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HOXC12 co-ordinates b2-adrenoceptor coupling to a cAMP/calcium feedforward loop to drive invasion.

Mr Terrance Lam

Oral presentation 1: Drug Discovery Theme, Eureka Room 1, December 2, 2024, 9:00 AM - 10:30 AM

Biography:
Terrance is a PhD student from Monash University. His research focuses on understanding compartmentalized signaling of the β2-adrenoceptor within the context of triple-negative breast cancer.

HOXC12 co-ordinates β_2-adrenoceptor coupling to a cAMP/calcium feedforward loop to drive invasion.

Terrance Lam[1], Bailey Cardwell[1], Bonan Liu[1], Alastair C Keen[1], Aeson Chang[1], Erica K Sloan[1], Michelle L Halls[1].

[1]Drug Discovery Biology Theme, Monash Inst Pharm Sci, Monash University, Parkville, VIC, Australia

Introduction. Noradrenaline released from sympathetic nerves during chronic stress accelerates cancer metastasis by activating β_2-adrenoceptors (β_2ARs) on tumour cells to promote invasion. We previously identified that the β_2AR drives invasion via a cAMP/calcium (Ca^{2+}) feedforward loop in the highly metastatic triple negative breast cancer (TNBC) cell line MDA-MB-231^{HM} (Pon et al, 2016). However, the commonality of this mechanism remains unknown.
Aims. To determine whether the β_2AR-cAMP-Ca^{2+}-invasion pathway is a common feature of TNBC.
Methods. Formoterol activation of the endogenous β_2AR was assessed in 11 TNBC cells. Interplay between cAMP and Ca^{2+} signalling was determined by measuring cAMP or Ca^{2+} in the presence of a Ca^{2+} chelator (BAPTA-AM) or an adenylyl cyclase inhibitor (2',3'-dideoxyadenosine, ddA), respectively. Invasion was assessed using microscopy. Principle component analysis (PCA) of transcriptomic and proteomic data was conducted to identify differentially expressed genes/proteins between cells that possess the feedforward loop compared to those that do not.
Results. There was no effect of formoterol on cAMP or Ca^{2+} in two TNBC cells (HCC1937, MDA-MB-453). Formoterol increased cAMP and Ca^{2+} in six of the remaining nine TNBC cells: HCC38 (pEC_{50} cAMP 8.58±0.44, Ca^{2+} 7.90±0.22; n=6-8), HCC1143 (pEC_{50} cAMP 9.88±0.33, Ca^{2+} 9.70±0.25; n=4-6), HCC1806 (pEC_{50} cAMP 8.88±0.48, Ca^{2+} 8.98±0.38; n=4-6), BT549 (pEC_{50} cAMP 9.48±0.28, Ca^{2+} 9.65±0.70; n=4-5), MDA-MB-468 (pEC_{50} cAMP 9.08±0.40, Ca^{2+} 9.07±0.17; n=4-6), HCC1395 (pEC_{50} cAMP 8.26±0.31, Ca^{2+} 7.73±0.58; n=4). BAPTA-AM and ddA inhibited cAMP and Ca^{2+}, respectively, suggesting that a cAMP/Ca^{2+} feedforward loop exists in these cells. Activation of the cAMP/Ca^{2+} feedforward loop correlated with accelerated invasion following β_2AR stimulation. PCA identified higher expression of the *HOXC12* transcription factor in cells with the feedforward loop. CRISPR knockdown of HOXC12 uncoupled the β_2AR from the cAMP-Ca^{2+}-invasion pathway.
Discussion. High expression of HOXC12 drives the β_2AR-cAMP-Ca^{2+}-invasion pathway in TNBC cells.

Pon CK et al (2016) FASEB J 30:1144-1154

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Discovery of PDLIM7 and PTPN9 as novel β2-adrenoceptor protein interactors

Miss Shaqayeg Ramazani

Oral presentation 1: Drug Discovery Theme, Eureka Room 1, December 2, 2024, 9:00 AM - 10:30 AM

Biography:
Shaqayeq Ramazani completed a Bachelor of Pharmaceutical Sciences Degree at Monash University in 2023. She is currently an Honours student in the Drug Discovery Biology Theme at the Monash Institute of Pharmaceutical Sciences, Monash University. She is investigating protein interactors of the ß2-adrenoceptor in the Spatial Organisation of Signalling Lab under the supervision of Associate Professor Michelle Halls and Dr Alastair Keen. Shaqayeq is keen on pursuing her PhD.

Discovery of PDLIM7 and PTPN9 as novel β_2-adrenoceptor protein interactors

Shaqayeq Ramazani[1], Alastair C Keen[1], Michelle L Halls[1]. [1]Drug Discovery Biology Theme, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville 3052, VIC, Australia.

Introduction. G protein-coupled receptors (GPCRs) form dynamic complexes with various proteins, including signalling, regulatory, and adaptor proteins, enabling signalling within subcellular domains for spatiotemporally specific cellular responses. As such, GPCRs do not exist in isolation at the plasma membrane but are surrounded by numerous proteins that could influence their activity. The β_2-adrenoceptor (β_2-AR) is a prime example of a GPCR that has a highly regulated and compartmentalised signalling network (Irannejad et al., 2013). Despite this, the list of proteins that can interact with the β_2-AR is relatively short. We therefore employed proximity biotinylation proteomics to identify proximal proteins to the β_2AR. We selected 11 novel β_2AR-associated proteins to study their interaction further.
Aims. To determine if the 11 candidate proteins interact with β_2AR and investigate their influence on β_2 AR signalling.
Methods. We used bioluminescence resonance energy transfer (BRET) to quantify the interactions between the β_2-AR and 11 potential protein partners. For the top candidates, we will determine their subcellular localisation using confocal microscopy. We will then assess the impact of top protein interactors on breast cancer cell invasion, as β_2AR signalling can result in undesirable outcomes in triple-negative breast cancer (Chang et al., 2016).
Results. We observed saturable BRET between the β_2AR and 2 out of 11 proteins, suggesting a specific interaction. PTPN9 shows a non-specific or low-affinity interaction with β_2AR under basal conditions. However, after receptor activation, a specific and saturable interaction was evident ($BRET_{50}$ mean±SEM n=4: stimulated 0.008.0±0.001). In contrast, a specific and saturable interaction was observed with PDLIM7 under basal conditions and after receptor activation ($BRET_{50}$ mean±SEM n=4: basal 0.029±0.009, stimulated 0.014±0.008).
Discussion. These experiments suggest that PDLIM7 and PTPN9 interact with the β_2AR in a distinct manner. These studies will characterise novel interactions for the β_2AR and define how they influence β_2AR activity and whether this has a role in triple-negative breast cancer progression.

1. Irannejad R et al (2013) Nature 495(7442), 534-538.
2. Chang A et al (2016) Brain behave immun, 57, 106-115

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Tomentosenol A, isolated from bee propolis, inhibits TGF-β1/SMAD3 signalling in human fibroblasts

Ms Lisa Randall

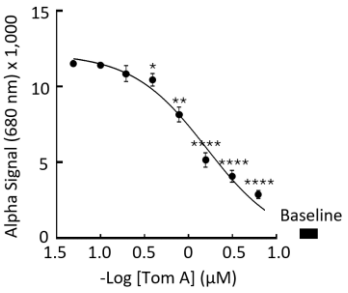
Oral presentation 1: Drug Discovery Theme, Eureka Room 1, December 2, 2024, 9:00 AM - 10:30 AM

Biography:
Lisa is a third year PhD candidate in the School of Health, Biomedicine discipline. Her PhD studies are centred around pharmacology, examining the cellular mechanisms of a novel, proposed anti-fibrotic compound isolated from the propolis produced by the Australian Stingless bee, Tetragonula carbonaria. This compound is Tomentosenol A. Her studies have enabled her to gain experience in a broad range of biochemical and molecular laboratory techniques, cell culture and animal models. She presents her findings wherever possible, winning the best poster presentation at the 2023 Australian Society for Medical Research, Post-Graduate Student Symposium. She represented the University of the Sunshine Coast and the Centre for Bioinnovation at the 2023 AusBiotech conference and is currently finalising her first research paper for submission for publication. She is a student member of ASCEPT, ASMR and APSA. In 2024 she has been accepted to present papers at the ASCEPT, APFP & APSA Joint Congress and the UniSC Research Conference.

Tomentosenol A, isolated from bee propolis, inhibits TGF-β1/SMAD3 signalling in human fibroblasts

Lisa J Randall[1,4], Sarah Bajan[1,2], Trong T Tran[3,4], Robert J Harvey[1,4], Fraser D Russell[1,4]. *School of Health, UniSC[1], Sippy Downs, QLD, Australia; School of Biotechnology and Biomolecular Sciences, UNSW[2], Sydney, Australia; School of Science, Technology and Engineering, UniSC[3]; Centre for Bioinnovation, UniSC[4], Sippy Downs, QLD, Australia.*

Introduction. We isolated and purified a meroterpenoid from Australian stingless bee propolis, called tomentosenol A (Tom A). Tom A inhibited TGF-β1-stimulated proliferation, migration and differentiation of human fibroblasts (Hamilton et al, 2022), suggestive of an anti-fibrotic compound. The mechanism of action Tom A is to be determined.
Aim. To examine the mechanism of action of Tom A in cultured adult human dermal fibroblasts and HEK293 cells, with a focus on the SMAD2/3 signalling pathway.
Methods. Normal adult human dermal fibroblasts were activated with TGF-β1 (10 ng/mL) in media containing DMSO (control), Tom A (0.05-6.25 µM), SIS3 (SMAD3 inhibitor; 10 µM) or GW788388 (TGF-βR1 inhibitor; 1 µM). Cell lysates were quantified for phosphorylation of SMAD3 (AlphaLISA assay), SMAD signalling (HEK293 cells expressing a SMAD3 reporter gene), and pro-fibrotic gene transcription (RTqPCR; *ACTA2*, *COL1A1, COL3A, CCN2*).



Results. TGF-β1 increased SMAD3 phosphorylation from baseline levels (Figure). Tom A (IC_{50}, 64.0 nM, n=3), SIS3 and GW788388 inhibited TGF-β1-stimulated SMAD3 phosphorylation. Tom A and SIS3 partially inhibited TGF-β1-stimulated SMAD3 reporter gene expression, while the combination of Tom A and SIS3 abolished the increased expression. TGF-β1 upregulated smooth muscle alpha actin (*ACTA2*), collagens 1A1 and 3A1 (*COL1A1*, *COL3A1*) and connective tissue growth factor (*CCN2*) transcription and this was reversed by 6.25 µM Tom A.
Discussion. The findings indicate inhibition of TGF-β1/SMAD3 signalling by Tom A. As this pathway is implicated in tissue fibrosis, Tom A is a compound that can be developed as a novel therapeutic approach for management of hypertrophic scars caused by deep dermal injuries that are associated with surgery, trauma, and burns.

Hamilton et al (2022) Antioxidants, 11:1604.

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Induction of S-phase arrest and apoptosis in glioblastoma via the HDAC8 PROTAC

Miss Jiranan Chotitumnavee

Oral presentation 1: Drug Discovery Theme, Eureka Room 1, December 2, 2024, 9:00 AM - 10:30 AM

Biography:
Jiranan Chotitumnavee is a lecturer in the Pharmacology Department at the Faculty of Dentistry, Mahidol University, Thailand. She received her Ph.D. in Medical Science from Kyoto Prefectural University of Medicine in 2022, supported by a scholarship from the Japanese government (MEXT). During her doctoral studies, she conducted research at Kyoto Prefectural University of Medicine and Osaka University, where she focused on developing a selective HDAC8 proteolysis-targeting chimera that promotes HDAC8 degradation through the ubiquitin-proteasome system. Her research interests include medicinal chemistry and the chemical biology of epigenetic modulators, particularly their mechanisms of action in cancer.

Induction of S-phase arrest and apoptosis in glioblastoma via the HDAC8 PROTAC

Jiranan Chotitumnavee[1], Chareerat Pruksaniyom[1], Rapeewan Settacomkul[2], Ratchanon Sukprasert[2], Sirada Srihirun[1], Yukihiro Itoh[3], Takayoshi Suzuki[3], Pornpun Vivithanaporn*[2]. Dept of Pharmacol, Fac of Dent, Mahidol Univ, BKK, Thailand[1], Chakri Naruebodindra Med Inst, Fac of Med Ramathibodi Hosp, Mahidol Univ, Samut Prakan, Thailand[2], Dept of Complex Molecular Chemistry, SANKEN, Osaka Univ, Osaka, Japan[3].

Introduction. Histone deacetylase 8 (HDAC8) is a crucial enzyme for growth and survival of glioblastoma cells. Unlike HDAC8 inhibitor, HDAC8 PROTAC modulates HDAC8 functions by inducing the proteasomal degradation of HDAC8 in cells. Recently, an HDAC8 inhibitor showed promise in inhibiting glioblastoma proliferation and improving survival rate in animal model. However, the novel strategy applying the HDAC8 PROTAC has yet to be explored.
Aims. To fill this gap, we intended to study effects and underlying mechanisms of the HDAC8 PROTAC in glioblastoma.
Methods. Initially, we investigated the HDAC8 reduction activity caused by the HDAC8 PROTAC through western blotting analysis. The cytotoxicity effect in glioblastoma and primary astrocytes was assessed using the MTT assay. The antiproliferative effect was investigated by employing the Deep Red Cytopainter® staining dye, and live-cell imaging was conducted using the Incucyte® analysis system. Cell cycle analysis was performed by applying the propidium iodide DNA labeling technique. The Annexin V-PE apoptosis assay was utilized to detect apoptotic cells. Lastly, we determined the levels of protein regulators involved in cell cycle and apoptosis through western blotting analysis.
Results. Our study revealed that the HDAC8 PROTAC reduced HDAC8 level in glioblastoma with a DC_{50} of 0.15 ± 0.07 µM. The HDAC8 PROTAC also reduced glioblastoma cell viability with IC_{50} of 4.87 ± 0.42 µM and showed less cell cytotoxicity effect in primary astrocytes. In addition, the HDAC8 Protac suppressed cell proliferation in a dose- and time-dependent manner. Interestingly, the HDAC8 PROTAC induced S-phase arrest by reducing the level of CDK2 and CDK4 in glioblastoma cells. As well as, the HDAC8 PROTAC regulated the level of Bax and Bcl-2 in glioblastoma, leading to the induction of glioblastoma cell apoptosis.
Discussion. By targeting HDAC8 for degradation, the HDAC8 PROTAC disrupts glioblastoma cell growth and survival by regulating the proteins involved in both cell cycle and apoptosis processes. These findings provide evidence for the potential therapeutic strategy of the HDAC8 PROTAC in glioblastoma treatment.

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Inhibition of CK1δ Attenuates IL-1α-Induced Epithelial-Mesenchymal Transition in Human Lung Epithelial Cells

Miss Jana Zielinski

Oral presentation 1: Drug Discovery Theme, Eureka Room 1, December 2, 2024, 9:00 AM - 10:30 AM

Biography:
Jana graduated from the University of Melbourne in 2020 with a Bachelor of Science majoring in Pharmacology. She received her Honours degree in 2021 under the supervision of Prof. Alastair Stewart, with the thesis titled: "The Art and Artefact of Static Culture". Jana then began her PhD in 2022 with Prof. Alastair Stewart focusing on the characterisation of Casein Kinase 1 delta in circadian rhythm and cancer tumorigenesis. Her research goals include advancing the use of microphysiological systems for in vitro drug discovery. She was a general committee member of the ASCEPT student forum in 2023.

Inhibition of CK1δ Attenuates IL-1α-Induced Epithelial-Mesenchymal Transition in Human Lung Epithelial Cells
Jana L Zielinski[1,2], Alastair G Stewart[1,2]. Dept of Biochemistry & Pharmacology, Univ of Melbourne[1], ARC Centre for Personalised Therapeutics Technologies[2], VIC, Australia.

Introduction. Casein Kinase 1 Delta (CK1δ) is a conserved serine/threonine protein kinase that is aberrantly expressed in lung tumour cells and involved in cellular processes, such as circadian rhythm and fibrogenesis. There is emerging evidence that pro-inflammatory cytokines promote metastasis. CK1δ/ε inhibition has previously been shown to mediate TGF-β-induced epithelial-mesenchymal transition (EMT) pathways (Keenan et al., 2018). The dual CK1δ/ε inhibitor PF670462 is therefore a potential anti-cancer therapeutic agent.
Aims. To explore whether IL-1α induction of EMT is CK1δ/ε-dependent in the human lung adenocarcinoma cell line A549 and in primary epithelial cells.
Methods. A549, immortalised primary cell line BCi NS and primary bronchial epithelial cells, were incubated with PF670462 (3 μM) for 30 min prior to stimulation with IL-1α (30 pM), TGF-β (100 pM) or a combination for 48h. CSNK1D and CSNK1E were transiently knocked down with siRNA prior to cytokine stimulation. EMT markers were measured with fluorescence microscopy and q-PCR. PAI-1, IL-6, IL-8 and IL-11 cytokine levels were measured by immunoassay. Cell migration, invasion and viability were measured with live cell microscopy. Global and phospho-proteomes were measured with LC-MS/MS Orbitrap Eclipse mass spectrometer.
Results. IL-1α-induced EMT-like morphology change and significantly increased gene markers such as Vimentin and TWIST in all cell lines ($p<0.01$, n=3-6). PF670462 or CSNK1D knockdown but not the TGF-β receptor kinase, ALK5, inhibitor (SB431542) inhibited IL-1α-induced EMT (n=5-6). IL-1α increased cell migration which was also inhibited by PF670462 (n=5). Cytokines induced paclitaxel resistance in A549 which is prevented by PF670462 (n=4).
Discussion. Fibrogens, morphogens and inflammagens may increase metastatic risk via fibrosis, EMT and migration. Cytokine attenuation by PF670462 indicates therapeutic potential for metastatic forms of cancer.
Keenan et al (2018) Casein kinase 1δ/ε inhibitor, PF670462 attenuates the fibrogenic effects of transforming growth factor-β in pulmonary fibrosis. *Frontiers in Pharmacology*, 9(738):1-15

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Exploring and Targeting Calcium Signaling Pathways in Cellular Senescence

Mr Vijayraghavan Seshadri

Oral presentation 1: Drug Discovery Theme, Eureka Room 1, December 2, 2024, 9:00 AM - 10:30 AM

Biography:

I am current final year PhD candidate at the department of pharmacology, university of Tasmania. I am currently doing my research at the department of Pharmacology, Biomedicine discovery institute, Monash university under the supervision of Dr Iman Azimi. My research investigates the role of calcium signalling in cellular ageing. In my current research, I have developed high throughput fluorescence microscopy-based methods for detecting cellular senescence markers. We have also discovered compounds that can be re-purposed to target age related pathologies. I am interested in the field of drug discovery in the field of ageing and age-related diseases.

Exploring and Targeting Calcium Signalling Pathways in Cellular Senescence

Vijayraghavan Seshadri[1,2], Iman Azimi[1,2], School of Pharmacy and Pharmacology[1], University of Tasmania, Hobart, TAS, Department of Pharmacology[2], Biomedicine discovery institute, Monash University, Clayton, VIC, Australia.

Introduction. Cellular senescence, characterised by irreversible cell cycle arrest and a secretory phenotype, is linked to age-related diseases. Emerging evidence highlights calcium signalling's role in senescence and its therapeutic potential. Repurposing calcium channel modulators offers promise for addressing senescence and associated disorders.

Aims. To study the re-modelling of calcium signalling pathways in different models of cellular senescence. To test calcium channel modulators for their potential senotherapeutic effect.

Methods. Human derived fibroblasts (HDF, < passage 10) were induced to senescence via Mitomycin C (MMC) (DNA damage) or D-galactose (oxidative stress). Cytosolic calcium was measured using Cal Red™ R525/650 AM (AAT Bioquest) by fluorescence microscopy. Endoplasmic reticulum (ER) Ca^{2+} release and store-operated Ca^{2+} entry (SOCE) were measured using Fluo-4 AM (Thermo Fisher Scientific) by plate reader and fluorescence imaging. Gene expression were assessed by qPCR. For drug screening, 140 small-molecule compounds targeting different calcium channels, were tested in our MMC-induced senescence. Senescence markers including SA-β-gal, nuclei area, cell area, P21, and EDU incorporation, were measured by fluorescence microscopy.

Results. Cytosolic Ca^{2+} increased 2-fold in MMC-induced senescence and 1.5-fold in D-galactose-induced senescence. SOCE response showed a 1.5-fold decrease in MMC-treated cells. This is while, ER Ca^{2+} release remained unchanged. SOCE components' expression increased over 2-fold in MMC-induced senescence. Markers of senescence-associated secretory phenotype (SASP) were upregulated in MMC-induced senescence and pharmacological suppression of SOCE reduced the expression of some of these markers, including IL-1α, MMP-1, and IL-8, by around two folds. Drug screening revealed specific Ca^{2+} channel modulators with senomorphic (reducing senescence marker levels) or senolytic (selectively killing senescent cells) abilities.

Discussion. This study identified a remodelling of Ca^{2+} signalling in two senescence models. In addition, calcium channel drug screening identified potential senotherapeutic compounds. These compounds can be tested in senescence-associated pathological conditions for their potential therapeutic effects.

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Pharmacokinetics, dosing, and effectiveness of allopurinol in dialysis: a scoping review

Miss Noha Kamel

Oral presentation 2: Pharmacy Practice & Clinical Pharmacology Themes, Eureka Room 2, December 2, 2024, 9:00 AM - 10:30 AM

Biography:

Noha Kamel is international PhD student at the University of Sydney and a recipient of the University of Sydney international stipend and tuition fee scholarships. She is working under supervision of Dr. Sophie Stocker and Dr. Ronald Castelino on pharmacokinetics and effectiveness of allopurinol in gout patients with end stage kidney diseases. She did her master's degree in Mansoura University, Egypt where she worked on a critical care project that resulted in a research paper entitled " Effect of Anti-inflammatory and Antimicrobial Cosupplementations on Sepsis Prevention in Critically Ill Trauma Patients at High Risk for Sepsis" in Frontiers in Pharmacology, impact factor 5.810, doi https://doi.org/10.3389/fphar.2021.792741 . She is highly interested in clinical pharmacy, pharmacometrics, modelling and simulation. Research gate profile: https://www.researchgate.net/profile/Noha-Kamel-6.

Pharmacokinetics, dosing, and effectiveness of allopurinol in dialysis: a scoping review

Noha Kamel[1,2], Michael Stokes[1,3], Daniel Wright[1], Kamal Sud[4], Surjit Tarafdar[5], Ronald Castelino[1,6], Sophie Stocker[1]. Sch. of Pharmacy, FMH, Univ. of Sydney[1], NSW, AUS; Clin. Pharm. & Pharm. Pract. Dept., Fac. of Pharm., Mans. Univ.[2], Mans., Egypt; Paed. ICU, Pharm. Dept., Westmead Child. Hosp.[3], NSW, AUS; Kid. Research Cent., Renal Med. Dept., Nepean Hosp.[4], NSW, AUS; Nephrol. Dept., Blacktown Hosp.[5], NSW, AUS; Pharm. Dept., Blacktown Hosp.[6], NSW, AUS

Introduction. Oxypurinol, the active metabolite of allopurinol, is mainly eliminated by the kidneys and many factors (including dialysis) can affect oxypurinol elimination in patients with compromised kidney function. Therefore, dosing allopurinol in patients with kidney failure receiving dialysis can be challenging.

Aims. To explore dosing practices, clearance of urate and oxypurinol with dialysis, and effectiveness (urate-lowering or frequency of gout flares) of allopurinol in patients with gout receiving haemodialysis (HD) or peritoneal dialysis (PTD).

Methods. Literature search was conducted in 5 databases (Ovid MEDLINE, Ovid Embase, EBSCOhost CINAHL, Scopus, and Web of Science). Abstract, full text screening and data extraction were done independently by 2 reviewers. Studies were grouped by dialysis modality.

Results. The 18 studies identified included 390 patients, most on HD (n=274, 70%). Allopurinol was commonly (6/8 studies) administered after dialysis. The average allopurinol dose per study was higher in HD (114-600 mg/day) than PTD (110-125 mg/day). The peritoneal dialytic clearance was 3.14 mL/min for oxypurinol (n=5) and 2.7-4 mL/min for urate (n=25). Haemodialytic clearance was 78-137 mL/min for oxypurinol (n=21) and 80-165 mL/min for urate (n=31). HD sessions decreased urate concentrations by 56-71% (n=7) compared to 8-13% with a 4-hour PTD dwell (n=5). Over time (1-106 days), urate concentrations in patients (n=84) on HD receiving allopurinol reduced by 14-41%. An average allopurinol dose of 121 ± 62 mg/day (HD) and 110 ± 72 mg/day (PTD) achieved target urate concentrations (serum urate <0.36 mmol/L) in 61% (20/33) and 47% (13/28) of HD and PTD patients, respectively. Gout flares decreased from 2 attacks/year to 0.1 /year after >2 years of HD or PTD (n=79) , with an initial transient increase in gout flares when starting HD (n=2).

Discussion. Oxypurinol and urate are similarly cleared by dialysis. Titration of allopurinol doses administered post-dialysis session, to achieve target urate is suggested. Future studies considering the dialysis modality subtype (e.g. haemodiafiltration, automated PTD) and current dialyser technology are required to inform optimal dosing.

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Reliably Quantifying Medicines Use Using Prescribing Data - Definitions Matter.

A/Prof Matthew Doogue

Oral presentation 2: Pharmacy Practice & Clinical Pharmacology Themes, Eureka Room 2, December 2, 2024, 9:00 AM - 10:30 AM

Biography:
Matt Doogue is a clinical pharmacologist passionate about applying clinical pharmacology principles to patient care. He has clinical and academic roles in clinical pharmacology and is a physician in a busy acute general medicine service. His interests include quality use of medicines, adverse drug reactions, clinical decision support, and therapeutic drug monitoring.

Quantifying Medicines Use Using Hospital Prescribing and Administration Data, What Should We Count?

Matthew Doogue[1,2], Lorna Pairman[1], Olivia Clendon[2], Milan Sundermann[1], Paul Chin[1,2], Richard McNeill[2]. Dept of Medicine, University of Otago; Dept of Clinical Pharmacology, Health New Zealand[2], Christchurch, New Zealand.

Introduction. Hospital prescribing systems hold rich data on medicines use both for research and to inform health policy and practice. Using these data well is challenging, a minor definitional change can affect results. What is a prescription, a medicine, a change in a medicine, and a hospital admission are not consistently defined. When these terms are used in the literature studies seldom provide definitions sufficient for replication. When used clinically, heterogeneity in definitions makes comparisons between institutions unreliable. We have encountered this challenge and wish to raise this issue for discussion.
Aims. To describe the complexity of using tertiary hospital medicines prescribing and administration data for research.
Methods. We have tested and refined definitions relating to medicines use using data from a large hospital prescribing and administration system (MedChart™) over several years. Prescribing data were extracted from the prescribing system into tables in the regional data warehouse. Reports have been developed for clinical use using different software tools and a series of research project undertaken. These projects have a range of requirements for numerators and denominators defined by their subjects, for example: patient treatment, medicines use, and prescribing activity,
Results: A 'medicine' is defined in law in New Zealand (and elsewhere) and standardised via the INN, but some are combination products. A medicine may be regular (long or short term) or PRN, and systemic or non-systemic. A 'medicine change' is initiation, cessation, change in dose rate (amount or frequency), or a change in route of administration. A 'prescription' is an order which has been administrated to the patient at least once, or for a PRN medicine 'live' for at least one hour. Additionally some queries pertaining to staff decisions/actions extend to all orders recorded in the system. A 'hospital admission' has two levels and which definition is used depends on the question. The time from admission to hospital until discharge to the community is a 'stay' and being under a 'service' is an 'event'.
Discussion. Medicine use in hospital is complex and commonly used descriptors of medicine use are insufficient for valid and reliable numerators and denominators of medicines. Standardised detailed definitions are needed to use medicines data consistently in research and clinical practice.

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Strategies to facilitate continuity of in-hospital medication changes post-discharge: a systematic review

Miss Kate Johnstone

Oral presentation 2: Pharmacy Practice & Clinical Pharmacology Themes, Eureka Room 2, December 2, 2024, 9:00 AM - 10:30 AM

Biography:

I am a fifth year Bachelor of Pharmacy and Management (Honours) student studying at the University of Sydney. My research interest lies in geriatric medicine. Specifically, I am interested in improving the safety of medication use among older adults. This year, I have had the opportunity to collaborate with a team of supervisors from the Kolling Institute at Royal North Shore Hospital and the University of Sydney School of Pharmacy. Their guidance has been instrumental in developing my systematic review and final thesis on the continuity of in-hospital deprescribing after discharge. In addition to my research interests, I enjoy working as a pharmacy student at my local community pharmacy.

Strategies to facilitate continuity of in-hospital medication changes post-discharge: a systematic review

Kate Johnstone[1], Sarah N Hilmer[2], Bonnie M Liu[2], Sarita Lo[2], Lisa Kouladjian O'Donnell[1,2], Edwin CK Tan[1], Nashwa Masnoon[2]. Sydney Pharm School, Faculty of Med and Health, The Univ of Sydney[1], Sydney, NSW, Australia; Laboratory of Ageing and Pharmacol, Kolling Institute[2], The Univ of Sydney and Northern Sydney Local Health District, Sydney, NSW, Australia.

Introduction. Older adults frequently undergo medication changes in hospital. Several strategies have been investigated to facilitate continuity of in-hospital medication changes post-discharge.
Aims. To summarise i) strategies that have been investigated to facilitate post-discharge continuity of in-hospital medication changes in older adults and ii) their impact on continuity of medication changes and clinical, health service utilisation and patient-reported outcomes.
Methods. A systematic review was conducted using MEDLINE and EMBASE databases to identify existing strategies and their impact on continuity, health service utilisation, clinical and patient-reported outcomes post-discharge in older adults, with mean/median age ≥60 years.
Results. Forty-nine out of 800 articles identified were included. Strategies commonly identified included providing discharge medication lists to patients and/or their general practitioners (GPs) (36/49, 73.5%), discharge counselling (28/49, 57.1%) and medication reconciliation (28/49, 57.1%). Most studies used multicomponent strategies (39/49, 79.6%) implemented by multidisciplinary teams (28/49, 57.1%). Twenty-five of the 49 studies (51.0%) reported significant improvements in continuity, while the remaining studies did not report significant impact on continuity. For example, of the 28 studies investigating medication discrepancies, 13 (46.4%) showed reduction in discrepancies following intervention. There were no significant impacts on clinical (n=12) or health service utilisation outcomes (n=17). Two of three studies reported significant improvements in patient-reported quality of life.
Discussion. Strategies to facilitate continuity of in-hospital medication changes focus on communicating medication changes to patients and GPs. There is evidence of positive impact of existing strategies on continuity of medication changes and quality of life. Future analyses investigating strategy complexity and cost-effectiveness may inform their translation into practice.

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A real-world analysis of AI chatbot performance for medicines information enquiries

Mr Duncan Yorkston

Oral presentation 2: Pharmacy Practice & Clinical Pharmacology Themes, Eureka Room 2, December 2, 2024, 9:00 AM - 10:30 AM

Biography:
Duncan Yorkston is a specialist Medicines Information Pharmacist within the Department of Clinical Pharmacology at Christchurch Hospital. In addition to a bachelor's degree in pharmacy, Duncan has completed a graduate certificate in analytics and has a special interest in health informatics and therapeutic drug monitoring.

A real-world analysis of AI chatbot performance for medicines information enquiries

Duncan Yorkston[1], Tracey Borrie[1], Paul Chin[1,2]. Department of Clinical Pharmacology, Health New Zealand - Te Whatu Ora Waitaha[1], Christchurch, New Zealand; Department of Medicine, University of Otago[2], Christchurch, New Zealand.

Introduction. The provision of medicines information (MI) services often requires interpretation and clinical judgment of complex scenarios by experienced pharmacists. To date, few studies have assessed the performance of artificial intelligence (AI) chatbots to assist pharmacists providing MI advice (Morath et al, 2023).
Aims. To evaluate the performance and risk associated with two readily accessible AI chatbots (Microsoft Copilot and Google Gemini) to answer medicines-related questions.
Methods. A sample of 20 questions from 4 categories (pregnancy and breastfeeding, pharmaceutical, dosage and administration, drug interaction and adverse drug reaction) answered by the Christchurch MI service (NZ) in November 2023 were entered in the chatbot applications during January 2024. All questions were preceded with the prompt "I'm a pharmacist". Chatbot answers were evaluated by comparing with the reference answer given by the Christchurch MI service using a consensus process involving two MI pharmacists and one clinical pharmacologist in the domains of content (correct, incomplete, false), patient management (possible, insufficient, not possible), risk of patient harm (no risk, low risk, high risk) and whether the chatbot answer prompted review of the reference answer.
Results. Only 6/40 (n=2 for Gemini, n=4 for Copilot) answers provided by the chatbots were considered correct and with adequate information to commence patient management with no risk of harm. Most were incomplete (70%, 28/40) regarding content but deemed to be low risk (85%, 34/40) of causing patient harm. There were no answers considered to be high risk of causing patient harm. 30% of answers (12/40) resulted in a prompt to review the reference answer.
Discussion. Our study results show that the selected chatbots provided answers that were typically suboptimal, albeit a significant minority prompted further review of the MI service answer, which potentially may have improved the answers. Further investigation of MI questions is required to determine differences in inter-category performance of the chatbots.

Morath B et al (2023) Eur J Hosp Pharm 0:1-7

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Pharmacists and community health workers to improve medication adherence: a systematic review

Dr Carole Bandiera

Oral presentation 2: Pharmacy Practice & Clinical Pharmacology Themes, Eureka Room 2, December 2, 2024, 9:00 AM - 10:30 AM

Biography:
A pharmacist by training, Carole graduated with a PhD in 2023 (University of Geneva, Switzerland). During her PhD she coordinated two randomised controlled trials to evaluate the impact of a pharmacist-led interprofessional medication adherence program on medication adherence in patients with chronic conditions. In 2023, she received a fellowship from the Swiss National Science Foundation to conduct a 2-year post-doctorate at the University of Sydney (Prof Parisa Aslani's research group), where she is investigating the interprofessional collaboration between pharmacists and community health workers, and how they can synergistically work together.

Pharmacists and community health workers to improve medication adherence: a systematic review

Carole Bandiera[1], Ricki Ng[1], Sabuj Kanti Mistry[2], Elizabeth Harris[3], Mark Harris[3], Parisa Aslani[1]. School of Pharmacy, The University of Sydney[1], Sydney, NSW, Australia; School of Population Health, University of New South Wales[2], Sydney, NSW, Australia; Centre for Primary Health Care and Equity, University of New South Wales[3], Sydney, NSW, Australia.

Introduction. There is increasing evidence to support the effectiveness of interventions involving community health workers (CHWs) in improving patient health outcomes, which reinforces their growing integration in healthcare teams. However, little is known about the interprofessional collaboration between pharmacists and CHWs.
Aims. To explore the impact of interventions involving pharmacists and CHWs on improving medication adherence.
Methods. The English scientific literature published in Embase, MEDLINE, Web of Science, CINAHL, Scopus, plus the grey literature were searched in April 2024. Using the software Covidence, two researchers screened article titles and abstracts and assessed full-text articles for eligibility. Studies were included if i) the intervention was delivered by pharmacists and CHWs and ii) reported on medication adherence outcomes. Data were extracted using a customized template using Excel. The Effective Public Health Practice Project quality assessment tool was used to assess the studies' methodological quality.
Results. Eight studies met the inclusion criteria, including a total of 1494 participants. Seven studies were conducted in the United States, and five were published in the last 4 years. The interventions consisted of medication therapy management, medication reconciliation, and repeated education sessions. The CHW shared clinical and non-clinical patient information and ensured a culturally safe environment while the pharmacist delivered the intervention. In six studies, medication adherence was evaluated through patient self-reported measures. Two studies used objective measures such as, pharmacy refill records and proportion of days covered. Three studies showed a significant improvement in medication adherence. Half of the studies were of weak quality.
Discussion. There were a small number of studies identified which focused on the interprofessional collaboration between pharmacists and CHWs to improve medication adherence. The impact of the interventions on medication adherence was limited. Further studies of higher quality are needed to better evaluate the impact of such collaboration on patient health outcomes.

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A model of shared responsibility in pharmacy practice.

Mr William Olsen

Oral presentation 2: Pharmacy Practice & Clinical Pharmacology Themes, Eureka Room 2, December 2, 2024, 9:00 AM - 10:30 AM

Biography:
Will is a PhD candidate entering the final year of his project. Having completed a Bachelor of Pharmacy with honours in 2018, Will is a practicing pharmacist with clinical experience in a range of community settings. His PhD project is in pharmacy ethics, exploring the responsibilities of pharmacists in the context of the opioid crisis. Will is also passionate about education, with a particular interest in teaching ethical decision-making.

A model of shared responsibility in pharmacy practice.
William Olsen[1], Chris Freeman[1,2,3], & Adeleke Adewumi[1], Adam La Caze[1]
School of Pharmacy, The University of Queensland[1], Brisbane, QLD, Australia; Faculty of Medicine, The University of Queensland[2], Brisbane, QLD, Australia; Metro North Hospital and Health Service[3], Brisbane, QLD, Australia

Introduction: Healthcare demands collaboration. When practitioners collaborate, the responsibility they have for the outcomes of their patients is shared. The exact nature of shared responsibility is inconsistently described in professional guidance. When more than one actor is responsible for an outcome, the risk is that individuals do not take certain actions because they are not individually accountable. Patients may be harmed if their health practitioners fail to meet certain obligations as a result of this inaction.
Aim: This study seeks to outline a model of shared responsibility that addresses the risks of inaction that are inherent in situations where more than one practitioner is responsible for a patient. This work attempts to resolve the ambiguity leading to the multiplicity of interpretations of shared responsibility as a concept in pharmacy practice.
Methods: Arguments are presented which determine the nature of pharmacist responsibility in collaborative settings. The model draws on supporting literature in the field of pharmacy practice research as well as research relating to shared responsibility in the context of international co-operation and law.
Results: The presented model of shared responsibility addresses the risk of diffusion of responsibility by attributing responsibility to individual actors with respect to their role, in relation to the role of other practitioners, in collaborative healthcare. Discussed within the model is the fact that the responsibility for a shared health outcome does not rest on the group of involved practitioners as one entity. Rather, this responsibility should be distributed among all involved practitioners as individuals. Pharmacist obligations in specific cases, referring to how a practitioner should act to bring about a certain outcome, are dependent on the obligations and actions of other actors.
Discussion: The proposed model is applied to three hypothetical cases involving a pharmacist and a prescriber to demonstrate the determination of (1) sole prescriber accountability, (2) joint prescriber and pharmacist accountability, and (3) sole pharmacist accountability. The proposed model of shared responsibility in pharmacy practice provides a basis to support pharmacists in recognising and acting upon their obligations in collaborative healthcare contexts.

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‘Omics and organoids: human cardiac fibrosis modelling for therapeutic target discovery

Dr Harley Robinson

Oral presentation 3: Cardiovascular & Urogenital & Gastrointestinal Themes, Eureka Room 3, December 2, 2024, 9:00 AM - 10:30 AM

Biography:
Dr Harley Robinson is an early career research officer at QIMR Berghofer Medical Research Institute. As an aspiring leader in multi-omics with an emphasis in mass spectrometry, Dr Robinson’s larger body of work focusses on the underlying mechanisms driving disease progression.

Her Bachelor in Biomedical Science (Hons, University of Queensland), and subsequent PhD (UQ/QIMRB) work focussed on mechanisms underpinning advanced prostate cancer, supported by the Australia Research Council Discovery scheme, lending to non-invasive prognostic biomarker discovery. Following candidature, she joined the Cardiac Bioengineering group and currently leads the proteomics and phosphoproteomics research in heart failure for novel drug target discovery.

‘Omics and organoids: human cardiac fibrosis modelling for therapeutic target discovery
Harley R Robinson[1], James E Hudson[1], Simon R Foster[1,2]. Cardiac Bioengineering, QIMR Berghofer Medical Research Institute[1], Brisbane, QLD, Australia; Dept of Pharmacol[2], Monash University, Clayton, VIC

Introduction. Cardiac fibrosis, defined by the excess deposition of extracellular matrix (ECM) associated with myocardial stiffness and diastolic dysfunction, is a pathological feature in >90% of heart failure patients. There are currently no effective cardiac anti-fibrotics, with previous approaches failing due to 1) multiple drivers of cardiac fibrosis, and 2) limited cardiac models capturing underlying human pathophysiology.
Aims. To define pro-fibrotic mechanisms that regulate the development of fibrosis in human cardiac organoids (hCO).
Methods. The direct effects of pro-fibrotic stimuli (endothelin-1, 0.1μM; angiotensin II, 1μM; TGFβ, 10μM; PAR1, 1μM; and “fibrotic cocktail” mix of these stimuli) on hCO contractile force, rate and contraction kinetics were analysed from 10 second videos using custom Matlab scripts (Mills et al, 2021; Voges et al 2023). These functional measures were complemented with mass spectrometry-based proteomics to identify cardiac proteome changes by each fibrotic driver, utilising correlation and differential abundance analyses.
Results. Individual fibrotic stimuli generated a range of different effects on hCO contraction at 24hrs, with endothelin-1 leading to a 37% prolongation of relaxation time (p.adj <0.0001), characteristic of diastolic dysfunction. Combination of fibrotic stimuli led to contrasting effects on contractile function. Equally, fibrotic stimuli alone and in pro-fibrotic cocktail differentially modulated ECM proteins, including thrombrospondin-1, which increased abundance by 14% with ET-1, 65% with PAR1 and 80% with TGFβ versus untreated hCOs, but 285% with the fibrotic cocktail (p.adj=0.02).
Discussion. While each stimuli led to changes in ECM and its regulatory proteins, the composition of matrix components seemed to govern contractile dysfunction rather than total ECM production. The complex interactions between the multiple cardiac fibrosis drivers highlight possible new signalling pathway targets and an exciting opportunity to dissect the underlying nuance underpinning cardiac fibrosis. By combining ‘omics technologies with functional analysis in cardiac organoids we hope to identify new anti-fibrotic targets.

Mills R et al (2021) Cell. 184(4):2167–2182.
Voges et al (2023) Cell Rep. 42(5):112322.

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Mechano-sensitive protein TXNDC5 promotes AVF neointimal hyperplasia through EndoMT and eNOS suppression

Mrs Laura Ianalieva

Oral presentation 3: Cardiovascular & Urogenital & Gastrointestinal Themes, Eureka Room 3, December 2, 2024, 9:00 AM - 10:30 AM

Biography:
Laura Ianalieva is a Ph.D. student at the National Taiwan University College of Medicine in Taipei. She is investigating the pathological role of specific proteins in neointimal hyperplasia and the dysfunction of arteriovenous fistulas. She also gained hands-on experience at Academia Sinica's Institute of Biological Chemistry, where she contributed to proteasome research using cryo-electron microscopy.

Her research and academic contributions reflect her commitment to advancing the field of pharmacology, with a focus on understanding complex protein interactions in vascular biology. Laura Ianalieva is preparing to complete her Ph.D. in the coming years and aims to leverage her expertise in a future role within the pharmaceutical or biomedical sectors.

Mechano-sensitive protein TXNDC5 promotes AVF neointimal hyperplasia through EndoMT and eNOS suppression

Laura R. Ianalieva[1], Chih-Fan Yeh[1,2], Yu-Shan Lin[1], Chien-Yin Su[1], Chih-Cheng Wu[3], Kai-Chien Yang[1,2,4]. Graduate Institute and Department of Pharmacology, National Taiwan University College of Medicine[1], Taipei, Taiwan; Division of Cardiology, Department of Internal Medicine and Cardiovascular Center[2], National Taiwan University Hospital, Taipei, Taiwan; Division of Cardiology, Department of Internal Medicine, NTU Hsin-Chu Hosptial[3], Hsin-Chu City, Taiwan; Institute of Biomedical Sciences, Academia Sinica[4], Taipei, Taiwan

Introduction. Arteriovenous fistula (AVF) is the preferred access for hemodialysis in end-stage renal disease. Neointimal hyperplasia (NH) near fistulas, induced by disturbed blood flow (DF) and low shear stress, contributes to AVF stenosis and failure. The underlying molecular mechanisms of NH and AVF dysfunction remain poorly understood. Combining bioinformatics, clinical and basic experiments, we identified an endoplasmic reticulum protein, thioredoxin domain containing 5 (TXNDC5), as a novel mediator of DF-induced endothelial dysfunction and AVF failure.
Aims. This study aimed to explore the role of TXNDC5 in NH formation in AVF and assess if targeting TXNDC5 can prevent AVF failure.
Methods. HUVECs were subjected to laminar and oscillatory flow in a cone flow device to mimic hemodynamic stress. siRNA transfection targeted TXNDC5, followed by qRT-PCR. AVF surgery in vivo model and further IF staining studies.
Results. TXNDC5 was markedly upregulated in the vascular wall of stenotic AVF from hemodialysis patients and in the neointima of mouse aortocaval fistula. Endothelium-specific deletion of Txndc5 in mice significantly reduced AVF neointimal volume, venous wall thickness and collagen deposition 42 days post AVF creation, which was accompanied by a restoration of the expression level of endothelial nitric oxide synthase (eNOS), a vasoprotective enzyme downregulated in the endothelium by DF, suggesting the essential role of endothelial TXNDC5 in AVF neointima formation. Lineage-tracing experiments revealed that endothelial cells contribute to neointima via endothelial-to-mesenchymal transition (EndoMT). In human endothelial cells, DF decreased eNOS while increasing TXNDC5 and mesenchymal markers, linking TXNDC5 to DF-induced NH and dysfunction via EndoMT and eNOS suppression.
Discussion. TXNDC5 is a pivotal mediator of DF-induced NH and AVF dysfunction through regulating EndoMT and eNOS. Targeting endothelial TXNDC5 could be an effective therapeutic strategy to combat AVF dysfunction in hemodialysis patients.

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The evolutionary loss of cardiac regeneration; the impact of the ectotherm-to-endotherm transition

Ms Lynn Devilee

Oral presentation 3: Cardiovascular & Urogenital & Gastrointestinal Themes, Eureka Room 3, December 2, 2024, 9:00 AM - 10:30 AM

Biography:
Lynn Devilée obtained her Bachelor's degree in Biomedical Sciences and Master's degree in Molecular Mechanisms of Disease at the Radboud University in Nijmegen, the Netherlands. In 2021, she started her PhD in the Cardiac Bioengineering Laboratory at QIMR Berghofer Medical Research Institute in Brisbane, Australia, where she studied the mechanisms underlying the loss of cardiac regeneration in the endotherm heart using human cardiac organoids. Lynn has recently submitted her PhD thesis and is now continuing her career in the Cardiac Bioengineering Laboratory, shifting her focus to studying cardiac fibrosis.

The evolutionary loss of cardiac regeneration – the impact of the ectotherm-to-endotherm transition

Lynn Devilée[1,2], Janice Reid[1,3], Sean Humphrey[4], Rebecca Fitzsimmons[1], Mary Lor[1], Michael Doran[2,5], James Krycer[1], Qing-Dong Wang[6], Richard Mills[1,4], James Hudson[1,2,3]. QIMR Berghofer Medical Research Institute[1], Brisbane, QLD, Australia; Faculty of Health, QUT[2], Brisbane, QLD, Australia; Faculty of Medicine, UQ[3], Brisbane, QLD, Australia; MCRI[4], Melbourne, VIC, Australia; Oncology R&D, AstraZeneca[5], Gaithersburg, MD, USA; BioPharmaceuticals R&D, AstraZeneca[6], Gothenburg, Sweden

Introduction. The heart of endotherms such as humans and mice loses the ability to regenerate shortly after birth, leading to a compromised ability to recover following injury. In contrast, ectotherms like zebrafish and newts can effectively regenerate their hearts, even as adults. Understanding why this loss occurs and what prevents endogenous cardiac regeneration of the mature endotherm heart could uncover new targets for cardiac regeneration.
Aims. To assess whether the high metabolic/energetic demand of endothermy prevents regeneration of mature endotherm cardiomyocytes (CM).
Methods. To inhibit the primary energy-consuming processes in CM, Ca^{2+} cycling and contraction, we treated mature human cardiac organoids (hCO) (Mills et al, 2021 & Voges et al, 2023) with nifedipine (nif, 3 µM) or mavacamten (mav, 0.3 µM), respectively. Cell cycle dynamics were studied by immunofluorescent detection of cell cycle markers. Using RNA-sequencing and phosphoproteomics we assessed if transcriptional or post-translational changes drive the cell cycle response. Metabolic flux analysis was used to assess the changes in oxidative and glycolytic metabolism in hCO.
Results. Functional inhibition by nif or mav (48 h) increased the proportion of CM in mitosis (pHH3+) (nif 0.53% ± 0.06 ($p=0.009$) vs control 0.20% ± 0.05, mav 0.53% ± 0.07 ($p=0.02$) vs control 0.31% ± 0.05) and the number of CM nuclei (NKX2.5+) (nif +10% ($p=0.0015$), mav +12% ($p<0.0001$)). Both the transcriptional (8 h) and phosphorylation (15 min) changes suggested diminished signalling associated with cardiac structure and function. A new metabolic homeostasis characterised by reduced oxidative metabolism without changes in glycolysis was established within 2 h of treatment.
Discussion. These results highlight the importance of a temporary reduction in functional energy demand to release the cardiac cell cycle blockade. Our future experiments will aim to determine how the metabolic changes could be harnessed to aid the development of metabolic reprogramming strategies for cardiac regeneration.
Mills RJ et al (2021) Cell 184: 2167-2182, Voges HK et al (2023) Cell Reports 42(5):112322

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Gallic acid strengthens intestinal barrier: Mechanisms of action and its anti-colitogenic application

Miss Purisha Kulworasreth

Oral presentation 3: Cardiovascular & Urogenital & Gastrointestinal Themes, Eureka Room 3, December 2, 2024, 9:00 AM - 10:30 AM

Biography:
Purisha Kulworasreth is a 3rd year medical student at Princess Srisavangavadhana College of Medicine, Chulabhorn Royal Academy, Bangkok, Thailand.

Gallic acid strengthens intestinal barrier: Mechanisms of action and its anti-colitogenic application

Purisha Kulworasreth[1], Supisara Treveeravoot[1,2], Apiwan Arinno[2,3], Pawin Pongkorpsakol[1,2,*]. International Collaborative Medical Research Laboratory, Princess Srisavangavadhana College of Medicine, Chulabhorn Royal Academy[1]., Laboratory of Epithelial Tight Junction Pathophysiology[2]., Center of Excellence in Natural Products Chemistry (CENP), Department of Chemistry, Faculty of Science, Chulalongkorn University[3]., Bangkok, Thailand.

Introduction. Inflammatory bowel disease (IBD) results from immune imbalance and intestinal epithelial barrier function impairment with no FDA-approved therapies to recover intestinal tight junction assembly. Gallic acid, a polyphenol mainly found in several types of medicinal plants, was reported to suppress intestinal inflammation. Nevertheless, its direct effects on intestinal tight junction assembly and underlying mechanism have never been fully elucidated.
Aims. To investigate whether gallic acid promotes intestinal tight junction-dependent epithelial barrier property, its cellular mechanism of action and *in vivo* anti-colitogenic effects.
Methods. Intestinal epithelial-like T84 cell monolayers were used as an *in vitro* model to assess the effect of gallic acid on intestinal barrier function by transepithelial electrical resistance (TER) measurement. Dextran sulphate sodium (DSS)-induced colitis mouse model and pathohistological analyses were also used to study pharmacologically *in vivo* effects of gallic acid. Permeability assay, western blotting analysis, molecular docking, and immunofluorescence staining were performed to demonstrate mechanistic insights into gallic acid-induced intestinal tight junction assembly and its anti-colitogenic effect.
Results. Our *in vitro* experiments suggested that gallic acid increased TER value across T84 cell monolayers by suppressing tight junction-dependent leak pathway permeability and enhancing re-organization of tight junction proteins (ZO-1 and occludin) to cell junction region via CaMKK/AMPK/SIRT-1/ERK-dependent mechanism. Our *in vivo* study indicated that gallic acid improved all clinical symptoms related to colitis demonstrated by body weight change, shortening colon length, disease activity index, and survival rate. In addition, gallic acid was shown to upregulate intracellular signalling related to tight junction regulation in colon tissues.
Discussion. This study, not only shed some light on the anti-colitogenic mechanism of gallic acid but may also lead to a successful discovery of tight junction-enhancing bioactive compound for the treatment of associated diseases.

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Determining the mechanisms underlying BCG-immunotherapy induced lower urinary tract side effects

Ms Georgia Bourlotos

Oral presentation 3: Cardiovascular & Urogenital & Gastrointestinal Themes, Eureka Room 3, December 2, 2024, 9:00 AM - 10:30 AM

Biography:
Georgia Bourlotos is a currently in her second year of her PhD at Flinders University in the Neurourology Research Group. She graduated with a Bachelor of Medical Science and Honours in Medical Science from Flinders University. Her research focuses on bladder cancer and improving patient outcomes and their wellbeing. Georgia has previously published a review titled "BCG induced lower urinary tract symptoms during treatment for NMIBC - Mechanisms and management strategies" (DOI: 10.3389/fnins.2023.1327053) in Frontiers in Neuroscience. She was awarded the Flinders Health and Medical Research Institute PhD Scholarship and the Australian Governement Research Training Program Scholarship. Georgia is passionate in exploring potential pathways to reduce pain in patients suffering from superficial bladder cancer.

Determining the mechanisms underlying BCG-immunotherapy induced lower urinary tract side effects
Georgia Boulotos,1, Aaron Clark1, William Baigent1, Steven Taylor2, Luke Selth1, Natalie Stevens2, Feargal Ryan2, Luke Grundy1. FHMRI, Flinders University1, Adelaide, SA, Aus; SAHMRI2, Adelaide, SA, Aus.

Introduction: Non-muscle invasive bladder cancer (NMIBC) is typically treated by local tumor resection followed by intravesical (instilled into the bladder) Bacillus Calmette-Guerin (BCG) immunotherapy. While BCG therapy is effective in preventing cancer progression and recurrence, up to 70% of patients experience lower urinary tract symptoms (LUTS) including bladder pain, urinary urgency, and urinary frequency that significantly reduce quality of life during treatment. In 7-20% of patients these side effects are so severe that they require cessation of therapy.
Aims: The aim of this study was to determine the mechanisms underlying the development of BCG-induced LUTS.
Methods: To do this we developed a mouse model of BCG-immunotherapy, consisting of once weekly instillations of BCG (2.5x108
CFU/ml) for 6 consecutive weeks. One day after the final infusion, we assessed the development of inflammation via RNAsequencing and flow cytometry of bladder single cell suspensions. Bladder sensory signalling was assessed utilising an ex-vivo bladder afferent nerve recording technique during bladder distension (0-50mmHg). Referred pelvic pain was measured in vivo as the withdrawal threshold to electronic von-Frey hair (eVFH) stimulation of the pelvic region.
Results: In this study we show that our mouse model of BCG develops significant inflammation, characterised by significant upregulation of key Hallmark inflammatory pathways, and a significant increase in the number of infiltrating CD45+ immune cells ($P<0.01$, N=10/group) including, dendritic cells ($P<0.05$), inflammatory monocytes ($P<0.001$), natural killer cells ($P<0.001$) and CD4+ ($P<0.001$) and CD8+ $P<0.05$) T cells. Ex-vivo afferent recordings revealed BCG-treated mice develop bladder afferent sensitivity to distension ($P<0.0001$, N=5/group), with the sensitisation of both low ($P<0.01$) and high threshold ($P<0.01$) single afferent units. Mice also developed pelvic pain, as indicated by a significant decrease in the withdrawal threshold to pelvic eVFH stimulation ($P<0.05$, N=10/group).
Discussion: Our study reveals that BCG-treatment in mice induces inflammation, bladder afferent hypersensitivity, and pelvic pain. Bladder afferent hypersensitivity is a common feature underlying the development of multiple bladder pain disorders, and our study suggests it may underlie the development of BCG-induced LUTS. Targeting hypersensitive bladder afferents may represent a novel therapeutic target for the relief of BCG-induced LUTS.

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Mucosa-innervating bladder afferents regulate urinary tract infection severity and persistence

Miss Cindy Tay

Oral presentation 3: Cardiovascular & Urogenital & Gastrointestinal Themes, Eureka Room 3, December 2, 2024, 9:00 AM - 10:30 AM

Biography:
Cindy Tay is a final-year PhD candidate with the NeuroUrology Group at Flinders University, supported by the Australian Government Research Training Program (AGRTP) scholarship. Her research focuses on unravelling the mechanisms behind chronic bladder pain disorders, particularly urinary tract infections. Cindy is dedicated to characterizing the contribution and function of different subsets of bladder sensory nerves in regulating bladder pain disorders through the development of a novel bladder mucosal denervation technique. Cindy has published a literature review titled "Animal Models of Interstitial Cystitis/Bladder Pain Syndrome" in Frontiers in Physiology (https://doi.org/10.3389/fphys.2023.1232017). She has also presented her research at various national and international conferences, including ASMR, ASCEPT, ANS, ICS, and the EMBL PhD Symposium, where she was awarded a travel grant to attend.

Mucosa-innervating bladder afferents regulate urinary tract infection severity and persistence

Cindy Tay[1], Stewart Ramsay[2], Vladimir Zagorodnyuk[1], Natalie Stevens[3], Steven Taylor[3], Luke Grundy[1]. FHMRI, Flinders University, Adelaide, SA [1]; Adelaide Medical School, The University of Adelaide, Adelaide, SA[2]; SAHMRI, Adelaide, SA[3].

Introduction: Most sensory nerves in the bladder, about 80-90%, are found in the bladder muscle and are designed to detect when the bladder stretches. The remaining 10-20% of sensory nerves, termed mucosal nerves, are located within or near the bladder epithelium but don't sense bladder stretch. The role of these mucosal afferents in maintaining bladder homeostasis is still unknown. Due to their position close to the bladder lumen, we hypothesise that mucosal afferents are part of a surveillance system for detecting and aiding the response to bacterial infections.
Aims: To identify the role of bladder mucosal afferents in regulating urinary tract infection persistence and severity.
Methods: To achieve this, we developed a model of bladder mucosal denervation via infusion of Resiniferatoxin into the bladder (RTX; 30μM for 30min) across three consecutive days. Seven days following RTX infusions, urinary tract infection (UTI) was induced in mice through infections with 50μl of $1x10^9$ CFU/ml of uropathogenic *Escherichia Coli* (UPEC). Changes in mucosal nerve excitability were determined by *ex-vivo* bladder afferent recordings at 1-day post UTI. Bacterial severity and persistence were determined by the CFU of UPEC in urine, bladder and kidney at 1- and 7-days post UTI. Bladder immune cell phenotyping was achieved by flow cytometry.
Results: Mice infected with UPEC exhibited significant mucosal afferent hypersensitivity, which was lost by prior RTX treatment (N=5; 10mg $p<0.001$, 50mg $p<0.001$, 100mg $p<0.05$). Mice undergoing UPEC infection following mucosal denervation with RTX exhibited significantly elevated bacterial counts in bladder and kidneys at 1d-post UTI (N=5; $p<0.01$ and $p<0.05$). At 7d-post UTI, 75% of UPEC mice had cleared the infection vs only 20% of RTX-UPEC treated mice. In correlation with bacterial persistence studies, immune cell phenotyping of bladders using flow cytometry showed persistent neutrophil counts in RTX-UPEC treated mice compared to UPEC mice (N=10; $p<0.0001$).
Discussion: Bladder mucosal denervation with RTX prevented bladder afferent hypersensitivity during UTI. Mice with mucosal denervation that received UTI developed more severe infections in the bladder wall and kidneys, and persistent neutrophil infiltration into the bladder wall. These data suggest that mucosal afferent signalling of infection is a crucial component of the host-defence to urinary tract infection.

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Does noroxycodone counter oxycodone analgesia: evidence from a clinical study

Prof Andrew Somogyi

Oral presentation 4: Drug Disposition and Response & Toxicology Themes, Courtyard Room 1&2, December 2, 2024, 9:00 AM - 10:30 AM

Biography:

Andrew Somogyi graduated in Pharmacy from Tasmania and completed a PhD from the University of Sydney (Pharmacy-Anaesthetics). He then undertook postdoctoral clinical pharmacology training in Bonn (Germany) under the guidance of Michel Eichelbaum, and for the past 40 years has been at the University of Adelaide. Apart from teaching in medical, dental, health sciences, nursing and physiotherapy courses, he has an active research programme examining interindividual variation in drug response through clinical pharmacokinetic, pharmacodynamic and outcomes studies underpinned by pharmacogenomics. His current research covers the fields of acute postoperative and cancer pain and psychiatry with a specific focus on ketamine and opioids and, HIV therapy in Papua New Guinea. He is a contributing member of the Clinical Pharmacogenetics Implementation Consortium (CPIC) and an honorary fellow of the Faculty of Pain Medicine (FFPMANZCA), a Fellow of the British Pharmacological Society and an ASCEPT Fellow.

Does noroxycodone counter oxycodone analgesia: Evidence from a clinical study

Andrew A Somogyi[1], Aaron K Wong[2], Jennifer Philip[2], Stefan T Musolino[1]. Discipline of Pharmacology[1], University of Adelaide, Adelaide, SA, Australia; Department of Palliative Care[2], Peter MacCallum Cancer Centre[2], Melbourne, Vic, Australia.

Introduction. Opioids are the mainstay of cancer pain management and oxycodone is the most widely-prescribed opioid in Australia. However the dosage range for optimal pain control and tolerable adverse effects can be more than 50-fold due to patient characteristics, biochemical, pharmacokinetic and genetic factors.
Aims. To determine whether variability in the pharmacokinetics of oxycodone and its metabolites (CYP2D6 oxymorphone- opioid active and (CYP3A4 noroxycodone- opioid inactive)) contribute to this large dose variability.
Methods. We conducted a multi-centre prospective longitudinal study in 33 people with advanced cancer taking oxycodone. Clinical data (demographics, opioids), validated instruments (pain, adverse effects) and blood samples (pharmacokinetic (LC-MS/MS), genetic) were collected
Results. The higher the oxycodone dose, the higher the likelihood of uncontrolled average pain (score < 4 vs >4) [OR 4.32 (95%CI: 1.1-17), P=0.04] and breakthrough pain (<4 vs >4 episodes/day) [OR 6.4 (1.4 -29, P=0.02)]. Higher plasma noroxycodone was associated with uncontrolled pain [OR 2.44 (95% CI 1.0 – 6.0), P=0.05] (score > 4 = median 29 ng/ml) vs 7 ng/ml (score <4) and higher plasma noroxycodone/oxycodone concentration ratio [OR 10.5 (95% CI 1.4 -77), P=0.02; 1.6 vs 0.45]. The plasma noroxycodone/oxycodone ratio was inversely correlated with serum CRP (r=-0.38), a measure of inflammation. Plasma oxycodone and oxymorphone had no effect on pain or adverse effects.
Discussion. We hypothesise that noroxycodone is a major pharmacological moiety that contributes to variability in oxycodone analgesia in cancer pain patients likely due to an immunomodulatory effect via TLR4 glial activation and the production of pro-inflammatory mediators.

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Intratumoral drug metabolism: does it affect anti-cancer drug efficacy?

Prof Robyn Meech

Oral presentation 4: Drug Disposition and Response & Toxicology Themes, Courtyard Room 1&2, December 2, 2024, 9:00 AM - 10:30 AM

Biography:

Dr. Meech is a molecular pharmacologist and cell biologist who trained at Flinders University and the Scripps Research Institute. She has extensive expertise in drug metabolic enzymes (DME) and their roles in endogenous metabolic homeostasis and drug/xenobiotic response. She also has a background in developmental and stem cell biology. Much of her current work focusses on cancer biology and treatment. Ongoing projects study the role of DMEs in regulating levels of small molecules involved in cancer initiation and progression. These processes, including lipid and steroid signaling involve effectors such as nuclear receptors that may recapitulate developmental pathways within the cancer cells, including stemness. She is also exploring models to study the role of intratumoral drug metabolism in acquired resistance to anti-cancer drugs. These projects span a number of cancer types including breast, prostate and colon.

Intratumoral drug metabolism: does it affect anti-cancer drug efficacy?

Radwan Ansaar, Quinn Martin, , Julie-Ann Hulin, Dong Gui Hu, Peter Mackenzie, **Robyn Meech**. Discipline of Clinical Pharmacology, Flinders Health and Medical Research Institute, Flinders University, Adelaide, SA, Australia

Introduction. Breast cancer (BCa) is heterogenous disease with a wide range of treatment modalities. Hormone receptor positive (HR+) BCa is commonly treated with tamoxifen while triple negative breast cancer (TNBC) and some advanced HR+ BCa may be treated with chemotherapies including taxanes and anthracyclines. BCa cells express a variety of ADME factors including drug metabolic enzymes (DMEs) that may impact intratumoral drug disposition; this idea is supported by clinical associations between intratumoral expression of some DMEs and drug-specific outcomes. However, local metabolism is often overlooked as contributor to drug efficacy. Here we tested the hypothesis that expression of UDP-glucuronosyltransferases (UGTs) within BCa cells is a determinant of drug efficacy.

Aims. To define the roles of UGT2B7 and UGT2B15 in modulating anticancer drug responses in breast cancer models.

Methods. HR+ BCa and TNBC cell lines were generated that over-express fluorescently-tagged UGTs. Drug metabolism was measured via UPLC-MS based glucuronidation assays. Drug resistance was assessed by measuring cell proliferation and survival in 2D and 3D models including long term cell-competition assays.

Results. Elevated UGT2B7 expression increased clearance of epirubicin (EPI) and induced drug-resistance in HR+ BCa and TNBC lines. Elevated UGT2B15 expression increased resistance of HR+ BCa cells to active tamoxifen (TAM) metabolite 4-OH-tamoxifen (4OHTAM). Moreover, TAM was found to be a potent inhibitor of UGT2B7-mediated EPI glucuronidation (Ki ~ 2µmolar), revealing a new UGT2B7-mediated drug-drug interaction (DDI) between TAM and EPI. Co-treatment studies suggested that TAM can act as a pharmacoenhancer by increasing intratumoural EPI exposure. Analysis of public clinical datasets revealed that higher intratumoural UGT2B15 expression is associated with poorer-TAM-specific survival, while patients co-administered EPI and TAM may have reduced risk of relapse [1].

Discussion. These findings suggest that intratumoral UGTs control local anti-cancer drug exposure and efficacy. Altering ADME gene expression may be an adaptive response of cancer cells to treatment, and may facilitate the evolution of tumour drug resistance. Moreover, beneficial DDIs that enhance local exposure could be investigated as a strategy to enhance outcomes, particularly with drugs that have a low risk of toxicity, such as TAM.

[1] Wils et al. (1999). *J Clin Oncol,* 17**,** 1988-98.

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Entry and impacts of effective cystic fibrosis drug Elexacaftor/Tezacaftor/Ivacaftor on fetal cortex

Miss Danni Li

Oral presentation 4: Drug Disposition and Response & Toxicology Themes, Courtyard Room 1&2, December 2, 2024, 9:00 AM - 10:30 AM

Biography:

Danni Li is a PhD student with Dr Elena Schneider-Futschik in the Department of Biochemistry and Pharmacology at the University of Melbourne. As a first-year PhD student, she has published 3 manuscripts as first author and has contributed to >5 conferences abstracts. Work conducted by her, has led to national and international grant success including funding from the US Cystic Fibrosis Foundation and Cure4CysticFibrosis in 2023. Danni has received awards including being named on the Dean's Honours List. Furthermore, she is supported by the University of Melbourne Research Scholarship and CFWA Post Graduate Top Up Scholarship.

Entry and impacts of effective cystic fibrosis drug Elexacaftor/Tezacaftor/Ivacaftor on fetal cortex

Danni Li[1], Mark D. Habgood[1], Elena K. Schneider-Futschik[1*]. [1] Department of Biochemistry and Pharmacology, The University of Melbourne [1], Melbourne, VIC, Australia.

Introduction. The novel cystic fibrosis modulators therapy Elexacaftor /Tezacaftor/Ivacaftor (ETI) is currently the most recommended drug targeting cystic fibrosis. However, its safety and efficiency in pregnancy and breastfeeding remain hugely unknown.

Aims. This study aims to assess the impacts of *in utero* ETI exposure on fetal brain.

Methods. Pregnant Sprague Dawley rats were fed with ETI (human equivalent dose: 6.7 mg/kg/d Elexacaftor + 3.5 mg/kg/d Tezacaftor + 25 mg/kg/d Ivacaftor) orally twice daily from embryonic day (E) 12 to E19. Fetal brain, plasma and other tissue were collected at E19 and analyzed with 3 techniques: (1) liquid chromatography mass spectrometry; (2) RNA sequencing; (3) histopathology with hematoxylin & eosin (H&E) staining.

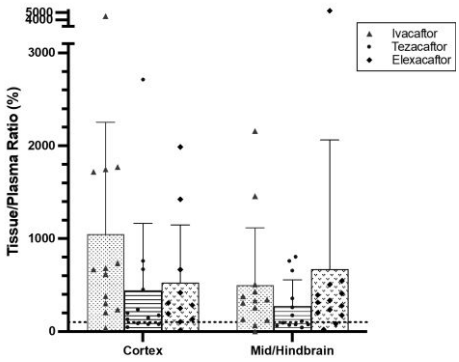

Fig 1. Drug distribution of ETI in fetal brain

Results. For all three ETI components, the fetal cortex/plasma ratio is higher than 100%, and the entry to cortex is as comparably high as to other fetal tissues. After chronic ETI exposure in late pregnancy, 44 downregulated genes were identified, some of which were associated with neurogenesis and neuronal differentiation. However, no visible histological changes were identified in terms of cortical layer thickness and cell density.

Discussion. The highly lipophilic ETI components can penetrate the placenta and fetal blood brain barrier, accumulate in fetal brain and potentially affect the central nervous system development. However, given that no visible structural damages were identified in fetal cortex, the significance of those impacts requires longer-term investigation, including behavioral study.

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Ceftolozane/tazobactam plus meropenem against ST235-clone Pseudomonas aeruginosa isolates in hollow-fibre infection model (PAGANZ)

Ms Siobhonne Breen

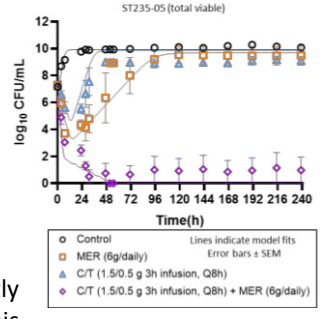
Oral presentation 4: Drug Disposition and Response & Toxicology Themes, Courtyard Room 1&2, December 2, 2024, 9:00 AM - 10:30 AM

Biography:
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 received oral presentations at international and national conferences.

Ceftolozane/tazobactam plus meropenem against ST235-clone *Pseudomonas aeruginosa* isolates in hollow-fibre infection model

Siobhonne K.J. Breen[1], Kate E. Rogers[1], Wee Leng Lee[1], Megan Faith[1], Jessica R. Tait[1], Alice E. Terrill[1], Carla López-Causapé[2,3], Roger L. Nation[1], Antonio Oliver[2,3], Cornelia B. Landersdorfer[1]. Monash Institute of Pharmaceutical Sciences[1], Monash University, Parkville, Vic, Australia. Servicio de Microbiología, Hospital Universitario Son Espases-IdISBa[2], Palma de Mallorca, Spain.

Introduction. 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.
Aims. 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).
Methods. Three multidrug-resistant ST235 isolates were investigated in 240h HFIM studies (n=1-2 replicates; inoculum ~$10^{6.8}$ CFU/mL). The pharmacokinetics of intermittent C/T ($t_{1/2}$=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.



Results. 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 $\log_{10}$ 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 (Figure).
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.

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Longitudinal linkage of hospitalised paracetamol poisoning in NSW using the PAVLOVA cohort

Miss Annabelle Chidiac

Oral presentation 4: Drug Disposition and Response & Toxicology Themes, Courtyard Room 1&2, December 2, 2024, 9:00 AM - 10:30 AM

Biography:
Annabelle Chidiac is a pharmacist and a PhD candidate in the School of Pharmacy at The University of Sydney. After completing her honours project on lithium toxicity in adults she has gone on to participate in various projects observing the occurrence and impact of poisoning in Australia. Her current thesis aims to look at paracetamol poisoning in an effort to identify at risk populations and reduce its occurrence.

Longitudinal linkage of hospitalised paracetamol poisoning in NSW using the PAVLOVA cohort

Annabelle S Chidiac[1,2], Nicholas A Buckley[1,2], Firouzeh Noghrehchi[1], Rose Cairns[1,2]. School of Pharmacy, Univ of Sydney[1], Sydney, NSW, Australia; New South Wales Poisons Information Centre, The Children's Hosp at Westmead[2], Sydney, NSW, Australia.

Introduction. Paracetamol is one of the most easily accessible medications worldwide and its use in poisonings is common and increasing, forming one of the top causes of acute liver failure in many high-income countries. Within New South Wales (NSW) the Poisoning And enVenomation Linkage to evaluate Outcomes and clinical Variation in Australia (PAVLOVA) cohort is a large data linkage project established to evaluate risk factors and outcomes of toxicological events.
Aims. To describe patterns and characteristics of paracetamol poisonings and adverse drug reactions recorded in PAVLOVA's hospital admissions data including the type of poisoning, demographics, co-ingestants, the need for n-acetylcysteine, ICU admissions, hepatotoxicity, liver transplants, deaths and repeat poisonings.
Methods. Events coded as T39.1 (poisoning by or adverse effect of 4-Aminophenol derivatives) were extracted from the NSW Admitted Patient Data Collection within the PAVLOVA cohort between January 2011-June 2020. Data was screened and analysed using R statistical software.
Results. There were 24092 events of a paracetamol poisoning or adverse event admitted to NSW hospitals between January 2011 and June 2020. The median age was 28.5 (IQR 18.7-44.9) and 71.0% (n=17095) were female. 18987 (78.8%) of these events were intentional poisonings followed by 4210 (17.5%) accidental poisonings. Drug induced liver injury occurred in 397 (1.6%) events. There were 2041 (8.5%) events that were admitted to the ICU and there were 104 (0.4%) deaths. After the index paracetamol admission a total of 2378 (12%) patients were readmitted to hospital for a poisoning or adverse event.
Discussion. Paracetamol is a common cause amongst poisonings and adverse events admitted to NSW hospitals. Intentional poisonings constitute the majority of events which supports government decisions to reduce paracetamol pack sizes. However, outcomes such as hepatotoxicity and deaths are common regardless of the type of poisoning. Additional focus should be placed on accidental poisonings and therapeutic misadventure to identify risk factors and targets for prevention.

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Active Learning for hERG Risk Modelling in Drug Development

Dr Slade Matthews

Oral presentation 4: Drug Disposition and Response & Toxicology Themes, Courtyard Room 1&2, December 2, 2024, 9:00 AM - 10:30 AM

Biography:
Slade Matthews is a researcher and educator whose career has been marked by his dedication to the intersection of biomedical science and machine learning. He is committed to fostering mathematical literacy among students and has made contributions to both research and education in the field. He holds two teaching awards for university teaching. Recognizing the importance of effective pedagogy, Slade completed a Graduate Certificate in Higher Education in 2011. He has a Bachelor of Medical Science, Honours (1995) which included an investigation into the venom of the Australian copperhead snake using classical pharmacological bioassays, chromatography, and electrophysiology. His doctoral research (PhD 2007) focussed on the integration of machine learning techniques for cell classification tasks and modelling relationships in clinical data. Slade's primary research focus centres on the fusion of experimental design, statistical analysis, and machine learning to investigate biomedical problems, especially in toxicology. He has published 43 publications in peer-reviewed journals and has been cited 1275 times.

Active Learning for hERG Risk Modelling in Drug Development
Slade Matthews, CPT Lab, Sydney Pharmacy School, The University of Sydney, Sydney, NSW, Australia

Introduction. The human Ether-à-go-go-Related Gene (hERG) encodes a protein that forms potassium channels critical for cardiac repolarization. Binding at IKr/hERG channels is among many important preclinical drug safety assays. It is essential to estimate hERG binding risk early due to the severity of the adverse patient outcomes (QT prolongation, arrhythmia, DtP). Several in silico approaches have been reported in the literature using traditional machine learning approaches which use an entire training set for model development. Active learning starts with a reduced training set and iteratively refines the model with incorporation of the most informative data points.
Aims. This study will evaluate the potential contribution to assay modelling that can be gained by employing the active learning machine learning paradigm.
Methods. Data for inclusion in the model was gleaned from the literature and machine learning models were programmed in Python using Pandas, ScikitLearn, and TPOT on a 12th gen i7, Z790 PC running Linux.
Results. Preliminary results were generated using a genetic algorithm approach to search for the best model and model parameterisation using the whole dataset for later comparison with the active learning approach. The GA approach produced a model that could learn relationships between physicochemical properties and binding at hERG channels resulting in an overall 5-fold cross validation accuracy of 81%. The performance on the hold-out test set included a balanced accuracy of 78% and F1 score (harmonic mean of precision and recall) of 0.79. The results from incorporation of active learning will be compared to these traditional (whole training set) modelling results.
Discussion. The significance of development of active learning models is that they are known to require fewer data points than more traditional approaches. Given that the availability of data is a key sticking point in the development of in silico toxicity models this reveals great promise for future assay modelling studies. Globally there is a more away from animal-based toxicity assessments. The positions in silico toxicity assay models at the forefront of toxicology in the 21st century.

Konda et al (2019) Computational Toxicology, 12.
Ramirez-Loaiza et al (2016) Data Mining and Knowledge Discovery, 31(2), 287-313.

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Chemoproteomics approaches to deconvolute drug targets for novel anti-malarial candidates

Prof Darren Creek

Oral presentation 5: Drug Discovery Theme, Eureka Room 1, December 2, 2024, 2:15 PM - 3:45 PM

Biography:
Professor Darren Creek is Director of the Drug Target Identification node of the Monash Proteomics and Metabolomics Facility, and is co-coordinator for the MIPS Global Health Therapeutic Program Area. He completed his B.Pharm and PhD at Monash University in 2007, and has worked in Uganda, Scotland and Australia on malaria drug discovery, clinical trials, and parasite metabolism. He developed new analytical tools for metabolomics, and has used metabolomics and proteomics to discover new metabolic pathways and drug mechanisms, as described in over 150 publications. He has served on the Boards of National and International Metabolomics Societies and was awarded the Inaugural Metabolomics Society Medal in 2019.

Chemoproteomics approaches to deconvolute drug targets for novel anti-malarial candidates

Darren J. Creek[1], Carlo Giannangelo[1], Christopher A. MacRaild[1], Sheena McGowan[1], Peter J. Scammells[1], and Ghizal Siddiqui[1]. Monash Institute of Pharmaceutical Sciences, Monash University[1], Parkville, VIC, Australia

Introduction: Phenotypic screening has provided many starting points for antimicrobial drug discovery, providing over 30,000 compounds for the malaria drug discovery pipeline. However, further progression of these hits is limited by a lack of understanding about the targets responsible for the antiparasitic activity. Several chemoproteomic approaches have recently been described that allow unbiased discovery of drug targets from a whole cellular proteome.
Aims: We aim to establish a suite of chemoproteomic methods to assist with drug target identification, and apply these to identify new drug targets in malaria parasites.
Methods: Label-free chemoproteomics methods were established based on proteolytic, thermal and solvent-based protein stability, which allow detection of differential stability of target proteins due to ligand binding when the test compound is added to a whole cell protein extract. Label-based approaches using click-chemistry, photoactivatable linkers and halo-tag biotinylation were also established. Proteomics analysis utilised DIA-based LC-MS with Orbitrap and Astral mass analysers.
Results: The label-free methods were validated using the current antimalarial drug, pyrimethamine, which selectively stabilised its known target, DHFR-TS. These methods were then applied to a range of novel aminopeptidase inhibitors, and successfully differentiated inhibitors that targeted M1 aminopeptidase, M17 aminopeptidase or both M1 and M17. These findings were independently confirmed by metabolomics-based peptide fingerprinting of treated parasites, and biochemical enzyme assays on purified aminopeptidase enzymes. The label-based target enrichment method was applied to a novel series of aminobenzimidazole antimalarials, and identified a novel target, exportin 1, which was independently confirmed by *in vitro* resistance evolution.
Discussion: Chemoproteomic approaches allow unbiased detection of drug targets for novel bioactive compounds. In addition to the confirmed drug targets identified using these methods, other potential targets were often observed, suggesting a combination of untargeted approaches, followed by targeted validation studies, are required to confirm specific drug targets responsible for activity. These approaches will significantly enhance the ongoing discovery of new medicines for malaria, and can be applied more broadly to identify new drug targets for other diseases.

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Structural analysis and Nanobody development on the relaxin receptor, RXFP1.

Prof Ross Bathgate

Oral presentation 5: Drug Discovery Theme, Eureka Room 1, December 2, 2024, 2:15 PM - 3:45 PM

Biography:
Professor Ross Bathgate is the leader of the Neurotherapeutics theme at the Florey Institute and is an Honorary Professorial Fellow in the Department of Biochemistry and Pharmacology at the University of Melbourne, Australia. He is a molecular pharmacologist with broad expertise in bioactive peptides and their G protein-coupled receptors (GPCRs). He has authored over 300 publications, is an inventor on 15 patents and was listed in the 2019 and 2020 world's most highly cited researchers for Pharmacology and Toxicology (Web of Science). He works closely with a number of pharmaceutical companies interested in the clinical development of GPCR-targeted therapeutics.

Structural analysis and Nanobody development on the relaxin receptor, RXFP1.
Ross AD Bathgate[1,2], Tiffany Myint[1,2], Bradley L Hoare[1], Lisa Williams[1], Isabelle Magiatzis[1,2], Paul Gooley[2], Daniel J Scott[1,2], Chris Draper-Joyce[1,2]. Florey Institute[1], and Department of Biochemistry and Pharmacology[2], University of Melbourne, Parkville, VIC, Australia.

Introduction. Drugs targeting RXFP1, the G protein-coupled receptor (GPCR) for the peptide hormone relaxin are being developed by multiple pharmaceutical companies for the treatment of heart failure. However, structural details of the interaction of relaxin and other agonists with RXFP1 and the mechanism of receptor activation are still lacking. Such information is essential to fully inform the clinical outcomes from the various RXFP1 agonists, especially small molecule agonists and peptidomimetic which have unique modes of RXFP1 interaction. Furthermore, there are limited tools available to study RXFP1 function including specific antibodies or RXFP1 antagonists.
Aims. The aim of this study was to utilize an engineered RXFP1 receptor (RXFP1#35) which has enhanced cellular expression to solve RXFP1 structures and to immunize Alpacas for the development of specific Nanobodies.
Methods. RXFP1#35 was produced in high purity and yield from mammalian cells and reconstituted into detergent micelles for Alpaca immunization or peptidiscs for structure determination via cryo-EM. A Nanobody library was produced from the immunized Alpaca and panned for RXFP1 binders using fluorescence-activated cell sorting (FACS).
Results. We have solved a cryo-EM structure of RXFP1 in the absence of ligand (Apo-RXFP1) with good overall resolution (~3Å) including the leucine rich-repeat domains of the ectodomain the site of ligand binding. Importantly, this is one of the first GPCR structures without ligand/G-protein/antibody or other fiducial markers. We also have preliminary structures of relaxin bound to an RXFP1-mini $G\alpha_s$ fusion complexed with $G_{\beta\gamma}$. Alpaca immunization with RXFP1 protein resulted in a good immune response in a post-immunisation serum test on RXFP1-expressing cells. Panning of the Nanobody library with RXFP1 protein by FACS enriched a population of anti-RXFP1 Nanobodies. Functional screening of purified antibodies has identified agonistic Nanobodies.
Discussion. Our engineered RXFP1 protein has facilitated RXFP1 structural analysis and anti-RXFP1 nanobody production. The RXFP1 structures will provide molecular detail of apo-, inactive- and active-state structures of relaxin, peptidomimetic and small molecule bound RXFP1 complexes which will inform clinical outcomes from these drugs. Anti-RXFP1 Nanobodies will be valuable research tools for receptor localization or potential drug leads.

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Cryo-EM structure of monomeric CXCL12-bound CXCR4 in active state

Prof Richard Ye

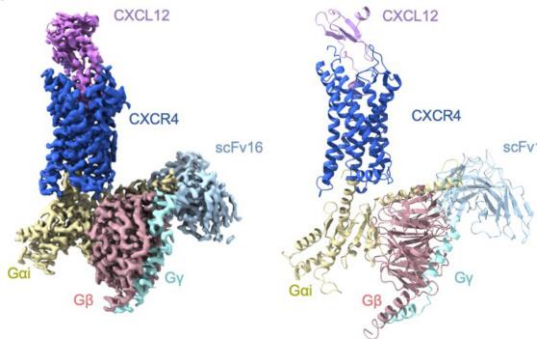
Oral presentation 5: Drug Discovery Theme, Eureka Room 1, December 2, 2024, 2:15 PM - 3:45 PM

Biography:

Dr. Richard Ye is a Presidential Chair Professor and Associate Dean of Biomedical Research & Innovation at School of Medicine, The Chinese University of Hong Kong (CUHK) in Shenzhen, China. He received a Ph.D. in cell and integrative biology from Washington University in St. Louis and established his lab at The Scripps Research Institute and University of Illinois, where he worked on gene cloning and pharmacological characterization of formyl peptide receptors. His lab focused on innate immunity and host defense when he joined Shanghai Jiao Tong University as Dean of School of Pharmacy in 2010. In recent years, Prof. Ye's lab used cryogenic electron microcopy to investigate the structural and functional correlation of G protein-coupled receptors including CXCR4, KSHV-GPCR, succinate receptor 1 and FPR1. He has published more than 230 research papers and is a Clarivate Highly Cited Researcher. Besides lab research, Prof. Ye serves as Associate Editor of Pharmacological Reviews.

Cryo-EM structure of monomeric CXCL12-bound CXCR4 in active state

Yezhou Liu[1,*], Aijun Liu[1,2,*]. Xinyu Li[3], Qiwen Liao[1], Weijia Zhang[1], Lizhe Zhu[3], Richard D. Ye[1,4] Kobilka Institute of Innovative Drug Discovery, School of Medicine, The Chinese University of Hong Kong[1], Shenzhen, Guangdong, China; Dongguan Songshan Lake Central Hospital, Dongguan Third People's Hospital[2]. Dongguan, Guangdong, China; Warshel Institute for Computational Biology, School of Medicine, The Chinese University of Hong Kong[3], Shenzhen, Guangdong, China; *Equal contribution to this work.



Introduction. CXCR4 binding of CXCL12 leads to diverse functions including bone marrow retention of hematopoietic progenitors and cancer metastasis. However, the structure of a CXCL12-bound CXCR4 remains unresolved despite available structures of CXCR4 in complex with small molecule antagonists and a viral chemokine.

Aims. This work uses cryo-EM to solve the structure of CXCR4 bound to its endogenous agonist CXCL12.

Methods. A cryo-EM structure of CXCL12-CXCR4-Gi protein complex was obtained at 2.65 Å. Site-directed mutagenesis and functional assays were carried out to determine CXCR4-ligand interactions at chemokine recognition sites.

Results. CXCL12 forms a 1:1 stoichiometry complex with CXCR4, with its N-terminus inserting into the transmembrane (TM) binding pocket involving TM1/2/3/7. The first 8 amino acids of CXCL2 are crucial for activation of CXCR4 and interact with $C186^{ECL2}$ and $D187^{ECL2}$ through polar interactions and $E288^{7.39}$ and $D262^{6.58}$ through hydrogen bonding. The distance of 3.2Å between V3 and the 'toggle switch' $W^{6.48}$ marks the deepest insertion among all chemokine-receptor pairs, leading to conformational changes of CXCR4 at the intracellular interface for G protein activation. Outside the TM pocket, CXCL12 binding is further stabilized through polar interaction of P10 with $C28^{NT}$ of the PC motif of CXCR4.

Discussion. These results provide the structural basis for CXCR4 activation by CXCL12. CXCR4 activation in relation to its monomeric and higher-order structure will be discussed.

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Bombesin 3 receptor: a novel target for the deadliest cancer

Ms Mariah Stavrou

Oral presentation 5: Drug Discovery Theme, Eureka Room 1, December 2, 2024, 2:15 PM - 3:45 PM

Biography:
Mariah is a PhD candidate in A/Prof Nicola Smith's Orphan Receptor Lab at UNSW Sydney. She has been a member of ASCEPT since 2021 and has served on ASCEPT's student committee for 2 years. She has a keen interest in GPCRs, with a focus on taste receptors and the forgotten bombesin receptor, BB3.

Bombesin 3 receptor: a novel target for the deadliest cancer
Mariah R Stavrou[1], Zoe A Eastwood[1], Sara Ballouz[2], Nicola J Smith[1]. Department of Pharmacology, School of Biomedical Sciences, UNSW Sydney[1], NSW, Australia; School of Computer Science and Engineering, UNSW Sydney[2], NSW, Australia.

Introduction. Despite significant treatment advances, lung cancer remains one of the biggest killers of Australians. Highly innovative strategies are urgently needed to target lung cancer with a limited side effect profile. Early evidence suggests that the orphan G protein-coupled receptor, bombesin 3 (BB_3), may be overexpressed in cancer and functionally absent in healthy tissue, presenting a unique opportunity for a biologically selective target for cancer.
Aims. First, to characterise expression of BB_3 and determine the extent of its biological selectivity in cancer. Then, to validate recently described synthetic ligands and the pharmacological properties of BB_3 that have otherwise been poorly characterised. Finally, to develop a highly disease-relevant model to measure the impact of BB_3 activity in cancer.
Methods. Gene expression data was mined from RNA-sequencing databases and extracted as transcripts per million RNA reads (TPM) for BB_3 and control genes. To measure constitutive and synthetic agonist activity at BB_3, HEK293 cells were co-transfected with BB_3 and luciferase reporter plasmids with and without agonist stimulation. A high-throughput GCaMP assay was used to measure increases in Ca^{2+} following BB_3 agonism. Human lung cancer organoids expressing BB_3 were incubated with BB_3 agonists and changes to disease phenotype and cell viability were measured.
Results. BB_3 mRNA was found exclusively in lung adenocarcinoma (LUAC), and not in adjacent healthy lung, other cancers and other healthy human tissue. BB_3 expression in LUAC was more prevalent (83%) than any other LUAC marker (<44%). BB_3 signals in the absence of ligand via the $G\alpha_{q/11}$, $G\alpha_{12/13}$, and $G\alpha_{s}$ pathways, and agonism increases Ca^{2+}. Lung cancer organoids expressing BB_3 were assessed for morphological and molecular characteristics of cancer in the absence and presence of BB_3 ligands.
Discussion. The exclusive expression of BB_3 in LUAC offers the possibility of selective and targeted treatment in a disease with high resistance to chemotherapy and other clinically used drugs. Barriers to BB_3's development as a LUAC target have been overcome with our characterisation of the receptor's pharmacology and development of a disease-specific model. This study awards us the opportunity to engineer targeted therapies that exploit BB_3's unique pharmacology in lung cancer.

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HDX-MS studies on the relaxin receptor, RXFP1

Dr Bradley Hoare

Oral presentation 5: Drug Discovery Theme, Eureka Room 1, December 2, 2024, 2:15 PM - 3:45 PM

Biography:
Currently working as Post Doctoral researcher under the leadership of Professor Ross Bathgate. Ongoing projects are centred around understanding signalling bias at the relaxin receptor, RXFP1, as well as general pharmacological investigation of other important GPCR drug targets.

Interest include:
- GPCR pharmacology, incorporating binding/signalling kinetics and structural biology.
- Novel drug discovery
- Assay development and optimisation
- Resonance energy transfer (eg. BRET, TR-FRET, FRET) and its applications to understanding ligand:receptor and protein:protein interactions.
- Using smartphone cameras and BRET to develop diagnostic tests for biomolecules. Please get in touch if you have any interest/expertise at all in this.

HDX-MS studies on the relaxin receptor, RXFP1

Bradley L Hoare[1], Tiffany Myint[1,2], Shatabdi Chakraborty[2,3], Ching-Seng Ang[3], Paul Gooley[2,3], Daniel J Scott[1,2], Chris Draper-Joyce[1,2], Ross AD Bathgate[1,2]. Florey Institute[1], Department of Biochemistry and Pharmacology[2], and Bio21 Molecular Science and Biotechnology Institute[3], University of Melbourne, Parkville, VIC, Australia

Introduction. The relaxin receptor, RXFP1, is a Family A G Protein-coupled receptor (GPCR) containing a large extracellular domain (ECD) responsible for binding relaxin and subsequent receptor activation. Whilst RXFP1 is already the target for clinical trials using relaxin mimetics or small molecule agonists, there remains a lack of structural information about the mechanism of relaxin binding and the concerted conformational rearrangements leading to receptor activation. This information is important as there are different modes by which different RXFP1 agonists can activate the receptor, which may lead to different clinical outcomes. Biophysical methods studying purified RXFP1 ectodomain (RXFP1-ECD) protein could provide more detail on this, however previous attempts at purifying RXFP1-ECD have been unsuccessful, largely due to issues with protein instability, aggregation, and low yield.
Aims. Purify sufficient quantities of RXFP1-ECD and perform hydrogen deuterium exchange mass spectrometry (HDX-MS) to investigate protein structure and dynamics upon relaxin binding.
Methods. A stable HEK293F suspension cell line with constitutive secretion of RXFP1-ECD protein was developed via lentiviral transduction. RXFP1-ECD protein was purified via immobilised metal affinity chromatography (IMAC) and subsequent size-exclusion chromatography (SEC). RXFP1-ECD was then confirmed to bind relaxin in biolayer interferometry (BLI) experiments, and HDX-MS experiments were undertaken on relaxin-bound and -unbound RXFP1-ECD protein.
Results. RXFP1-ECD protein was successfully purified with a yield of ~0.15 mg/L. BLI experiments confirmed that purified RXFP1-ECD was relaxin binding competent (Kd ~ 1 nM). The resulting HDX-MS dataset achieved good sequence coverage (~80%) and supported previous reports of relaxin binding sites within the ECD. Excitingly, other regions of RXFP1-ECD demonstrated conformational change upon relaxin binding which were previously unknown.
Discussion. Insights gained from HDX-MS are complementary to parallel cryoEM datasets of RXFP1 structure. Future experiments will assess how different relaxin mimetics or small molecule agonists interact differently with the receptor, and it is hoped that these insights will clarify any differences in clinical outcomes from these drugs.

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An intracellular lipid pocket at Frizzled receptors regulates transducer activity

Dr Wessel Burger

Oral presentation 5: Drug Discovery Theme, Eureka Room 1, December 2, 2024, 2:15 PM - 3:45 PM

Biography:
Dr. Burger is an early career researcher who completed his PhD in 2022 at the Monash Institute of Pharmaceutical Sciences, Monash University. In 2023 Dr. Burger moved to WEHI to the lab of Dr Alisa Glukhova. His research is aimed at unraveling the molecular mechanisms of Frizzled signalling, a crucial area of study due to its dysregulation in numerous human cancers. Currently, there is a lack of understanding of the molecular events involved in this process. To address this gap, Dr. Burger employs a combination of cryogenic electron microscopy, biochemistry, and molecular pharmacology techniques.

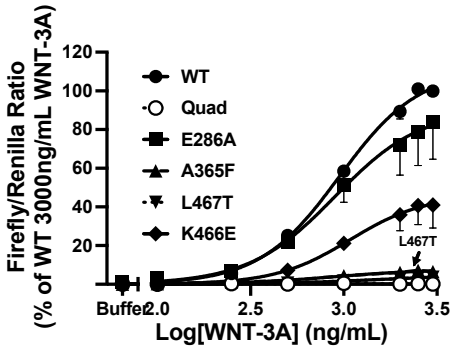
An intracellular lipid pocket at Frizzled receptors regulates transducer activity

Wessel A. C. Burger[1,2], Tin Nguyen[1], Susovan Das[1], Joshua R. Prendergast[1], Alisa Glukhova[1,2]. Structural Biology Division, Walter and Eliza Hall Institute of Medical Research[1], Parkville, VIC, Australia; Australian Research Council Centre for Cryo-Electron Microscopy of Membrane Proteins, Monash University[2], Parkville, VIC, Australia.

Introduction. Frizzleds (FZDs) are class F G protein coupled receptor (GPCRs) that signal through G proteins and Dishevelled (Dvl). Our 2.6 Å cryo-EM structure of FZD7-Gs complex revealed that a small molecule, Lauryl Maltose Neopentyl Glycol (LMNG) occupies an intracellular lipid binding pocket at the FZD-G protein interface. This unique interface is not seen in any other GPCR structure. LMNG likely replaces a cellular phospholipid during sample preparation and stabilises the FZD7-mGs complex providing an explanation for the long-standing observation that FZD7 displays high constitutive activity. Excitingly, Alphafold2 predicts a similar pocket in the FZD7-Dvl complex. Within the pocket, four residues are conserved across all ten FZD subtypes but differ at the most closely related GPCR, Smoothened, that does not signal through Dvl.

Aims. Determine the role of conserved lipid pocket residues on Dvl signalling and constitutive G protein signalling through mutagenesis and signalling assays.

Methods. Four individual mutants and a mutant with all four residues (Quad mutant) mutated to their Smoothened equivalent were characterised in A) Dvl signalling through Wnt-3a dose response curves in the TopFlash assay and B) Constitutive G protein activity in the TruPath assay. Differences in receptor expression were accounted for by fluorescence-activated cell sorting (FACS).



Results. All mutants showed a decrease in Wnt-3a mediated Dvl signalling with all Dvl signalling lost at the A365F, L467T and Quad mutants. Constitutive G protein activity of FZD7 was increased at the mutants.

Discussion. Our results indicate that conserved residues form a lipid pocket that regulates transducer coupling and activity at FZD receptors.

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How are deprescribing guidelines disseminated and implemented? Survey of international organisational stakeholders

Mr Chun Hei Justin Cheng

Oral presentation 6: Pharmacy Practice Theme, Eureka Room 2, December 2, 2024, 2:15 PM - 3:45 PM

Biography:
I am a first-year PhD student with a background in community pharmacy. Currently, I work at a sleep and respiratory clinic, focusing on managing patients with sleep apnoea. My passion lies in the importance of deprescribing, particularly in recognising and reducing unnecessary medications, aiming to optimise patient outcomes and quality of life. My academic journey seeks to explore the development of a gabapentinoid deprescribing guideline.

How are deprescribing guidelines disseminated and implemented? A survey of international organisational stakeholders
Chun Hei Justin Cheng[1], Danijela Gnjidic[1], Stephanie Mathieson[2], Barbara Farrell[3], Lisa McCarthy[4], Wade Thompson[5], Aili Langford[1], Carl R Schneider[1]. School of Pharmacy, Faculty of Medicine and Health, Univ of Sydney[1], Sydney, NSW; Sydney Musculoskeletal Health, Faculty of Medicine and Health, Univ of Sydney[2], Sydney, NSW; Bruyère Research Institute[3], Ottawa, ON; Leslie Dan Faculty of Pharmacy[4], Univ of Toronto, Toronto, ON; Dept of Anaesthesiology, Pharmacol & Therapeutics[5], Faculty of Medicine, Univ of British Colombia, Vancouver, BC.

Introduction. Deprescribing guidelines have gained traction internationally over recent years. However, there is limited understanding of the strategies used by organisations and policy bodies to disseminate and implement current deprescribing guidelines and their impact.
Aims. To identify dissemination and implementation strategies on deprescribing guidelines across international organisations.
Methods. A survey containing 44-items mirroring components of the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework was distributed by international deprescribing networks via targeted email invitations, newsletters and social media. Stakeholders from organisations with experience in implementing deprescribing guidelines were invited to respond. Ethics approval was obtained prior to recruitment.
Results. Of the 69 responses, 46 participants across 14 countries provided analysable data. Almost half (45%) of respondents reported organisational tailoring of guidelines for local context. Three quarters (75%) reported a lack of planning for implementation, dissemination, and or evaluation. Almost 80% reported that their organisation does not monitor outcomes of the strategies used. Whilst 75% reported provision of on-going training and support, only 8% reported monitoring of guideline uptake by individual members. Most respondents (78.1%) believed that guideline uptake could be improved.
Discussion. International reach of deprescribing guidelines was confirmed. However, despite active tailoring and training, most organisations reported little effort in evaluating the adoption or outcomes post-implementation with lack of planning for on-going maintenance. Opportunities exist to improve implementation and evaluation planning to promote effective long-term maintenance. Subsequent research can focus on implementing on-going maintenance.

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Patient Focused Pharmacy Practice in Sri Lanka: A Scoping Review

Miss Ciera Summers

Oral presentation 6: Pharmacy Practice Theme, Eureka Room 2, December 2, 2024, 2:15 PM - 3:45 PM

Biography:
Miss Ciera Summers holds a Bachelor's degree in Biomedical Science and is currently in her final year of the Bachelor of Pharmacy (Hons) program at The University of Queensland. She is completing her Honours research project, which focuses on the role of pharmacists within the Sri Lankan healthcare system and their integration into clinical settings. This research is being conducted in collaboration with Professor Ian Coombes, Dr. Judith Coombes, Professor Amanda Wheeler, and Professor Yasakalum Bagyawantha.

Patient Focused Pharmacy Practice in Sri Lanka: A Scoping Review

Ciera F Summers[1], Judith Coombes[1,2], Amanda Wheeler[2,3], Yasa Kalum Bagyawantha[4], Ian Coombes[1,2,3,5],
1 =School of Pharmacy, University of Queensland[1], Brisbane, QLD, Australia; 2= Collaborative of Australian Sri Lankans for Pharmacy Practice, Education and Research (CASPPER); 3= Centre for Mental Health, Griffith University, Brisbane; 4 = Dept of Pharmacy University Peradeniya 5 = Pharmacy Dept, Royal Brisbane and Women's Hospital, Brisbane.

Introduction. The National Medicines Regulatory Authority Act in Sri Lanka promotes safe, effective and economic use of medicines; however the country's current model of pharmacy practice is predominantly supply focused and unable to uphold these objectives, due to the lack of clinical pharmacy education available. In Sri Lanka, there are currently 6 Bachelor of Pharmacy (BPharm) degrees, commencing in 2006. Due to lack of previous clinical pharmacy knowledge, international academics have assisted in the development of these programmes. Therefore, the pharmacist workforce in Sri Lanka is not integrated into the multidisciplinary healthcare team, and often not participating in clinical roles.
Aims. To describe the scope of evidence regarding the need for, and impact of, pharmacists on the safe and quality use of medicines in Sri Lanka, how pharmacists are perceived and utilised, and what improvements can be carried out to Sri Lanka's medicine focused healthcare service.
Methods. A systematic search of online databases was conducted, using PubMed, Embase, Scopus, as well as ResearchGate. Keywords used to search included a combination of 'pharmacy' 'Sri Lanka' 'healthcare' 'clinical pharmacist' 'pharmacy'. EndNote was used to remove any duplicated studies, and then imported into Covidence to be screened and data extraction conducted.
Results. Of 143 initial articles screened, 20 met the inclusion criteria. The evidence suggested a need for, and acceptance of, pharmacists by medical colleagues to undertake clinical roles and improve the quality use of medicines. Evidence also suggested that implementing pharmacists in a multi-disciplinary team helped improve patient knowledge of, and adherence to, medicines and improved health outcomes such as reduced unplanned re-admissions.
Discussion. This evidence suggests that pharmacists can make important contributions to overall patient health outcomes; preventing hospitalisations and medication-related problems. In order for Sri Lankan pharmacy services to integrate this role into routine multidisciplinary healthcare, provision of training to build and apply clinical knowledge, skills, and confidence is critical in Sri Lankan undergraduate pharmacy and continuing professional development programs.

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Stakeholders' perspectives of perinatal depression and anxiety screening in primary care:a meta-synthesis

Ms Lily Pham

Oral presentation 6: Pharmacy Practice Theme, Eureka Room 2, December 2, 2024, 2:15 PM - 3:45 PM

Biography:
Lily Pham is a pharmacist and a University of Sydney PhD candidate focussing on how pharmacists can support other primary care providers in the early detection and screening of perinatal depression and anxiety.

Stakeholders' perspectives of perinatal depression and anxiety screening in primary care: a meta-synthesis
Lily Pham[1], Claire L O'Reilly[1], Rebekah J Moles[1], Jack C Collins[1], Sarira El-Den[1]. Sydney Pharmacy School, The University of Sydney[1], Sydney, NSW, Australia.

Introduction. The perinatal period, a time during pregnancy and 12 months pot-birth, involves physiological, emotional, and social changes that put new parents at risk of experiencing perinatal depression and anxiety (PNDA), resulting in increased health and lifetime impact costs. Screening in primary healthcare settings provides consumers with opportunities for early detection of and intervention for PNDA.
Aims. To comprehensively review the evidence pertaining to stakeholders' perspectives on PNDA screening in primary care settings.
Methods. The search strategy explored four key concepts: (i) the perinatal period, (ii) depression and anxiety disorders, (iii) qualitative research and (iv) screening. The search was conducted across Medline, PsycINFO, CINAHL, and JBI databases on 3rd November 2023 to identify records published from database inception to the search date. To be eligible for inclusion, studies had to qualitatively explore perspectives of any stakeholders who are affected by PNDA screening (e.g., parents, healthcare professionals). Included studies had to be written in English, contain quotes (e.g., from interview transcripts), and refer to screening in a primary healthcare setting. Publications were excluded if they reported on non-primary research. The research team took an interpretivist, epistemological approach to the qualitative thematic analysis.
Results. Nineteen studies were included in the meta-synthesis, of which five explored consumers' and eleven explored healthcare professionals' and three explored both perspectives. Study designs included interviews, focus groups and written responses to questionnaires. Through qualitative analysis, three overarching consumer themes were identified: screening engagement, screening environment and screening process. Four overarching healthcare professionals' themes were established: knowledge and skills, stigma, screening approach and value of screening.
Discussion. Understanding stakeholders' perspectives of PNDA screening allows for the consumer experience to be considered in future design and development of PNDA screening services. Addressing consumers' and healthcare professionals' knowledge of PNDA and screening may also improve engagement with and delivery of PNDA screening services.

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Do type 2 diabetes guidelines consider older adults in the Western Pacific?

Ms Darshna Goordeen

Oral presentation 6: Pharmacy Practice Theme, Eureka Room 2, December 2, 2024, 2:15 PM - 3:45 PM

Biography:
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 limited life expectancy. 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. Prior to commencing her PhD, Darshna was involved in various research projects at the Centre for Medicine Use and Safety at Monash University. Of note, she was a part of the evidence review team for the Clinical Practice Guidelines for the Appropriate Use of Psychotropic Medications in People Living with Dementia and in Residential Aged Care, which has been approved by the National Health and Medical Research Council of Australia.

Do type 2 diabetes guidelines consider older adults in the Western Pacific?

D Goordeen[1], Y Elsedfy[2], S Fariman[3], J Simon Bell[1], S Hamada[4], K Wang[5], M Abu Al Shieh[1], Y Hattori[6], M Nunan[7], E Reeve[1]. Centre for Medicine Use and Safety[1], Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Vic, Australia; School of Pharmacy[2], University of Queensland, QLD, Australia; Eshelman School of Pharmacy[3], University of North Carolina at Chapel Hill, NC, United States; Institute for Health Economics and Policy[4], Association for Health Economics Research and Social Insurance and Welfare, Tokyo, Japan; School of Health and Biomedical Sciences[5], Royal Melbourne Institute of Technology, Vic, Australia; Department of Home Care Medicine[6], Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; Beyond Essential Systems[7], Vic, Australia.

Introduction: The Western Pacific Region (WPR) has the fastest ageing population and 38% of the world's diabetes population, with most of these being Type 2 Diabetes (T2D). It is unknown to what extent medication management recommendations are included for these populations in T2D Clinical Practice Guidelines (CPGs).
Aims: To identify T2D CPGs within the WPR and investigate the nature of medication management recommendations and whether they consider older adults, frailty, dementia, and those receiving end of life care.
Method: MEDLINE, Embase, Scopus, guideline-specific registries and grey literature searches were performed (inception-August 2023). 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 Appraisal of Guidelines, Research and Evaluation (AGREE II) tool.
Results: From the 39 countries and areas of the WPR**,** 14 CPGs were included from 10 countries. Ten CPGs recommended reduced and/or individualised glycaemic targets focused on reducing hypoglycaemia in older adults. Six CPGs included deprescribing recommendations about de-intensification/simplification of complex regimens in older adults, people with co-morbidities associated with ageing and those receiving end of life care. Quality of CPGs varied, the domain with the highest scores was scope and purpose and the largest discrepancies between ratings were rigour of development and editorial independence.
Discussion: Relevant recommendations were sparse across the included CPGs. Further research is needed to support CPG development in these areas while considering the diversity of the WPR, such as differences in remoteness, population, health infrastructure, medication access and socioeconomic status.

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Where are my mob at? Analysing the representation of Australian Indigenous pharmacists

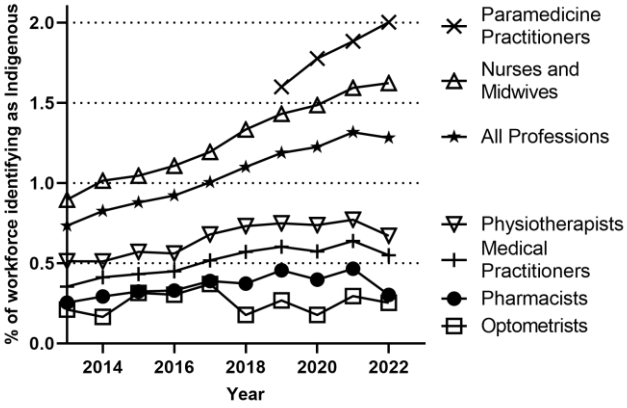
Dr Jared Miles

Oral presentation 6: Pharmacy Practice Theme, Eureka Room 2, December 2, 2024, 2:15 PM - 3:45 PM

Biography:
Jared is a proud Yuwi man, pharmacist and early-career researcher with interests spanning from culturally safe and effective pharmacy practice through to new technologies for pharmaceutical development and delivery. He is a Senior Lecturer with UQ School of Pharmacy, and is passionate about supporting First Nations students coming into university and becoming health professionals. Jared also works with mob as a pharmacist with the Institute of Urban Indigenous Health (IUIH).

Where are my mob at? Analysing the representation of Australian Indigenous pharmacists

Jared A Miles[1,2], Tasneem Mahomedy[1], Meng-Wong Taing[1]. School of Pharmacy, The University of Queensland[1], Woolloongabba, QLD, Australia; Poche Centre for Indigenous Health[2], The University of Queensland, St Lucia, QLD, Australia.



Introduction. Despite comprising approximately 3% of the national population, Australian First Nations peoples remain underrepresented in the health workforce. Increasing representation is a key step to improving culturally safe healthcare.

Aims. This study aims to understand trends in the demographics of registered pharmacists in Australia who identify as Aboriginal and/or Torres Strait Islander, compare these with other health professions, and identify potential professional and societal factors that have impacted their representation.

Methods. Analysis was primarily performed using the National Health Workforce Dataset spanning 2013-2022, supported by data from the Pharmacy Board of Australia and other professional organisations.

Results. As of 2023 there are 118 Australian First Nations registered pharmacists, constituting only 0.3% of the pharmacist workforce. This is the lowest representation in the profession since 2014. Further analysis of representation across demographics, professional roles, and geographical locations will be presented.

Discussion. All registered health professions underrepresent First Nations peoples; however, pharmacists are the second lowest despite the ease of access and visibility to the public. Some of this may be related to post-COVID attrition of the workforce, but it is clear that a profession-wide approach is necessary to attract and train more First Nations pharmacists and to improve retention towards developing cultural capacity and safety in pharmacy.

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Navigating cultural diversity in diabetes care: insights from Australian healthcare professionals

Ms Diane Gargya

Oral presentation 6: Pharmacy Practice Theme, Eureka Room 2, December 2, 2024, 2:15 PM - 3:45 PM

Biography:
Diane Gargya is a general practice and credentialed pharmacist with over ten years of experience in community pharmacy. She is also a credentialled diabetes educator in private practice and works as a casual academic. Diane is pursuing a PhD at RMIT University, focusing on patient-centred diabetes care for culturally and linguistically diverse communities. Her expertise and interests include diabetes education and management, medication management, and health coaching. She served as an Expert Advisory Group for the 'FIP Diabetes Prevention, Screening, and Management: A Handbook for Pharmacists, published in 2021. She is a member of the Australasian Pharmaceutical Science Association (APSA), the Pharmaceutical Society of Australia (PSA), and the Australian Diabetes Educators Association (ADEA).

Navigating cultural diversity in diabetes care: insights from Australian healthcare professionals
Diane Gargya[1,2], Ieva Stupans[1], Thilini Thrimawithana[1], Vincent Chan[1], Barbora de Courten[1,2], Chiao Xin Lim[1,2]. Pharmacy, School of Health and Biomedical Sciences, RMIT University, Bundoora, VIC, Australia[1];
Medicine Department, School of Clinical Sciences, Monash University, Clayton, VIC, Australia[2].

Introduction. Australia's diverse, multicultural landscape necessitates culturally competent healthcare delivery, particularly in managing chronic conditions like diabetes. Individuals from culturally and linguistically diverse (CALD) backgrounds often encounter unique challenges in diabetes care. These challenges stem from a combination of cultural beliefs, language barriers, and socioeconomic factors. Despite the increasing diversity in Australian society, little is known about how healthcare professionals (HCPs) deliver culturally appropriate diabetes care.
Aims. The primary aim of this study is to explore the experiences and perspectives of HCPs in delivering type 2 diabetes care to CALD patients.
Methods. Using the constructivist grounded theory methodology, in-depth interviews were conducted in-person and online with a diverse group of ten HCPs, including doctors, nurses, pharmacists, dieticians, and diabetes educators. Data were collected using open-ended guided questions and analysed iteratively, with coding, memo-writing, and constant comparison to identify emerging patterns and themes to develop a substantive theory capturing the complexities of delivering diabetes care to CALD patients.
Results. An emergent theory, 'lifelong learning and adaptability', highlights the importance of patient-centred approaches, continuous learning, and adaptation to cultural contexts. Key themes include HCP self-awareness, building trust and rapport, genuine interest in patients' cultural backgrounds, understanding and integrating cultural and economic nuances of patients, culturally specific resources and support systems, and patient and community involvement in diabetes care development and delivery. These themes underscore the dynamic and collaborative nature and process of providing diabetes care to patients from CALD backgrounds.
Discussion. This research highlights the importance of HCPs' lifelong learning and adaptability to provide culturally adapted and patient-centred diabetes care to improve patient outcomes in multicultural settings. Insights gained from this study could inform the development of tailored interventions and training programs, thereby enhancing the quality of diabetes care for individuals from diverse cultural backgrounds.

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AIM2 inflammasome inhibition improves cognition in a mouse model of vascular dementia

Dr Quynh Nhu Dinh

Oral presentation 7: Neuropharmacology Theme, Eureka Room 3, December 2, 2024, 2:15 PM - 3:45 PM

Biography:
Dr Quynh Nhu Dinh is a research fellow working in the Centre for Cardiovascular Biology and Disease Research at La Trobe University under the mentorship of Prof Thiruma Arumugam. She completed her PhD in 2017 in the Department of Pharmacology at Monash University, and her thesis examined the roles of inflammation, ageing and sex differences in hypertension. Dr Dinh specialises in using mouse models of hypertension and vascular dementia. Her current research focuses on understanding the pathophysiology of hypertension and vascular dementia, and also evaluates potential therapeutic interventions. She has published in leading journals such as Cardiovascular Research and British Journal of Pharmacology (>1000 citations). Currently, Dr Dinh is a co-program manager for the Annual Scientific Meeting of Hypertension Australia and a co-lead for the Australian National Hypertension Taskforce Working Group: raising and maintaining awareness at all levels.

AIM2 inflammasome inhibition improves cognition in a mouse model of vascular dementia

Quynh Nhu Dinh[1], Kylie Agnew-Francis[2], Xin-yi Chai[1], Nishat Tabassum[1], Christopher G Sobey[1], Grant R Drummond[1], Nigel C Jones[3], Avril AB Robertson[2], Thiruma V Arumugam[1]. Centre for Cardiovascular Biology and Disease Research, Department of Microbiology, Anatomy, Physiology and Pharmacology, La Trobe Institute for Molecular Science, La Trobe University[1], Bundoora, VIC, Australia; School of Chemistry and Molecular Biosciences, Institute for Molecular Bioscience, The University of Queensland[2], Brisbane, QLD, Australia; Department of Neuroscience, Central Clinical School, Monash University[3], Clayton, VIC, Australia.

Introduction. There are no disease modifying drugs available for dementia. Our lab and others have shown that the AIM2 inflammasome contributes to the pathophysiology of the two most common forms of dementia – vascular dementia and Alzheimer's disease. Our collaborators have developed the world's first AIM2 inflammasome inhibitor.
Aims. To determine whether a novel AIM2 inflammasome inhibitor (AR23) can improve cognition and reduce brain injury in mouse models of vascular dementia and Alzheimer's disease.
Methods. 3 month old male C57Bl6 mice underwent bilateral carotid artery stenosis (BCAS) surgery to model vascular dementia. Two weeks after surgery, the mice were administered either an AIM2 inhibitor (AR23, 5 mg/kg/d) or vehicle (50% DMSO, 50% PEG300) for 2 weeks via an osmotic minipump. Male and female 5xFAD mice were used as a genetic model of Alzheimer's disease. 3 and 5 month old 5xFAD were administered the AIM2 inhibitor or vehicle for 6 and 4 weeks respectively. Spatial and learning memory was assessed using the Barnes maze test.
Results. AR23 improved cognition in BCAS mice (n=16, $P<0.05$). 36 days after surgery, BCAS mice had reduced cerebral blood flow compared to sham (n=16, $P<0.05$) but AR23 increased cerebral blood flow in BCAS mice (n=16, $P<0.05$). 5 month old 5xFAD mice had impaired cognition compared to WT (n=10-11, $P<0.05$) but AR23 did not influence this impairment in either sex. AR23 also had no effect on the density of amyloid-beta in the brain of 5xFAD mice (n=6, $P>0.05$). AR23 administration at an earlier age of 3 months also did not influence cognition, however, AR23 reduced the density of amyloid-beta in the cortex of female 5xFAD mice but not males (n=6, $P<0.05$).
Discussion. A novel AIM2 inflammasome inhibitor was protective in experimental vascular dementia mice demonstrating its potential as a therapy for vascular dementia. Neurodegeneration may be irreversible at 5 months in 5xFAD mice but AIM2 inhibition may have protective effects in female 5xFAD at a younger age.

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Understanding the interplay of STING and TOLLIP in driving secondary injury post-TBI.

Miss Amelia Fryer

Oral presentation 7: Neuropharmacology Theme, Eureka Room 3, December 2, 2024, 2:15 PM - 3:45 PM

Biography:
Amelia is in the final year of her PhD with the Neuropharmacology research group in the Department of Biochemistry and Pharmacology at the University of Melbourne. Her research focuses on CNS innate immunity and understanding the cGAS-STING pathway and its role in driving neuroinflammation and neurodegeneration in traumatic brain injury (TBI). She has first-authored two publications during her candidature, the most recent of which was published in May in the British Journal of Pharmacology titled 'Pharmacological inhibition of STING reduces neuroinflammation-mediated damage post-traumatic brain injury.'

Understanding the interplay of STING and TOLLIP in driving secondary injury post-TBI.

Amelia L Fryer[1], Amar Abdullah[2], Juliet M Taylor[1] and Peter J Crack[1] Dept of Biochem and Pharmacol, Univ of Melbourne[1], Parkville, VIC, Australia; Dept of Biol Sci, Sunway University[2], Selangor, Malaysia

Introduction. Traumatic brain injury (TBI) is a major cause of death and disability worldwide with limited pharmacological interventions available to slow the inflammation and neurodegeneration that ensues post-injury. Our lab has demonstrated the cGAS-STING pathway as a key driver of neuroinflammation-mediated neurodegeneration in TBI and other neuropathologies. Known to be a regulator of type-I interferon production, there is increasing evidence for additional roles for STING in mediating cell death and ER-stress. Toll interacting protein (TOLLIP), is an endogenous negative regulator of TLR signaling with roles in misfolded protein trafficking. Recently, TOLLIP has been identified to regulate STING activity, by stabilising STING at its resting state on the ER.
Aims. This study aims to evaluate the role of TOLLIP in regulating STING and ER-stress activity in the CNS post-TBI.
Methods. 10–12-week-old male C57Bl/6 mice anaesthetized with an ip injection of ketamine (100mg/kg)/xylazine (10mg/kg) and were exposed to brain injury using the controlled-cortical impact model (CCI). 30-minutes post-injury, mice were administered a single iv 750nmol dose of the STING inhibitor, C-176 or saline (vehicle). Analysis was conducted 2 and 24-hours post-TBI (n=7-9 mice for each treatment group).
Results. Western blot analysis revealed a significant reduction in the expression of TOLLIP and total STING in the cortex 24h-post TBI and not 2h-post TBI in both C-176 (0.65±0.08, n=9 $p<0.0001$) and vehicle-treated mice (0.65±0.10, n=9 $p<0.0001$) when compared to sham (1.55±0.15). C-176-treated mice alone exhibited significantly increased phosphorylation of the unfolded protein response (UPR) regulator IRE1-α (6.14±1.24, $p<0.001$ n=9) compared to both sham (1.00±0.12) and vehicle-treated TBI mice (1.37±0.28). Striatal mRNA expression levels of its downstream mediator *Xbp1* were also elevated at 24h-post TBI when compared to sham mice (C-176=1.24±0.11; sham=1.03±0.08, $p<0.05$ n=9).
Discussion. Together these findings suggest TOLLIP and its stabilising activity on resting-state STING is lost-post TBI with the pharmacological inhibition of STING increasing activation of the IRE1-XBP1 branch of the unfolded protein response. This study provides novel mechanistic insight into the regulation and activity of STING post-TBI in mice.

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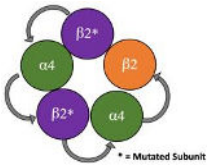
Functional assay controlling nAChR assembly provides new insights into ADSHE receptor function

Mr Lucas David

Oral presentation 7: Neuropharmacology Theme, Eureka Room 3, December 2, 2024, 2:15 PM - 3:45 PM

Biography:
Lucas is currently completing his Honours year for a Bachelor of Medical Science with the Ion Channel Drug Discovery Group at the Brain and Mind Centre, The University of Sydney. His research aims to address the current gap in knowledge on the effects of variants on nicotinic acetylcholine receptor (nAChR) function through creating functional assays that are able to determine the functional profile of variant nAChRs found in Autosomal Dominant Sleep-related Hypermotor Epilepsy (ADSHE) patients. These assays will be able to assign pathogenicity to novel variants. Following the completion of his degree, Lucas aspires to continue to study and work within the medical and health field.

Functional assay controlling nAChR assembly provides new insights into ADSHE receptor function
Lucas David[1], Han Chow Chua[1], Mary Chebib[1], Philip K. Ahring[1], Vivian Liao[1]. Brain and Mind Centre, University of Sydney[1], Sydney, NSW, Australia



Introduction. Genetic variants in the α4 and β2 subunits of neuronal nicotinic acetylcholine receptors (nAChRs) are associated with Autosomal Dominant Sleep-Related Hypermotor Epilepsy (ADHSE). However, the exact effect of how these variants interfere with the function of the resulting receptors is yet to be completely understood. This is because expressing heteromeric receptors (two or more different subunits) *in vitro* systems, such as *Xenopus* oocytes, creates the possibility of forming multiple receptor subtypes within the same cell, which may lead to incorrect conclusions. Our study addresses this by utilising receptor concatenation technology which involves linking the subunits in a predetermined stoichiometry to ensure only the receptor of interest is expressed (See figure).
Aims. To develop a new functional assay that can distinguish between pathogenic and benign nAChR α4 and β2 variants from a cohort of 26 patients and healthy individuals (gnomAD database) with a pool of 8 different variants.
Methods. Site-directed mutagenesis and receptor concatenation were performed using basic molecular biology techniques. The desired concatenated receptors were then expressed in *Xenopus* oocytes. Two-electrode voltage clamp electrophysiology was conducted with increasing concentrations of acetylcholine (ACh) applied to oocytes to generate dose-response curves (analysed using GraphPad Prism).
Results. We created functional assays to test novel mutations; H331Y (α4) and P96T (β2), published mutations; S284L (α4), S280F (α4), V287M (β2), I312M (β2) and benign variants (gnomAD database); V287I (α4) and A275V (β2). The results showed certain variants cause hypersensitive (gain-of-function) receptor compared to wild type (WT) in terms of their response to ACh. Other variants presented a decrease in sensitivity (loss-of-function) to ACh compared to WT, whereas the benign control respond similarly to ACh as WT, indicating our assay can distinguish pathogenicity.
Discussion. Our novel functional assay provides absolute control over receptor assembly, allowing for a precise understanding of how variants affect receptor function. This validated assay can be clinically used to determine variant pathogenicity. Additionally, it can also be used to screens drugs for precision medicine, personalising treatments for gain- and loss-of-function variants.

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N-linoleyltyrosine improves cognitive dysfunction in obese mice through fatty acid amid hydrolase

Adj A/Prof Sha Liu

Oral presentation 7: Neuropharmacology Theme, Eureka Room 3, December 2, 2024, 2:15 PM - 3:45 PM

Biography:

Liu Sha, an Associate Professor and Graduate Supervisor at Chengdu Medical College, obtained a Ph.D. in Medicine from the Pharmacology Department of Shanghai Jiao Tong University School of Medicine in 2015. Our team is dedicated to the development, optimization, and exploration of new targets and mechanisms of unsaturated fatty acyl amino acids in the central nervous system, obesity, and tumors. As the first and corresponding author, I have published 14 research papers in domestic and international journals, such B.R.B, J.P.S etc. Additionally, our research has received support from the National Natural Science Foundation of China, the Science and Technology Department of Sichuan Province, and other projects, with three national invention patents granted or applied for. We also emphasize talent cultivation by forming the "running snail" and guiding undergraduate students to achieve various awards, such as the Silver Award in the International University Student Competition. Our primary research interests include:

- *Investigating new compounds, specifically unsaturated fatty acyl amino acids, to discover those with significant pharmacological activity and to explore their potential mechanisms.*
- *Utilizing molecular docking and molecular dynamics techniques to calculate the binding modes and binding energies between unsaturated fatty acyl amino acids and their targets, thereby predicting possible action targets.*
- *Conducting research on metabolic diseases such as tumors, obesity, diabetes, and Alzheimer's disease by integrating multi-omics and bioinformatics methods with newly synthesized compounds from this project, aiming to discover new therapeutic targets.*

N-linoleyltyrosine improves cognitive dysfunction in obese mice through fatty acid amid hydrolase

Sha Liu[1], Ze-Cheng Xu[1], Yuan-Ting Liu[1], Shu-Ping Han[1]. School of Pharmacy, Chengdu Medical College[1], Chengdu, Si Chuan, China

Introduction. Obesity is often accompanied by mild cognitive impairment. Previous studies showed that N-linoleyltyrosine (NIT) exerted neuroprotective activities, but its effect on obesity-induced cognitive impairment remained unknown.
Aims. This study aims to investigate the effects and mechanisms of NIT in an obese mouse model.
Methods. Mice were fed a 60% kcal fat diet to establish an obesity mouse model and then orally administered 100 mg/kg/day of NIT for 7 weeks. Body weights of mice were recorded weekly, and the learning and memory functions were assessed using the Morris water maze. Brain pathology was examined with HE staining. The gut microbiota structure was analysed using 16S rRNA sequencing. Non-targeted metabolomics analysis was conducted to detect intestinal contents, plasma, and brain tissues. Network pharmacology predicted potential signalling pathways of NIT. Molecular docking and molecular dynamics simulations investigated the interaction between NIT and fatty acid amide hydrolase (FAAH).
Results. NIT reduced body weight and improved learning and memory impairment in obese mice. Additionally, NIT ameliorated brain damage in the DG region. Results from 16S rRNA sequencing indicated that NIT didn't affect α-diversity but affected β-diversity analysis. Furthermore, NIT significantly decreased Proteobacteria and Veillonellaceae abundance in the intestines of obese mice. Non-targeted metabolomics revealed that NIT significantly reduced 3-dehydrocholic acid levels in gut and decreased the stearic acid levels in plasma. In brain tissues, NIT increased the levels of phosphatidylcholine

metabolites such as PC (16:0/16:0), N-acetyl aspartate-glutamate-glutamine, and N-acetyl aspartate. Network pharmacology results indicated that NIT affected the ERK signalling pathway. Molecular docking and molecular dynamics simulations showed that the docking score of NIT with FAAH was -10.7 kcal/mol, and the binding free energy was -48.7 kcal/mol, indicating a strong binding affinity between NIT and FAAH.
Discussion. In summary, NIT reduced body weight, improved learning and memory functions, balanced gut microbiota, and improved metabolic profiles. These processes may be related to FAAH involvement.

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Investigating the relationship between CGRP and the calcitonin receptor in the brain.

Dr Michael Garelja

Oral presentation 7: Neuropharmacology Theme, Eureka Room 3, December 2, 2024, 2:15 PM - 3:45 PM

Biography:
In 2020, Michael obtained his PhD in Biological Sciences from the University of Auckland. He then moved to the University of Otago to help Prof. Debbie Hay to establish a research lab. In 2022 Michael was awarded with a Neurological Foundation of New Zealand First Fellowship to investigate CGRP and its related peptides and receptors in brain regions relevant to migraine. Michael is currently co-Principal Investigator on Marsden Funded project, alongside his mentor Prof Debbie Hay, continuing his work with CGRP in the context of migraine.

Investigating the relationship between calcitonin gene-related peptide and the calcitonin receptor in the brain of rats and mice.
ML Garelja[1], LM Forrester[1], and DL Hay[1,2]. Department of Pharmacology & Toxicology, University of Otago[1], Dunedin, New Zealand. Maurice Wilkins Centre for Molecular Biodiscovery, School of Biological Sciences, University of Auckland[2], Auckland, New Zealand.

Introduction. The calcitonin receptor (CTR) can dimerise with receptor activity-modifying proteins to form several distinct receptors for calcitonin gene-related peptide (CGRP) and/or amylin in vitro. However, deconvoluting the physiological relevance of each receptor for each ligand is challenging because of the complexity of the system. In the brain, CGRP is abundant and a key player in the pathophysiology of pain. Amylin, however, does not have widespread expression in the brain. We hypothesize that CTR-based receptors could act as receptors for CGRP, rather than amylin in many brain regions.
Aims. This study aimed to address this by investigating the spatial relationship between CGRP and CTR in a subset of brain regions.
Methods. Brains were collected from three male and three female adult (8-10 weeks) Sprague-Dawley rats and C57BL/6J mice. Sections were selected containing the amygdala, parabrachial nucleus (PBN), locus coeruleus (LC), and spinal trigeminal nucleus (Sp5). Fluorescent immunohistochemistry was performed using validated antibodies against CGRP and CTR. Fluorescence was visualized using confocal microscopy on an Opera PHENIX High Content Imager and analysed qualitatively using ImageJ.
Results. CGRP and/or CTR like-immunoreactivity (IR) were detected in each region. In the amygdala, PBN, and Sp5, CGRP and CTR like-IR were detected in close proximity. Conversely, in the LC, CTR, but not CGRP, like-IR was detected. Within each region, CGRP like-IR was detected predominantly in fibres, whereas CTR like-IR was detected in both fibres and cell bodies. The data were broadly consistent between rats and mice, and male and female.
Discussion. The close proximity of CGRP and CTR in some locations suggests that CTR could be responsible for some CGRP signalling in the brain. In other locations, such as the LC, where only CTR was detected, other ligands may be involved. These data contribute to understanding CGRP receptor biology and which molecular entities may contribute to its modulation of pain signalling and beyond.

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Evaluating Anti-TNF and Small molecules impact on Depression and Anxiety for IBD

Mr Irwin Kashani

Oral presentation 7: Neuropharmacology Theme, Eureka Room 3, December 2, 2024, 2:15 PM - 3:45 PM

Biography:
Dr. Irwin Kashani is an Advanced Trainee in Clinical Pharmacology at Flinders Hospital, where he plays a pivotal role in both clinical practice and research. Under the mentorship of Professor Arduino Mangoni and Dr TIlenka Thynne, Dr. Kashani actively contributes to the Southern Oncology Clinical Research Unit (SOCRU) and is a co-investigator in multiple oncology clinical trials. His work spans oncology, complex hypertension, endocrinology, and gastroenterology clinics, reflecting his comprehensive expertise in multidisciplinary patient care.
Dr. Kashani's research focus includes evaluating the impact of biologics and small molecule therapies on mental health outcomes in autoimmune conditions. He is currently developing a systematic review and meta-analysis on this topic, employing rigorous methodologies such as the JBI framework. His clinical trials experience also extends to large IBD studies conducted at the Royal Brisbane and Women's Hospital, where he completed advanced GCP training.
A committed educator, Dr. Kashani regularly presents at journal clubs, teaches junior staff, and participates in quality improvement initiatives. His leadership and adaptability have been honed through roles in high-pressure medical and surgical settings, and he brings a patient-centered approach to his practice.
Dr. Kashani is passionate about the intersection of molecular therapies and clinical pharmacology, combining his interest in acute medicine with chronic disease management. With several international publications and oral presentations to his name, he strives to advance evidence-based practice while fostering therapeutic relationships with patients.

Evaluating the impact of Anti-Tumor Necrosis Factor and Small molecules Therapy on Depression and Anxiety for Inflammatory Bowel Disease Patients.
Irwin Kashani, Reme Mountifield, Alex Barnes, Arduino Mangoni and Tilenka Thynne. Department of Clinical Pharmacology, Flinders Hospital and Flinders University, Adelaide, SA, Australia

Introduction. Depression and Anxiety are common in patients with inflammatory bowel disease. There has been investigation into the influence of anti-tumor necrosis factor (TNF) biologics on depression and anxiety in patients with and without IBD, with longitudinal studies and small randomized controlled trials showing conflicting results.
Aim. We performed an analysis of the relationship between anti-TNF biologics and small molecule therapies on depression and anxiety in patients with IBD.
Methods. An online questionnaire was administered through IBD clinics at Flinders Medical Center, South Australia. Data on IBD activity (Simple Clinical Colitis Activity Index and Harvey–Bradshaw Index), IBD, Medical history including previous mental illness, smoking history, surgical history, family history, demographics, and IBD medication were recorded. Depression was assessed with Patient Health Questionnaire 9 (PHQ9), with clinically significant depression defined as PHQ9 score >15. Anxiety was assessed with the General Anxiety Disorder-7 (GAD-7) Questionnaire, with definition of mild anxiety (5-9), moderate anxiety (10-14) and severe anxiety (15-21). Inadequate completion of any score or index led to that result not being included.

Results: Our preliminary data included 220 responses to the online questionnaire, with 106 from patients with Crohn's disease, 56 from patients with ulcerative colitis (UC), 12 from patients with indeterminate colitis, and 36 undefined. The median age of respondents was 44 years, with 63% being female, and the median duration of inflammatory bowel disease (IBD) was 12 years. Of the participants, 65 reported having depression or anxiety. Additionally, 15% were active smokers, and 72 were former smokers. Fifteen participants reported consuming more than 10 alcoholic drinks per week, while 31 reported consuming between 4 and 8 drinks per week. Clinically significant depression was observed in 20.8% of the cohort, with 17.6% experiencing moderate to severe anxiety and 21.4% reporting mild anxiety. Anti-TNF therapy was used by 34.3% (n=72) of participants, while small molecule therapy (Tofacitinib or Upadacitinib) was used by 10.5% (n=22). The rate of clinically significant depression among those using anti-TNF therapy was 22% (n=15/67) compared to 14% (n=14/98) in non-users (P=-0.179). For those using anti-TNF therapy, the rate of mild anxiety was 28% (n=19/67) compared to 24% (n=24/99) in non-users (P=0.553), and the rate of moderate to severe anxiety was 21% (n=14/67) compared to 21% (n=21/99) in non-users (P=0.961). Regarding small molecule therapies, the rate of clinically significant depression was 28.5% (n=6/21) compared to 16% (n=23/144) in non-users (P=-0.151). Notably, among patients with Crohn's disease, the rate of clinically significant depression in those using small molecule therapies was 57% (n=4/7) compared to 18% (n=17/92) in non-users (P=-0.016). The rate of moderate to severe anxiety among small molecule therapy users was 19% (n=4/21) compared to 21% (n=31/145) in non-users (P=0.807), and the rate of mild anxiety was 42% (n=9/21) compared to 23% (n=34/145) in non-users (P=0.058). In UC, the rate of mild anxiety among small molecule therapy users was 50% (n=7/14) compared to 20% (n=8/40) in non-users (P=0.031). Clinically significant depression and moderate-severe anxiety were associated with female sex (P=0.036 and P=0.009, respectively), but not with previous surgery for IBD (P=0.338). There was no difference in the anti-TNF/small molecule and non-anti-TNF/small molecule groups for any of these variables.

Discussion: Our study indicates a trend towards higher rates of mild anxiety among anti-TNF users but no significant association with depression or anxiety. However, small molecule therapy, particularly in Crohn's disease, was linked to a higher prevalence of clinically significant depression and mild anxiety. These findings underscore the need for heightened monitoring of mental health in patients on small molecule therapies, especially those with Crohn's disease. Further research is warranted to elucidate the mechanisms underlying these associations and guide clinical management.

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A clinical decision support alert to promote timely laxative prescribing with clozapine

Mr Milan Sundermann

Oral presentation 8: Pharmacogenomics & Clinical Pharmacology Themes, Courtyard Room 1&2, December 2, 2024, 2:15 PM - 3:45 PM

Biography:
Milan is a PhD student in his last year of study at the University of Otago – Christchurch. His PhD project is focused on evaluating and optimising digital clinical decision support tools in hospital to promote medication safety. Milan is interested in harnessing the large volumes of routinely collected healthcare data in hospitals to inform and improve medicine use. As a current student, Milan is part of the ASCEPT student forum committee and the organising committee for the ASCEPT New Zealand forum

A clinical decision support alert to promote timely laxative prescribing with clozapine.
Milan Sundermann[1], Susanna Every-Palmer[2], and Paul KL Chin[1]. Department of Medicine, University of Otago[1], Christchurch, New Zealand; Department of Psychological Medicine, University of Otago [2], Wellington, New Zealand.

Introduction. Clozapine can cause constipation and sometimes life-threatening gastrointestinal complications. Hence, laxatives should be prescribed with clozapine. However, this is not consistently done. Clinical decision support (CDS) alerts within electronic prescribing systems can facilitate this co-prescribing.
Aims. To assess whether implementation of a CDS alert which prompted prescribing of a laxative with clozapine at our institution on 09/09/2019 improved laxative co-prescribing with clozapine in hospital inpatients.
Methods. Inpatient prescriptions were extracted from the local data warehouse before (01/01/2017-08/09/2019) and after (09/09/2019-31/12/2023) alert implementation and linked in R software. The primary outcome was co-prescription of any regularly scheduled laxatives (other than bulk-forming) within 24 hours of the first clozapine prescription. The secondary outcome was co-prescribing of any laxative within 24 hours of the first clozapine prescription. The proportions of outcome measures were compared before and after alert implementation using chi-squared tests. Multivariable logistic regression was performed to assess the effect of the alert whilst adjusting for covariates such as age, sex, ethnicity, disease burden, co-prescribing of other constipating medicines.
Results. There were a total of 1194 first clozapine prescriptions included. Regular laxatives were co-prescribed for 67.0% (301/449) of clozapine prescriptions within 24 hours pre-alert implementation and 76.1% (567/745) post-alert implementation ($p < 0.001$). The multivariable regression model showed that the likelihood of regular laxative co-prescribing within 24 hours for clozapine prescriptions increased after the alert was implemented (OR = 1.36, 95% CI 1.04-1.80). The proportion of clozapine prescriptions co-prescribed any laxative within 24 hours was 87.3% (392/449) pre-alert implementation and 96.5% (719/745) post-alert implementation ($p < 0.001$). The likelihood of any laxative being co-prescribed for clozapine prescriptions within 24 hours increased after the alert was implemented (OR = 3.66, 95% CI 2.22-6.04)
Discussion. Implementation of the alert was associated with improved laxative co-prescribing within 24 hours of clozapine. These findings support adoption of this alert type in other electronic prescribing systems. The effect of this intervention on patient outcomes (e.g. constipation) needs to be investigated.

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Reprogramming histone methylation status as a therapeutic approach for MPNST therapy

A/Prof Chung-Ping Liao

Oral presentation 8: Pharmacogenomics & Clinical Pharmacology Themes, Courtyard Room 1&2, December 2, 2024, 2:15 PM - 3:45 PM

Biography:

Dr. Chung-Ping Liao received his PhD from Indiana University School of Medicine and completed postdoctoral training at the University of Texas Southwestern Medical Center. Dr. Liao is currently an Associate Professor at the Graduate Institute of Medical Sciences, Taipei Medical University in Taiwan. His research focuses on the pathogenic mechanisms of tumors associated with the human genetic disorder neurofibromatosis type 1 (NF1). By leveraging comprehensive genetic mouse models, his study has identified the critical contributions of the immune microenvironment to neurofibroma tumorigenesis. His research group is also interested in the vulnerability of malignant peripheral nerve sheath tumors (MPNST) by targeting their epigenetic regulations. The ultimate goal of the Liao lab is to identify novel therapeutics for NF1 treatment.

Reprogramming histone methylation status as a therapeutic approach for MPNST therapy

Guan-Yi Lai[1], Chung-Ping Liao[1]. [1]Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University, Taipei, Taiwan

Introduction. Malignant peripheral nerve sheath tumor (MPNST) poses a significant challenge in cancer treatment, being largely resistant to current therapies. With no FDA-approved medication for MPNST, the need for novel treatment strategies is urgent. Our preliminary research has identified an overexpression of lysine-specific demethylase 1 (LSD1) in MPNST, suggesting LSD1 as a potential oncogenic driver. LSD1 demethylates histone H3 on lysine 4 and lysine 9 to modulate epigenetic reprogramming for gene repression and activation. Addressing the specific roles of LSD1 in the MPNST epigenome might reveal a novel therapeutic target for this unmet medical need.

Aims. This study aimed to delineate the contributions of LSD1-mediated epigenetic reprogramming to MPNST tumorigenesis.

Methods. We took the approach of LSD1 knockdown by LSD1 siRNA and LSD1 pharmaceutical inhibition by SP-2577 to address the role of LSD1 in MPNST tumorigenesis. The transcriptome of LSD1 modulation was profiled by NGS RNA-sequencing. MPNST xenograft mouse model was utilized to evaluate the therapeutic potential of LSD1 inhibitor SP-2577.

Results. LSD1 was found to be overexpressed in clinical human MPNST samples, experimental mouse MPNST models, and cultured MPNST cell lines. Suppression of LSD1 by LSD1 siRNA or LSD1 inhibitor SP-2577 significantly induced cell apoptosis and arrested the cell cycle at the G1 phase. Transcriptome analysis revealed that LSD1 knockdown or inhibition induced the expression of oxidative stress regulator TXNIP. Overexpression of TXNIP induced the levels of ROS to promote cell apoptosis and arrest the cell cycle, resulting in a potent anti-MPNST activity. MPNST xenograft mice treated with SP-2577 revealed a reduction in tumor growth rate.

Discussion. In conclusion, the modulation of LSD1 activity demonstrates promising anti-MPNST activity by altering the epigenetic background of MPNST cells. This underscores the potential of LSD1 as a promising target for MPNST therapy. Furthermore, the LSD1 inhibitor SP-2577 used in our study could be a potent anti-MPNST small molecule, offering hope for the future of MPNST treatment. These findings suggest a potential therapeutic strategy for MPNST, which is currently a challenging cancer to treat.

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"Reaching for a pill" - a qualitative systematic review of gabapentinoid misuse

Dr Evan Browne

Oral presentation 8: Pharmacogenomics & Clinical Pharmacology Themes, Courtyard Room 1&2, December 2, 2024, 2:15 PM - 3:45 PM

Biography:
Evan Browne is a Clinical Pharmacology, Toxicology and Nephrology Advanced Trainee based in Sydney with an interest in equity of care and the quality use of medicines.

"Reaching for a pill" - a qualitative systematic review of gabapentinoid misuse

Evan Browne[1,2], Amy Mc Neilage[2], Suzanne Nielsen[3], Claire Ashton[2] & Bridin Murnion[1,2]
Clinical Pharmacology, St Vincent's Hospital[1], Darlinghurst, NSW; University of Sydney,[2] Camperdown, NSW; Monash Addiction Research Centre[3], Clayton, VIC

Introduction: The use of gabapentinoids (GP) has been increasing, parallel with increasing harms related to toxicity and misuse[1]. Health care practitioner (HCP) perspectives provide important information on practice and beliefs that can inform strategies to modify prescribing and dispensing practice to reduce harms.

Aim: To systematically review and synthesise the qualitative literature on the perspectives of HCPs and other stakeholders on GP misuse and dependence.

Methods: A systematic review of 6 databases from inception to September 1, 2023. Phenomena of interest were misuse or dependence of GP, extracting any data with a qualitative component. Data were iteratively reviewed using reflexive thematic analysis to create themes. The CASP tool was used for quality appraisal.

Results: 1288 non-duplicated studies were identified, of which 48 progressed to full text screens. 7 studies met inclusion criteria. 4 main themes were identified (Table 1). There was awareness of increasing misuse via prescription and diversion ("pump this stuff out like it is candy") among addiction HCP, with GP often substituted for opioids or continuing after off-label management of other withdrawal. Stigma was considered an important, but under identified barrier to addressing misuse.

Theme 1: Awareness and perceptions of misuse and dependence
Theme 2: Reasons for misuse
Theme 3: Signs of misuse and/or dependence
Theme 4: Strategies to mitigate misuse and diversion
Subtheme: Provider centric approaches
Subtheme: Scheduling to reduce inappropriate gabapentinoid access
Subtheme: Access to gabapentinoid alternatives

Patient expectation of and access to pain management were considered problematic. HCPs had varied opinions on the benefits of regulatory changes to GP supply. HCPs supported additional practitioner education, audit and monitoring programs.

Discussion: This qualitative systematic review demonstrates complexity in HCP understanding of causes and responses to gabapentinoid misuse providing useful nuance to inform future medicines policies.

1: Crossin R, Scott D, Arunogiri S, Smith K, Dietze PM, Lubman DI. Pregabalin misuse-related ambulance attendances in Victoria, 2012–2017: characteristics of patients and attendances. Med J Aust. 2019;210(2):75–9.
2:Braun V, Clarke V. Reflecting on reflexive thematic analysis. Qual Res Sport Exerc Health. 2019 Aug 8;11(4):589–97.

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Factors contributing to variability in response to follitropins: a systematic review

Ms Toni Michael

Oral presentation 8: Pharmacogenomics & Clinical Pharmacology Themes, Courtyard Room 1&2, December 2, 2024, 2:15 PM - 3:45 PM

Biography:
Toni is a PhD student at the University of Sydney, School of Pharmacy. Her research is focused on understanding factors which contribute to the variability in urate response to gout medications and ovarian response to IVF medications (supervised by Dr. Sophie Stocker). She has received two awards for oral conference presentations.

Factors contributing to variability in response to follitropins: a systematic review

Toni Michael[1], Ranita Kirubakaran[2], Tanay Parab[1], Mark Grosser[3], Beverley Vollenhoven[4], Vinayak Smith[3,4,5], Sophie Stocker[1]. Sch of Pharm, Univ of Sydney[1], NSW; Dept of Pharm, Ministry of Health[2], Malaysia; 23Strands Pte Ltd[3], NSW; Dept of Obst and Gynaecol, Monash Univ[4], VIC. Virtus Health Pte Ltd[5], NSW.

Introduction. Controlled ovarian hyperstimulation (COH) for in vitro fertilisation (IVF) involves the administration of follicle-stimulating hormones, such as follitropin alfa, beta, or delta (follitropins). Oocyte response to COH is uncertain and variable, with many women requiring multiple IVF cycles to become pregnant. Understanding the factors contributing to the variability in response to follitropins is a strategy to improve individual response to COH therapies.
Aims. To identify factors contributing to variability in response to follitropins in women undergoing COH.
Methods. The EMBASE, PubMed and SCOPUS databases, and the references of included articles were systematically searched from database inception up to 14 January 2024. The search strategy included follicle-stimulating hormones, pharmacokinetics, dose, and IVF terminology. Studies conducted in women undergoing IVF with data on the duration of COH therapy, the total dose of follitropin administered, and the number of oocytes retrieved, were included. Descriptive (median [range]) and linear regression analysis ($P<0.05$) were performed on summary statistics.
Results. From the 3,849 studies identified, 329 were eligible. Of these, 126 studies reported on follitropin alfa, beta, and/or delta. The age and BMI of the women undergoing IVF were 32 years [20–42] and 22.8 kg/m^2 [20.2–61.3]. The average total dose of follitropin alfa, beta and delta was 2000 IU [1008–4538], 1800 IU [700–4040], and 84 µg [50–124], respectively, with COH lasting for 10 days [6–18]. On average, 11 [2–21] oocytes were retrieved. For follitropin alfa, a longer duration of COH ($P=0.03$), and older age ($P<0.0001$) decreased the number of oocytes retrieved ($R^2=0.28$, $P<0.0001$). Similarly, for follitropin beta, a longer duration of COH ($P=0.02$) and older age ($P=0.01$) reduced the number of oocytes retrieved ($R^2=0.15$, $P=0.002$). For follitropin delta, a lower total dose administered ($P<0.0001$) and older age ($P=0.02$) reduced the number of oocytes retrieved ($R^2=0.72$, $P<0.0001$).
Discussion. In addition to the age of a woman undergoing COH for IVF, the total dose of follitropin administered and the duration of COH impact the success of oocyte retrieval. These factors should be considered when individualising follitropin dosing to improve COH treatment response. The impact of other factors on oocyte retrieval, such as previous cycle number, should be explored further to additionally inform follitropin dosing.

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Optimizing Clinical Impact of Isoniazid Treatment Through Pharmacogenomics and Drug Level Implementation

Associate Professor Pajaree Chariyavilaskul

Oral presentation 8: Pharmacogenomics & Clinical Pharmacology Themes, Courtyard Room 1&2, December 2, 2024, 2:15 PM - 3:45 PM

Biography:

Dr. Chariyavilaskul received her first degree as a Medical Doctor with honours from the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, in 2001. She underwent post-graduate training and received an M.Sc. in Clinical Pharmacology with Distinction from the University of Glasgow, Glasgow, UK, in 2004 and a Ph.D. in Medical Science from the University of Edinburgh, Edinburgh, UK in 2010.

Dr. Charivavilaskul is currently an Associate Professor of Pharmacology and an Assistant Dean of Research Affairs, Faculty of Medicine, Chulalongkorn University. She is also the Head of Center of Excellence in Clinical Pharmacokinetics and Pharmacogenomics, the Head of Pharmacogenetics Laboratory Services, Center for Medical Diagnostic Laboratories, and an executive member of the Advisory Board of the Maha Chakri Sirindhorn Clinical Research Centre under the Royal Patronage, Faculty of Medicine, Chulalongkorn University.

She is responsible for teaching pharmacology in both undergraduate and postgraduate training programs of the Faculty of Medicine. She is also an active researcher, focusing on the areas of clinical pharmacokinetics, pharmacodynamics, and pharmacogenomics.

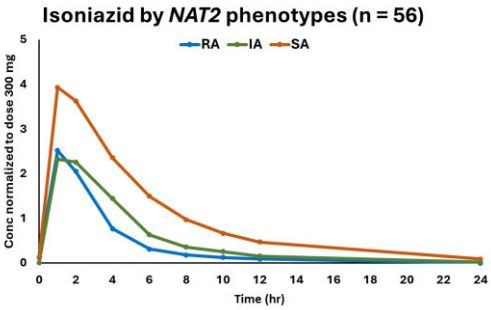
Optimizing Clinical Impact of Isoniazid Treatment Through Pharmacogenomics and Drug Level Implementation

Pajaree Chariyavilaskul[1], Weeraya Phaisal[1], Kamon Kawkitinarong[2], Gompol Suwanpimonkul[2], Anchalee Avihingsanon[3]. Center of Excellence in Clinical Pharmacokinetics and Pharmacogenomics, Chulalongkorn University[1], Bangkok, Thailand; Department of Medicine, Faculty of Medicine, Chulalongkorn University[2], Bangkok, Thailand; HIV-NAT, Thai Red Cross Society[3], Bangkok, Thailand.

Introduction. Genetic variations in the N-acetyltransferase 2 gene (*NAT2*) can significantly affect the efficacy and toxicity of isoniazid, leading to interindividual variability in drug response.

Aims. To display the distribution of *NAT2* genotypes and phenotypes in Thai TB patients and to investigate the pharmacokinetic profile of isoniazid according to *NAT2* genotypes and phenotypes.

Methods. 679 TB patients were enrolled. 28 *NAT2* SNPs were investigated using the MassARRAY system. The subsequent cohort of 60 TB patients were entered into the intensive pharmacokinetic study. Pharmacokinetic profiles (Tmax, Cmax, AUC, T1/2, Kel, Vz/F, and CL/F) were analyzed according to *NAT2* genotypes and phenotypes.



Results. *NAT2**6/*7 (23.6%), *6/*6 (19.6%), and *4/*4 (16.1%) were highly found in our TB cohort. About half (52.4%) of the patients were *NAT2* slow acetylators (SA). Cmax, $AUC_{0\text{-}24hr}$, and $AUC_{0\text{-}inf}$ of SA were two times higher than those of the rapid (RA) and intermediate acetylators (IA) [Cmax (mg/L): SA 4.17±1.73 vs RA 2.70±0.59 vs IA 2.59±0.93, p = 0.001; $AUC_{0\text{-}24hr}$ (mg.hr/L): SA 23±12 vs RA 8±2 vs IA 11±4, p = 0.000; $AUC_{0\text{-}inf}$ (mg.hr/L): SA 24±13 vs RA 9±2 vs IA 12±4, p = 0.000]. Vz/F and CL/F of SA were significantly decreased compared to RA and IA [Vz/F (L): SA 76±41 vs RA 187±81 vs IA 125±68, p = 0.000; CL/F (L/hr): SA 17.92±12.20 vs RA 34.36±7.13 vs IA 28.39±12.66, p = 0.000].

Discussion. Alleles of *NAT2* reduce enzyme function and the *NAT2* SA phenotype are highly found in the Thai population affecting the pharmacokinetic profiles of isoniazid. The *NAT2*-guided dose, together with the therapeutic drug monitoring of isoniazid, should be clinically implemented to help improve the outcome of TB treatment.

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Prolonged off-label antipsychotic therapy and cardiometabolic outcomes in children: a systematic review

Ms Ramya Padmavathy Radha Krishnan

Oral presentation 8: Pharmacogenomics & Clinical Pharmacology Themes, Courtyard Room 1&2, December 2, 2024, 2:15 PM - 3:45 PM

Biography:
Ramya is a PhD candidate at the University of Sydney in the Faculty of Medicine and Health. With a Masters in Bio-Technology, her prior experience of working in the drug discovery and pharmacovigilance field has inculcated a passion for Pharmacoepidemiology and drug safety. Her research utilises population-based health data to generate real-world evidence on medicine use and safety in the mental health space. She has further undergone training in Epidemiological methods and Health economic evaluations. Ramya's PhD is focussed on the investigation of cardiometabolic adverse effects associated with antipsychotic treatments given at low doses in off-label disorders, using Australian administrative datasets. Her aim is to improve patient health and well-being through the quality use of medicines.

Prolonged off-label antipsychotic therapy and cardiometabolic outcomes in children: a systematic review
Ramya Padmavathy Radha Krishnan[1], Monika Dzidowska[1], Danni Zheng[1], Zoie Shui-Yee Wong[2], Nicholas A Buckley[1], Jacques Eugene Raubenheimer[1] Faculty of Medicine and Health, The University of Sydney[1], Sydney, NSW, Australia; Graduate School of Public Health, St. Luke's International University[2], Tokyo, Japan.

Introduction. Paediatric antipsychotic use for non-psychotic illnesses is increasing and may be prescribed at low doses for many years. The resulting safety issues have not been adequately examined.
Aims. This systematic review investigated the cardiometabolic safety of antipsychotic use for a year or more in children with non-psychotic disorders.
Methods. We performed a systematic search for both randomised and observational studies with any comparator, examining cardiometabolic outcomes. Data synthesis through vote counting was depicted in an effect direction plot (upward, downward and sideways arrows indicating increase, decrease and no change respectively; size indicating number of participants).

Study	Study Design	Weight gain	Hyperglycemia	Dyslipidemia	Hypertension	Metabolic syndrome
Calarge et al (2014)	PC	▲4	▲3	◄►4	◄►	▲2
Gulisano et al	PC				▲2	
Rizzo et al	PC	▲	▲	▲2		
Calarge et al (2009)	RC	▲	▲3	▲4	◄►2	▲2
Degrauw et al	RC	▲3				
Pringsheim et al	RC	▲		◄►4		
Wei et al	RC	▲	▲	▲	◄►	
Wink et al	RC	◄►				
Yoon et al	RC	▲				
Ondo et al	RC	▲				
Croteau et al	NCC	▲				
Lee et al	NCC		▲			
Roke et al	CS	▲				
Srisawasdi et al	CS		▲2	▲5		
Vanwong et al	CS	▲				

Results. There were 15 observational studies with 114,141 participants (mean age 10.93 years) and no clinical trials. Autism and Tourette syndrome were studied in two-thirds of the studies. Prolonged antipsychotic treatment was associated with hyperglycaemia (100%, n=6), metabolic syndrome (100%, n=2), weight gain (91.6% studies, n=12) and dyslipidaemia (66.6%, n=6) as shown by the effect direction plot. Results were inconclusive for hypertension while no studies investigated ischemic heart disease or thrombosis. All studies had moderate to high methodological quality.

Discussion. Prolonged antipsychotic exposure in children, who are still undergoing physiological development, has the potential to disrupt metabolic processes that can have lasting repercussions. It is crucial that healthcare providers consider safety issues carefully in their approach to antipsychotic prescription in children.

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Activation and allosteric modulation of the human GLP-1R by small-molecule ligands

Dr Xin Zhang

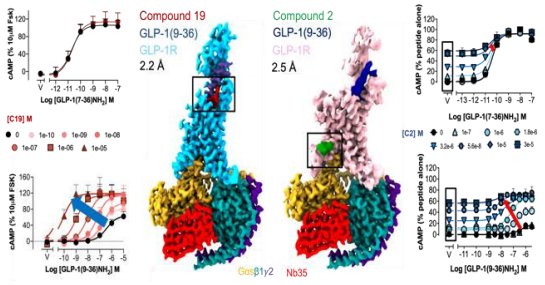
Bellberry New Investigator Award, Eureka Room 1, December 2, 2024, 4:15 PM - 6:15 PM

Biography:

Dr Xin (Cindy) Zhang received her PhD in 2021 and was awarded the 2021 Mollie Holman Medal for doctoral thesis excellence by Monash University for studies on the glucagon-like peptide-1 receptor (GLP-1R) in the lab of Profs. Patrick Sexton and Denise Wootten. She was then recruited as a Postdoctoral Fellow in the same laboratory on projects aligned to the Australian Research Council (ARC) Centre for Cryo-EM of Membrane Proteins (CCeMMP), and was recently awarded an ARC Discovery Early Career Researcher Award (DECRA) fellowship (2023-2026). Her research program incorporates cell biology, biochemistry, structural biology (in particular cryo-EM) and pharmacology to gain molecular insights into G protein-coupled receptors (GPCRs). Her particular interest is in the structure-function relationships of glucagon family GPCRs to understand how diverse ligands bind to and activate these receptors, which are clinically important drug targets for the treatment of type II diabetes and obesity.

Activation and allosteric modulation of the human GLP-1R by small-molecule ligands

Xin Zhang[1,2], Hariprasad Venugopal[3], Samantha McNeill[1], Matthew J. Belousoff[1,2], Patrick M. Sexton[1,2], Denise Wootten[1,2]. Drug Discovery Biology[1], and ARC CCeMMP[2], Monash Institute of Pharmaceutical Sciences, and Ramaciotti Centre for Cryo-Electron Microscopy[3], Monash University, Melbourne, VIC, Australia.



Introduction. The glucagon-like peptide 1 receptor (GLP-1R) is a well-established clinical target for type II diabetes and obesity. A variety of GLP-1R non-peptidic agonists and positive allosteric modulators (PAMs) have been identified, however, how they bind and modulate GLP-1R function is poorly understood.

Aims. Determine structures of GLP-1R-Gs complexes bound to different endogenous peptide agonist (GLP-1, GLP-1(9-36)NH_2, oxyntomodulin), biased small-molecule agonists (PF 06882961, CHU-128) or PAMs (compound 19, compound 2), and correlate these with their pharmacological profiles.

Methods. Structures of GLP-1R-Gs complexes were determined using cryo-electron microscopy (cryo-EM). Pharmacological profiles were assessed using assays of well-studied downstream signalling (cAMP production and calcium mobilisation) and regulatory (arrestin recruitment, internalisation) events.

Results. The binding site for PF 06882961 exhibits substantial overlap with that of endogenous peptide agonists within the receptor core. In contrast, CHU-128 displays limited overlap, which aligns with its divergent pharmacological properties (Deganutti et al 2022, Zhang et al 2020). Surprisingly, compound 19 engages at the extracellular side of the receptor, while compound 2 binds to the intracellular end. This correlates with the probe dependent properties of these PAMs, which differently modulate the metabolite signalling of endogenous peptides (Figure 1).

Discussion. Structural differences can be correlated to functional data revealing molecular insights into activation and modulation of small-molecule ligands. These findings will facilitate rational structure-based discovery of non-peptidic drugs targeting the GLP-1R and other related class B1 G protein-coupled receptors.
Deganutti G*, Liang YL*, Zhang X* et al (2022) Nat Commun 13:92; Zhang X et al (2020) Mol Cell 80:1–16

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Advancing Geriatric Pharmacology through Big Data Analytics with International Collaboration

Dr Kenji Fujita

Bellberry New Investigator Award, Eureka Room 1, December 2, 2024, 4:15 PM - 6:15 PM

Biography:
After completing a Master of Science in Clinical Epidemiology followed by a Doctor of Pharmacy at the University of Sydney, Dr. Fujita has been working as a Postdoctoral Research Fellow at the Kolling Institute Ageing and Pharmacology Laboratory since 2020. His unique combination of expertise in clinical pharmacology, epidemiology, and big data analytics, along with his previous experience in developing web applications, positions him to lead several innovative projects. His research focuses on improving medication management for older adults, particularly through deprescribing, frailty assessment, and monitoring the quality of care. Dr. Fujita, who previously worked as a pharmacist in Japan, currently serves as the co-lead of the working group on guidelines and indicators within a pharmacy practice research group in Europe, Pharmaceutical Care Network Europe (PCNE). He is also an executive committee member of the Social and Administrative Pharmacy Section in the International Pharmaceutical Federation (FIP) and the chairperson of a research committee within the Association of Pharmacist Home Visiting Service in Japan (J-HOP)

Advancing Geriatric Pharmacology through Big Data Analytics with International Collaboration

Kenji Fujita
Departments of Clinical Pharmacology and Aged Care, Kolling Institute, Faculty of Medicine and Health, the University of Sydney and the Northern Sydney Local Health District, Sydney, NSW, Australia

Dr. Fujita is a Postdoctoral Research Fellow at the Kolling Institute Ageing and Pharmacology Laboratory. His expertise in clinical pharmacology and advanced data analytics positions him to create scalable, internationally applicable solutions that can drive improvements in geriatric pharmacology. His research focuses on improving medication management for older adults, particularly through deprescribing, frailty assessment, and monitoring quality of care.
In Australia, his main role has been leading the analysis of big data from NSW Hospitals for a pilot, followed by a stepped-wedge cluster randomised trial across six hospitals, investigating the effectiveness of a comprehensive intervention bundle with a stewardship program to facilitate the deprescribing of sedative and anticholinergic medications in older inpatients. Recognising that hospital clinicians are more likely to recommend deprescribing medications to GPs through discharge summaries than to deprescribe during admission, Dr. Fujita developed a Natural Language Processing model to extract deprescribing recommendations from discharge summaries of older adults with polypharmacy, achieving high accuracy. Pre-defined subgroup analysis of the randomised trial results by frailty required further development and validation of a frailty index using data routinely available in the electronic health record. Future applications of the frailty index are planned to help identify subgroups of vulnerable older adults who may benefit from multidisciplinary interventions to enhance therapeutic outcomes and minimise adverse drug events.
He also applied his analytic skills to preclinical research at the Kolling. Using pre-trained convolutional neural network models in aging mice, he evaluated the effects of chronic monotherapy, polypharmacy, and deprescribing over time.

Dr. Fujita's contributions extend internationally. He co-leads a working group to develop quality indicators (QIs) for pharmaceutical care, involving 19 researchers from 13 countries. In addition, his leadership in an international collaborative project between Australia and Japan has involved analysing data from over 2 million older adults across 2,000 community pharmacies to evaluate pharmacists' deprescribing initiatives for older adults with polypharmacy. The success of a series of his studies on developing and validating QIs for pharmaceutical care in Japan, along with the development of interactive web applications, led to an ongoing Japanese government-funded QI project.

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Translating evidence to practice: pharmacist-led deprescribing and the SaferMedsNL initiative.

Dr Justin Turner

Bellberry New Investigator Award, Eureka Room 1, December 2, 2024, 4:15 PM - 6:15 PM

Biography:
Dr Justin Turner has extensive experience providing patient care and leading research across aged care, primary care, tertiary care and academia in Australia, Europe and North America. His research seeks to answer the question, "How can we optimise medication use in older adults?" Dr Turner's research is driven by a passion for improving medication management and reducing medication-related harm.
Dr. Turner completed his Master of Clinical Pharmacy at the University of South Australia and his PhD at Monash University. He then undertook a Postdoctoral Fellowship at the University of Montreal, where he focused on designing, implementing, and evaluating evidence-based deprescribing interventions at a population level. Notable achievements during his time in Canada include conducting the first nationwide survey on deprescribing, leading a randomized controlled trial on opioid reduction, and instigating policy changes to incentivize pharmacists to deprescribe. His leadership in the SaferMedsNL initiative educated and engaged residents of Newfoundland and Labrador about the risks of medication-related harm and the importance of deprescribing.
As an inaugural member of the Australian Deprescribing Network (ADeN) and Co-Director of the Canadian Appropriate Medication Use and Deprescribing Network (CADeN), Dr. Turner has been at the forefront of deprescribing internationally. Dr Turner has been an investigator on successful grants and scholarships totalling over $10 million and received awards for research excellence from both the Canadian Geriatrics Society and the American Geriatrics Society.
Dr. Turner's current research seeks to adapt international best practices in patient-led deprescribing to the contexts of Australia, Canada, and the United States. His work continues to influence health policies and clinical practice, leading to safer and more effective medication use for older adults globally.

Translating evidence to practice: pharmacist-led deprescribing and the SaferMedsNL initiative
Justin P Turner[1-2], Kelda Newport[3], Cara Tannenbaum[4], Deborah V. Kelly[3]. Centre for Medicines Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences[1], Monash University, VIC, Australia. Faculté de Pharmacie, Université de Montréal[2], QC, Canada School of Pharmacy, Memorial University of Newfoundland[3], NL, Canada. Faculté of Médicine, Université de Montréal[4], QC, Canada

Introduction: Newfoundland and Labrador (NL) has among the highest rates of potentially inappropriate medications (PIMs) in Canada, specifically chronic use of sedatives and proton pump inhibitors (PPIs). The SaferMedsNL intervention adapted the D-PRESCRIBE trial to the contexts of NL via stakeholder engagement. New funding was provided for pharmacists to identify PIMs and initiate deprescribing conversations with patients and healthcare providers.

Aims: To evaluate the changes in medication across NL for people who did or did not receive the pharmacist deprescribing intervention.
Methods: Prescription claims data for all NL adults from 2019 to 2021 were analysed to identify prescription and pharmacist deprescribing intervention claims. Propensity score matching assessed changes in mean daily defined doses (DDD) for chronic sedative or PPI users who did or did not receive the deprescribing intervention. Sub-analysis investigated age categories.
Results: Reductions in DDD varied across medication classes and age groups. A significant reduction in PPI DDD was observed after 3 months, increasing to a 30% reduction at 10 months. The intervention group continued to have significantly lower DDD until the end of the 40-month follow-up. No significant reduction in sedative DDD was observed in the all-ages analysis. However, among adults aged ≥70, sub-analysis indicated a significant impact of the intervention, with PPI DDD reducing by 20% and sedative DDD reducing by 12% during the follow-up period.
Discussion: The evidence-based D-PRESCRIBE trial was effectively adapted and scaled up at a population level, leading to reductions in PIM use. The reductions observed in older adults are important because this age category is most susceptible to adverse drug events. Further research should investigate the differences in effect observed between medication classes and across age groups.

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Reduced oral absorption and brain-penetration of caffeine in amyotrophic lateral sclerosis mice

Dr Liam Koehn

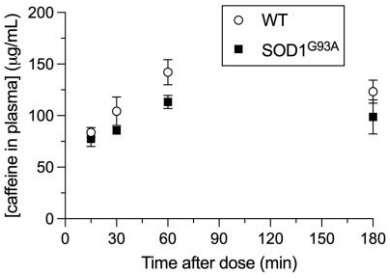
APSA Emerging Leaders Award, Eureka Room 1, December 3, 2024, 8:00 AM - 8:50 AM

Biography:

Liam completed his PhD in Professor Norman Saunders' laboratory at the University of Melbourne, investigating the permeability of medicines across the blood-brain barrier at different stages of development. He then undertook a postdoctoral fellowship in Professor Barbara Stonestreet's laboratory at Brown University, where he investigated the efficacy and mechanism of action of a novel treatment for neonatal hypoxic-ischemic brain injuries. Liam joined Professor Nicolazzo's laboratory at the Monash Institute of Pharmaceutical Sciences in 2022, where he investigates the pathophysiology of motor neurone disease and the efficacy of novel neuroprotective treatments.

Reduced oral absorption and brain-penetration of caffeine in amyotrophic lateral sclerosis mice

Liam M Koehn[1], Joel R Steele[2], Roshan Jalaldeen[1], Joseph Pelle[1], Ralf B Schittenhelm[2], Bradley J Turner[4], Joseph A Nicolazzo[1]. Drug Delivery, Disposition and Dynamics, Monash University[1], Parkville, VIC, Australia; Monash Proteomics and Metabolomics Platform, Monash University[2], Clayton, Victoria, 3800, Australia; The Florey Institute of Neuroscience and Mental Health, University of Melbourne[4], Parkville, VIC, 3052, Australia.



Introduction. Amyotrophic lateral sclerosis (ALS) is a member of the motor neurone disease family of neurodegenerative disorders. It is unknown whether there are disease-induced changes to pharmacokinetics after oral administration in ALS, as has been reported in other neurodegenerative disorders.

Aims. To compare plasma, brain and spinal cord concentrations of digoxin, caffeine and sulfasalazine orally administered to wild-type (WT) and SOD1^{G93A} mice (model of familial ALS, superoxide dismutase 1 mutation) and investigate underlying mechanisms contributing to differences between genotypes.

Methods. Postnatal day 110-120 male and female SOD1^{G93A} and WT mice were administered digoxin (2 mg/kg), sulfasalazine (50 mg/kg) or caffeine (130 mg/kg) via oral gavage, anaesthetised with isoflurane (<5% in oxygen) and plasma, brain and spinal cord collected at 15, 30, 60 or 180 min post-dose (n=3/genotype/sex/time-point). *Ex vivo* intestinal permeability was assessed, alongside untargeted, quantitative proteomics of the small intestine and liver.

Results. AUC of caffeine, but not digoxin and sulfasalazine, was significantly ($z<1.96$, Bailer's) lower in plasma, brain and spinal cord of SOD1^{G93A} compared to WT mice. Brain-to-plasma ratios were not different between genotypes. AUC of caffeine in stomach was significantly higher in SOD1^{G93A} mice and the *ex vivo* intestinal permeability of caffeine was lower in male SOD1^{G93A} compared to WT mice. Proteomics identified male-specific differences in hepatic and intestinal transporters/enzymes relevant to pharmacokinetics, however major caffeine-metabolising enzymes were unchanged.

Discussion. A drug-specific reduction in oral absorption was identified in SOD1^{G93A} mice, which may be due to reduced gastric emptying and intestinal permeability. Male-specific changes to the hepatic and small intestinal proteome of SOD1^{G93A} mice highlight that additional studies are warranted to assess if other drugs exhibit altered pharmacokinetics in SOD1^{G93A} mice, as well as whether these differences are evident in individuals with ALS.

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Risk of aortic aneurysm or dissection following exposure to systemic fluoroquinolone antibiotics

Dr Jack Janetzki

APSA Emerging Leaders Award, Eureka Room 1, December 3, 2024, 8:00 AM - 8:50 AM

Biography:

Jack is a Lecturer in Pharmacy and Pharmacology. Jack is a practicing Pharmacist and has worked in several pharmacies in both rural Victoria and urban South Australia. Jack has a strong interest in improving medication safety which is evident in his clinical practice, research and education of future health professionals. Maintaining clinical practice allows him to draw on real world experiences and incorporate this into his contemporary teaching and research endeavours. Jack is a member of the Quality Use of Medicines and Pharmacy Research Centre (QUMPRC) at UniSA. He is also a member of the Local Advisory Committee for Pharmaceutical Defence Limited, a not-for-profit organisation which support pharmacists with risk management advice.

Risk of aortic aneurysm or dissection following exposure to systemic fluoroquinolone antibiotics

Jack Janetzki[1], Jung Ho Kim[2], Seng Chan You[2], Nicole Pratt[1], University of South Australia[1], Adelaide, South Australia, Australia, Yonsei University College of Medicine[2], Seoul, South Korea

Introduction. Medicine regulators have issued safety warnings regarding the risk of aortic aneurysm or dissection (AA/AD) with fluoroquinolones (FQ) antibiotics. Risk remains uncertain as prior studies due to inconsistencies in study design, approaches to identifying exposures, outcomes and methods to address confounding.

Aims. To estimate the risk of AA/AD following FQ exposure compared to other standard treatments for urinary tract infection (UTI).

Methods. A distributed network analysis was conducted across 14 databases standardised to the OMOP Common Data Model. Patients were included if they were aged 35 years or older and initiated an antibiotic for treatment of UTI between 2010 and 2019. Patients initiating systemic FQ were compared to trimethoprim (TMP) and cephalosporin (CPH). The primary outcome was hospitalisation for aortic aneurysm or dissection (AA/AD). A large-scale propensity score (PS) model using covariates measured at baseline was generated using regularised regression. Target and comparator cohorts were matched using a 1:1 ratio. Covariate balance was assessed using standardised difference of means between the matched cohorts, clinical equipoise was assessed by determining overlap in preference score distributions and systematic error was assessed by evaluating the expected absolute systematic error across 50 negative controls. Cox proportional hazards models were used to model outcome risk for each time at risk window (30, 60, 90 or 365 days). Hazard ratios were pooled across databases using Bayesian meta-analysis among those databases that passed study diagnostics.

Results. Seven databases contributed data to the meta-analysis of the association between FQ and AA/AD compared with TMP; pooled calibrated hazard ratio (HR) for the 60-day risk window was 0.91 (95% Confidence Interval (CI) 0.73-1.10). Nine databases contributed to meta-analysis of association between FQ and AA/AD compared with CPH; pooled calibrated HR for the 60-day risk window was 1.01 (95% CI 0.82-1.25).

Discussion. There was considerable variation in patient characteristics and treatment patterns, however limited heterogeneity in treatment effect estimates. We found no association between use of FQ and risk of AA/AD compared to other broad spectrum antibiotics in patients with UTI.

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“Almost like crickets”: Impact of the COVID-19 pandemic on hospital education

Dr Sarah Hassan

APSA Emerging Leaders Award, Eureka Room 1, December 3, 2024, 8:00 AM - 8:50 AM

Biography:
Sarah Hassan is a pharmacist and PhD graduate from RMIT University. Her research primarily focuses on how antibiotics can be better utilised in the hospital setting, with her thesis investigating surgical antimicrobial prophylaxis in orthopaedic surgery and the factors that influence antibiotic guideline adherence. She also has an interest in understanding how education delivery in the hospital system influences guideline uptake and the strategies that can be implemented to enhance uptake of guideline recommendations. She currently works as a community pharmacist and as a sessional academic with the Discipline of Pharmacy at RMIT University.

“Almost like crickets…”: Impact of the COVID-19 pandemic on hospital education

Sarah Hassan[1], Vincent Chan[1], Julie E Stevens[1,2,3], Ieva Stupans[1]. Pharmacy, School of Health and Biomedical Sciences, RMIT University[1], Bundoora, VIC, Australia; Clinical and Health Sciences, University of South Australia[2], Adelaide, SA, Australia; Adelaide Medical School, Faculty of Health and Medical Sciences, University of Adelaide[3], Adelaide, SA, Australia

Introduction: Continuing professional development equips healthcare professionals with contemporary knowledge. The COVID-19 pandemic has placed excessive strains on the healthcare system in Victoria, Australia and has impeded routine activities conducted in hospitals. It is unclear to what extent hospital education has been impacted due to the pandemic.
Aim: To qualitatively explore education pharmacist perspectives on the general impact of the COVID-19 pandemic on the hospital system, the barriers and enablers to providing education during this time and the overall lessons – both positive and negative – learnt as a result of the experience.
Methods: Clinical education pharmacists (n=24) across Victorian public hospitals were invited to participate in this study. Semi-structured interviews were conducted between December 2021 and February 2022, with questions focusing on the barriers and enablers to providing education during the pandemic. Results were analysed using a content analysis approach and the Systems Engineering Initiative for Patient Safety (SEIPS) 101 model ‘PETT Scan’ tool.
Results: Ten education pharmacists participated in the study. An increase in workload and demand for clinical services were highlighted by all pharmacists, resulting in reduced education sessions. Education provision was further impacted by the lack of infrastructure to adequately support the use of virtual platforms. Enablers included the capability to record virtual education sessions as well as the development of online modules to disseminate knowledge.
Discussion: The COVID-19 pandemic has greatly impacted the provision of education across Victorian public hospitals, with many hospitals experiencing reduced opportunities to provide education. By identifying barriers to providing education and by increasing support and resources, hospitals can improve access to knowledge during rapidly changing circumstances.

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Pharmacological inhibition of interleukin-18 attenuates deoxycorticosterone/salt-induced hypertension, renal inflammation and capillary rarefaction

Miss Buddhila Wickramasinghe

ASCEPT Garth McQueen Oral Student Prize Session, Eureka Room 1, December 3, 2024, 9:00 AM - 10:30 AM

Biography:
Buddhila Wickramasinghe is a third-year PhD candidate in the Hypertension and Diabetes division at the Centre for Cardiovascular Biology and Disease Research, La Trobe University, Melbourne, Australia. Her research focuses on understanding the role of the immune system in hypertension and chronic kidney disease by utilizing various animal models and in vitro techniques. As she continues to develop her research profile, she has presented her work at both national and international conferences, including the High Blood Pressure Research Council of Australia ASM and International Society of Hypertension Scientific Sessions. In addition to her research, Buddhila advocates for HDR students as the student representative for the Cardiovascular SIG of ASCEPT. She is also dedicated to promoting STEM education and inspiring the next generation of scientists by engaging with primary and high school students.

Pharmacological inhibition of interleukin-18 attenuates deoxycorticosterone/salt-induced hypertension, renal inflammation and capillary rarefaction

Buddhila Wickramasinghe[1], Narbada Saini[1], Jordyn Thomas[1,2], Brooke Huuskes[1], Henry Diep[1,2], Christopher G Sobey[1], Maria Jelinic[1], Grant R Drummond[1], Antony Vinh[1]. Centre for Cardiovascular Biology and Disease Research, La Trobe Institute for Molecular Science, La Trobe University, Bundoora, VIC, Australia[1]; Victorian Heart Institute, Monash University, Clayton, VIC, Australia[2].

Introduction. Circulating levels of the pro-inflammatory cytokine, interleukin-18 (IL-18), are elevated in patients with hypertension and chronic kidney disease (CKD). Moreover, genetic IL-18 deletion prevents the development of hypertension and renal injury in uninephrectomised mice treated with deoxycorticosterone acetate and high salt (1K/DOCA/salt, a model of CKD). Thus, IL-18 represents a novel drug target to treat hypertension and CKD.
Aims. Determine if pharmacological inhibition of IL-18 protects against 1K/DOCA/salt-induced hypertension and CKD.
Methods. Male C57BL/6 mice (n=11-12/group, 12 weeks old) were randomly assigned to receive a control IgG or anti-IL-18 neutralising monoclonal antibody (30 mg/kg, *i.p.*) 3 days prior to induction of hypertension, and every 3 days thereafter. Isoflurane anaesthetised mice (induction: 2 L/min, 5% in O_2; maintenance: 0.4 L/min, 2.5% in O_2) received uninephrectomy and implantation of a DOCA pellet (2.4 mg/d, *s.c.*) with saline drinking water (0.9% NaCl). Normotensive controls received a placebo pellet (*s.c.*) with normal drinking water. Blood pressure (BP) was measured weekly (tail-cuff). After 21 days, mice were humanely killed and kidneys were collected to assess fibrosis (picrosirius red staining), immune cell infiltration (flow cytometry) and renal capillary density (immunofluorescence).
Results. Anti-IL-18 treatment did not affect systolic BP in placebo mice (118±2 mmHg Vs 122±3 mmHg in control IgG), but significantly blunted hypertension in 1K/DOCA salt mice (139±6 mmHg Vs 159±6 mmHg in control IgG; $P<0.05$). 1K/DOCA/salt-induced leukocyte ($CD45^+$) accumulation in the kidneys was reduced in anti-IL-18-treated mice (0.9±0.1 x10^5 cells/kidney) compared to control IgG treatment (1.6±0.3 x10^5 cells/kidney; $P<0.05$). Further analysis revealed reductions in myeloid cells ($CD11b^+$; $P<0.05$), specifically macrophages ($F4/80^+$; $P<0.05$). 1K/DOCA/salt-induced renal capillary rarefaction but not fibrosis was significantly prevented in anti-IL-18-treated mice ($P<0.05$).
Discussion. Neutralisation of IL-18 prevents experimental hypertension possibly via a reduction in renal inflammation and renal capillary rarefaction. IL-18 may represent a novel drug target to treat hypertension and kidney disease.

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Proteomic analysis of BALF from silicotic Victorian engineered-stone workers reveals secretome landscape

Ms Claudia Sim

ASCEPT Garth McQueen Oral Student Prize Session, Eureka Room 1, December 3, 2024, 9:00 AM - 10:30 AM

Biography:
Claudia Sim is a final-year PhD candidate from the Respiratory Pharmacology Laboratory at Monash University. Her research seeks to establish novel methods and metrics to quantify silica in alveolar macrophages and proteomic profiling of bronchoalveolar lavage fluid (BALF) from silicosis patients. Her work aims to deepen the understanding of disease mechanisms, establish ex vivo models of silicosis using human precision-cut lung slices for therapeutic testing, uncover potential biomarkers, and improve differential diagnosis in interstitial lung diseases. Claudia has presented her work at both national and international conferences. As an active member of the respiratory research community, she collaborates with industry partners like Owlstone Medical to advance breath-based diagnostics to support early disease detection, with an aim to empower individuals and healthcare providers to make timely, informed health decisions.

Proteomic analysis of BALF from silicotic Victorian engineered-stone workers reveals secretome landscape.
Claudia Sim[1], Joel Steele[2], Terry Lim[2], Paris Papagiannis[1], Simon G Royce[1], Ryan Hoy[3,4], Tracey Leong[5], Ralf B Schittenhelm[2], Jane E Bourke[1] [1]Pharmacology, Biomedicine Discovery Institute, [2]Proteomics and Metabolomics Platform and [3]School of Public Health, Monash University, Clayton VIC, Australia [4]Respiratory Medicine, The Alfred Hospital, Melbourne, VIC; Australia [5] Respiratory and Sleep Medicine, Austin Hospital, Heidelberg, VIC, Australia

Introduction. Silicosis is a major occupational health issue, with increased cases associated with the unsafe cutting of high silica artificial stone benchtops[1]. There is no cure, partly due to a limited understanding of disease pathogenesis.

Aims. To establish a metric of silica load and identify proteomic signatures and pathways associated with silicosis.
Methods. Bronchoalveolar lavage fluid (BALF) from silicosis (n=22) and control (n=6) subjects. Silica load in BALF macrophages (macs) was quantitated based on #birefringent particles/mac x %particle-containing macs x #macs /mL. BALF was subjected to targeted (Olink®) and untargeted (LCMS) proteomic analysis for Gene Set Enrichment Analysis (GSEA) and visualization of Protein-protein Interaction (PPI) networks by Cytoscape and STRING.

Results. *Silica load:* Higher proportion of silica-containing macs associated with disease severity. *Targeted analysis*: Sixteen differentially expressed proteins (DEPs) - 14 DEPS increased inc MCP-1, -2, -3; two DEPS decreased *cf* control ($p<0.05$). *Untargeted quantitative analysis:* Six DEPs - 4 increased, 2 decreased ($p<0.05$). *Qualitative analysis:* 1784 potentially silicosis-unique proteins - only osteopontin present in 21/22 samples, differential expression validated by ELISA ($p<0.001$). *GSEA:* Enriched pathways associated with ribosome ($p<0.05$, FDR<1) and spliceosome ($p<0.005$, FDR<1). *PPI analysis:* heterogenous ribonucleoprotein C (HNRNPC, involved in mRNA synthesis) is the hub protein
Discussion. Our comprehensive characterization quantitates silica-containing macs, DEPS and unique proteins and their associations with silicosis. From *GSEA* and *PPI* analysis, silicosis-unique proteins interact primarily with targets related to ribonucleoproteins, including the spliceosomal complex involved in regulating mRNA transcripts and subsequent generation of functional mRNA. Unraveling the secretome landscape has provided mechanistic insights into silicosis disease processes for potential therapeutic targeting in this occupational lung disease.

Hoy R et al (2023) Prevalence and risk factors for silicosis among a large cohort of stone benchtop industry workers. *Occup Environ Med* 80:439-446.

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Feasibility and Acceptability of a Nurse-Pharmacist Post-Discharge Telehealth Heart Failure Service

Mr Joshua Bennetts

ASCEPT Garth McQueen Oral Student Prize Session, Eureka Room 1, December 3, 2024, 9:00 AM - 10:30 AM

Biography:
Joshua is a clinical pharmacist and PhD candidate from the University of Newcastle. Joshua has a particular interest in cardio-oncology — an emerging field that focusses on mitigating cardiovascular disease secondary to cancer treatment. His research focusses primarily on pharmacist-led models of care to support people with cardiovascular disease and cancer as they transition between hospital and home.
Joshua has presented his research at national and international conferences and is an active member of the International Cardio-Oncology Society (IC-OS) pharmacist working group. Joshua is also a credentialed pharmacist who continues to provide domiciliary medication management review services for his community and has broad clinical experience across both hospital and community pharmacy.

Feasibility and Acceptability of a Nurse-Pharmacist Post-Discharge Telehealth Heart Failure Service
Joshua Bennetts[1,2], Cameron Robson[3], Dawn McIvor[3], Trent Williams[3], Aaron Sverdlov[2,3], Doan Ngo[1,2]. School of Biomedical Sciences and Pharmacy, University of Newcastle[1], Callaghan, NSW, Australia; Hunter Medical Research Institute[2], New Lambton Heights, NSW, Australia; Hunter New England Local Health District[3], New Lambton Heights, NSW, Australia.

Introduction. Poor medication compliance, use of harmful medications and withdrawal of beneficial medications are common contributors to hospital readmissions and mortality for heart failure patients (HFPs). However, few studies have evaluated the implementation of a nurse-pharmacist model of care into a HFPs transition-of-care journey.
Aims. To determine the feasibility and acceptability of a nurse-pharmacist telehealth service for transition-of-care HFPs discharged from the John Hunter Hospital, Australia.
Methods. HFPs were referred to an existing telehealth service and offered medication reconciliation and education in addition to their usual care; a service we termed 'MedRec'. Primary outcomes were feasibility — measured by calculating recruitment and successful completion of a MedRec — and acceptability — measured by an investigator-developed survey. Secondary outcomes were medication-related issues detected during MedRec.
Results. In total 100 HFPs were offered a post-discharge MedRec. Mean age of patients was 68.5 years (±14.2). HFPs were mostly male sex (62%). Pharmacist MedRecs were requested by 80% of HFPs. In total 62 MedRecs (77.5%) were performed; 9 HFPs declined MedRec during follow-up and an additional 9 HFPs were uncontactable. Mean time to MedRec following nurse referral was 10.98 days (±9.74). At the time of MedRec, 25 recipients (40.3%) were experiencing drug-related toxicity or adverse events, 13 recipients (20.9%) were experiencing medication compliance issues, and undertreated comorbidities, such as symptomatic heart failure or chronic pain, was identified in 12 recipients (19.4%). Drug and/or disease management information was requested by 35 MedRec recipients (56.4%). Post-MedRec surveys were completed by 35 (56.5%) HFPs. All survey participants agreed that a telehealth MedRec was an acceptable form of education provision. Engagement with a pharmacist MedRec was perceived to ease anxiety associated with understanding medication-related changes and empowered greater medication self-management.
Discussion. A post-discharge nurse-pharmacist telehealth service is a feasible and acceptable model of care. Inclusion of a routine MedRec post-discharge may be an effective means of maintaining continuity of care for HFPs.

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Characterisation of the pro-atherosclerotic orphan G protein-coupled receptor, GPR146

Mr Brendan Wilkins

ASCEPT Garth McQueen Oral Student Prize Session, Eureka Room 1, December 3, 2024, 9:00 AM - 10:30 AM

Biography:
Brendan recently completed his PhD in the laboratory of Nicola Smith at UNSW Sydney. He is now a Lecturer in the Department of Pharmacology in the School of Biomedical Sciences at UNSW Sydney. Brendan has a special interest in G protein-coupled receptors, particularly those that do not yet have an identified endogenous ligand which are termed "orphans". Brendan is the chair-elect of the ASCEPT Equity, Diversity, and Inclusion Committee and is committed to improving the visibility of the ASCEPT LGBTQIA+ community.

Characterisation of the pro-atherosclerotic orphan G protein-coupled receptor, GPR146

Brendan P Wilkins[1], Jack Zhang[1], Asuka Inoue[2], Marianne Martinello[3], Blake Cochran[1], Rowena Bull[3], Nicola J Smith[1]. School of Biomedical Sciences, UNSW Sydney[1], NSW, Australia; Graduate School of Pharmaceutical Sciences, Tohoku University[2], Sendai, Japan; The Kirby Institute, UNSW Sydney[3], NSW, Australia.

Introduction. GPR146 is an orphan G protein-coupled receptor that has a convincing pro-atherosclerotic role through upregulation of the cholesterol biosynthesis pathway. Inhibition of this receptor may be particularly useful with treatment-refractory familial hypercholesterolaemia. However, the molecular pharmacology of this receptor remains understudied. Proinsulin C-peptide and foetal bovine serum (FBS) are proposed activators of GPR146, although the pairing with C-peptide has not yet been reproduced by an independent research group and the active component in FBS has not yet been identified.
Aims. The aim of this study was to validate previously proposed ligands for GPR146.
Methods. C-peptide and FBS were tested using the following assays: reporter gene assays to investigate Gαs, Gαi/o, Gαq/11, and Gα12/13 signalling; a NanoBiT assay for β-arrestin recruitment; and Western blot or a BRET1-based biosensor for ERK1/2 phosphorylation (pERK1/2). A panel of 58 human sera was screened at GPR146 using Western blot probed for pERK1/2; the threshold for "hit" selection was set at ±2xSD. Human sera identified as "hits" were then further characterised using G protein- and arrestin-deficient HEK293A cells.
Results. Neither C-peptide nor FBS activated GPR146 in any assays tested (n=5); assay validity was confirmed by multiple positive controls. An overall increase in pERK1/2 was observed in response to human serum in GPR146-expressing cells compared to cells not expressing GPR146 ($P<0.0001$, paired t-test). 47/58 human serum samples elevated pERK1/2, with 5 surpassing the upper hit threshold indicating activation of GPR146.
Discussion. In this study, previously proposed ligands for GPR146 were not reproduced, indicating that C-peptide is not, and FBS does not contain, the endogenous ligand for GPR146. Instead, human serum was identified as an activator of GPR146. Future studies with human serum may identify the endogenous ligand for GPR146.

Yu et al. 2019. Cell. 179(6):1276-1288.e14.
Yosten et al. 2013. J Endocrinol. 11;218(2):B1-8.

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Maternal Thirdhand E-vapour exposure impacts offspring lung health in experimental asthma model

Miss Andie Thorpe

ASCEPT Garth McQueen Oral Student Prize Session, Eureka Room 1, December 3, 2024, 9:00 AM - 10:30 AM

Biography:
Andie Thorpe is a second-year PhD student at the University of Technology Sydney and the Woolcock Institute of Medical Research. Her research centres on the pulmonary effects of e-cigarette exposure, with a current focus on investigating the in-utero impacts of e-cigarette use and its implications for chronic respiratory diseases.

Maternal Thirdhand E-vapour exposure impacts offspring lung health in experimental asthma model

Andrew E Thorpe[1,2], Chantal Donovan[1,2,3], Richard Kim[1,2,3,] Meng Wang[1,2], Xu Bai[1,2], Rochelle Yarrak[1], Hui Chen[1], Brian Oliver[1,2]. School of Life Sciences, University of Technology Sydney[1], Sydney, NSW, Australia; Woolcock Institute of Medical Research, Respiratory Cellular and Molecular Biology[2], Sydney, NSW, Australia; University of Newcastle, Immune Health Program, Hunter Medical Research Institute[3], Newcastle, NSW, Australia

Introduction. Women of childbearing age (14 - 45) comprise the highest demographic of e-cigarette usage globally, with little regulation around exposure, due to the perception that e-cigarettes are harm-free. Third hand exposure to e-cigarette vapour has been shown to cause negative biologic effects including immune regulatory and pulmonary effects [1, 2]. Aims. To determine the impact that in utero exposure on foetal health outcomes specifically chronic respiratory diseases including asthma.
Methods. 6-week-old Female Balb/c mice were exposed to third hand e-vapour encompassing a variety of e-cigarette usage behaviours (Low power (LP)& High power (HP), +/- nicotine (NIC)) for 15 weeks; inclusive of pre-exposure, gestation, and weaning periods. Female offspring from maternal ($_M$) exposed mice were intraperitoneally administered ovalbumin (OVA) followed by intranasal OVA challenges (12,13 & d33,34) to induce experimental asthma. At the endpoint (d35), lung function analysis was conducted with a methacholine challenge to test for airway hyperresponsiveness and bronchoalveolar lavage fluid was collected to measure airway inflammation.
Results. Maternal third hand e-vapour exposure affected offspring lung health. Airway hyperresponsiveness was observed $_M$LP-NIC vs $_M$SHAMOVA ($P<0.001$). Airway inflammation was increased in high power setting groups regardless of nicotine concentration $_M$HP-NIC and $_M$HP+NIC vs $_M$SHAMOVA ($P<0.05$). These findings were confirmed by histological inflammation scoring.
Discussion. Nicotine and non-nicotine containing e-cigarettes can produce harmful effects at a third-hand exposure level. These findings indicate the potential public health impact that third hand e-cigarette exposure can have during pregnancy and maternal exposure on respiratory health outcomes.
[1] Thorpe, A.E., et al., Third-Hand Exposure to E-Cigarette Vapour Induces Pulmonary Effects in Mice. Toxics, 2023. 11(9): p. 749. [2] Chen, H., et al., Evidence from a mouse model on the dangers of thirdhand electronic cigarette exposure during early life. ERJ Open Research, 2020. 6(2): p. 00022-2020.

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AT2R agonists C21 and NAc inhibit IPF-fibrogenesis in precision cut lung slices

Miss Olivia Young

ASCEPT Garth McQueen Oral Student Prize Session, Eureka Room 1, December 3, 2024, 9:00 AM - 10:30 AM

Biography:
Olivia Young is a third-year PhD student in the Respiratory and Integrative Cardiovascular Pharmacology Laboratories at Monash University. Her research focuses on the therapeutic potential of anti-fibrotic components in the renin-angiotensin system, specifically angiotensin type II receptors (AT2R), in the treatment of Idiopathic Pulmonary Fibrosis (IPF). She is particularly interested in modelling IPF ex vivo using precision cut lung slices, allowing efficient screening of novel AT2R agonists in human tissue. She has presented her work at national and international conferences, and is currently a fellow of the Centre for Research Excellence in Pulmonary Fibrosis (CREATE Fellow).

AT2R agonists Compound 21 and NAc inhibits ex vivo IPF fibrogenesis in human precision cut lung slices
Olivia N Young1 , William R Studley1 , Paris C Papagianis1 , Elizabeth A Richards1 , Yi Chen2 , Phil G Bardin3 , Glen P Westall4 , Robert E Widdop1 , Jane E Bourke1 . 1Pharmacol., Monash Uni., Clayton, VIC, Australia (Aus), 2VHH, Clayton, VIC, Aus, 3CIIID, Hudson Institute, Clayton, VIC, Aus, 4Allergy, Immunol. and Resp. Medicine, The Alfred, Prahran, VIC, Aus.

Introduction. Idiopathic pulmonary fibrosis (IPF) is an incurable lung disease with current treatments unable to reverse fibrosis. The angiotensin type 2 receptor (AT2R) agonist Compound 21 (C21) abrogates fibrosis in a bleomycin mouse model1 and is in trials in IPF patients2 . NAc is a novel AT2R agonist with higher selectivity over AT1R than C21. **Aims.** To compare antifibrotic effects of AT2R agonists C21 and NAc with current IPF treatment pirfenidone in human precision-cut lung slices (PCLS).
Methods. Matched PCLS from agarose-inflated lung resection specimens were treated with vehicle or stimulated with fibrotic cocktail (FC = TGFβ1, TNFα, LPA, PDGF) ± C21, NAc (both 1 and 10μM) or pirfenidone (500μM) for 120h. In situ fibrosis was assessed by Masson's trichrome staining. Conditioned media was collected at 48h and 120h to measure secreted procollagen 1α1 and fibronectin by ELISA, and MMP-2 and -9 activity via gelatin zymography.
Results. s. Collagen (% tissue area) was unchanged with FC treatment (n=18). However, FC induced a 5-fold increase in procollagen 1α1 (ng/mL: vehicle 34.4 ± 12.8; FC 187.1 ± 31.19, n=16, $p<0.001$, paired t-test) and a 3-fold increase in fibronectin (ng/mL: vehicle 1293.0 ± 321.1; FC 4180.0 ± 417.4, n=9, $p<0.001$). C21 and NAc, but not pirfenidone, significantly reduced FC-induced secretion of both procollagen 1α1 (by 71.1% and 61.2%, respectively) and fibronectin (by 57.5% and 52.4%, respectively) ($p<0.01$, one-way ANOVA, n=14-16, n=8-9). FC significantly increased total MMP-2- and -9 activity at 120h, with a trend to reduced activity following treatment with C21, NAc, and pirfenidone.
Discussion. Fibrogenesis can be modelled ex vivo as increased procollagen 1α1 and fibronectin secretion from human PCLS using a cocktail of IPF-relevant mediators. C21 and NAc significantly reduced fibrogenic markers in hPCLS more effectively than pirfenidone. A mismatch between effects of FC on % collagen and secreted collagen in PCLS may be due to FC-induced increase in MMP-2 and -9. This research demonstrates that AT2R agonists are as effective as pirfenidone, an approved IPF treatment, and clinical trials have shown that they are also more well-tolerated.
1Rathinasabapathy et al. (2018), Front Physiol, 9:180
2NCT04533022

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New Approaches to treat organ failure via inhibition of pancreatic enzymes

Mr Zijun Lu

Oral presentation 9: Traditional Medicines & Pharmaceutical Sciences Themes, Eureka Room 2, December 3, 2024, 9:00 AM - 10:30 AM

Biography:

Zijun Lu is a third-year PhD student at Monash University, specialising in lymphatic drug delivery, lipid-based formulation, and acute critical illness. Zijun's work aims to improve therapeutic strategies and patient outcomes in critical care settings.

New approaches to treat organ failure via inhibition of pancreatic enzymes in the gut and gut lymph

Zijun Lu[1], Benjamin J. Boyd[1], Christopher J.H. Porter[1], Ian K. Styles[1], John A. Windosor[2], Anthony R.J. Philips[2], Jiwon Hong[2], Natalie L. Trevaskis[1]. [1]Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC, Australia. [2]Surgical and Translational Research Centre, University of Auckland, Auckland, New Zealand

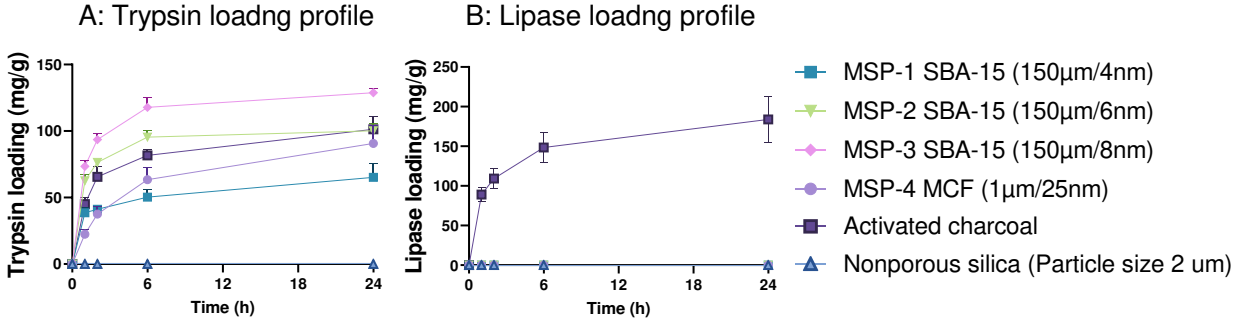
Introduction. Acute and critical illnesses (ACIs) are typically managed in emergency and intensive care settings in hospitals. Recently, the 'gut-lymph model' has demonstrated that 'toxic factors' from the gut, including pancreatic protease, lipase and lipase generated lipotoxins, enter the lymph and the blood circulation in ACIs to promote systemic inflammation and organ dysfunction/failure. Currently there are no specific and effective treatments for organ failure in ACIs. Therefore, we investigated if delivering adsorbent materials into the gut lumen could bind to and reduce pancreatic enzyme activity in the intestine fluid.

Aims. To determine the optimal properties of adsorbent materials to bind to and inhibit the activity of lipase (from rhizomuscor miehei) and protease (e.g. trypsin from bovine pancreas) enzymes in vitro. To compare the in vivo effect of different adsorbent materials on pancreatic enzyme activity (e.g. analysed by BAPNA substrate) after intestinal administration to rats.

Methods. The in vitro loading and inhibition of pancreatic enzymes by different adsorbent materials, including MSP with different pore size (4 – 12 nm), and activated charcoal, were tested in Tris buffer by BCA assay. The in vivo pancreatic enzyme inhibition was assessed following infusion of adsorbent materials into isolated intestinal segments in rats.

Results. MSP (SBA-15) with a pore size of 8 nm was found to have the highest trypsin binding (128.9 mg/g). Activated charcoal was found to be an extremely effective platform to adsorb both trypsin (101.4 mg/g) and lipase (183.9 mg/g) in buffer (Figure below). Both MSP and activated charcoal reduced pancreatic enzyme (trypsin) activity in rat intestine.

Discussion. Adsorbent materials can bind to and load pancreatic enzyme in vitro and reduce pancreatic enzyme activity in vivo. It appeared that pore size but not particle size was the critical factor that influences enzyme loading, where the highest binding which is likely linked to pore size (8 nm) being not too small or too large to bind the enzyme. These materials may provide a novel medical approach to reduce the progression of ACI to organ dysfunction and failure.



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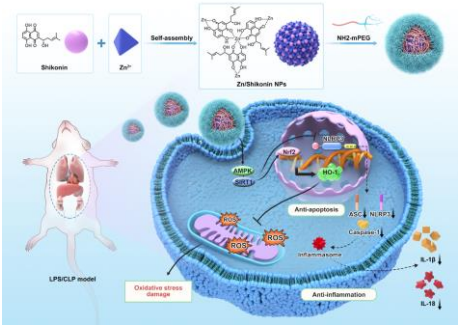
Nanosized shikonin: An effective therapeutic agent against sepsis and other inflammation-related disease

Dr Yuqing Miao

Oral presentation 9: Traditional Medicines & Pharmaceutical Sciences Themes, Eureka Room 2, December 3, 2024, 9:00 AM - 10:30 AM

Biography:
Yuqing Miao received his PhD degree from the Northwest University in 2021. Following this, he began working at Shaanxi University of Chinese Medicine. His current research interests focus on the design and synthesis of magnetic and metal-polyphenol nanomaterials for bioimaging and therapy of diseases.

Nanosized shikonin: An effective therapeutic agent against sepsis and other inflammation-related disease
Yuqing Miao[1], Haifa Qiao[1,2]. Shaanxi Collaborative Innovation Center of TCM Technologies and Devices, Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, China; Shaanxi Key Laboratory of Integrated Acupuncture and Drugs, College of Acupuncture and Tuina [2], Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, China.



Introduction. Previous studies have reported that shikonin (Shik), a component of Chinese herbal medicine, also known as “Zi-cao”, possess prominent anti-inflammatory and antioxidant effects and holds promise as a potential therapeutic drug for inflammation related disease, such as sepsis and diabetic foot ulcers. However, the poor water solubility and the relatively high toxicity of shikonin hamper its clinical application.
Aims. A metal-polyphenol coordination-based organic-inorganic hybridization strategy was used to improve the efficacy and further decrease toxicity.
Methods. we constructed nanosized shikonin, based on an organic-inorganic hybridization strategy of metal-polyphenol coordination to improve the aqueous solubility and biosafety of shikonin. The therapeutic efficacy of Zn-Shik-PEG nanoparticles was evaluated by in vitro and in vivo experiments.
Results. Nanosized shikonin effectively improved the aqueous solubility and biosafety of shikonin. Mechanistic studies suggest that Shikonin NPs could effectively clear intracellular ROS via regulating the Nrf2/HO-1 pathway, meanwhile Shikonin NPs could inhibit NLRP3 inflammasome-mediated activation of inflammation and apoptosis by regulating the AMPK/SIRT1 pathway. As a result, the Shikonin NPs demonstrated excellent therapeutic efficacies in sepsis and diabetic foot ulcers model.
Discussion. These findings suggest that Nanosized shikonin may have therapeutic potential for the treatment of sepsis and other inflammatory diseases.

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Delivery of siRNA via Bone-targeting LNP efficiently inhibits prostate cancer bone metastasis

Dr Yanlun Gu

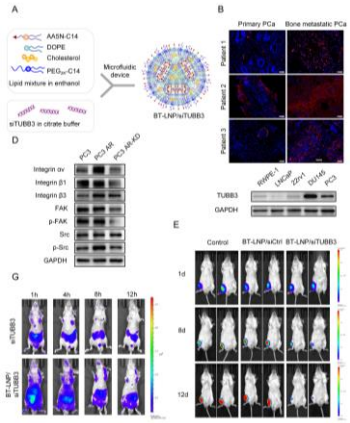
Oral presentation 9: Traditional Medicines & Pharmaceutical Sciences Themes, Eureka Room 2, December 3, 2024, 9:00 AM - 10:30 AM

Biography:

Yanlun Gu is currently a Ph.D. candidate in School of Pharmaceutical Sciences, Peking University. He also received M.S. and B.S. from Peking University. His research focuses on the pathological mechanisms of prostate cancer, the identification and validation of drug targets and biomarkers, as well as the development of novel small-molecule drugs for prostate cancer treatment.

Delivery of siRNA via Bone-targeting LNP efficiently inhibits prostate cancer bone metastasis

Yanlun Gu[1,2,3#], Bingqi Dong[4#], Xiaojiao Sun[3#], Qingqing Xiong[5*], Xiaocong Pang[1,2*], Yimin Cui[2,3*], Institute of Clinical Pharmacology, Peking University[1], Beijing, China; Department of Pharmacy, Peking University First Hospital[2], Beijing, China; School of Pharmaceutical Sciences, Peking University[3], Beijing, China; Department of General Surgery, Peking University First Hospital[4], Beijing, China; Department of Hepatobiliary Cancer, Liver Cancer Center, Tianjin Medical University Cancer Institute & Hospital[5], Tianjin, China.



Introduction. Bone metastases occur in more than 70% of advanced prostate cancer (PCa) patients. Resistance to detachment-induced apoptosis, also known as anoikis, plays a crucial role in the onset of tumor metastasis.

Aims. To discover novel targets involved in PCa bone metastasis and develop a rational targeted therapy.

Methods. Bioinformatics analysis was used to identify novel targets involved in anoikis resistance in PCa. RNA-Seq, and western blotting were used to investigate the effect of TUBB3 knockdown on gene expression patterns and biological pathways. Microfluiding mixing was utilized to construct bone-targeting lipid nanoparticles (BT-LNP) for the delivery of siRNA targeting TUBB3. The PCa bone metastasis mouse model was established to evaluate the effect of BT-LNP/siTUBB3

Results. We established an anoikis-related prognostic risk model of PCa and identified *TUBB3* as a key prognostic gene highly correlated with bone metastasis. TUBB3 expression is increased in bone metastatic tissues and anoikis-resistant PCa cells, and TUBB3 depletion significantly reverses anoikis resistance. TUBB3 knockdown reduces αvβ3/FAK/Src axis activation, blocking its downstream oncogenic signalling. In addition, BT-LNP/siTUBB3 based on bisphosphonate-modified ionizable lipid with localization in the bone microenvironment significantly attenuate PCa bone metastasis progression in vivo upon intravenous administration.

Discussion. These findings not only demonstrate for the first time that TUBB3 can be explored as an effective therapeutic target for bone metastatic PCa, but also that provide BP-LNP-mediated siRNA delivery may also serve as an efficient tool for future bone-targeted drug discovery.

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Kidney-targeted antioxidant salvianolic acid B nanoparticles for acute kidney injury therapy

Prof Xiao-Ming Zhu

Oral presentation 9: Traditional Medicines & Pharmaceutical Sciences Themes, Eureka Room 2, December 3, 2024, 9:00 AM - 10:30 AM

Biography:

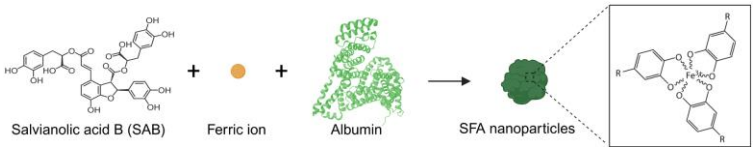
Dr. Zhu obtained his PhD degree in pharmacology from Peking Union Medical College in 2008, and then took postdoctoral training in Nanyang Technological University and the Chinese University of Hong Kong. In 2014, he joined Macau University of Science and Technology. His current research interests include drug discovery targeting protein degradation and design of novel drug delivery systems for natural products, especially focusing on the synergistic pharmacological activities of the nanocarriers. In 2017, he got the CNPHARS-Servier Prize for Young Investigators in Pharmacology in China.

Kidney-targeted antioxidant salvianolic acid B nanoparticles for acute kidney injury therapy

Xiao-Ming Zhu, Jian-Li Chen. State Key Laboratory of Quality Research in Chinese Medicine, Macau University of Science and Technology, Taipa, Macau SAR, China.

Introduction. Acute kidney injury (AKI) is highly correlated with oxidative stress, and the application of antioxidants is one of the promising treatments.

Aims. Salvianolic acid B (SAB) is a natural polyphenol with powerful antioxidant effects. Due to its inherent characteristic of inferior bioavailability, its clinical application is impeded. Aided by the advantages of nanotechnology, the SAB-based nanoparticles were synthesized to improve SAB's therapeutic efficacy for treating AKI.



Methods. In this study, small SAB-incorporated nanoparticles (SFA) were synthesized via the self-assembly of SAB, ferric ions, and bovine serum albumin (BSA). The in vivo distribution of SFA were studied in the AKI model mice induced by glycerol. The effects of SFA and SAB were compared in both in vitro and in vivo studies.

Results. Apart from antioxidant activity, the SFA nanoparticles were found to efficiently restore lysosome dysfunction induced by reactive oxygen species (ROS) in human kidney proximal tubular epithelial HK-2 cells. The small size and BSA incorporation make the SFA nanoparticles to be promising AKI-targeting nanoparticles. They are rapidly accumulated and long-term retained in injured kidneys of glycerol-induced AKI mice, especially in the proximal tubules which are the key lesion location during AKI. In vivo studies indicate that SFA nanoparticles show a superior protective effect compared with the free drug by suppressing oxidative stress and maintaining lysosome homeostasis indicated by enhanced heme oxygenase-1 (HO-1) expression and restored cathepsin B (CTSB) activity, respectively.

Discussion. In summary, this study develops a delivery system for the antioxidant SAB enhancing local delivery and offering additional lysosome restoring mechanism for AKI therapy.

Acknowledgements. This work was funded by The Science and Technology Development Fund, Macau SAR (File no. 0035/2022/A1, 0168/2019/A3).

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Effect of lipopolysaccharide and anti-inflammatory compounds on murine microglial transporters

Mr Ethan Kreutzer

Oral presentation 9: Traditional Medicines & Pharmaceutical Sciences Themes, Eureka Room 2, December 3, 2024, 9:00 AM - 10:30 AM

Effect of lipopolysaccharide and anti-inflammatory compounds on murine microglial transporters
Ethan Kreutzer[1], Jennifer L Short[2], Dorothy C C Wai[1], Katherine A Morgan[3], Paul S Donnelly[3], John K Fallon[4], Jacqueline B Tiley[5], Kim L R Brouwer[5] & Joseph A Nicolazzo[1]. Monash Institute of Pharmaceutical Sciences[1] & Monash Centre for Advanced mRNA Medicines Manufacturing & Workforce Training[2], Monash University, Melbourne, VIC, Australia; School of Chemistry & Bio21 Institute[3], Univ of Melbourne, Melbourne, VIC, Australia; Div of Pharmacoengineering & Molecular Pharmaceutics[4] & Div of Pharmacotherapy & Experimental Therapeutics[5], UNC-Chapel Hill, NC, USA.

Introduction. Microglia have been suggested to play a role in drug disposition within the CNS due to their expression of functional drug transporters (Ronaldson et al, 2022). Reduced abundance and function of key efflux transporters, including P-glycoprotein (P-gp) and breast cancer resistance protein (Bcrp), have been observed in microglia stimulated with lipopolysaccharide (LPS) (Gibson et al, 2012). In addition, modulation of fatty acid binding protein 4 (FABP4) and copper homeostasis have been shown to reduce LPS-mediated microglial inflammation. The impact of modulating these pathways on LPS-mediated effects on drug transporters in microglia is unknown.
Aims. To investigate the impact of LPS and two therapeutic interventions, namely Cu(ATSM), a copper-modulating compound, and BMS309403, an FABP4 inhibitor, on transporter abundance and function in BV-2 microglia.
Methods. BV-2 cells were exposed to 1 µg/mL LPS alone and to either 100 nM Cu(ATSM) or 50 µM BMS309403 with and without LPS 1 µg/mL for 24 h. Transporter abundance was assessed via targeted LC-MS/MS and western blot.
Results. LPS exposure demonstrated a reduction in microglial P-gp (~32%) and Bcrp (~40%) abundance, whilst increasing both glucose transporter 1 (~14%) and organic anion transporting polypeptide 4a1 (~29%). Although Cu(ATSM) or BMS309403 did not reverse LPS-mediated transporter changes, Cu(ATSM) treatment trended toward increased P-gp abundance, whilst BMS309403 treatment downregulated several efflux transporters.
Discussion. Our targeted proteomic analysis supports existing literature demonstrating that inflammatory pathways play a role in microglial efflux transporter and solute carrier regulation. These results also highlight a potential role for FABP4 in microglial transporter regulation, the mechanism of which will be the focus of future studies.

Gibson C et al (2012) J Pharmacol Exp Ther 343:650-60
Ronaldson P & Davis T (2022) Pharmaceutics 14:1501

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Tetrastigma hemsleyanum polysaccharide enhances the anti-cancer efficacy of anti-PD-L1 therapy

Prof Jinjian Lu

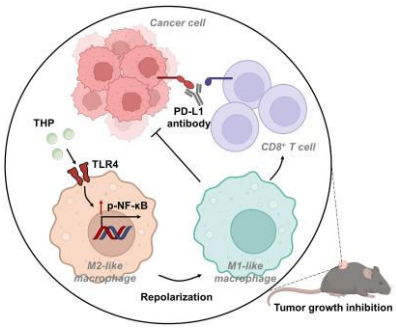
Oral presentation 9: Traditional Medicines & Pharmaceutical Sciences Themes, Eureka Room 2, December 3, 2024, 9:00 AM - 10:30 AM

Biography:

Dr. Jin-Jian Lu is an Associate Professor in University of Macau and received his Ph.D. degree in Shanghai Institute of Meteria Medica, Chinese Academy of Sciences in 2009. Currently, Dr. Lu is mainly engaged in the discovery and mechanism study of anti-cancer compounds based on tumor microenvironment. He is also interested in studying the new targets and strategies for cancer therapy. He has been the recipient of more than 10 research grants funded by National Science Foundation of China, Science and Technology Development Fund Macao S.A.R and so on. Dr. Lu has published more than 200 scientific papers in the SCI journals including J Hematol Oncol, Acta Pharm Sin B and Pharmacol Ther (Total citations 10000+, H-index 54, Scopus). He is the editorial or youth editorial board member for 11 professional journals including Transl Oncol and Chin J Nat Med, and the referee for 100+ peer-reviewed journals. He was awarded as the 2nd Prize of Natural Science: Macao Science and Technology Awards (twice) and CNPHARS Annual Young Pharmacologists. (2/8/2024)

***Tetrastigma hemsleyanum* polysaccharide enhances the anti-cancer efficacy of anti-PD-L1 therapy**

Yu-Chi Chen[1], Mu-Yang Huang[1], Wei Shi[1], Yan-Ming Zhang[1], Wei-Bang Yu[1], Can-Yu Huang[1], Xiuping Chen[1], Ting Li[1], Xin Chen[1], Zhi-Shan Ding[2], Jin-Jian Lu[1]. State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau[1], Macao, MO, China; School of Medical Technology and Information Engineering, Zhejiang Chinese Medical University[2], Hangzhou, ZJ, China.



Introduction. Despite the effectiveness of programmed cell death receptor-1 (PD-1) and programmed cell death ligand-1 (PD-L1) antibodies, many patients are unresponsive due to the immunosuppressive tumor microenvironment. Innovative approaches to enhance PD-1 or PD-L1 blockades are needed.

Aims. To explore the effect of *Tetrastigma hemsleyanum* polysaccharide (THP) on enhancing anti-cancer effects of anti-PD-L1 and its potential mechanism.

Methods. Murine tumor models evaluated the anti-cancer effect of anti-PD-L1 combined with THP. Flow cytometry analyzed tumor-infiltrating immune cells. *In vitro* studies examined THP's impact on macrophage polarization and underlying mechanisms using flow cytometry, qRT-PCR, and western blot. Co-culture assessed THP-primed macrophages' effects on cancer cell growth inhibition and T cell proliferation. The roles of $CD8^+$ T cells and TLR4 in combination therapy were tested using anti-CD8 antibody and TLR4 inhibitor.

Results. THP enhanced the anti-cancer effects of anti-PD-L1 in mouse MC38 colorectal and 4T1 breast cancer models. Combination treatment further increased tumor-infiltrating T cells, and $CD8^+$ T cell depletion nullified the anti-tumor effect. The M1/M2 macrophage ratio in the tumor microenvironment increased with THP and anti-PD-L1 combination treatment. *In vitro*, THP repolarized macrophages to an M1-like phenotype, inhibiting cancer cell growth and promoting $CD8^+$ T cell proliferation. TLR4 inhibition blocked THP-induced macrophage repolarization and reduced the combination therapy's anti-cancer effect.

Discussion. Our results suggest that THP may be used as an adjuvant to enhance anti-tumor efficacy of anti-PD-L1 therapy, and this notion merit further investigation.

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Translational proteomic biomarkers of casein kinase inhibition in macrophages

Dr Qianyu Helen Chen

Oral presentation 10: Respiratory & Inflammation Theme, Eureka Room 3, December 3, 2024, 9:00 AM - 10:30 AM

Biography:
Qianyu Chen received her Master degree in pharmaceutical sciences from Peking University and her PhD in pharmacology from University of Melbourne in 2022.
She is now a postdoctoral researcher at the University of Melbourne, working on TianLi Biotech projects to develop innovative therapeutics for idiopathic pulmonary fibrosis and other inflammatory lung diseases.

Translational proteomic biomarkers of casein kinase inhibition in macrophages
Qianyu Chen[1,2], Shenna Langenbach[1,2], Meina Li[1,2], Alastair G Stewart[1,2].
Department of Biochemistry and Pharmacology, University of Melbourne[1]; ARC Centre for Personalised Therapeutics Technologies, Department of Biochemistry and Pharmacology, University of Melbourne[2], Parkville, VIC, Australia.

Introduction. Expression of casein kinase 1 delta and epsilon (CK1δ/ε) is elevated in patients with chronic pulmonary disease, such as idiopathic pulmonary fibrosis and asthma. Anti-fibrogenic and anti-inflammatory effects of the CK1δ/ε inhibitor, PF670462 suggest CK1δ/ε as potential therapeutic target in respiratory diseases. Identification of pharmacodynamic and disease-related biomarkers are critical for drug development from pre-clinical to clinical stage.
Aims. We performed an exploratory study on biomarkers in CK1δ/ε inhibitor PF670462-exposed macrophages.
Methods. Peripheral blood mononuclear cells (PBMCs) were isolated from human whole blood. After monocyte-to-macrophage maturation, macrophages were exposed to PF670462. Cells collected from pseudo-bronchoalveolar lavage performed in whole lobe of non-transplanted human lung were used to assess concentration-response relationships of PF670462. Peptide samples were analysed by LC-MS/MS using Orbitrap Eclipse spectrometer.
Results. PF670462 suppressed pro-inflammatory cytokines IL-6 and GM-CSF production induced by LPS or poly I::C in human whole blood and blood isolated macrophages Comparing the global proteome of macrophages treated with PF670462 to vehicle, sparse Partial Least Squares Regression (PLS) discriminant analysis showed that PF670462 treatment at 24h is well separated from vehicle group. Highest protein abundance changes were selected out from receiver operating characteristic (ROC) curve analysis for further validation. Potential biomarkers were validated in PF670462 concentration-response curve, identifying counter-regulatory increases in CK1δ and CK1ε as highly correlated, as also observed with mRNA for CK1δ and CK1ε in macrophages.
Discussion. Global Proteomics efficiently enables the discovery and qualification of exploratory biomarkers. We identified several protein concentration-dependent responses to CK1δ/ε inhibitor PF670462 in macrophages that will be used to estimate PF670462 effectiveness by inhalation in phase one clinical trials.

Funding: Tianli Biotech Pty Ltd

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Carnosine enhances the cardiovascular benefits of pulmonary rehabilitation on COPD

Mr Suleman Almerdasi

Oral presentation 10: Respiratory & Inflammation Theme, Eureka Room 3, December 3, 2024, 9:00 AM - 10:30 AM

Biography:
Suleman Almerdasi is a third-year PhD candidate in Biomedical Science within the Respiratory Research Group at the school of Health and Biomedical Science at RMIT university. He is supervised by Professor Ross Vlahos, with co-supervision from Dr. Stanley Chan, Professor Stavros Selemidis. His doctoral research focuses on novel pharmacological strategies to treat cigarette smoking-induced atherogenesis in COPD. He aims to investigate whether carnosine supplementation combined with exercise training can mitigate cardiovascular disease in a preclinical COPD model.

Carnosine enhances the cardiovascular benefits of pulmonary rehabilitation on COPD

Suleman Almerdasi[1], Stanley M.H. Chan[1], Rana Alateeq[1], Wei Wang[1], Alina Akhtar[1], Simone N. De Luca[1], Stavros Selemidis[1], Ross Vlahos[1].
[1]Centre for Respiratory Science and Health, School of Health and Biomedical Sciences, RMIT University, Melbourne, VIC 3083, Australia

Introduction. Pulmonary rehabilitation addresses critical aspects of chronic obstructive pulmonary disease (COPD) such as exercise intolerance but may not adequately mitigate the heightened risk of cardiovascular disease (CVD). Oxidative stress is a common driver in both COPD and CVD, highlighting the necessity for antioxidant strategies in conjunction with rehabilitation. Carnosine is a bioactive dipeptide, which may protect against oxidative stress and reduce exercise fatigue.
Aims. Examine if carnosine supplementation with exercise training may mitigate CVD in a preclinical COPD model.
Methods. Male BALB/c mice were exposed to either room air or cigarette smoke (CS; 9 cigarettes per day, 5 days per week) for up to 8 weeks with or without carnosine supplementation (1 mg/mL dissolved in drinking water). Additionally, mice underwent involuntary treadmill exercise (50% of maximal speed) for 30 minutes per day, 5 days per week. Exercise tolerance, airway inflammation and vascular function were assessed.
Results. Chronic CS exposure reduced body weight gain, exercise capacity, and blood pressure $p<0.0001$, $n=14$), and caused significant airway inflammation ($p<0.0001$, $n=6$). This was associated with a blunted ACh-induced vasodilatation, indicating endothelial dysfunction ($p<0.0001$, $n=6$). Immunofluorescence showed increased platelet adhesion to the vascular endothelium and CD62p positive stains indicating their activation ($p<0.0001$, $n=6$). Exercise alone had no effect, but carnosine with exercise mitigated the negative impacts on weight, exercise capacity, and heart rate, preserving endothelial function and lessening platelet adhesion and activation.
Discussion. Exercise training alone may be insufficient in fully addressing the heightened CVD risk associated with CS-induced COPD. Carnosine supplementation appears to have added benefits on the vasculature, which may offer a more comprehensive and tailored approach to the management of COPD.

Grant Support: NHMRC project grant APP1138915

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A novel pro-resolution therapy approach to treat pulmonary arterial hypertension

Miss Ting Fu

Oral presentation 10: Respiratory & Inflammation Theme, Eureka Room 3, December 3, 2024, 9:00 AM - 10:30 AM

Biography:

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. Ting's studies and research have been supported by the Monash Graduate Scholarship (MGS) and the Monash International Tuition Scholarship (MITS). 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

A novel pro-resolution therapy approach to treat pulmonary arterial hypertension.

Ting Fu[1], Chloe Landy[1], Miles J De Blasio[1], Jaideep Singh[1], Anida Velagic[1], Owen L Woodman[1], Barbara Kemp-Harper[2], Peishen Zhao[1], Rebecca H Ritchie[1,2], Chengxue Qin[1*].[1]Drug Discovery Biology and [2]Department of Pharmacology, Monash Univ, VIC; Australia.

Introduction. Chronic low-grade inflammation is a key contributor to the pathogenesis of pulmonary arterial hypertension (PAH). A crucial aspect of a self-resolving inflammatory response is its ability to limit the production of pro-inflammatory mediators and promote tissue healing. The nonselective formylpeptide receptor (FPR) agonist, Compound17b (Cmpd17b) has shown pro-resolution effects in the pulmonary vasculature *ex vivo*[1], but the impact of FPR agonists on PAH is not known.

	Normoxia + Vehicle	SuHx + Vehicle	SuHx + Cmpd17b	SuHx + Sildenafil
RVSP (mmHg)	29±1 (n=12)	40±2**** (n=12)	33±1$$$ (n=13)	34±13$ (n=13)
RV/(LV+S) weight	0.33±0.01 (n=11)	0.47±0.02*** (n=7)	0.49±0.02 (n=10)	0.50±0.02 (n=10)
Lungs : tibia length (mg/mm)	14.7±0.6 (n=7)	21.6±0.9**** (n=7)	19.6±0.5 (n=10)	18.8±0.4$ (n=10)
m*Il6* (fold increase)	1.0±0.2 (n=11)	1.9±0.3* (n=13)	0.6±0.1$$$ (n=11)	1.0±0.3 (n=10)
m*Tnf-α* (fold increase)	1.0±0.2 (n=11)	1.8±0.5 (n=13)	0.5±0.1$ (n=11)	1.0±0.1 (n=10)
m*Ctgf* (fold increase)	1.0±0.1 (n=11)	1.1±0.2 (n=13)	0.6±0.1$ (n=11)	0.4±0.1$$ (n=10)

*P<0.05, ***P<0.001, ****P<0.0001 vs Normoxia + vehicle;$P<0.05, $$P<0.01,$$$P<0.001 vs SuHx + vehicle,(One-way ANOVA with Šídák's multiple comparisons test). RVSP: Right ventricular systolic pressure, RV: Right ventricular, LV: Left ventricular, S: Septum, m*Il6*: Interleukin6, m*Tnf-α*: Tumor necrosis factor-α, m*Ctgf*: Connective tissue growth factor.

Aim. To investigate the therapeutic effects of FPR agonist in PAH.

Methods. 9-week-old male C57BL/6J mice were randomly allocated to either normoxia (21% O_2) or hypoxia (10% O_2) cohorts. The hypoxia cohort received subcutaneous injections of sugen 5416 (20mg/kg) weekly for 4 weeks and was exposed to hypoxia for 28 days. In this study, the sugen/hypoxia (SuHx) cohort was randomly divided into three groups: (i) treatment-vehicle, (ii) Cmpd17b (50 mg/kg/day), or standard clinical treatment (iii) sildenafil (0.3 mg/kg/day). The normoxia cohort received the treatment-vehicle (10% DMSO in 0.8% tween 80 in saline). Mice were culled and lungs were collected for analysis of gene expression by qPCR.

Results. SuHx mice displayed elevated right ventricular systolic pressure (RVSP) and elevation in lung weight and a higher RV/(LV+S), upregulated expression of the pro-inflammatory cytokine m*Il-6*. Cmpd17b not only lowered the RVSP in SuHx mice, but also downregulated pro-inflammatory cytokines m*Il6* and m*Tnf-α,* as well as the pro-fibrotic mediator m*Ctgf* (Table).

Discussion. Our study demonstrated that Cmpd17b not only lowers the RVSP as current clinical treatment do, but also limits inflammation, which might be beneficial for preventing organ remodelling.

[1.] Studley WR et al. (2023) Br J Pharmacol DOI10.1111.bph.16231.

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Validation of a novel precision-cut lung slice fibrosis model from TGFβ-overexpressing mice

Dr Paris Papagianis

Oral presentation 10: Respiratory & Inflammation Theme, Eureka Room 3, December 3, 2024, 9:00 AM - 10:30 AM

Biography:
Dr Paris Papagianis is a Postdoctoral Research Fellow in the Respiratory Pharmacology Lab within the Biomedicine Discovery Institute (BDI) at Monash University. Paris' research focus is on lung health and disease spanning early life to adulthood. Paris was awarded a joint PhD from Monash University and the University of Western Australia (2019), exploring anti-inflammatory and anti-fibrotic therapeutics for ventilator-induced lung injury in preterm birth care.
In 2022, Paris joined the Respiratory Pharmacology Laboratory, led by A/Prof Jane Bourke. Paris maintains a strong interest in lung health and diseases, working with Jane on the occupational lung disease, silicosis. Paris and the Respiratory Pharmacology Lab are also developing new tools to help understand how chronic lung diseases develop and progress to eventual lung fibrosis and lung function decline.

Validation of a novel precision-cut lung slice fibrosis model from TGFβ-overexpressing mice

Paris Papagianis[1], Julia G Chitty[1], ZK[1,3], Janette Burgess[3], Philip Bardin[2], Jane E Bourke[1], Belinda Thomas[2].
[1]Pharmacology, Biomedicine Discovery Institute, Monash University, Australia; [2]Monash Lung & Sleep, Hudson Institute of Medical Research, Australia; [3]Biological & Medical Research, Universitair Groningen, Netherlands.

Introduction. Transforming growth factor β (TGFβ) is elevated in fibrotic lung diseases, contributing to both fibrogenesis and disease progression. Transgenic mice (TGM) with lung-specific TGFβ over-expression (induced by doxycycline (DOX) in drinking water) have lung fibrosis (Lee et al, 2014). Multiple precision cut lung slices (PCLS) containing all resident cells in the native lung matrix can be prepared from individual mice. DOX-induced overexpression of TGFβ in PCLS from TGM mice *ex vivo* may provide a higher throughput approach to explore fibrogenesis compared to *in vivo* models.
Aims. To establish DOX-induced TGFβ overexpression and lung fibrosis *ex vivo* in PCLS for comparison with *in vivo* model.
Methods. Transgenic C57Bl/6 mice with inducible lung-specific TGFβ over-expression were either (1) administered water (TGM) or DOX (TGM-DOX) *in vivo* for 8 weeks or (2) used to prepare PCLS for culture in the absence (TGM-PCLS) or presence of DOX (TGM-PCLS-DOX) for 5 days. TGFβ levels were measured in (1) bronchoalveolar lavage (BAL) or (2) conditioned PCLS media. Fibrosis was assessed by Masson's trichrome or Histoindex in both (1) whole lungs (*in vivo*) or (2) PCLS (*ex vivo*).
Results. TGFβ levels in BAL from TGM-DOX mice at 8 weeks was 20-fold higher than TGM mice (5.8±0.6 vs 0.3±0.1 pg/ml; n=14/group, $p<0.001$). Fibrosis was localised to airways in TGM-DOX mice, with 3-fold higher subepithelial thickness (TGM-DOX 16.5±0.9 vs TGM 5.1±1.1 µm, $p<0.001$) and Histoindex analyses confirming increased %airway collagen (TGM-DOX 68±2% vs TGM 52±3% $p<0.001$). In PCLS from TGM, viability was maintained with DOX treatment *ex vivo* at 5 days. TGFβ levels were higher in in PCLS media from TGM-PCLS-DOX than TGM-PCLS (4.6±0.9 vs 0.4±0.1 ng/ml, n=10 per group, $p<0.05$), as were secreted pro-collagen1α1 (323.7±63.1 vs 175.8±31.9 ng/ml; $p<0.05$) and osteoprotegerin (9.0±0.6 vs 5.8±0.9 ng/ml TGM-PCLS; $p<0.05$). Fibrosis (% PCLS tissue area) assessed by Histoindex was also higher in TGM-PCLS-DOX (11.5±0.91 vs 7.51±0.93%; $p<0.05$).
Discussion: We are the first to establish DOX-induced overexpression of TGFβ in PCLS *ex vivo*. We show comparable responses to DOX treatment *ex vivo* and *in vivo*, validating the use of PCLS to reduce animal use. Treating PCLS from these TGM with DOX will allows us to test drugs to inhibit fibrogenesis or reverse established fibrosis in future experiments where *ex vivo* DOX exposure is extended beyond 5 days.

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Sexual Dimorphism in the Sugen-Hypoxia Mouse Model of Pulmonary Arterial Hypertension

Miss Chloe Landy

Oral presentation 10: Respiratory & Inflammation Theme, Eureka Room 3, December 3, 2024, 9:00 AM - 10:30 AM

Biography:
Chloe is a PhD student in the Cardiovascular Pharmacology Lab at the Monash Institute of Pharmaceutical Sciences. Chloe completed her B.PharmSci(Adv)Hons in 2021. Her honours project explored the efficacy of novel FPR agonists in treating pulmonary arterial hypertension (PAH). Chloe's current research aims to identify whether a class of lipids known as specialised pro-resolving mediators (SPMs) are differentially expressed between the sexes in PAH.

Sexual Dimorphism in the Sugen-Hypoxia Mouse Model of Pulmonary Arterial Hypertension

Chloe Landy[1], Ting Fu[1], Ruby Tang[1], Miles J De Blasio[1], Kristy L Jackson[1], Owen L Woodman[1], Cheng Xue Qin[1]. Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences[1], Parkville, VIC, Australia

Introduction. Pulmonary arterial hypertension (PAH) is an inflammatory vascular disease that ultimately results in right ventricular (RV) failure. Women with PAH have a better prognosis than men however underlying mechanisms, particularly as it relates to inflammation-resolution pathways, are poorly understood.

Aims. To compare inflammatory signalling in male (M) and female (F) mice using the sugen-hypoxia (SuHx) PAH model.

Methods. C57BL/6J mice were subjected to either hypoxia (10% O_2) with sugen (20mg/kg, sc, weekly in first 4 weeks) or normoxia (NmOx) with vehicle (0.5% carboxymethyl cellulose, 0.9% tween 80 and 0.4% benzyl alcohol in saline, sc) for 2 or 8 weeks (wk). Mice were anaesthetised (ketamine/xylazine/atropine, 100/20/1.2 mg/kg, ip) and RV systolic pressure (RVSP), a surrogate for pulmonary pressure in mice, was measured. RV hypertrophy (RV/LV+S) was assessed.

Results. SuHx mice exhibited significantly elevated RVSP and right ventricular hypertrophy. Female mice had a lower RVSP than males at 2 weeks after PAH induction but a higher RVSP at 8 weeks. Over time, RVSP increased in female SuHx mice but not in males. While RV/LV+S was not influenced by sex, it did increase significantly over time in both male and female SuHx mice, indicating progressive right ventricular hypertrophy in this model.

Discussion. The SuHx model effectively replicates sexual dimorphism observed in clinical setting of PAH. The substantial differences in RVSP between male and female mice warrants the need for further research into the underlying mechanisms contributing to sexual dimorphisms in PAH pathophysiology. This knowledge could pave the way for the development of sex-tailored therapies, enhancing the effectiveness of PAH treatment.

	2wk + M + NmOx	**2wk + F + NmOx**	**8wk + M + NmOx**	**8wk + F + NmOx**	**2wk + M + SuHx**	**2wk + F + SuHx**	**8wk + M + SuHx**	**8wk + F + SuHx**
RVSP	25.0±0.9 (7)	24.4±0.6 (11)	24.0±0.7 (11)	24.3±0.5 (11)	36.4±1.0 (12)****	30.6±1.0 (12)***/###	32.8±0.8 (12)****	37.4±2.4 (8)****/#/ †
RV/LV+S	0.34±0.01 (6)	0.28±0.01 (6)	0.31±0.01 (6)	0.33±0.01 (6)	0.41±0.01 (6)*	0.42±0.02 (6)****	0.49±0.02 (6)****/†	0.54±0.02 (4)****/ †

Mean ± SEM (n). *p<0.05, ***p<0.001, ****p<0.0001 compared to NmOx counterparts; #p<0.05, ###p<0.001 compared to male counterparts; †p<0.05 compared to 2-week counterparts

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Phosphoproteome changes induced by the CK1δ inhibitor PF670462 in modulating TGF-β-induced fibrogenesis

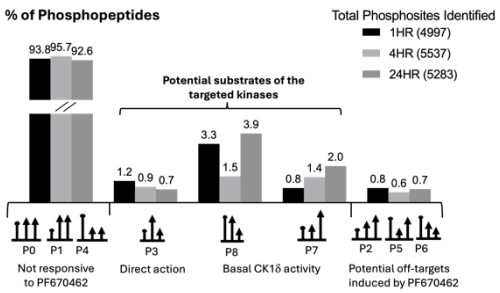
Miss Stephanie Zhang

Oral presentation 10: Respiratory & Inflammation Theme, Eureka Room 3, December 3, 2024, 9:00 AM - 10:30 AM

Biography:
Stephanie Zhang is a PhD candidate in the Department of Pharmacology and Biochemistry at the University of Melbourne. Stephanie's research investigates the role of casein-kinase 1 delta (CK1δ) in TGF-β induced fibrogenesis, with a particular interest in the potential therapeutic use of the compound PF670462 for treating Idiopathic Pulmonary Fibrosis (IPF). Stephanie explores the signalling pathways targeted by PF670462 using proteomics, aiming to uncover biomarkers and develop targeted therapies for IPF. Through her work, she contributes to advancing the understanding of CK1δ's role in disease and the potential of targeted treatments.

Temporal dynamics of the phosphoproteome changes induced by the Casein Kinase 1 delta (CK1δ) inhibitor PF670462 in modulating TGF-β-induced fibrogenesis.

Stephanie S. Zhang[1], Alastair G. Stewart[1,2]. Dept of Biochemistry & Pharmacology, Univ of Melbourne[1], Parkville, VIC; ARC Centre for Personalised Therapeutics Technologies[2], Parkville, VIC.



Introduction. TGF-β plays a critical role in the development and progression of Idiopathic pulmonary fibrosis (IPF). Modulation of specific components of the TGF-β pathway provides attractive targets for developing IPF therapies. The CK1δ/ε dual inhibitor PF670462 reduced myofibroblast activation and collagen deposition in *in vitro* and *in vivo* models of fibrogenesis[1]. However, understanding of the mechanism of action is limited.

Aims. To investigate the phosphoproteome changes exerted by PF670462 in TGF-β-induced fibrogenesis to provide further molecular detail on its mechanism of action, and to ascertain physiological substrates of CK1δ.

Methods. The phosphoproteomic changes in primary human lung fibroblasts from non-IPF donors induced by 3μM PF670462 alone and in response to 100pM TGF-β1 at 1hr, 4hr and 24hr were measured by LC/MS/MS. Bioinformatics analyses were performed to generate insights into the phosphorylation events.

Results. Phosphopeptides identified at the three time-points were grouped into nine response patterns according to phosphorylation changes in response to TGF-β1 and any further phosphorylation induced by PF670462. Patterns P3, P8 and P7 showing PF670462 effects were analysed to identify putative substrates of CK1δ matching with its consensus motif (Figure 1). Gene set enrichment analysis identified major biological processes and pathways associated with the individual phosphorylation patterns.

Discussion. The phosphorylation footprint of PF670462 identified some significant pharmacodynamic biomarkers that may be useful for assessing target engagement and TGF-β modulation. The identification of putative substrates of CK1δ will enable the reconstruction of the signalling network of CK1δ in response to TGF-β-induced fibrogenesis.

[1]Keenan CR et al. (2018) Fibrosis. Front. Pharmacol. 9:738.

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Co-designing novel medication management tools for people impacted by dementia during hospitalisation

Mr Alexander Clough

Oral presentation 11: Pharmacoepidemiology Theme, Courtyard Room 1&2, December 3, 2024, 9:00 AM - 10:30 AM

Biography:
Alexander Clough is a PhD student in the Sydney Pharmacy School at the University of Sydney, conducting research into improving the medication management of people with dementia by addressing key information gaps and empowering people with dementia and carers. He is focussed on increasing the visibility of people impacted by dementia in research, reducing the barriers between participants and researchers, and ultimately enhancing research and health outcomes. He is supported by an Australian Government Research Training Program scholarship.

Co-designing novel medication management tools for people impacted by dementia during hospitalisation

Alexander J Clough[1], Danijela Gnjidic[1], Natali Jokanovic[2], Jane Thompson[3], Yun-Hee Jeon[4], Elizabeth Manias[5], Carl Schneider[1], Timothy F Chen[1], Mouna J Sawan[1]. Sydney Pharmacy School, Univ of Sydney[1], Camperdown, NSW, Australia; Department of Infectious Diseases, Monash Univ[2], Melbourne, VIC, Australia; Member of the public[3], Canberra, ACT, Australia; School of Nursing & Midwifery, Univ of Sydney[4], Camperdown, NSW, Australia; School of Nursing & Midwifery, Monash Univ[5], Clayton, VIC, Australia.

Introduction. People impacted by dementia (people with dementia and carers) commonly experience medication-related issues in hospital and at discharge with limited support and information. User-centred, collaboratively designed tools for people impacted by dementia are needed in order to improve health literacy in medication management.
Aims. To co-design medication management guidance tools for people impacted by dementia during hospitalisation and at discharge.
Methods. This multi-methods study was an integration of four sequential explanatory phases using experience-based co-design to create two tools, one for people with dementia and one for carers of people with dementia: 1) literature review, qualitative study, and carer survey; 2) input from expert advisory panels involving people impacted by dementia; 3) five focus groups (seven carers, six people with dementia, and three healthcare professionals) to gather feedback on the tools; and 4) quantitative analysis of readability and suitability. The tools were refined based on feedback at every stage, a graphic designer modified the design, and final hard copies produced as 12-page A5-size booklets.
Results. The first phase generated content topics of: shared decision-making; medications that may affect cognition; question prompts; and the hospital processes and a person's role. The advisory panels suggested introducing informed consent and a discharge checklist. Analysis of the focus groups indicated that people with dementia liked the visual appeal of the tools, but simpler and more active language was required. Carers also proposed similar language changes and wanted clearer information on how to discuss goals of care and asking for a second opinion. The tools were deemed to be suitable, and participants indicated the tools should be provided on admission for use throughout hospitalisation.
Discussion. This co-design study involving people impacted by dementia successfully generated novel user-centred tools to improve medication management health literacy. This approach can serve as a framework to co-design other clinical tools and educational materials for vulnerable patient groups across healthcare settings.

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Impact of in-hospital medication changes on clinical outcomes: the journey and destination

Dr Nashwa Masnoon

Oral presentation 11: Pharmacoepidemiology Theme, Courtyard Room 1&2, December 3, 2024, 9:00 AM - 10:30 AM

Biography:

Dr. Nashwa Masnoon is a Postdoctoral Research Fellow at the Laboratory of Ageing and Pharmacology, Kolling Institute, University of Sydney and Northern Sydney Local Health District and a Pharmacist at Royal North Shore Hospital. She completed her PhD in 2020 from the University of South Australia, which focused on identifying older adults at risk of harm from inappropriate polypharmacy. Her research areas are deprescribing, continuity of care during transitions and more broadly, the quality use of medicines.

Impact of in-hospital medication changes on clinical outcomes: the journey and destination

Nashwa Masnoon[1], Sarita Lo[1], Danijela Gnjidic[2], Andrew McLachlan[2], Fiona Blyth[2], Patrick Kelly[2], David Le Couteur[3], Rosalie Viney[4], Rosemary Burke[3], Ana Capuano[5], Sarah Hilmer[1]. Kolling Institute[1], Univ of Sydney & NSLHD, Sydney, NSW, Australia; Faculty of Medicine & Health[2], Univ of Sydney, Sydney, NSW, Australia; SLHD[3], Sydney, NSW, Australia; Univ of Technology[4], Sydney, NSW, Australia; Rush Univ[5], Chicago, IL, USA.

Introduction. Impact of in-hospital medication review in older adults on post-discharge clinical outcomes is unknown.
Aims. To assess the impact of medication changes made during hospitalisation in older inpatients, on Emergency Department (ED) visits, hospital readmissions, and mortality within 28 days of discharge.
Methods. This was a retrospective cohort study of 2000 inpatients aged ≥75 years, consecutively admitted for ≥48 hours to six hospitals in NSW, under General Medicine, Geriatrics, and Rehabilitation. Medication changes included the number of drugs started or dose increased and drugs stopped or dose decreased for i) all drug classes, ii) Drug Burden Index (DBI)-contributing medications (anticholinergic and sedative burden), and iii) Beers criteria 2015 (potentially inappropriate medications, PIMs). Medication changes also included the differences in drugs at discharge versus admission in the i) number of all drugs, ii) number of PIMs, and iii) DBI score. The effects of medication changes on clinical outcomes were ascertained with logistic regression adjusted for age, gender, and principal diagnosis. For 28-day mortality, sensitivity analysis excluded palliative patients. Because the effect may be differential as per total number of discharge drugs, patients were stratified by the number of discharge drugs: i) ≤4, ii) 5-9 and iii) ≥10.
Results. Patients were on average 86 years old (SD=5.8), with 41% males. For patients on 5-9 discharge medications, decreasing PIMs reduced risks of ED visits (adjusted Odds Ratio, aOR 0.55, 95% CI 0.34-0.91, p=0.02) and readmission (aOR 0.62, 95% CI 0.38-0.99, p=0.04). Decreasing DBI drugs reduced readmission risk (OR 0.71, 95% CI 0.51-0.99, p=0.04). The difference in the number of PIMs at discharge compared to admission reduced ED visit risk (aOR 0.65, 95% CI 0.43-0.99, p=0.04). Medication changes did not impact ED visits and readmission risk in patients taking ≤4 or ≥10 discharge medications. Medication changes had no impact on 28-day mortality after excluding palliative patients.
Discussion. Our findings demonstrate that the journey (medication increases and decreases) and the destination (differences in medication use from admission to discharge) support the usefulness of medication review interventions in older inpatients, especially those on 5-9 medications.

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DPYD genotype based fluoropyrimidine dosing in variant carriers, and patient clinical outcomes

Ms Deirdre Landsberg

Oral presentation 11: Pharmacoepidemiology Theme, Courtyard Room 1&2, December 3, 2024, 9:00 AM - 10:30 AM

Biography:
Deirdre Landsberg is a PhD candidate at the University of South Australia, Clinical & Health Sciences, undertaking a doctorate in pharmacogenomics. The primary focus of her research is dihydropyrimidine dehydrogenase (DPYD/ DPD) genotype-based dosing for fluoropyrimidines in cancer patients, and DPD phenotype approaches.
In addition to Deirdre's PhD studies, she works as an academic pharmacogenomic pharmacist on the national MARVEL-PIC study to advance personalised medicines in paediatric oncology patients. Deirdre has been a paediatric clinical pharmacist at the Women's and Children's hospital in Adelaide since 2014. She is passionate about contributing to the development of pharmacogenomics, and is a member of the International Society of Pharmacovigilance (ISoP) specialist interest group in pharmacogenomics.

***DPYD* genotype based fluoropyrimidine dosing in variant carriers, and patient clinical outcomes.**
Deirdre Landsberg[1], Helen Martin[2], Ganessan Kichenadasse[2], Alan Boddy[1], Stephanie E Reuter[1]. [1]UniSA Clinical & Health Sciences, University of South Australia, Adelaide, SA, Australia; [2]Flinders Medical Centre, Flinders Centre for Innovation in Cancer, Bedford Park, SA, Australia.

Introduction. *DPYD* genotype screening for targeted variants (c.1905+1G>A [*DPYD**2A]; c.1679T>G [*DPYD**13]; c.2846A>T; c.1236G>A/HapB3) prior to systemic fluoropyrimidine (FP) treatment (i.e. 5-fluorouracil and capecitabine) lends itself to critical advancement in personalised chemotherapy. Pre-emptive genetic testing can identify individuals with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency and dose recommendations are available from international guidelines, allowing dose adaptations based on *DPYD* genotypes. *DPYD* genotype-based dosing strategies and patient clinical outcomes remains largely understudied within the adult Australian population.
Aims. The primary objective of this study aimed at evaluating *DPYD* genotype-guided dosing strategies (initial FP dose and attempted dose titrations) in real-world clinical care. Clinical dosing was evaluated against recommendations from the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline. The secondary objective was to evaluate patient clinical outcomes (toxicity, treatment outcomes, toxicity related death and hospitalisation).
Methods. Targeted *DPYD* testing was implemented in a tertiary hospital, from which service and patient outcomes were examined over an 18-month period. Data collected included administered FP doses, toxicity, patient and disease characteristics. Toxicity was assessed using the Common Terminology Criteria for Adverse Events (CTCAE).
Results. Between 1 June 2022 and 31 December 2023, a total of 225 patients were screened, of whom 20 (8.89%) patients were *DPYD* variant carriers. Of the 20 patients, 19 were heterozygous carriers and received FP chemotherapy; one patient was a homozygous c.1236G>A/HapB3 carrier and did not receive FP chemotherapy. Initial (cycle 1) dose reductions were reported in 17 out of 19 variant carriers; however, significant variation in dose intensities was observed. Most variant carriers did not report grade ≥ 3 toxicity and completed their planned treatment.
Discussion. The clinical integration of *DPYD* genotype-based dosing to personalise FP chemotherapy was successful. However, given the heterogeneity in dosing requirements, additional strategies such as expanded *DPYD* testing and/or quantification of FP exposure may be required to comprehensively inform personalised dosing for FP.

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Glucose lowering medicines utilisation before and after entry into residential aged care

Mr Yohanes Wondimkun

Oral presentation 11: Pharmacoepidemiology Theme, Courtyard Room 1&2, December 3, 2024, 9:00 AM - 10:30 AM

Biography:
Yohanes Wondimkun is a PhD candidate at the University of South Australia. Yohanes' PhD research focuses on improving the use of diabetes medicines among older people living in aged care homes using linked health and aged care data from the Registry of Senior Australians (ROSA). Yohanes holds a bachelor's degree in pharmacy from Gondar University and master's in pharmacy practice from Addis Ababa University, and has previously worked in research and academic roles in higher education institutions, including as Head of School of Pharmacy at Haramaya University.

Glucose lowering medicines utilisation before and after entry into residential aged care

Yohanes A Wondimkun Msc[1,2], Gillian E Caughey PhD[1,2], Maria C Inacio PhD[1,2], Tracy Air MBiostat[2], Catherine Lang BSc (Hons)[2], Janet K Sluggett PhD[1,2]. [1]University of South Australia, UniSA Allied Health and Human Performance, Adelaide, SA; [2]Registry of Senior Australians, South Australian Health and Medical Research Institute, Adelaide, SA

Introduction. Transitioning to a residential aged care facility (RACF) is a critical point in an older person's care trajectory. Little is known about changes in glucose lowering medicine (GLM) use during this period.

Aims. To examine changes in GLM use in the 12-months before and 12-months after RACF entry among older people with diabetes.

Methods. A national retrospective cohort study was conducted using linked health and aged care data from the Registry of Senior Australians (ROSA). Individuals with diabetes aged ≥65 years who entered an RACF between January 2015 and December 2018 were included. Prevalence of GLM use and number of defined daily doses (DDDs) dispensed per 1000 resident-days were determined in the 12-months before and 12-months after RACF entry on a quarterly (91-day) basis. Point estimates and 95% confidence intervals (CIs) were estimated using Generalised Estimating Equation Poisson regression models, or negative binomial regression when overdispersion was present.

Results. Among the 50,993 residents studied (median age 84 years (interquartile range 78-88)), prevalence of GLM use was 58.4% (95%CI 58.0-58.8) in the 9-12 months prior to RACF entry and 56.3% (95%CI 55.9-56.8) in the 9-12 months post-entry. GLM use in the 3-months before RACF entry was 56.8% (95%CI 56.4-57.2) compared with 61.7% (95%CI 61.3-62.1) in the 3-months post-entry. Insulin use increased from 13.3% (95%CI 13.0-13.6) in the 3 months prior to RACF entry to 20.5% (95%CI 20.1-20.8) in the 3-months post-entry while the use of other GLM classes only changed slightly. The number of DDDs/1000 resident-days increased from 1015 (95%CI 1002-1028) in 9-12 months before entry to 1254 (1168-1339) 9-12 months after entry. Among 22,792 individuals dispensed a GLM in the 3 months prior to RACF entry and were alive at study end, 50.2% received the same GLMs, 15% withdraw from ≥1 GLM, 13.8% had no record of supply, 15% added another GLM, and 6% switched in the 9-12 months post-RACF entry.

Discussion. Use of insulin peaked in the first 3-months following RACF entry, with little change in other GLM use in the year before and after entry. Residents with diabetes may benefit from close monitoring of their diabetes treatment, particularly for individuals receiving insulin in the 3-months post-RACF entry.

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Consumers' Knowledge and Experiences of Adverse Drug Reaction Reporting in Australia

Mr Mohammed Dedefo

Oral presentation 11: Pharmacoepidemiology Theme, Courtyard Room 1&2, December 3, 2024, 9:00 AM - 10:30 AM

Biography:
Mohammed Gebre Dedefo is a PhD candidate and casual research assistant at the University of South Australia. Prior to commencing his PhD, Mohammed worked as a researcher and a lecturer of Clinical Pharmacy at Addis Ababa University and Wollega University, Ethiopia. His PhD project focuses on Adverse drug reaction reporting by consumers in Australia

Consumers' Knowledge and Experiences of Adverse Drug Reaction Reporting in Australia

Mohammed Gebre Dedefo[1], Renly Lim[1], Gizat M. Kassie[1], Elizabeth Roughead[1], Lisa Kalisch Ellett[1]. Quality Use of Medicines and Pharmacy Research Centre, UniSA Clinical and Health Sciences, University of South Australia[1], Adelaide, SA, Australia.

Introduction. Adverse drug reactions (ADRs) are a major cause of mortality, morbidity, and increased healthcare costs. Worldwide, consumers' knowledge and practice of adverse drug reaction (ADR) reporting is low.
Aims. To investigate the current knowledge and experiences of consumers in Australia on ADR reporting and their reasons for reporting or not reporting ADRs, with a focus on the use of digital tools for ADR reporting.
Methods. A cross-sectional online survey was conducted among adults who had taken medicine in Australia. A structured questionnaire with multiple choice or Likert scale responses with an option for participants to provide free-text responses, pretested for face validity was used. Consumer characteristics, knowledge and ADR reporting practices were analysed using descriptive statistics and chi-square test or Fisher's exact test.
Results. A total of 544 survey responses were included in the analysis. The majority of respondents were women (68%), and 22% were aged between 65-74 years. Fifty-eight percent (n=317) of respondents knew that they could report ADRs to either the Therapeutic Goods Administration (TGA), state or territory government health department or healthcare professionals. Three-quarters (n=405) of respondents stated that they had experienced an ADR; of these, 36% reported an ADR to either the TGA, state or territory government health department or healthcare professionals. Among those who reported ADRs, 58% were unaware that they could use digital tools to report ADRs. The main reason for reporting was that they were worried about their own situation (45%) and the main reason for not reporting was that they did not think the ADR was serious enough to report (39%).
Discussion. Over half of consumers who responded to our survey knew that they could report ADRs; however, their knowledge of ADR reporting methods, using digital tools for ADR reporting, and practices of ADR reporting were low. Addressing awareness of digital tools for reporting ADRs, privacy and security concerns are crucial in order to encourage the use of digital tools for ADR reporting, as a large proportion of respondents described these as barriers to ADR reporting using digital tools.

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Which care setting are antidepressants initiated on entry to residential aged care?

Ms Georgina Hughes

Oral presentation 11: Pharmacoepidemiology Theme, Courtyard Room 1&2, December 3, 2024, 9:00 AM - 10:30 AM

Biography:
Georgina is a pharmacist and PhD Candidate at UniSA and the Registry of Senior Australians (ROSA). Her PhD is exploring real-world use and safety of antidepressant medicines among older people living in aged care homes across Australia. Georgina is a pharmacist and pharmaceutical scientist, with practice experience extending across research & development, manufacturing, hospital and community pharmacy practice areas.

Which care setting are antidepressants initiated on entry to residential aged care?

Georgina A Hughes[1,2], Maria C Inacio[2,3], Debra Rowett[1,4], Catherine Lang[2], Robert N Jorissen[2,3], Megan Corlis[5], Janet K Sluggett[2,3]. UniSA Clinical & Health Sciences, Univ of SA[1], Adelaide SA; Registry of Senior Australians, SAHMRI[2], Adelaide SA; UniSA Allied Health & Human Performance, Univ of SA[3], Adelaide SA; Drug and Therapeutics Information Service, South Australian Local Health Network[4], Adelaide, SA, Australian Nursing & Midwifery Federation SA Branch[5], Adelaide SA.

Introduction. Antidepressant use increases around residential aged care facility (RACF) entry and initiation during hospitalisations may contribute to this.
Aims. This study characterised the care setting where antidepressants were initiated and determined associated resident characteristics.
Methods. A cross-sectional study including non-Indigenous individuals aged 65-105 years who entered RACFs in two Australian states (South Australia and Victoria) during 2015-2019, and were dispensed an antidepressant within two months, was conducted. Care settings (community-based, hospital, RACF) were determined from linked RACF records, and hospitalisations ≤30 days before entry. Pharmaceutical claims before and after RACF entry were screened to determine antidepressant initiation. Multinomial logistic regression estimated adjusted odds ratios (aORs) and 95% confidence intervals (95%CIs) for resident characteristics associated with care settings of antidepressant initiation.
Results. 34,525 residents from 1,046 RACFs were included. Overall, 27,160 (78.7%) commenced antidepressants prior to RACF entry, 2,552 (7.4%) in hospital immediately prior to RACF entry, and 4,813 (13.9%) in RACFs. Mirtazapine constituted 44.8% (n=1,143) of antidepressants initiated in hospitals and 39.5% (n=1,902) in RACFs. Residents who were ≥90 years were more likely to start an antidepressant in the RACF compared to community-based settings (aOR=1.97, 95%CI 1.74-2.23). Residents recently using an antipsychotic were less likely to start an antidepressant in hospital (aOR=0.40, 95%CI 0.33-0.47) or RACF (aOR=0.51, 95%CI 0.45-0.58) compared to community-based settings.
Discussion. Individuals receiving antidepressants during transition to RACFs often commence antidepressants before entry. Interventions to optimize antidepressant use in RACFs should consider setting, recency and indication for antidepressant initiation, ongoing safety monitoring and the influence the hospital setting has on choice of antidepressant.

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Prevalence and risk factors for psychotropic medication use in Australian older adults

Trong Hieu (Harry) Le

Oral presentation 12: Late breaking Abstracts, Eureka Room 1, December 3, 2024, 2:15 PM - 3:45 PM

Biography:
I am a pharmacist in Vietnam and currently a Master of Philosophy student at School of Pharmacy, the University of Sydney, specializing in quality use of medicines, dementia, and digital health. My recent work focuses on the quality use of psychotropic medication in older adults and development of clinical prediction models to optimize psychotropic use.

Prevalence and risk factors for psychotropic medication use in Australian older adults.

Trong H. Le[1], Edward C.Y. Lau[1], Weisi Chen[1], Christine Y. Lu[1,2], Tuan A. Nguyen[3], Lee-Fay Low[1], Sarah N Hilmer[2], Yun-Hee Jeon[1], and Edwin C.K. Tan[1,2]. Faculty of Medicine and Health, The University of Sydney, Sydney, NSW[1]; Kolling Institute, Royal North Shore Hospital, St Leonards, NSW[2]; National Aging Research Institute, Parkville, VIC[3].

Introduction. Psychotropic medications are widely used among older adults, yet national data on their prevalence and the sociodemographic factors influencing their use in Australia are limited.
Aims. To estimate the national prevalence of psychotropic medications prescribed to older Australians across age groups and identify associated sociodemographic factors.
Methods. This retrospective cross-sectional study used national linked data from the 2021 Census and the Pharmaceutical Benefits Scheme (PBS) to analyse psychotropic medication prescribing in Australians aged 65 and older. Psychotropics, classified under the Anatomical Therapeutic Chemical (ATC) code N, were examined between August 1st and October 31st, 2021. Psychotropic prevalence was analysed by 5-year age strata, with multivariate logistic regression models used to assess associated factors for overall and specific drug classes. Statistical analyses were conducted using R version 4.3.0.
Results. Among 3,850,281 older adults from the Census 2021, 31% were prescribed psychotropic medications during a 3-month study period. Prevalence increased with age across all subclasses except antiepileptics. Those needing assistance with core activities (OR 2.05, 95% CI 2.03–2.06) and living in non-private dwellings (OR 2.02, 95% CI 1.99–2.05) were more likely to receive psychotropics. Higher education, higher socioeconomic status, and speaking a language other than English were linked to lower use. Aboriginal and Torres Strait Islander status was associated with increased benzodiazepine (OR 1.15, 95% CI 1.10–1.20) and opioid (OR 1.20, 95% CI 1.16–1.23) use. Dementia was strongly linked to antipsychotic (OR 2.59, 95% CI 2.52–2.66), antidepressant (OR 1.42, 95% CI 1.40–1.44), and antiepileptic (OR 1.25, 95% CI 1.21–1.29) use. Arthritis significantly increased opioid use (OR 2.03, 95% CI 2.02–2.05).
Discussion. Nearly a third of older adults are prescribed psychotropics. Socioeconomic status, sociodemographic factors, and cultural influences significantly affect their use, highlighting potential discrepancies in access to care. Future research should address the observed variation in psychotropic medication use and evaluate clinical appropriateness and outcomes.

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Highly porous inhalable N-acetyl-L-cysteine microparticles developed using spray freeze drying for COPD

Prof Shyamal Das

Oral presentation 12: Late breaking Abstracts, Eureka Room 1, December 3, 2024, 2:15 PM - 3:45 PM

Biography:

Professor Shyamal Das is a Professor and the Associate Dean of Research at the School of Pharmacy, University of Otago, New Zealand. He completed his PhD in Pharmaceutics and a research fellowship at the Monash Institute of Pharmaceutical Sciences.

Over the past 20 years, his primary research focus has been on powder characterization and innovative inhaler powder formulations for lung diseases. His recent projects include inhaled biologics, such as nanoparticulate miRNA delivery for COPD, and cannabidiol for asthma and COPD, as well as high-dose antibiotics for respiratory infections, including COVID-19. One of his inhaled antibiotic powders for tuberculosis has secured funding from the Health Research Council of New Zealand for a clinical trial. Professor Das has received several awards for research, teaching, and supervision. He is currently the President of the Controlled Release Society New Zealand Chapter and the Otago Medical School Research Society. He also serves on the editorial boards of two pharmaceutical science journals, Pharmaceutics and the International Journal of Pharmaceutics. Since 2015, he has been the only member from the Southern Hemisphere on the Drug Delivery to the Lung Scientific Committee.

Highly porous inhalable N-acetyl-L-cysteine microparticles developed using spray freeze drying for COPD

Rishi M. Shah[1,2], Greg Walker[1], Rajesh Katare[2], Shyamal C. Das[1] [1]School of Pharmacy, University of Otago, Dunedin, New Zealand [2]Department of Physiology, University of Otago, Dunedin, New Zealand

Introduction: Chronic obstructive pulmonary disease (CODP) is a global health issue. N-acetyl-L-cysteine (NAC) is used as a mucolytic agent that helps individuals with chronic lung diseases including CODP. However, NAC has poor clinical efficacy with the current high oral doses because of limited bioavailability caused by first-pass hepatic metabolism. To overcome this limitation and to provide a rapid onset of action, the direct administration of NAC to the lungs through inhalation would be a rational approach. However, the production of microparticles of NAC is challenging as it is thermosensitive. Spray freeze drying (SFD) is an emerging technique to develop microparticles of thermosensitive compounds for inhalation. Formulation components can influence the particle structure and aerosolization properties.

Aim: To develop highly porous inhaled NAC dry powder using the spray freeze drying method and investigating the influence of inulin on particle structure integrity and of leucine on aerosolization of resultant powders.

Methods: A 9-run experimental design was produced to construct a linear model using a custom design function in Design-Expert® v13 software, with NAC and inulin proportions at 30-70% $^{w}/_{w}$ and leucine at 0-10% $^{w}/_{w}$ proportion. The physicochemical and aerosolization performances of the prepared SFD powders were assessed. and characterise for their physicochemical and aerosolisation performance using the Next Generation Impactor.

Results: All the SFD powders appeared as white fluffy powders that were highly porous, spherical in morphology and had irregular protrusions on the surface. The SFD powders also had geometric particle size of 37–50 µm, total yield of 20–38% $^{w}/_{w}$, water content <5% $^{w}/_{w}$ and were crystalline in nature. In addition, the emitted dose was >93% and fine particle fraction (FPF) was >45% for all SFD powders. The SFD powder formulation containing leucine showed better aerosol performance (FPF >57%) compared to those without leucine. All SFD powders had mass median aerodynamic diameter ≤4.5 µm suggesting their suitability for inhalation and a low GSD ≤1.6 µm suggesting a narrow particle size distribution.

Conclusion: Highly porous NAC dry powder, suitable for inhaled delivery was successfully developed using SFD method. In addition, inulin provided structural integrity to the prepared NAC SFD microparticles, and leucine improved the aerosolization performance.

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Stakeholders' views on a virtual pharmacy discharge service for First Nations patients

Bushra Haque

Oral presentation 12: Late breaking Abstracts, Eureka Room 1, December 3, 2024, 2:15 PM - 3:45 PM

Biography:
Bushra is a 4th year pharmacy honours student at the University of Sydney. She is passionate about patient-centred and equitable healthcare and strives to improve culturally safe healthcare for First Nations peoples. She is currently undertaking an honours research project based in Dubbo to inform the culturally safe implementation of a transition of care program. She has worked in a small community pharmacy in Maroubra for almost 4 years and has found it extremely rewarding. Thank you to the Virtual Clinical Pharmacy Service team in the Western New South Wales Local Health District for their support and invaluable knowledge towards the project.

Stakeholders' views on a virtual pharmacy discharge service for First Nations patients

Bushra Haque[1], Siniti Herath[1], Kingston Yeung[1], Jonathan Penm[1]. School of Pharmacy, University of Sydney[1], Sydney, NSW, Australia

Introduction. The transition from hospital to home remains a prominent issue that leads to negative health outcomes when not addressed appropriately. Risks of negative outcomes at these transitions for First Nations peoples may be inflated due to a lack of culturally safe healthcare (AIHW, 2024; Australian Commission on Safety and Quality in Health Care, 2024). As a result, a virtual transition of care stewardship (TOCS) pharmacist who facilitates a post-discharge Home Medication Review (HMR) is to be implemented in rural/regional New South Wales to increase patient safety regarding medications, and to reduce medication-related hospital readmissions.

Aims. To explore the thoughts, beliefs and perceptions of key stakeholders involved in First Nations peoples' healthcare on the implementation and cultural safety of a virtual TOCS pharmacist service that facilitates a post-discharge HMR for First Nations patients.

Methods. Semi-structured one-on-one interviews were conducted with key stakeholders including doctors, nurses, pharmacists, Aboriginal Health Workers, and allied health workers. All interviews were transcribed manually and analysed according to the methodology described by Bernard and Ryan.

Results. The study included 20 interviews with clinicians. Clinicians stressed the importance of informing the patient of what to expect, why the service will be used, and how it can assist them with managing their medications. Additionally, building rapport with First Nations patients to increase the acceptability of both the virtual TOCS service and HMR service was emphasised. It was also suggested that understanding of culturally safe healthcare may be lacking in clinicians that do not identify as First Nations.

Discussion. The study suggests the need for regular cultural safety training in the context of First Nations peoples, approaching the implementation of HMRs for First Nations patients with a holistic understanding of their healthcare needs, and ensuring patient awareness of the services being provided both in and out of hospital.

Australian Commission on Safety and Quality in Health Care, 2017. Safety Issues at Transitions of Care: Consultation report on perceived pain points relating to clinical information systems

Australian Institute of Health and Welfare (AIHW) 2024. Aboriginal and Torres Strait Islander Health Performance Framework: summary report March 2024

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Causality, severity and avoidability of adverse drug reactions in children

Dr Duaa Gaafar

Oral presentation 12: Late breaking Abstracts, Eureka Room 1, December 3, 2024, 2:15 PM - 3:45 PM

Biography:

Dr Duaa Gaafar is a general paediatrician at the Royal Children's Hospital and an honorary research fellow at the Murdoch Children's Research Institute (MCRI). She specialises in paediatric clinical pharmacology and focuses on adverse drug reactions, drug allergies, and pharmacogenomics. Duaa is actively involved in research projects exploring drug-related adverse effects in children as part of her PhD, contributing to safer prescribing practices and advancing the field of paediatric pharmacology.

Causality, Severity and Avoidability of Adverse Drug Reactions in Children over an 11-year period

D. Gaafar [1,2,3]*, H. Weerdenburg[1,2,3], R. Dimond[4], M. Iles[4], J. Christodoulou [2,3], N. Cranswick[1,2,3] and A. Gwee[1,2,3]
1 Infectious Diseases, Children's Cancer Centre and Clinical Pharmacology Units, Department of General Medicine, Royal Children's Hospital, Parkville, Australia; 2 Department of Paediatrics, The University of Melbourne, 50 Flemington Rd, Parkville, VIC 3052, Australia; 3 Murdoch Children's Research Institute, Parkville, Australia;4 Grampian Health Ballarat Pharmacy Department.

Background: Adverse Drug Reactions (ADRs) are a frequent cause of emergency admissions and extended hospital stays in children,, leading to increased healthcare costs and patient morbidity. However, ADRs' causality, severity, and avoidability in children remain underexplored.
Objective: This study aims to assess the causality, severity, and avoidability of ADRs in hospitalised children over an 11-year period at The Royal Children's Hospital, a tertiary paediatric hospital in Melbourne.
Methods: Retrospective cohort study of ADRs in children aged 0-18 years from January 2012 to December 2022. ADRs were evaluated using the Naranjo criteria for causality, the Hartwig scale for severity, and the Modified Schumock and Thornton scale for avoidability. ADR types were classified as Type A (dose-related) and Type B (unrelated to dose or idiosyncratic).
Results: Of 599 children with ADRs, the median age was 8.7 years (range 3 weeks-18 years), with 44% female. Most ADRs were mild (74%), with 25% moderate and 1% severe. The most commonly implicated drugs were antimicrobials (46%), analgesics (9%), and antiepileptics (8%). ADRs were type A in 44%, with neurological symptoms being the most common. Type B reactions (56%) most commonly occurred with antimicrobials (87%). Additionally, allergy label documentation was inconsistent, with 15% lacking appropriate flags despite a history of previous ADRs. One in six ADRs were potentially avoidable, with 9% definitely and 6% probably avoidable. Most avoidable ADRs were due to failure to consider documented allergies, inappropriate dosing, drug interactions, or not applying preventative measures (e.g. premedication).
Conclusion: Our study shows that 1 in 6 ADRs in children could be avoided, highlighting the need for further clinician education. In the era of widespread use of hospital electronic medical records, future strategies should focus on developing automated tools to support prescribing decisions and ensure adherence to safety protocols.

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Primary healthcare provider perceptions of a pharmacist-led transition of care service

Prof Michael Barras

Oral presentation 12: Late breaking Abstracts, Eureka Room 1, December 3, 2024, 2:15 PM - 3:45 PM

Biography:
Prof Michael Barras is the Director of Pharmacy at the Princess Alexandra Hospital, Brisbane, and a Research Conjoint with the School of Pharmacy, The University of QLD (Hospital 0.8 FTE / UQ 0.2 FTE). He currently supervises 8 HDR students who are conducting research related to medication safety, health informatics and advanced scope clinical pharmacy.

Primary healthcare provider perceptions of a pharmacist-led transition of care service

Karen Bettenay[1], Kelvin Robertson[2], Ian Coombes[3,4], Michael Barras[4,5]. [1]Office of the Chief Allied Health Officer, Clinical Excellence QLD; [2]Townsville University Hospital, Townsville, QLD; [3]Royal Brisbane and Women's Hospital, QLD; [4]School of Pharm, The University of QLD, Brisbane; [5]Princess Alexandra Hospital, Brisbane, QLD.

Introduction: A pharmacist-led transition of care (ToC) service to improve communication and medication handover between hospitals and primary healthcare providers was implemented at three tertiary hospitals over 2-years (2022-23). Identified high-risk patients were reviewed at discharge. A co-designed post-discharge medication management plan (MMP) was sent to the patient's general practitioner (GP) and community pharmacist (CP).
Aim: To evaluate primary healthcare provider perceptions of a pharmacist-led ToC service.
Methods: A link to an online survey was emailed to GPs and CPs who were sent an MMP. A convenience sample of providers participated in semi-structured interviews. Interviews were conducted by telephone and audio recorded. Transcripts underwent inductive coding using NVivo® to identify themes.
Results: Survey responses were received from 48 GPs and 57 CPs (response rate 9% and 13% respectively). Interviews were conducted (KB) with three GPs, four CPs and one general practice pharmacist. Most GP and CP respondents agreed the MMP was received within an appropriate time frame (74% and 86%), was easy to understand (80%, 90%), was useful (74%, 86%), and improved their understanding of medication changes (71%, 81%). Most respondents agreed with (77%, 83%) and were likely to act on (74%, 83%) the MMP information. Unfortunately, 9% of GP and 26% of CP respondents stated they did not have time to act on recommendations. Despite this, over 85% of GPs and CPs indicated they would like to receive an MMP for more of their high-risk patients. Two interview themes were identified: health performance and service delivery. Participants reported continuity of care benefits but highlighted poor project awareness and issues with information transfer due to the lack of medication software integration.
Discussion: Primary healthcare providers held positive views towards the ToC model of care and supported service continuation. Issues with information transfer and project awareness were identified.

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Sexually dimorphic effects of chronic cerebral hypoperfusion in mice

Dr Michael De Silva

Oral presentation 12: Late breaking Abstracts, Eureka Room 1, December 3, 2024, 2:15 PM - 3:45 PM

Biography:

Dr Michael De Silva is a Senior Lecturer in the Department of Microbiology, Anatomy, Physiology and Pharmacology and Head of the Cerebrovascular Disease Division in the Centre for Cardiovascular Biology and Disease Research at La Trobe University. Michael earned his PhD from Monash University in 2011 and has completed a postdoctoral research position at the University of Iowa, USA. Michael's current research interests include examining the effects of cardiovascular diseases (such as stroke and hypertension) on the regulation of cerebral microvascular function and cognitive function. He has been as ASCEPT member since 2008 and was co-chair of the Cardiovascular SIG (2019-2020).

Sexually dimorphic effects of chronic cerebral hypoperfusion in mice.

T. Michael De Silva, Tarunpreet Rajput, Thiruma V. Arumugam, Christopher G Sobey & Quynh Nhu Dinh[1]. [1]Centre for Cardiovascular Biology and Disease Research and Department of Microbiology, Anatomy, Physiology and Pharmacology, La Trobe University, Bundoora, Victoria 3086, Australia.

Introduction. Vascular dementia (VaD) is a cerebrovascular disease resulting from compromised cerebral blood flow (CBF) leading to chronic cerebral hypoperfusion (CCH). Interestingly, VaD is more prevalent in men than in women, suggesting that sex may be an important determining factor for the onset and progression of this disease. However, the mechanism(s) accounting for this sex-dependent effect are unclear.
Aims. To determine the effect of biological sex on cognitive function and brain injury in a model of CCH.
Methods. Bilateral common carotid artery stenosis (BCAS) was used to induce CCH in 12-week-old male and female C57Bl6 mice (n=96). Cortical CBF was measured using laser speckle contrast imaging (before and after surgery and prior to euthanasia at 36 days. Cognitive function (spatial reference memory and executive function) was assessed for 6 consecutive days using the Barnes maze with days 1-3 being the acquisition phase (learning) and days 4-6 being the reversal phase (cognitive flexibility). Neuron and microglia cell numbers were quantified in the pre-frontal cortex using immunofluorescence. Expression of sex hormone receptors in the brain was measured using qPCR.
Results. CBF was similarly reduced by ~35% in males and females ($P<0.05$ vs sham, n=11-12) immediately after BCAS, and recovered by ~17% in in both sexes over 36 days. Escape latency (measure of executive function) for males with CCH was slower than for male shams during the acquisition phase (day 2: 61.8±11.4s vs 26.4±2.6s; and day 3:42.9±9.9s vs 15.0±1.4s) ($P<0.05$, n=11-12) but not the reversal phase of Barnes maze testing. Primary latency (spatial reference memory) was preserved in male mice after BCAS. In contrast, no changes were observed in primary or escape latency in females with CCH in either phase of testing. The number of neurons (NeuN+ cells) in pre-frontal cortex was reduced by ~50% in males with CCH compared to sham ($P<0.05$, n=5-6) but did not differ between females with CCH and sham females. No differences in microglia cell size or number were observed between any groups (n=5-6). Gene expression of sex hormone (estrogen, progesterone, testosterone) receptors was not altered by CCH in either sex.
Discussion. These findings suggest that female mice are less sensitive than males to some of the deleterious effects of CCH. Further studies are required to identify the precise mechanisms underlying this protection.

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Development of Post Graduate Support Programs for Pharmacy Alumni During Internship

Mr Matthew West

Oral presentation 13: Education Theme, Eureka Room 2, December 3, 2024, 2:15 PM - 3:45 PM

Biography:
Matthew West is a dedicated practicing clinician and academic with over 20 years' experience in a variety of roles within the pharmacy profession. With an initial career in private hospital pharmacy, Matt has expanded his scope to include rural and remote healthcare, academia, consultancy and aged care clinical pharmacy roles. Passionate about supporting early career pharmacists, Matt is pursuing a PhD in Education Frameworks for pharmacist competencies and early career suport. Matt is focussed on innovative teaching initiatives in a rapidly changing educational and professional environment.

Development of Post Graduate Support Programs for Pharmacy Alumni During Internship

Matthew West[1], Anna Barwick[1], Anna Marie Babey[2]. School of Health[1] and School of Science and Technology[2], University of New England, Armidale, NSW, Australia.

Introduction. Uncertainty and a rapidly changing pharmacy profession create stressors and barriers for early career pharmacists (ECPs). Professional and personal support for ECPs, particularly in rural and remote areas, can be difficult to obtain. UNE Pharmacy graduates can find this particularly challenging, as they study predominantly online, missing the opportunities to establish networks akin to those created by students in on-campus programs.
Aims. To develop an extended support program for pharmacy graduates to facilitate transition from guided learners to independent practitioners.
Methods. A strategic plan for a UNE Pharmacy Alumni (UNEPhA) group was created in 2019. UNE pharmacy students elect to provide their contact information during their final year, and were subsequently invited to collaborate in the design and organisation of events to facilitate the transition from intern to practitioner.
Results. On average, one-third of final year pharmacy students nominate to be on the Alumni list. These graduates identified that online peer-peer mentoring, intern guidance and online clinical update sessions may be beneficial for interns and ECP. Eight registered pharmacists from the UNE alumni volunteered to be intern mentors, with 9 pairs of peer-peer mentoring undertaken over two offerings in 2020 and 2021. Both mentors and mentees experienced a positive impact from their interactions and expressed a desire to continue contributions/participation. Eight online sessions, focused on the intent of the registration examinations and refining individual professional processes, were hosted and all intern alumni who attended were successful in the registration exams. These events were identified as both engaging and rewarding by attendees.
Discussion. Professional development and the creation of interpersonal networks are essential to combat the tyranny of isolation that can be experienced by interns in rural and remote areas. Pre-COVID, UNE students were unique placed to develop resilience to isolation, studying predominantly online with limited face-to-face networking opportunities. The post-graduate support program will continue to be developed with UNE alumni in consultation with academic staff. This will provide a framework to facilitate and nurture professional development, particulary in regional Australia, where security of the health workforce is an area of priority.

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Design, development, and evaluation of continuing professional development modules for community pharmacists

Dr Anna-Marie Babey

Oral presentation 13: Education Theme, Eureka Room 2, December 3, 2024, 2:15 PM - 3:45 PM

Biography:
Dr Anna-Marie Babey received her PhD from McGill University in Montreal, undertook post-doctoral work on opioid tolerance with Prof Gavril Pasternak at the Memorial Sloan-Kettering Cancer Center in New York, and with Prof Ping-Yee Law in the Department of Pharmacology at the University of Minnesota. She is currently a member of the School of Science & Technology at the University of New England, and has an extensive history of teaching and curriculum development across 9 different degree programs at 2 Australian universities. She is particularly interested in developing learning activities that enhance students' creativity, adaptability, and critical-thinking skills as part of her commitment to education quality. She is an active member of the ASCEPT Education Forum, having previously served as Secretary, a Councillor of the IUPHAR-Education Section, a member of the Australasian core concepts of pharmacology project, and a member of the IUPHAR-Education core concepts of pharmacology research team.

Design, development, and evaluation of continuing professional development modules for community pharmacists
Bridgette Caccamo[1], Joanna Dearden[1], Kristie Gill[1], Aleisha O'Brien[1], and Anna-Marie Babey[2]. School of Health[1] and School of Science & Technology[2], University of New England, Armidale, NSW, Australia

Introduction. While the number of oral anticancer agents (OAAs) has increased exponentially, dispensing and patient management has devolved to community pharmacies, despite a lack of dedicated guidelines and educational materials for the community setting. Community pharmacists have identified a lack of knowledge and confidence in dispensing OAAs, creating challenges for, and barriers to professional practice and potentially, patient outcomes.
Aims. To create continuing professional development (CPD) modules on a set of common OAAs intended to augment community pharmacist' drug knowledge and risk awareness; and to obtain their feedback for module optimisation.
Methods. The Pharmaceutical Society of Australia's online compendium of CPD modules and the published literature were scrutinised to inform best practice in module design, format, depth and breadth of content, and duration. Once the preliminary modules had been created, community pharmacists were recruited using convenience sampling (UNE HREC Approval HE23-020). Interviews were then conducted as the pharmacists worked through and assessed the modules. With participants' permission, sessions were recorded, transcribed, and de-identified for inductive thematic analysis. Recruitment continued until saturation of opinion was achieved. Common themes that arose were critically evaluated and used to optimise the final version of each module.
Results. Four CPD modules were created in PowerPoint that included drug mechanisms, counselling points, risks to staff and patients, and links to additional resources. A total of 21 pharmacists across 3 states were recruited for module assessment. Unanimously, pharmacists found that the module they reviewed was an appropriate length, engaging, and relevant to their practice. Additionally, they thought the module would be of benefit to their colleagues if it were made available. By contrast, there was no consensus on the section of the module that was considered the most engaging, although the preference aligned with the range of their professional experience.
Discussion. Feedback from participating pharmacists demonstrated that the modules may assist in upskilling their colleagues to meet the changing demands of their practice, although no particular section was thought to have primacy. UNE Pharmacy students gained valuable insight into the creation of CPD modules and their benefit to the profession, with some expressing an interest in contributing to the creation of other modules once registered.

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Non-remunerated services provided by community pharmacies: an observational study by pharmacy students

Dr Jack Janetzki

Oral presentation 13: Education Theme, Eureka Room 2, December 3, 2024, 2:15 PM - 3:45 PM

Biography:
Jack is a Lecturer in Pharmacy and Pharmacology at the University of South Australia. Jack has a strong interest in improving medication safety which is evident in his clinical practice, research and education of future health professionals.
Jack's research focuses on integrating methodologies to understand how adverse drug events happen at both a molecular level and also at the population level. Jack is a member of the Quality Use of Medicines and Pharmacy Research Centre at UniSA and an active contributor to the Observational Health Data Sciences and Informatics (OHDSI) network, an international collaborative who generate evidence to promote better health care.

Non-remunerated services provided by community pharmacies: an observational study by pharmacy students
Jack Janetzki[1], Vijayaprakash Suppiah[1], Michael Ward[1], Daniella Amato[1], Wern Chai[1], Kirsten Staff[1], Jacinta Johnson[1], Debra Rowett[1], Lisa Kalisch-Ellett[1], Clinical and Health Sciences, University of South Australia, Adelaide, SA, Australia

Introduction. Government funding, dispensing of medicines and direct sale of products have historically offset costs of providing non-remunerated professional services. Recent changes to pharmacy funding mechanisms have affected pharmacists' ability to absorb such costs.
Aims. Identify the range of non-remunerated services in South Australian community pharmacies that are not reimbursed by government or paid for by consumer.
Methods. Direct observational study by pharmacy students enrolled in placement. Three two-hour observation periods of pharmacist duties were performed per student. Number, type and duration of non-remunerated services were recorded. Results were summarised descriptively.
Results. Over 78 unique observations periods, there were 329 total service observations. 156 (47.4%) were for non-remunerated prescription services and 94 (28.6%) for primary healthcare, usually lasting between 1-5 minutes (155 observations). Prescription medicine scenarios commonly involved queries regarding availability of medicine (n=74), provision of information (n=45), changes to dose administration aid without charge (n=28) or troubleshooting medication administration devices (n=17). Primary health care scenarios commonly involved vaccination inquiries (without administration) (n=39), health condition advice (without a product supplied) (n=28) or patient monitoring (without payment) (n=12). Return of unwanted medicine at no charge was also commonly observed (n=28).
Discussion. Pharmacists undertake a diverse range of non-remunerated activities that make significant contributions to quality use of medicines by consumers. Pharmacy students will be able to use findings to understand the value of remunerating such services and consider diversified revenue streams on a background of cost-benefit analysis.

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VitOOLs VIRTUAL LEARNING PLATFORM for integrated learning in physiology and pharmacology

A/Prof Lisa BG Tee

Oral presentation 13: Education Theme, Eureka Room 2, December 3, 2024, 2:15 PM - 3:45 PM

Biography:
Lisa Tee is an Associate Professor and Biomedical Scientist with over 30 years' experience in research and teaching. Lisa commenced research in Clinical Pharmacology while undertaking her PhD in London University and has been actively engaged in teaching and research in Australia since 1986. As chief investigator, she was awarded funding from several resources including NHMRC and Cancer Foundation. Lisa's excellence and innovation in teaching has been recognised with the Australian Excellence and Innovation in Teaching (2011) and the National Teaching Fellowship (2016). Lisa's teaching aims to empower students with the learning skills to understand difficult concepts leveraging on current technology. She is the founder of MyCourseMap (interactive curriculum mapping tool) and co-founder of VitOOLs (immersive virtual learning platform) and recognised with a Curtinnovation Award (2021). Lisa is presently working collaboratively with colleagues and clinicians in the transformation of 2D medical imaging into 3D visualisation, creating the "3D virtual patient".

VitOOLs VIRTUAL LEARNING PLATFORM – an integrated approach to learning physiology and pharmacology

Lisa BG Tee[1], Ajanthy Shan[1], James Alex[2], Mauro Vaccarezza[1], Ricky Chen[3], Zhonghua Sun[1], Rima Caccetta[1]. Curtin Medical School[1], School of Elec Eng, Comp and Math Sci[2], Curtin University, Bentley, WA, Australia; School of Biomedical Sciences, Pharmacology & Toxicoloy[3], UWA, Nedlands, WA, Australia.

Introduction. For deep understanding of the complexity of pharmacological effects of drugs, the VitOOLs Team at Curtin has developed a virtual learning platform for an integrated, immediate, and immersive approach in linking physiology to pharmacology effects at body, tissue, cell and molecular levels. The VitOOLs platform offers a Virtual Patient Simulation (VPS) and VR Pharmacology laboratory (VR Lab). In this paper we present the use of the VPS in a large year one human biology class and VR Lab in the second- and third-year pharmacology class.
Aims. This project aims to evaluate the usability of the VitOOls platform for teaching physiology and pharmacology. Specifically, to evaluate the benefits and challenges in using VitOOls in health Sciences and medical education, and to determine aspects that needs further refinement.
Methods. The evaluation was conducted in two phases. In phase 1, students undertaking the Human, Structure and Function unit (Year 1) use VPS and Pharmacology units (Year 2 and 3) used VPS and VR Lab to supplement the workshop activities. Following the workshop, students were invited to complete a system usability scale (SUS) questionnaire [1]. In Phase 2, a one-on-one session was conducted with students using a moderated in-person assessment model.
Result and Discussion. SUS generated 200 responses for the use of VPS and 150 for VR Lab. The SUS score for the simulated patient is acceptable at 79. Users perceived the VR LAB and Body model to be effective as learning tools. The perceived learning outcome benefits include engagement, repeatability and seeing the actual and immediate physiological changes. The SUS quantitative data indicated a usability score for the VR LAB that corresponded to a marginally acceptable usability score (62.5). Whilst students who were unfamiliar with use of VR headset controller in conducting experiment indicated low confidence, majority commented the better learning of drug action in organ and molecular levels. Students also commented having a better understanding of the link between physiology and pharmacological effect. The VitOOLs team is currently exploring ways to using the SUS score for usability.
Reference. 1. Bangor, A., Kortum, P. & Miller, J. (2009). *Journal of Usability Studies*, **4** (3) 114-123.

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Comparing self-regulated learning approaches between school leavers and mature learners.

Miss Alexandra Steel

Oral presentation 13: Education Theme, Eureka Room 2, December 3, 2024, 2:15 PM - 3:45 PM

Biography:
Alexandra Steel is an Intern Pharmacist with Barwon Health and is completing her Masters of Pharmacy with Monash University after the completion of a Bachelor of Pharmacy (Honours) in 2023 as a graduate-entry student. Prior to this, she completed her undergraduate studies of a Bachelor of Biomedical Science and Commerce. She has participated in projects exploring education and learning amongst mature learners, as well as the environmental impact of the health care system and hopes to continue delving into these areas

Comparing self-regulated learning approaches between school leavers and mature learners.
Alexandra Steel[1], Nilushi Karunaratne[1], Betty Exintaris[1], Simon James[2], David Wei Dai[3], Suzanne Caliph[1], Angelina Lim[1,2], Faculty of Pharm and Pharmaceutical Sci, Monash Univ.[1], Melbourne, VIC, Australia; School of IT, Deakin Univ.[2], Burwood, VIC, Australia, UCL Instit of Education, Univ College London[3], London, UK; Murdoch Childrens Research Instit[4], Royal Children's Hosp, Melbourne, VIC, Australia.

Introduction. Diversity amongst student populations could result in varied learning approaches, such as between school leavers and mature learners. These learning approaches can be explored using Zimmerman's self-regulated learning approach, which consists of three phases: forethought; performance; and self-reflection (Zimmerman, 1990).
Aims. This study aimed to explore the differences in self-regulated learning approaches between mature learners (graduate entry) and school leavers.
Methods. A sequential explanatory mixed methods design was used along with Zimmerman's three phase approach. 272 students were recruited: 208 undergraduate students and 64 graduate entry students. The learning approaches between the two groups were compared using factor and correlation analyses of four assessments: a practical exam, an oral exam, a multiple-choice quiz, and a written exam. Additionally, semi-structured interviews were conducted to gain a more detailed understanding of the learning approaches of both groups and how they were applied.
Results. Both groups showed the adoption of similar learning approaches for the different assessments, however graduate entry students tended to spend more time studying outside of class when compared to the undergraduate cohort. Graduate entry students also showed more self-belief with regards to understanding concepts and maintaining focus when being taught. With regards to results, the graduate entry learning approaches were slightly more effective, especially for practical and oral exams, when compared to undergraduate students.
Discussion. This study enabled the comparison of learning approaches of graduate entry students with school leavers studying identical content and how these influenced their ability to succeed in assessments. Although both groups showed similar learning approaches, minor differences lead to slightly better outcomes for mature age learners, which is valuable finding to consider as educators are now catering for more diverse learning cohorts.

Zimmerman BJ (1990) Educ Psychol 25:3-17

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Harnessing Generative AI for Objective Structured Clinical Examinations Preparation in Pharmacy Education

Dr Angelina Lim

Oral presentation 13: Education Theme, Eureka Room 2, December 3, 2024, 2:15 PM - 3:45 PM

Biography:
Dr. Angelina Lim is a lecturer at Monash University and her key interests are simulation, authentic assessment, generative artificial intelligence, antimicrobial stewardship and paediatric endocrinology. Angelina's main expertise lies in designing and evaluating Objective Structured Clinical Examinations. Angelina has embarked on many pharmacy related career paths, starting with hospital pharmacy, then community pharmacy (still practicing), public health sector and research. She still maintains links with the Murdoch Children's Research Institute (MCRI) working on projects in disability and paediatric endocrinology. Angelina is dedicated to teaching and education research and aims to use evidence based pedagogical approaches to drive her teaching and curriculum design.

Harnessing Generative AI for Objective Structured Clinical Examinations Preparation in Pharmacy Education
Emily Stokes[1], Angelina Lim[1], Ethan Kreutzer[1], Yeap Li Ling[2], Amna C. Mazeh[3], Joel Moore[3]. Pharmacy and Pharmaceutical Sciences Education[1], Monash University, Melbourne, VIC, Australia; School of Pharmacy[2], Monash University, Malaysia; Dept. of Politics and International Relations[3], Monash University, Melbourne, VIC, Australia.
Introduction. Objective Structured Clinical Examinations (OSCEs) are widely utilised in pharmacy education to assess readiness for practice. There is demand for individualised simulations that allow students to prepare for OSCEs through repeated practice. These simulations can complement traditional face-to-face learning, providing additional tools and creating more opportunities for practice, while still offering individualised feedback and overcoming the logistical and budgetary challenges associated with traditional face-to-face formative OSCEs.
Aims. To evaluate the usability and acceptability of ATLAS (Authentic Teaching & Learning Application Simulations) as a tool for OSCE preparation. This technology harnesses cutting-edge Large Language Models (e.g. OpenAI's GPT-4) to provide students with real-time, tailored feedback on both clinical and communication skills.
Methods. A quasi-experimental study was conducted across two pharmacy units studied at Monash University. Data encompassing ATLAS attempt counts, OSCE scores, and tool perceptions were systematically collected and analysed. The study evaluated the influence of ATLAS on both domestic and international students' OSCE performance. Additionally, a content analysis of qualitative feedback pinpointed the advantages and challenges of integrating generative AI using ATLAS into OSCE preparation.
Results. Out of the 328 students who participated, 263 used ATLAS. Median OSCE scores improved with increased ATLAS practice, from 0.80 with no attempts to 0.90 after six attempts. OLS regression analysis showed a significant impact of ATLAS usage on OSCE marks (p=0.01), with an estimated increase of 0.09 in scores from zero to six conversations. Survey feedback indicated students valued the simulations for OSCE preparation.
Discussion. The ATLAS platform's contribution to OSCE preparation was positively received, with students indicating that these simulations were realistic. The tool proved to be effective as students obtained an improvement in their clinical and communication skills. This highlights ATLAS's value as a supplementary educational tool, fostering enhanced patient interaction competencies. However, the lag in responding to the student's input and preference for in-person interactions revealed the limitations of the current technology and highlighted its potential to complement rather than replace in-person simulations.

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The role of cardiomyocyte cavin-1 in cardiac function and development

Miss Hui Yi Khoo

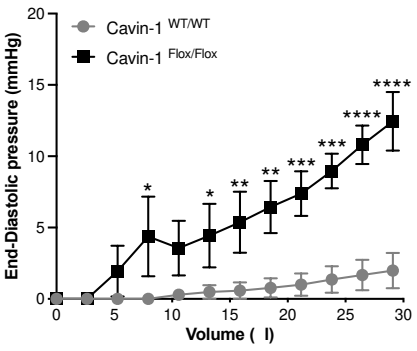
Oral presentation 14: Cardiovascular Theme, Eureka Room 3, December 3, 2024, 2:15 PM - 3:45 PM

Biography:
Hui Yi (Cathy) Khoo is a PhD candidate in the Cardiac Disease Therapy and Receptor Biology Group (CDT/RBG) at The University of Queensland since 2021. Her research focuses on the interactions between cardiomyocytes and endothelial cells in the heart, specifically examining the roles of neuregulin (NRG) and nitric oxide (NO). The CDT/RBG laboratories are keenly interested in developing adeno-associated viruses (AAVs) for the overexpression or deletion of genes of interest by targeting specific cell types in the heart using various promoters. Cathy's project primarily targets cardiomyocytes and endothelial cells to deliver the gene of interest, aiming to determine the resulting physiological changes or effects on the NRG/ErbB4 and cavin/caveolae/NO axes through AAVs. This approach enables her to further understand the underlying mechanisms of these axes in maintaining normal heart physiology.

The role of cardiomyocyte cavin-1 in cardiac function and development

Hui Yi Khoo[1], Tayla R. Bishop[1], Jake S. Russell[1], Walter G. Thomas[1], Melissa E. Reichelt[1]. School of Biomedical Science, Faculty of Medicine, The University of Queensland[1], Brisbane, QLD, Australia.

Introduction. Cavin-1, which is essential for the formation of caveolae, is expressed in multiple cardiac cell types. Global cavin-1 deficiency leads to diastolic dysfunction, an effect reversible with nitric oxide synthase inhibition and mimicked by a nitric oxide donor (Kaakinen et al, 2017). However, the contributions of specific cardiac cell types to this function are not well understood.
Aims. We aimed to delineate the specific role of cardiomyocyte cavin-1 in regulating cardiac function and development.
Methods. We generated a cavin-1 floxed mouse using CRISPR and used an adeno-associated virus serotype 9 (AAV9) with a chicken troponin T promoter to drive the expression of Cre recombinase in cardiomyocytes (AAV9;cTNT-iCre). The expression of transgenes and cavin-1 deletion were confirmed by RT-qPCR and immunofluorescent staining. Cardiac function was assessed using echocardiography and pressure-volume measurements both *in vivo* and *ex vivo.*



Results. The AAV-Cre approach successfully reduced cavin-1 mRNA in cardiomyocytes. This cavin-1 knockdown caused diastolic stiffness as evidenced by a steeper rise in end-diastolic pressure with increasing volume (see figure). Heart rate was also elevated, as was expression of atrial and brain natriuretic peptides.
Discussion. These findings highlight the importance of cardiomyocyte cavin-1 in regulating cardiac function, particularly in ventricular relaxation.

Kaakinen M et al (2017). Cavin-1 deficiency modifies myocardial and coronary function, stretch responses and ischaemic tolerance: roles of NOS over-activity. Basic Res Cardiol 112(3): 24

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Inhibition of the upregulated phosphodiesterase4D isoforms improves SERCA2a function in diabetic cardiomyopathy

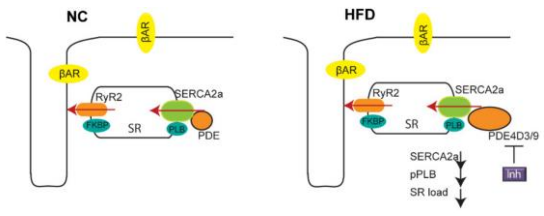
Dr Qingtong Wang

Oral presentation 14: Cardiovascular Theme, Eureka Room 3, December 3, 2024, 2:15 PM - 3:45 PM

Biography:
Dr. Wang received her Bachelor in Clinical Medicine (2002), Master in Pharmacology (2007) and Ph.D. in Pharmacology (2012) from Anhui Medical University, Hefei, China. She joined the Faculty of Anhui Medical University since July 2002 and completed her visiting scholar research at Department of Pharmacology, UCDavis. Her research interests focus on understanding the mechanisms of pathogenesis of inflammatory disease and inflammation-related cardiomyopathy, identifying novel targets for disease therapy and developing small-molecule compound with specific activity. She is now a professor of pharmacology and a principal investigator in Key Laboratory of Anti-inflammatory and Immune Medicine, Ministry of Education (Anhui Medical University).

Inhibition of the upregulated phosphodiesterase4D isoforms improves SERCA2a function in diabetic cardiomyopathy
Qingtong Wang[1,2], Zhenduo Zhu[1], Wei Wei[1], Yongsheng Han[3], & Yang K Xiang[2]. Institute of Clinical Pharmacology, Anhui Medical University[1], Hefei, 230032, China; Department of Pharmacology, University of California at Davis[2], CA 95616, USA; Department of Emergency Medicine, The First Affiliated Hospital of USTC[3], Hefei, 230001, China.

Introduction. Phosphodiesterases (PDEs) are implicated in the modulation of local cAMP-PKA activity essential for sarcoplasmic reticulum Ca^{2+}-ATPase 2a (SERCA2a) function in the heart.
Aims: We aim to characterize PDE isoforms that underlie decreased activities of SERCA2a and reduced cardiac contractile function in diabetic cardiomyopathy (DCM).
Methods. Wild-type mice were fed with either a normal chow or a high-fat diet (HFD). Cardiomyocytes were isolated for biosensor-based analysis of local cAMP-PKA activity, proximity ligation assays, and excitation-contraction coupling.
Results. HFD feeding induced selective upregulation of PDE 4D3 and 4D9 isoforms in hearts. The upregulated PDE4D isoforms in HFD cardiomyocytes specifically bound to SERCA2a but not ryanodine receptor 2 on the sarcoplasmic reticulum. The increased association of PDE4D isoforms with SERCA2a in HFD cardiomyocytes led to reduced local PKA activities and phosphorylation of phospholamban but minimally affected the PKA activities and phosphorylation of ryanodine receptor 2. These changes correlate with lower calcium load in the sarcoplasmic reticulum and attenuation of excitation-contraction coupling in high-fat diet cardiomyocytes. Moreover, selective inhibition of PDE 4D3 or 4D9 restored PKA activities and phosphorylation of phospholamban at the SERCA2a complex, recovered calcium load, and increased excitation-contraction coupling in high-fat diet cardiomyocytes. Therapies with PDE4 inhibitor rofluomilast and PDE4D inhibitor BPN14770 restored PKA phosphorylation of phospholamban and cardiac contractile function.
Discussion. The current study identifies upregulation of specific PDE4D isoforms that selectively inhibit SERCA2a function in the high fat diet-induced cardiomyopathy, indicating that this signaling remodeling can be targeted to restore cardiac contractility in diabetic cardiomyopathy.



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Formyl Peptide Receptor Agonism: A Novel Approach for Limiting Abdominal Aortic Aneurysm.

Mr Jaideep Singh

Oral presentation 14: Cardiovascular Theme, Eureka Room 3, December 3, 2024, 2:15 PM - 3:45 PM

Biography:

Jaideep is a final year PhD student at Monash University, Australia under the supervision of Dr. Helena Qin, Dr. Kristy Jackson, Prof. Geoff Head, and Prof. Rebecca Ritchie. His PhD project focuses on targeting formyl peptide receptors as a novel approach to treat hypertension-induced cardiovascular and renal damage. Prior to the commencement of his PhD, he was working in the drug discovery organisations for 11 years. He completed his Master of Pharmacology (2009) and Bachelor of Pharmacy (2006) at Rajiv Gandhi University of Health Sciences, India. He has also successfully filed four patents and published 18 articles in the peer-reviewed international journals.

Title: Formyl Peptide Receptor Agonism: A Novel Approach for Limiting Abdominal Aortic Aneurysm.

Jaideep Singh[1,2], Feng Tang[1], Kristy Jackson[1,2], Geoffrey Head[2], Owen Woodman[1], David Greening[2], Rebecca Ritchie[1,2], Cheng Xue Qin[1,2]. [1]Monash University, VIC, Australia; [2]Baker Heart and Diabetes Institute, VIC, Australia.

Introduction: Unresolved, chronic inflammation contributes to abdominal aortic aneurysm (AAA) development yet current standard-of-care poorly targets this, or the high AAA-associated mortality, warranting development of new pharmacological interventions for AAA. Formylpeptide receptors (FPRs) play a critical role in resolution of inflammation, but their regulation of AAA development and its management has not been sought. **Aim and hypothesis:** Here, we investigate the therapeutic potential of FPR-agonist compound17b (Cmpd17b) on blood pressure (BP), aortic remodelling, and function in AAA mice. **Methods:** Male C57BL/6 mice were implanted with angiotensinII (AngII-1.4-mg/kg/day)-containing osmotic-minipumps for 4-weeks to induce AAA (sham mice received saline). Tail-cuff BP was recorded at baseline and during 4-weeks treatment with Cmpd17b (50-mg/kg/day, i.p.), the antihypertensive hydralazine (12.5-mg/L, drinking-water), or vehicle. At endpoint, aortic function was assessed by ultrasound imaging, and remodelling, as well as quantitative proteomics. **Results:** Cmpd17b and hydralazine modestly reduced BP to a similar extent, however only Cmpd17b significantly attenuated AAA development (Table). Further, Cmpd17b more effectively limited adverse aortic remodelling (reduced aortic fibrosis and calcification plus elevated elastin, indicative of aortic elasticity and compliance) and ultrasound-derived aortic dysfunction (reduced aortic wall thickness, enhanced distensibility, and strain) in AAA mice (Table). Comprehensive interrogation of the mouse aortic proteome revealed the marked AAA-induced smooth muscle cell (SMC) contractile-to-synthetic phenotype shift correlates with published human data. This phenotype shift is blunted by Cmpd17b (superior to hydralazine). **Discussion:** Our study demonstrated that the FPR-agonist Cmpd17b provides superior efficacy in limiting AAA than BP reduction alone.

Mean±SEM (n=10-15)	Sham+ vehicle	AAA+ vehicle	AAA+ Hydralazine	AAA+ Cmpd17b
ΔBP (mmHg)	0±2	↑28±3*	↑17±4#	↑20±4#
Collagen deposition (%)	33±2	53±3*	46±3#	44±2#
Calcium deposition (%)	0.2±0.1	4.5±0.4*	3.7±0.3	3.1±0.2#
Elastin (%)	43±3	30±3*	38±2#	48±2#$
SMC contractile proteome	-	↓↓↓	↓↓	↓
SMC synthetic proteome	-	↑↑↑	↑↑↑	↑
Aortic diameter (mm)	0.8±0.0	1.3±0.1*	1.1±0.1	1.0±0.1#
Aortic thickness (µm)	109±4	193±11*	163±11#	134±4#$

*P<0.05 vs. sham, #P<0.05 vs. AAA, $P<0.05 between hydralazine and Cmpd17b (One-way ANOVA with Bonferroni correction)

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Simultaneously targeting RXFP1 and RXFP3 improves stroke outcomes in the photothrombotic model

Dr Adriana Knezic

Oral presentation 14: Cardiovascular Theme, Eureka Room 3, December 3, 2024, 2:15 PM - 3:45 PM

Biography:
Dr Adriana Knezic completed her PhD in the Department of Pharmacology at Monash University (in 2023), which focused on the pathophysiology and therapeutic targeting of stroke in several different stroke animal models, and is currently a Postdoc in the Department, under the mentorship of Prof. Chrishan Samuel and A/Prof. Brad Broughton. Her current research is investigating new therapeutics for stroke, including various stem cell-based therapies and compounds that target the organ-protective effects of either the angiotensin II type 2 receptor (AT2R) or Relaxin Family Peptide Receptor 1 (RXFP1). She is currently a member of the ECR Community Engagement Committee of the Monash Biomedicine Discovery Institute, the Hypertension Australia ECR committee and is the secretary of the ASCEPT Cardiovascular SIG.

Simultaneously targeting RXFP1 and RXFP3 improves stroke outcomes in the photothrombotic model
Adriana Knezic[1], Caylie E Moore[1], Charlotte M O Barker[1], Chrishan S Samuel[1], Brad R S Broughton[1]. Cardiovascular Disease Program Biomedicine Discovery Institute, Dept of Pharmacology, Monash University, Clayton, VIC, Australia

Introduction. Stroke is the second leading cause of death worldwide, with treatment limited to approximately 10% of patients. There are two main relaxin receptor subtypes expressed in the central nervous system (CNS): Relaxin Family Peptide Receptor (RXFP)1 and RXFP3. Targeting RXFP1 with the major circulating and stored form of relaxin, human gene-2 (H2) relaxin, improved functional outcomes when given 6 h post-stroke in the photothrombotic (PT) model (Truong et al, 2023). Whilst the neuropeptide, human gene-3 (H3) relaxin, which activates both receptors, limited stroke-induced infarct size when given 30 mins pre-middle cerebral artery occlusion (Bergeron et al, 2015). The effects of targeting RXFP3 alone or in combination with RXFP1 in stroke at a clinically relevant time-point are not known.
Aims. To examine the efficacy of the RXFP3-selective agonist, H3B10-27 (H3B10) alone or in combination with H2 relaxin, as a post-stroke treatment for ischaemic stroke in the PT model.
Methods. Male C57Bl/6 mice (8-10 weeks, n=8/group) underwent PT stroke or sham surgery. At 6 h post-stroke, mice were treated with vehicle (saline), H3B10 (0.2 mg/kg/day) or H3B10 (0.2 mg/kg/day) + H2 relaxin (0.5 mg/kg/day) i.v. Infarct volume was assessed at 72 h after stroke onset and motor function assessed via the hanging wire test at 24 and 72 h post-stroke. Immunofluorescence was used to assess measures of brain inflammation and apoptosis.
Results. H3B10 alone did not improve functional outcomes, however, H3B10+H2 relaxin improved motor function 2.7-fold on the hanging wire test. While both treatments did not influence infarct volume, they did significantly reduce apoptosis by >55%, increase the M2:M1 macrophage ratio by 30%, and decrease neutrophil and T cell infiltration into the brain by >60% ($P<0.05$). Administration of H3B10 also tended to reduce the level of astrocytes and macrophages within the peri-infarct, although this was only significant when administered in combination with H2 relaxin ($P<0.05$).
Discussion. The simultaneous targeting of RXFP1 and RXFP3 produced greater protection against stroke compared to RXFP3 alone. Although H3B10 did not improve motor function according to the hanging wire test, it reduced the adaptive and innate immune response in the brain. Further dose-ranging of H3B10 or the use of more functional tests may be necessary to fully elucidate RXFP3 in stroke. However, RXFP1 remains a promising target for stroke treatment.

Truong et al (2023) Pharmacol Res 187:106611; Bergeron et al (2015) Endocrinology 156:638-646

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AMPK attenuation of β-adrenergic receptor-induced cardiac injury via phosphorylation of β-arrestin-1-ser330

Prof Han Xiao

Oral presentation 14: Cardiovascular Theme, Eureka Room 3, December 3, 2024, 2:15 PM - 3:45 PM

Biography:

Dr. Han XIAO received her M.D. & Ph.D. from Peking University in 2008 and continued her postdoctoral work at the University of California, Riverside, USA, from 2010-2012. Her research mainly focuses on the inflammatory mechanisms of cardiac remodeling and the potential therapeutic strategy. Recently, she mainly focused on adrenergic signaling and cardiac remodeling.

As the first or corresponding author, she has published 40 papers in famous journals, including Circulation Research, European Heart Journal, Circulation, and the British Journal of Pharmacology.

As the chief principal investigator, she has acquired foundations from the National Science Fund for Outstanding Young Scholars, the National Natural Science Foundation of China Key program, and the National Key R & D program. She obtained the CNPHARS-SERVIER Young Investigator Award in Pharmacology (2017), the Chiang Pi-ning award-outstanding Young Investigator Award (2020), and the VCANBIO Award for Innovations and Breakthroughs in Life Sciences and Medicine (2021). She is currently the Deputy Secretary-General of the Chinese Committee of the International Society for Heart Research(ISHR).

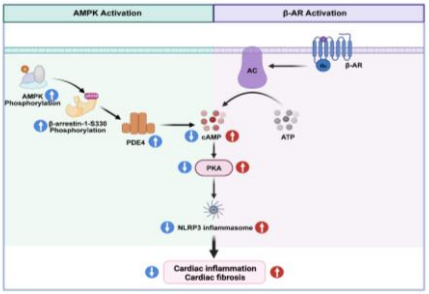
AMPK attenuation of β-adrenergic receptor-induced cardiac injury via phosphorylation of β-arrestin-1-ser330

Mingming Zhao[1], Youyi Zhang[1], John Y-J. Shyy[2], Han Xiao[1].
Department of Cardiology and Institute of Vascular Medicine, Peking University Third Hospital[1], Beijing, China; Department of Medicine, University of California, San Diego[2], La Jolla, CA, USA.

Introduction. β-adrenergic receptor (β-AR) overactivation is a major pathological cue associated with cardiac injury and diseases. AMP-activated protein kinase (AMPK), a conserved energy sensor, regulates energy metabolism and is cardioprotective.

Aims. To explore whether AMPK exerts cardioprotective effects via regulating the signaling pathway downstream of β-AR.

Methods. Using immunoprecipitation, MS, site-specific mutation, *in vitro* kinase assay, and *in vivo* animal studies, we determined whether AMPK phosphorylates β-arrestin-1 at serine 330 (Ser330). Wild-type mice and mice with site-specific mutagenesis (S330A KI/S330D KI) were subcutaneously injected with the β-AR agonist isoproterenol (ISO; 5 mg/kg) to evaluate the causality between β-adrenergic insult and β-arrestin-1 Ser330 phosphorylation.



Results. AMPK activator metformin could decrease cyclic AMP/protein kinase A (cAMP/PKA) signaling induced by ISO. AMPK bound to β-arrestin-1 and phosphorylated Ser330 with the highest phosphorylated MS score. Neonatal mouse cardiomyocytes (NMCMs) overexpressing β-arrestin-1-S330D (active form) inhibited the β-AR/cAMP/PKA axis by increasing phosphodiesterase 4 (PDE4) expression and activity. Cardiac transcriptomics revealed that the differentially expressed genes between ISO-treated S330A KI and S330D KI mice were mainly involved in immune processes and the inflammatory response. In S330D KI mice, the β-AR–activated cAMP/PKA pathways were attenuated, leading to repressed inflammasome activation, reduced expression of proinflammatory cytokines, and mitigated macrophage infiltration. S330D KI mice also showed diminished cardiac fibrosis and improved cardiac function upon ISO exposure.

Discussion. AMPK phosphorylation of β-arrestin-1 Ser330 potentiated PDE4 expression and activity, thereby inhibiting β-AR/cAMP/PKA activation. Subsequently, β-arrestin-1 Ser330 phosphorylation blocks β-AR-induced cardiac inflammasome activation and remodeling.

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Targeting drivers of HFpEF heart failure phenotype in human aortic endothelial cells

Dr Anida Velagic

Oral presentation 14: Cardiovascular Theme, Eureka Room 3, December 3, 2024, 2:15 PM - 3:45 PM

Biography:
Dr Anida Velagic is a Postdoctoral Research Fellow in the Heart Failure Pharmacology Laboratory at the Monash Institute of Pharmaceutical Sciences. Her research focuses on targeting pathways that drive cardiovascular disease development using animal models and human cells. Her research has been published in the American Journal of Physiology-Heart and Circulatory Physiology (featured as 'hot article', 2023), the British Journal of Pharmacology (selected as 'Editor-In-Chief's pick' and highlighted in a Monash University news article, 2022), the Handbook of Experimental Pharmacology (2021), Antioxidants and Redox Signaling (2020), and others. Her work has been recognised by awards from leading international cardiovascular societies including the International Society for Heart Research (ISHR; Student Publication Prize, 2022; Early Career Scientist Excellence Award, 2023) and American Heart Association (AHA; Paul Dudley White International Scholar Award, 2021). She has presented her work at well-attended and highly competitive prize sessions, or as an invited symposia speaker, at conferences hosted by leading national/international cardiovascular and pharmacology societies (AHA; Cardiac Society of Australia and New Zealand, CSANZ; World Congress of Basic & Clinical Pharmacology, WCP; Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists, ASCEPT). Dr Velagic is Co-Chair of the ASCEPT Cardiovascular Special Interest Group (CV SIG), and an Editor for Frontiers in Physiology.

Targeting drivers of HFpEF heart failure phenotype in human aortic endothelial cells
Anida Velagic[1,2], Alex M Parker[1,2], Cristina F Triffon[1], Miles J De Blasio[1], Jarmon G Lees[1,2], Shiang Y Lim[1,2], Rebecca H Ritchie[1]. Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences[1], Melbourne, VIC, Australia; O'Brien Department, St. Vincent's Institute of Medical Research[2], Melbourne, VIC, Australia.

Introduction. Heart Failure with preserved Ejection Fraction (HFpEF) is highly prevalent with poor patient prognosis (5-year mortality >70%), lacking effective treatment options that improve survival. HFpEF patients often exhibit comorbidities such as obesity, diabetes and hypertension. These conditions promote mitochondrial dysfunction, inflammation, fibrosis, and oxidative stress, which drive endothelial dysfunction and HFpEF progression.
Aims. Examine if cardiometabolic stress conditions induce key drivers of HFpEF in human aortic endothelial cells.
Methods. Male human aortic endothelial cells were subjected to 48 h of control media (basal media with 5.55 mM glucose, 14.45 mM mannitol), or cardiometabolic stress conditions (basal media with 20 mM glucose, 0.25 mM palmitate, 0.1 mM linoleic acid, 0.1 mM oleic acid, 10 nM endothelin-1, 1 µM cortisol). Mitochondrial superoxide production was quantified in live cells stained with MitoSOX Red using an Operetta CLS High-Content Analysis System. Gene expression of markers of inflammation (*Icam-1*, intercellular adhesion molecule 1; *Il-6*, interleukin 6), adverse tissue remodelling (*Tgf-β1*, transforming growth factor beta 1; *Ctgf*, connective tissue growth factor; *Timp-1*, tissue inhibitor of metalloproteinase 1; *Mmp-2*, matrix metalloproteinase 2), and oxidative stress (*Nox4*, NADPH oxidase 4) were measured by quantitative real-time reverse transcription polymerase chain reaction (qRT-PCR).
Results. Mitochondrial superoxide production, and gene expression of *Icam-1*, *Il-6*, *Tgf-β1*, *Timp-1*, *Mmp-2* and *Nox4* was ≥1.5 fold higher in human aortic endothelial cells in cardiometabolic stress conditions compared to control media.

Discussion. Human aortic endothelial cells in cardiometabolic stress conditions displayed mitochondrial dysfunction (elevated mitochondrial superoxide production), and upregulated gene expression of markers of inflammation, fibrosis, and oxidative stress. Our findings demonstrate that cardiometabolic stress conditions induce mechanisms implicated in HFpEF in human aortic endothelial cells, highlighting the utility of this *in vitro* model to test novel drug candidates for HFpEF. We are now investigating if therapies specifically targeting mitochondrial dysfunction, fibrosis, inflammation and inflammasome, benchmarked against standard care for heart failure, remain effective under cardiometabolic stress conditions in human aortic endothelial cells, and whether these effects are sex-dependent.

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3D printed tablets for personalised doses of prednisone using selective laser sintering

Mr ZHENG Zheng

Oral presentation 15: New Targets and Approaches, Courtyard Room 1&2, December 3, 2024, 2:15 PM - 3:45 PM

Biography:

Mr Zheng Zheng is a PhD candidate in the School of Pharmacy at the University of Queensland studying under Dr. Jared Miles. Before candidature, he completed a Master of Biotechnology degree from the Australian Institute for Bioengineering and Nanotechnology, University of Queensland. His current research interest includes oral dosage forms production using selective laser sintering technology, which is related to formulation selection, printing parameter optimisation, 3D model design, and post-printing tests.

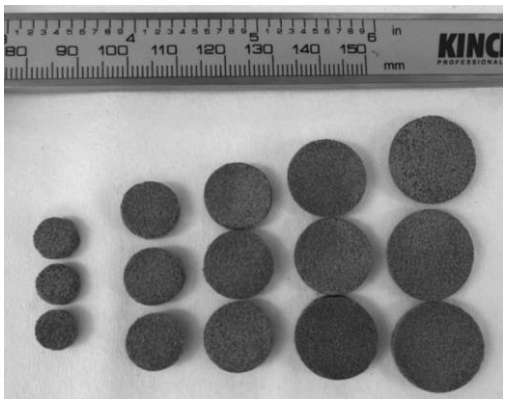
3D printed tablets for personalised doses of prednisone using selective laser sintering

Zheng Zheng[1], Liam Krueger[1], Angus C. F. Harrop[1], Benjamin P. Ross[1], Amirali Popat[1], Jared A. Miles[1]*. School of Pharmacy, The University of Queensland[1], Woolloongabba, QLD 4102, Australia.

Introduction. The recent emergence of three-dimensional (3D) printing in pharmaceutical development has enabled a shift away from standardised medication dosing and towards more precise and personalised medicines and treatments. However, few studies have demonstrated the translational ability of these developments using therapeutic doses of clinically relevant drugs.

Aims. Utilising the steroidal drug prednisone, this study aims to demonstrate the capability of selective laser sintering (SLS) 3D printing to produce custom tablets of various clinically relevant doses with high accuracy.

Methods. A Sintratec Kit SLS 3D Printer was used for powder feedstock printing. Formulation stability, printed tablets' morphology, content uniformity, disintegration and dissolution were tested.



Results. Across the five distinct dosage groups ranging between 5 and 25 mg, the formulation and 3D printing process produced highly accurate and uniform tablets, with less than 6% deviation in weight and less than 4% variation in prednisone content. The SLS printed tablets had a release rate comparable to the commercially available prednisone tablets, with both achieving 100% release within 25 minutes. The formulation also proved to be highly stable throughout SLS 3D printing, confirmed with HPLC, Fourier-transform infrared spectroscopy, differential scanning calorimetry, and thermogravimetric analysis.

Discussion. Utilising a single feedstock formulation for all tablet doses showed that it is feasible to produce customised prednisone tablets by changing the size of the 3D model *in silico*. This proof-of-concept study demonstrated the capability of SLS 3D printing to create therapeutic doses of clinically relevant medications, showing the viability of translation to clinical practice for the provision of personalised medications.

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Modulation of host antioxidant proteins' expression by novel antichikungunya virus agents

A/Prof Anna Krasilnikova

Oral presentation 15: New Targets and Approaches, Courtyard Room 1&2, December 3, 2024, 2:15 PM - 3:45 PM

Biography:
Anna Krasilnikova graduated with a Bachelor of Medicine and Bachelor of Surgery (MBBS) degree and later obtained her MD in Clinical Pharmacology at Volgograd State Medical University (VolgSMU), Russia. After obtaining her Ph.D. in the field of Clinical Pharmacology and Pharmacology in 2004 (VolgSMU) she started as Assistant professor in the Department of Clinical Pharmacology and Intensive Care and later headed the position of the director of Regional Center of Drug Safety Monitoring in Volgograd, Russia. From 2010 till 2023 Dr. Anna Krasilnikova held the position of Assoc. Prof of Pharmacology at the Faculty of Medicine Universiti Teknologi MARA (Malaysia). Since June 2023 she is Associate Professor of Pharmacology, at the department of Pathology and Pharmacology, School of Medicine, IMU University (Malaysia) and adjunct Associate Professor department of Clinical Pharmacology and Intensive care of Volgograd State Medical University (Russia).
Her research interests include experimental and clinical pharmacology of antiviral and antibacterial drugs, ocular Pharmacology and drug development. Currently, she is focused on the investigation of new antiviral drugs against Dengue and Chikungunya virus and antimicrobial peptides. Anna Krasilnikova has more than 30 publications in indexed journals and chapters in books and she presented her research findings at various national and international conferences. She is a member of British Pharmacology Society and Malaysian Society of Pharmacology and Physiology.

Modulation of host antioxidant proteins expression by novel antichikungunya virus agents
Anna Krasilnikova[1,2], Noor Fahitah Abu Hanipah[3,4], Wang Seok Mui[5,6]. Department of Pathology and Pharmacology, School of Medicine IMU University[1], Kuala Lumpur, Malaysia; Department of Clinical Pharmacology and Intensive Care, VSMU[2], Volgograd, Russia; Department of Pharmacology, Faculty of Medicine, UiTM[3], Selangor, Malaysia; IMMB, Faculty of Medicine, UiTM[4], Selangor, Malaysia; Department of Medical Microbiology & Parasitology, Faculty of Medicine, UiTM[5], Selangor, Malaysia; I-PPerForM, UiTM[6], Selangor, Malaysia.

Introduction. The new phenylaminouracil derivatives Z214 and Z364 synthesised at the Department of Pharmaceutical and Toxicological Chemistry (Volgograd State Medical University) previously showed activity against chikungunya virus (CHIKV), which is possibly related to their inhibitory effect on CHIKV-induced oxidative stress.
Aims. To determine protein targets that potentially involved in mechanism of antiviral action of Z214 and Z364 *in vitro.*
Methods. Vero 76 cells were either mock or infected with CHIKV at MOI=1 and when treated with 1% DMEM, 1% DMSO, Z214 (50 µM), or Z364 (100 µM). Protein analysis of supernatant was done using 2D gel electrophoresis and Progenesis same spot software. The proteins found to be significantly up or downregulated were subjected to MS analysis. Subsequently qPCR and determination of several antioxidant parameters were performed. Statistical analysis was performed using ANOVA.
Results. Annexin A2 (AnxA2) and Peroxiredoxin 1 (Prx1) were significantly upregulated in Z214 and Z364 treated Vero cells. A significant increase in AnxA2 and Prx1 genes expression was found at 18-24 hrs at the CHIKV-infected and non-infected cells treated with Z214 and Z364 compared to the non-treated cell and virus controls. CHIKV-infected cells showed significant increased MDA level and SOD activity compared to DMEM and DMSO treated groups. Both Z214 and Z364

significantly reduced MDA levels in CHIKV-infected cells and showed a downward trend in SOD activity, although this decrease was not significant.
Discussion. CHIKV infection causes an imbalance in the redox status of cells. The mechanism of anti-CHIKV action of Z214 and Z364 might be associated with modulation of the host antioxidative activity through the upregulation of annexin A2 and peroxiredoxin 1.

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Using a nano carrier for siRNA delivery to liver sinusoid endothelial cells

Laura Westwood

Oral presentation 15: New Targets and Approaches, Courtyard Room 1&2, December 3, 2024, 2:15 PM - 3:45 PM

Biography:
Lara is a current PhD student at the University of Sydney, working with the Biogerontology Lab at ANZAC Research Institute. Her research focuses on gene therapy delivery methods using nanotechnology as a delivery platform. Her team also focuses on developing nanotechnology platforms for the oral delivery of therapeutic peptides, proteins, antigens and RNA. Lara is also an ambassador at Sydney Nano where she works to utilise transdisciplinary methods and connections to share nanotechnologies' potential in all facets of life.

Using a nano carrier for siRNA delivery to liver sinusoid endothelial cells
Lara J. Westwood [1, 2, 4], Glen P. Lockwood [1, 4], David G. Le Couteur [1, 3, 4], Victoria C. Cogger [1, 3, 4], Maaike Kockx [1, 5], Nicholas J. Hunt [1, 2, 3, 4]. [1] Faculty of Medicine and Health, [2] Sydney Nano Institute, [3] Charles Perkins Centre, The University of Sydney, Camperdown, NSW, Australia [4] ANZAC Research Institute, Centre for Education and Research on Ageing, [5] Atherosclerosis Laboratory, Concord Repatriation General Hospital, Concord, NSW, Australia. Email: lwes2022@uni.sydney.edu.au

Introduction. Small interfering RNA (siRNA) is a repressive molecule that can cause gene inhibition leading to mRNA degradation. It is presently under investigation for use as a therapeutic intervention, however RNA cannot freely diffuse across the cell membrane and requires an efficient delivery system to facilitate uptake that also overcomes any potential for nonspecific off-target effects or immune stimulation. Previously, we utilised silver sulfide quantum dots (QDs) for targeted delivery of medications and peptides to liver sinusoid endothelial cells (LSECs) with no immune recognition.
Aims. Here we aim to demonstrate the effectiveness of the QDs for delivery of bioactive siRNA for their potential use in mRNA targeting therapy.
Methods. In this study, the delivery of GAPDH siRNA using a nano carrier of siRNA conjugated to a quantum dot and coated in various polymers that guide endocytosis, lysosomal determination and cytosolic release, has demonstrated a reduction in GAPDH gene expression following oral administration. In vitro and in vivo studies were conducted with isolated primary Bl6 mice liver cells at varying timepoints and concentrations.
Results. In vitro studies found a reduction in both LSEC and hepatocyte expression of GAPDH following 4, 24 and 48hr siRNA treatment compared to healthy controls, with no toxicity indicated by cell death and cell proliferation assays. In vivo studies demonstrated a dramatic reduction in LSEC GAPDH expression following orally delivered nano siRNA comparable to healthy controls. Gene knockdown of the nano carrier was comparable to a common treatment of galNAc tail vein injection treated mice. Hepatocytes demonstrated minimal GAPDH downregulation in vivo, indicating LSEC specific targeting and delivery.
Discussion. This preliminary work suggests that our nano carrier is a viable delivery agent for gene therapeutics and warrants further investigations.

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Inhibition of CSF1 receptor activation improves cigarette smoke-induced pulmonary and cognitive outcomes (ASCEPT Early Achievement Award for Women)

Dr Simone De Luca

ASCEPT Early Achievement Award for Women and Gillian Shenfield Early Educator Award, Eureka Room 1, December 3, 2024, 4:15 PM - 5:15 PM

Biography:
Dr De Luca is an RMIT University Vice Chancellor Postdoctoral Research Fellow. She completed her PhD in Neuroscience in 2018. Her research focus has been on elucidating how chronic lung diseases such as Chronic Obstructive Pulmonary Disease disrupts cognition and neuroinflammatory profiles in mice.

Inhibition of CSF1 receptor activation improves cigarette smoke-induced pulmonary and cognitive outcomes.
Simone N De Luca[1], Madison Coward-Smith[1], Hao Wang[1], Mehdi Zia[1], Rana Alateeq[1], Alina Akhtar[1], Ross Vlahos[1]. [1]Centre for Respiratory Science & Health, School of Health & Biomedical Sciences, RMIT University, Melbourne, VIC, Australia.

Introduction. Chronic obstructive pulmonary disease (COPD) is a global crisis, ranking as the fifth leading cause of death in Australia. It costs nearly $9 billion annually due to managing comorbidities and acute exacerbations triggered by infections. Cognitive dysfunction affects up to 61% of COPD patients, but the mechanism remains unclear, thus hampering the development of therapeutics. Lung macrophages and neutrophils may reach the brain thereby activating the brains immune cells, microglia causing cognitive impairment. Colony stimulating factor 1 (CSF1) and its receptor (CSF1R) play a role in regulating both macrophages and microglia.
Aims. To investigate the role of CSF1R in pulmonary macrophage-microglia communication, and whether utilising CSF1R antagonists can improve pulmonary and cognitive outcomes in a preclinical model of COPD.
Methods. Male BALB/c mice were exposed to room air or cigarette smoke (CS) for 8 weeks followed by a 4-week treatment with the CSF1R antagonist, GW2580 (75 mg/kg) or vehicle (0.5% CM-cellulose) alongside CS exposure (n=14/group). Recognition and spatial working memory were assessed (novel object recognition test and y-maze) and tissue collected to assess lung inflammation (flow cytometry) and neuroinflammation (immunofluorescence).
Results. CS vehicle mice displayed an increased percentage of interstitial lung macrophages compared to shams (p<0.0001) and GW2580 partially restored the percentage of interstitial lung macrophages although not to sham levels (p<0.0001). CS-exposed mice displayed impairments in both recognition and spatial working memory compared to sham mice (p<0.01) which were reversed by GW2580 treatment (p<0.05). CS exposure led to a robust reduction in hippocampal microglial complexity (p<0.05). Treatment with GW2580 restored microglial complexity with a shift from an “activated” morphology in CS mice toward a surveillant “ramified” morphology similar to sham mice.
Discussion. CS exposure induced pulmonary impairments alongside recognition and spatial working memory deficits like those seen in humans with COPD. A therapeutic treatment with the CSF1R antagonist; GW2580, partially restored pulmonary inflammation, improved recognition and spatial working memory and altered the microglial morphology. Future work will investigate if pharmacological modulation of CSF1R can resolve neuronal alterations.

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Implementing Educational Escape Rooms in Biomedical Science and Interprofessional Education (Gillian Shenfield Early Educator Award)

Dr Iris Lim

ASCEPT Early Achievement Award for Women and Gillian Shenfield Early Educator Award, Eureka Room 1, December 3, 2024, 4:15 PM - 5:15 PM

Biography:
Dr. Iris Lim is an Assistant Professor in Biomedical Sciences at Bond University. Her main research interests focus on investigating the physiology and pharmacology of the lower urinary tract to discover treatments for lower urinary tract disorders. Dr. Lim is also a passionate educator and is particularly dedicated to utilising innovative tools and methods, such as gamification and game-based learning, to enhance student learning experiences and engagement.

Implementing Educational Escape Rooms in Biomedical Science and Interprofessional Education
Iris Lim[1], Centre for Urology Research, Bond Unviersity[1], Gold Coast, QLD, Australia

Introduction. In contemporary education, innovative teaching methods are crucial for enhancing student engagement and learning outcomes. Educational escape rooms are interactive, themed environments where participants solve puzzles and complete tasks to achieve specific learning objectives within a set time (Veldkamp et al, 2020).
Aims. This study explored the application of themed escape rooms in two different educational settings demonstrating how they address specific educational challenges and participant engagement.
Methods. In this study, two different in-person physical educational escape rooms for two different education settings were developed: a room for a neurophysiology subject for biomedical science students and an interprofessional education activity for allied health students including those from the medical, physiotherapy, occupational therapy, nutrition and dietetics and exercise science programs within a private Australian university. In each of these settings, participants completed a survey post-completion of the room and/or debriefed with the facilitator of the rooms regarding perceived learning and effectiveness of the escape room format.
Results. The two educational escape rooms were successfully designed and implemented across 2022 – 2023. The subject-specific room was completed by a total of 92 students while the interprofessional activity involved 621 students. Participants reported that the interactive and immersive nature of the escape rooms was enjoyable and significantly enhanced their engagement and understanding of the material. Moreover, both students and facilitators noted that the escape rooms effectively promoted the development of essential soft skills, including teamwork, communication, and critical thinking. The qualitative feedback from debriefing sessions highlighted that the escape rooms were perceived as a valuable and effective tool for learning, with many participants expressing a desire for more of such interactive learning experiences in their curriculum. In the interprofessional escape room, 100% of students reported a preference for the escape room format over paper-based study.
Discussion. The implementation of educational escape rooms in both settings effectively enhanced student engagement and the development of essential soft skills, proving to be a valuable and preferred learning tool.

Veldkamp A et al (2020) Edu Rev 31:100364