101 Challenges and opportunities in drug discovery

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In the last decade there has been a transformation in the technologies available to the drug discovery scientist to understand disease, to identify novel drug targets and to stratify patient populations. Technologies including Genomics, Functional Genomics and Artificial Intelligence have been adopted to identify and validate novel drug targets. This transformation in our ability to identify novel drug targets with human validation and a direct line of sight to bespoke patient populations has created a major challenge as many of these targets are unprecedented in terms of drug discovery and may be intractable to small molecule discovery. This challenge is being met through advances in the discovery and development of a series of new therapeutic modalities to treat and maybe cure disease. This includes new small molecule modalities including PROTACs, molecular glues and small molecules targeting RNA, the many nucleotide therapeutics from short antisense oligonucleotides to mRNA medicines, many novel protein, peptide and antibody therapeutics and cell and gene therapies. Advances with the creation and development of these new therapeutic modalities are enabling the drug discovery scientist to address highly validated targets that have proven intractable to traditional small molecule discovery, while allowing the drug discovery scientist to progress highly novel targets, with human validation, towards the clinic. Through this innovation we are approaching the situation where the concept of an intractable target can be consigned to the past offering huge opportunity for the treatment of disease. In this presentation I will describe advances in the field in the last decade to address these challenges and how technology is transforming drug discovery

102 Early outcomes of video-assisted education for consumers prescribed oral anticoagulants

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Introduction: Education for consumers prescribed oral anticoagulants (OACs) improves engagement in their management and therapeutic outcomes. Challenges exist for time-poor health professionals in providing effective, efficient, comprehensive, COVID 19-safe education; best practice also recommends a multi-modal approach to education.
Aim: To develop a contemporary OAC consumer education video and evaluate its effect and acceptability in an Australian tertiary hospital.
Methods: Two videos (direct oral anticoagulants (DOACs) [15 min] and warfarin [20 min]) were developed informed by a literature review, expert panel and collaboration with people with lived experience of OAC therapy. Verbal/written OAC education ('standard care') and video-assisted education were compared in a prospective, non-randomised, before/after study involving hospital inpatients newly commenced on OACs. Outcomes evaluated were the change in short-term OAC knowledge using the Anticoagulation Knowledge Tool (AKT), and satisfaction with education.
Results: In the standard care group (n=54; median age 64 years [range: 26-90]; 63.0% male; 66.7% receiving DOACs), verbal/written OAC education was associated with a mean (± SD) increase in AKT score of 29.9% ± 20.1%; while in the video-assisted education group (n=18; median age 64.5 years [range: 31-89]; 61.1% male; 61.1% receiving DOACs), the mean AKT score increase was 31.8% ± 19.2% (p=0.72). Satisfaction with education was high across both modalities (standard care vs video-assisted education) on questions regarding ease of understanding (96.0% vs 100%), ability to inspire confidence in the OAC (94.0% vs 80.0%), and overall satisfaction (98.0% vs 100%) (p>0.05 for all comparisons between the groups).
Discussion: While evaluation of video-assisted OAC education is ongoing, it is reassuring that initial integration of the videos into hospital practice has resulted in equivalent educational and patient satisfaction outcomes to standard care. Future research will focus on confirming these findings, and investigating the potential benefits of the videos in the delivery of efficient, consistent and accessible OAC education.

103 Accuracy of best possible medication histories by pharmacy students: An observational study

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Introduction. The WHO reports that up to 97% of adult patients had at least one medication discrepancy upon hospital admission (WHO, TOC, 2019), with a quarter of the related adverse events being considered preventable (Forster et al, CMAJ, 2004). Medication reconciliation is an effective strategy to prevent medication errors upon hospital admission (Forster et al, CMAJ, 2004) and requires obtaining a patients' best possible mediation history (BPMH) (Meguerditchian AN et al, BMC, 2013). However, obtaining a BPMH is time-consuming and pharmacy students may assist pharmacists in this task (Meguerditchian AN et al, BMC, 2013). Aims. To evaluate the proportion of patients who have an accurate BPMH from the pharmacy student-obtained BPMH compared to the pharmacist-obtained BPMH. Methods. In this 8-week prospective observational study, 6 student-pairs were trained to obtain BPMHs in 2 tertiary hospitals. Students obtained BPMHs for patients taking 5 or more medicines. A pharmacist independently obtained and checked the student BPMH from the same patient for accuracy. Deviations were determined between student-obtained and pharmacist-obtained BMPH. An accurate BPMH was defined as having no-or-low risk medication deviations. Results. The pharmacy students took BPMHs for 91 patients. Of these, 65 patients (71.4%) had an accurate BPMH. Of the 1170 total medicines documented, 1118 (95.6%) were deemed accurate. For the student-obtained BPMHs, they were more likely to be accurate for patients who were older (OR: 1.04; 95% CI 1.03 – 1.06; $p<0.001$), had fewer medications (OR: 0.85; 95% CI: 0.75 – 0.97; $p=0.02$), and if students used two source types (administration and supplier) to obtain the BPMH (OR: 1.65; 95% CI: 1.09 – 2.50; $p=0.02$). Discussion. Pharmacy students may facilitate medication continuity upon hospital admission and reduce medication deviations under the supervision of a pharmacist.

104 Estimating value of a pharmacist-led obstetric medicines information service through user experience

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Introduction. Medicines information services should be routinely evaluated to ensure a robust, evidence-based approach is taken to deliver quality information to the callers and demonstrate value and impact of the service.
Aims. To conduct a user experience survey to identify knowledge, use and value of the King Edward Memorial Hospital (KEMH) Obstetric Medicines Information Service.
Methods. A telephone survey was designed with reference to an informal survey conducted by KEMH, and relevant literature. Users of the service were contacted by author NM within 24 hours of their enquiry. A minimum sample of 180 responses was anticipated based on a sampling protocol and available time. Fixed-response and qualitative data were collected in Qualtrics. Quantitative data were reported descriptively, with verbal feedback analysed thematically.
Results. A total of 181 user surveys were conducted over a three-month period. 66% (n=119) of participants were health professionals, and 34% (n=62) were health consumers. 118 respondents (65%) indicated prior use of the service. All respondents reported that they followed the advice provided, and all found the information either 'very useful' or 'useful'. All users rated the service positively, from three to five on a 5-point Likert-type scale, with 56% (n=101) users indicating a score of four. In the event of the service being unavailable, most health consumers reported the use of health professionals (47%), existing services for medicines information (17%) and Google® (3%). The majority of health professionals (72%) cited the use of current pharmaceutical resources as an alternative source of information. Feedback suggested a need for online capability, a larger social media presence, educational material and increased awareness of the service.
Discussion. The user survey identified high levels of satisfaction with the service and self-reported acceptance of the advice, with all users indicating personal value of the service. Increasing awareness and accessibility of the service to health consumers should reduce risks with self-management of medication, particularly given the increasing volume of open-access and often unverified information.

105 Community pharmacy training for people living with severe and persistent mental illness

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Introduction. People living with severe and persistent mental illness (SPMI) have reduced life expectancy compared to the general population. Community pharmacists, with appropriate training, can help support and manage mental and physical health problems experienced by people living with SPMI. The *PharMIbridge* Randomised Controlled Trial (RCT) was designed to test the effectiveness of a pharmacist-led support service for people living with SPMI.
Aims. The current study reports on the evaluation of the *PharMIbridge* training program, in terms of its impact on participants' knowledge and confidence towards metabolic health, as well as mental health stigma and attitudes.
Methods. Pharmacy staff from 55 community pharmacies across four Australian RCT regions attended training (n=140). Intervention Group (IG) and Comparator Group (CG) participants received Mental Health First Aid (MHFA) training, while IG participants received additional training on physical health, motivational interviewing and goal setting; and participated in simulated patient role-plays. Pharmacists' perceived knowledge and confidence of metabolic screening, and mental health stigma and attitudes were assessed using pre- and post-training surveys.
Results. Confidence and knowledge scores towards metabolic screening improved in IG, compared to CG ($p<0.001$). Both IG and CG participants had less-stigmatising attitudes after training ($p<0.001$). IG participants were more confident and comfortable in providing medication counselling ($p<0.05$) compared to CG, post-training.
Discussion. MHFA training improves mental health stigma. A purpose-designed training package can further improve pharmacists' knowledge about physical health issues and improve pharmacists' confidence in supporting the medication-related and physical health needs of people living with SPMI.
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106 The effect of COVID-19 on pharmacists' role as immunisers

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Introduction. Since 2013, when the Pharmacy Board of Australia determined that vaccination was within the scope of practice for pharmacists, they have progressively become more involved in immunisations, including influenza, measles-mumps-rubella, and meningococcal ACWY. In recent times, pharmacists have answered the call to action to join the COVID-19 vaccination rollout.
Aim. To create a timeline of events as documented by the AJP of the changes in pharmacists' role and evolving responsibilities as immunisers through the COVID-19 pandemic.
Methods. A keyword search was conducted in the AJP for articles tagged with the terms 'pandemic,' 'COVID-19', 'coronavirus' and 'vaccine' from September 2019 (the first mention of pharmacists' potential role in an upcoming pandemic) and July 19, 2022, as articles on COVID became more scarce.
Results. A total of 665 articles were identified, of which 228 were sub-categorised into a separate timeline on immunisation. Legislative and supply issues were the main reasons for pharmacists not being included in the COVID-19 vaccination rollout earlier, causing significant stress to both owner and employee pharmacists. However, the inclusion of pharmacists in the rollout in late 2021 led to many positive outcomes including greater access to vaccines. Pharmacist involvement in the program was followed by changes in provisions for pharmacists currently being able to vaccinate children as young as five years for both COVID-19 and influenza, with the exception of Tasmania and the Northern Territory, where administration of influenza vaccines is restricted to children aged ten and older.
Discussion. Including pharmacists in the COVID-19 vaccination program has enabled them to expand on their role as immunisers. Pharmacists have helped the Australian public reach COVID-19 vaccination goals and are in an advantageous position to help with other vital professional services in the future.

107 Perinatal depression screening recommendations and its implications in primary care

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Introduction. Perinatal depression (PND) affects 10-20% of women globally yet is often unidentified due to a lack of diagnosis and treatment. Screening can identify women at-risk of PND for further assessment however, there is debate in the literature regarding whether PND screening should be administered routinely.
Aims. To identify and compare PND screening recommendations across member countries of the Organisation for Economic Co-operation and Development (OECD).
Methods. A systematic review was conducted across all 37 OECD member countries. Publications providing PND screening recommendations were identified via an online systematic search using PubMed, Google and the Guidelines International Network. Recommendations made by or on behalf of an organisation for an OECD member country were included. Publications written in a language other than English or did not develop their own recommendations were excluded. Recommendations relating to PND screening endorsement, screening timing, frequency, screening tools used, healthcare provider responsible, follow-up and referral were extracted.
Results. Publications (n=21), from 5 countries, Australia, Canada, New Zealand, the United States and United States, were included. Most publications made recommendations in support of PND screening, using the Edinburgh Postnatal Depression Scale (EPDS). However, inconsistencies in screening recommendations across and within countries were found. These inconsistencies included screening timing, frequency and healthcare provider responsible.
Discussion. This systematic review is the first to identify and compare PND screening recommendations across OECD member countries. Inconsistencies in current recommendations highlight the need for the development of clear, evidence-based and standardised recommendations that also define roles of different healthcare providers in PND screening. This will facilitate effective early detection and intervention of PND, including in primary care and pharmacy.

108 Drug Burden Index for deprescribing anticholinergic and sedative medications in older inpatients

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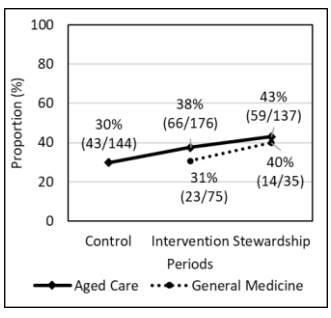
Introduction. The Drug Burden Index (DBI), a measure of a person's total exposure to medications with anticholinergic and sedative effects, may be a useful clinical risk assessment tool to target patients for deprescribing.
Aims. To evaluate how a comprehensive intervention bundle using the DBI impacts on the proportion of older inpatients with at least one DBI-contributing medication dose reduced or ceased on discharge, compared to hospital admission and identify which medications are most frequently deprescribed.
Methods. Inclusion criteria were patients aged ≥75 years admitted to the Aged Care or General Medicine services for ≥48 hours from December 2020 to October 2021 and had DBI >0 at admission to an Australian tertiary referral hospital. In the 'control' period, usual care was provided (only available for the Aged Care service). In the 'intervention', access to a multifaceted intervention bundle was provided, including displaying DBI score in the hospital Electronic Medical Record and deprescribing guides. In the 'stewardship' period, a stewardship pharmacist used the bundle to provide clinicians with individual patient recommendations on deprescribing of DBI-contributing medications.
Results. Overall, 567 patients were included. In the Aged Care service, the proportion of patients with at least one DBI-contributing medication dose reduced or ceased on discharge increased from 30% (control) to 38% (intervention, adjusted risk difference (aRD) = 6.5%, 95% confidence intervals (CI) = -3.2–17.5%) and 43% (stewardship, aRD = 12.1%, 95% CI = 1.0–24.0). The same trend was seen in the General Medicine service (31% in intervention and 40% in stewardship). The most deprescribed DBI-contributing medications during the study period for both services combined were antidepressants (n = 53 medications), followed by opioids (n = 46) and antipsychotics (n = 35).



Discussion. Integrating the comprehensive intervention bundle with an accompanying stewardship program is a promising strategy to facilitate deprescribing of sedative and anticholinergic medications in older inpatients.

109 Polypharmacy and the risk of QT prolongation in hospitalised patients on antipsychotics

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Introduction. Psychotropic polypharmacy is common in patients with mental illness. This can increase the risk of drug-drug interactions and adverse drug reactions (ADR). Psychotropic medications can cause QT-prolongation as an ADR leading to a potentially fatal ventricular arrhythmia called Torsades de Pointes (TdP). Taking combinations of such medications can compound this risk.
Aims. To investigate the difference in the prevalence of QT-prolonging drugs at admission and discharge in hospitalised patients taking at least one antipsychotic medication.
Methods. This retrospective observational study utilised existing inpatient data from three South Australian public hospitals between 1 January to 31 December 2019. Pre-admission and discharge medications were classified as having known, possible or conditional QT-prolonging potential according to the AZCERT classification system. Subgroup analyses comparing patients admitted to acute mental health units with non-acute wards were also conducted.
Results. For patients admitted to acute mental units (n=407), a total of 48 QT-prolonging drugs were used 815 times. Of these, the top five were olanzapine, quetiapine, aripiprazole, paliperidone and mirtazapine. The average prevalence of QT-prolonging medications increased significantly from 1.92 (SD=0.99) pre-admission to 2.01 (SD=1.02) on discharge (p=0.042). In patients admitted to non-acute wards (n=303), a total of 62 QT-prolonging drugs were used 765 times. Of these, the top 5 were quetiapine, risperidone, olanzapine, pantoprazole and furosemide. In contrast with patients admitted to acute mental units, the number of QT-prolonging medications decreased significantly from 2.77 (SD=1.68) pre-admission to 2.48 (SD=1.58) on discharge ($p=4.09x10^{-6}$).
Discussion. The decrease in number of QT-prolonging medicines from admission to discharge in patients admitted to non-acute wards may indicate that the risk of QT prolongation is being appropriately reviewed and managed within hospitals. Similarly, it may be reflective of a general deprescribing trend for medicines. However, the increase in the number of QT-prolonging medicines observed in patients admitted to acute mental units may suggest that these patients require more medications to manage their complex medical needs. Majority of patients in both cohorts were prescribed two or more QT-prolonging medications and patients taking multiple QT-prolonging medications at admission were often discharged with a similar number. This highlights the need for increased review of such medicines while patients are hospitalised. In addition, a majority of the commonly prescribed medications individually carried a conditional risk of causing QT-prolongation. Further research is required to assess how this risk changes when multiple medicines with conditional risk of causing QT-prolongation and TdP are used concurrently.

110 Carer Assessment of medicaTion management guidanCe for people living with dementia at Hospital discharge (CATCH): A national cross-sectional survey

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Introduction. Complexities in medication management for people with dementia is a major contributing factor to adverse events post-hospital discharge. There is limited information on how well guidance on medication management for people with dementia is provided to carers at discharge.
Aims. To evaluate the extent of medication management guidance provided to carers at hospital discharge.
Methods. The CATCH tool was distributed via a cross-sectional survey study. The CATCH tool contains 30 Likert-type items and was developed using content validation and pretesting with carers. Inclusion criteria were formal and informal carers responsible for managing the medications of the person living with dementia. Electronic and hardcopy distribution of the survey occurred across Australia. Data collection started on April 24th, 2022 and is currently ongoing. Quantitative data was descriptively analyzed and Mann-Whitney U and Chi-square tests were used to compare responses between formal and informal carers.
Results. To date, 113 informal carers and 68 formal carers (n=182) participants completed the survey. Most participants (43%) were provided guidance on the day of discharge by the doctor (66%) or nurse (34%) in written form. Over a third of participants (34%) stated that medication management guidance could be improved. Informal carers were significantly more likely to indicate that medication management guidance could be improved, compared to formal carers (38% vs 23%, p=0.038). Overall, the most common medication information provided related to medication purpose (72%), administration instructions (71%) and possible benefits of medications (70%). Informal carers reported insufficient information on drug-drug interaction, as compared to formal carers (23.7% vs 2.9%, p=0.03).
Discussion. Our preliminary findings suggest that informal carers for people with dementia at hospital discharge have information needs that are inadequately addressed to a greater extent, then formal carer information needs. This finding presents an opportunity for intervention.

111 Using electronic prescription and laboratory data to assess prescribing practice

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Introduction. A prescription in an electronic prescribing and administration (ePA) system creates a digital data trail of a treatment decision made by a clinician. Current clinical information relevant to a prescription includes laboratory test results. Linking laboratory and prescribing data allows for investigation of the relationship between a patient's laboratory test results and prescribing decisions. Currently these data sources are not linked, and automated audit reports are constrained to single data silos.
Aims. To link electronic prescription and laboratory data. To illustrate relationships between the two datasets and use this to describe prescribing decisions.
Methods. Prescription data and laboratory test result data from 2018 to 2022 was extracted from the Canterbury District Health Board (CDHB) data warehouse. The prescription data and laboratory test result data were linked by patient, hospital admission and date/time using SQL and a report developed using PowerBI®. The report was validated using dabigatran as a test medicine, and then applied to rivaroxaban and lithium to demonstrate wider applicability.
Results. An interactive report was developed of six graphs showing the relationship of prescribing decisions to laboratory test results. Firstly, initial prescribing decisions such as choice of medicine and dose were related to laboratory test results (such as eGFR) defined in clinical guidelines. Secondly, for specific prescribed medicines, relevant laboratory results used for monitoring were compared with subsequent prescribing decisions. Prescriber decisions in response to the laboratory result were categorised as 'appropriate' or 'inappropriate' by comparing the decision with the guideline recommendations. The report links to the CDHB data warehouse, providing access to near real time information.
Discussion. Prescribing and laboratory data were successfully linked at an individual prescription and test level. Prescribing decisions such as choice of medicine and medication dose can now be compared with guideline recommendations and be rapidly audited at a systems level with minimal further resource. The proof-of-concept report is intended for use by clinical services to monitor and evaluate complex clinical decisions in near real time.

112 Inappropriate prescribing and adverse health outcomes in hospitalised middle-aged and older adults: a systematic review and meta-analysis

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Introduction. Inappropriate prescribing is common in adults with multimorbidity. Middle-aged adults are the largest group of patients with multimorbidity in absolute terms but are often excluded from systematic reviews in this area. The presence of frailty may confer the highest risk of adverse health outcomes from inappropriate prescribing.
Aims. To determine whether hospitalised middle-aged and older adults exposed to inappropriate prescribing are at increased risk of mortality and hospital readmission.
Methods. We are conducting a systematic review and meta-analysis on inappropriate prescribing in hospitalised middle-aged (45-64 years) and older adults (≥65 years). This review will consider multiple types of inappropriate prescribing including inappropriate medicines, prescribing omissions and drug interactions. The outcomes of interest are mortality and hospital readmission. The databases being searched are MEDLINE (OVID), CINAHL (EBSCO), EMBASE, World of Science, SCOPUS and the Cochrane Library. Studies with an accepted measurement of the risk of exposure to inappropriate prescribing relative to a control or comparator group will be included. The risk of bias will be assessed using the Joanna Briggs Institute Critical Appraisal Checklists. Subgroup analyses will be performed for patients with frailty and based on the cause of readmission (e.g. readmission for medicine-related problems). Sensitivity analyses will be conducted to investigate the influence of study design and the tools used to define inappropriate prescribing (e.g. Beers criteria, START/STOPP, MAI, PROMPT, etc.) on the outcomes of interest.
Results. The search was conducted on 21 July 2022. There were 11846 studies imported for screening with 5519 duplicates removed. To date, 2994 studies have been screened by two reviewers with 2807 studies being excluded. There have been 153 full text studies assessed for eligibility with 76 being excluded and 77 being included.
Discussion. This review will identify the definitions of inappropriate prescribing in hospitalised middle-aged and older adults that are associated with adverse health outcomes including for those with frailty.

113 Patient-led gout management: self-monitoring urate by people with gout improves clinical outcomes

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Introduction. Despite safe and effective urate-lowering therapy, such as allopurinol, the management of gout is suboptimal. Negative experiences with gout medications and insufficient feedback on urate control contributes to poor adherence. Whilst several point-of-care urate devices are available, self-monitoring of urate remains uncommon.
Aims. To evaluate a patient-led model-of-care where people with gout use a self-monitoring urate device. Outcomes examined included adherence to allopurinol, attainment of target urate concentrations and gout flare frequency.
Methods. People with gout (N = 30) currently taking allopurinol in rural and urban Australia self-monitored their urate concentration using a point-of-care device (HumaSens2.0plus) at least once monthly for 12 months. Intra-individual urate variance was determined using coefficient of variation (c.v. %, SD/mean). Allopurinol adherence was monitored using medication event monitoring technology (Aardex). Overall adherence was calculated as proportion of days covered, with adequate adherence defined as ≥ 80%. Gout flares were self-reported.
Results. Most participants were male (94%), living in an urban area (55%). Participants monitored their urate on average 18 (IQR 11.5) times per year. Preliminary findings show 75% (IQR 36.7) of urate concentrations for each participant were less than target (≤ 0.36 mmol/L). Intra-individual variability in urate was 14% (IQR 7.3). Attaining urate targets was associated with good adherence (n = 20, P = 0.02). Almost half (n = 13) of participants experienced at least one gout flare, mainly within the first 6-months of self-monitoring. Overall, 20% (n = 6) of participants up-titrated their allopurinol.
Discussion. Patient-led self-monitoring of urate facilitated attainment of target urate concentrations, was associated with good adherence to allopurinol and informed optimisation of urate-lowering therapy. Gout flare frequency was reduced the longer self-monitoring was conducted, coinciding with improved urate control. Further research on the feasibility and cost-effectiveness of this model-of-care for gout management is warranted.

114 Adenosine receptor-mediated cardioprotection post-myocardial infarction in aged rats.

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Introduction. Myocardial infarction (MI) is a leading cause of morbidity and mortality worldwide. Adenosine receptors represent promising therapeutic targets to minimise cardiac damage and pathological remodelling post-MI. However, preclinical models have shown that the cardioprotective efficacy of A_1R prototypical agonists can decrease with advanced age (1). In juvenile rats, the adenosine A_1 receptor (A_1R) biased agonist, VCP746 (2), stimulates cardioprotection, without the dose-limiting on-target effects of hypotension and bradycardia. The cardioprotective efficacy of the biased agonist VCP746 in the context of advanced age, a common MI risk factor, is currently unknown.
Aim. To assess the influence of the cardiovascular risk factor, advanced age, on the *in vivo* cardioprotection and haemodynamic effects mediated by prototypical and biased adenosine receptor agonists.
Methods. Ischaemia (30-min) by left anterior descending coronary artery ligation followed by reperfusion (120-min) was performed in aged (70-72 week old) rats. Upon reperfusion, a single bolus dose of vehicle (10% v/v DMSO), NECA (10 µg/kg; prototypical agonist) or VCP746 (80.8 µg/kg; biased agonist) was administered. Infarct size and area at risk was determined (ImageJ) following staining with Evans blue (5% w/v) and 2, 3, 5-triphenyltetrazolium chloride (TTC, 1% w/v). Blood pressure (BP) and heart rate (HR) were measured using a combined catheter-micromanometer inserted into the right common carotid artery and left ventricle. Statistical analysis performed using GraphPad Prism 9.
Results. When administered upon reperfusion, VCP746 (n=9), but not NECA (n=10), significantly reduced infarct size relative to vehicle (n=8) in aged rats. Whereas NECA significantly reduced BP and HR upon infusion, VCP746 did not mediate significant haemodynamic effects.
Discussion. A_1R biased agonists represent a potential novel approach to stimulate cardioprotection post-MI, in the absence of dose-limiting unwanted effects on BP or HR, in the context of the common MI risk factor, advanced age.

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2. Valant C et al (2014) PNAS 111(12): 4614-4619

115 Interleukin-18 is a critical driver of angiotensin II-induced cardiac remodelling in mice

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Introduction: Heart failure is one of the leading causes of death worldwide and a frequent consequence of hypertension. Hypertensive heart failure is characterised by cardiomyocyte hypertrophy, inflammation and fibrosis, leading to stiffening and impaired diastolic function. Currently, there are no effective treatments for hypertensive heart failure, reflecting our limited knowledge of the disease mechanisms involved. Interleukin-18 (IL-18) is a pro-inflammatory, inflammasome-derived cytokine that is elevated in the circulation of hypertensive patients. However, whether IL-18 plays a role in promoting myocardial remodelling and heart failure is unknown.
Aim: To determine if IL-18-deficient (*Il18*$^{-/-}$) mice are protected from angiotensin II-induced cardiac remodelling.
Methods: Hypertension was induced in male wild-type and *Il18*$^{-/-}$ mice (C57BL/6 background) by infusion of high dose angiotensin II (1.44 mg/kg/d, s.c.) for 28 d via osmotic minipump. Normotensive controls were saline-infused. Systolic blood pressure (SBP) was measured via tail cuff, cardiac fibrosis was assessed by picrosirius red-staining, while cardiac hypertrophy/remodelling was assessed histologically with cross-sectional area of cardiomyocytes and by measuring heart weight:body weight. The left ventricular (LV) systolic and diastolic functions were assessed with in vivo echocardiography.
Results: Baseline SBPs were not different between WT (119 ± 10 mmHg) and *Il18*$^{-/-}$ mice (123 ± 11 mmHg), and angiotensin II evoked a similar degree of hypertension in each strain (158±26 and 166±13 mmHg in WT and *Il18*$^{-/-}$ mice, respectively). Despite having no impact on the pressor responses to angiotensin II, IL-18-deficiency was associated with marked protection against angiotensin II-induced cardiac hypertrophy (7.9 ± 1.1 *cf.* 6.6 ± 0.5 mg/g in WT and *Il18*$^{-/-}$, respectively; n≥7, P<0.01) and fibrosis (6.2 ± 4.3% *cf.* 2.1 ± 0.6% area collagen in WT and *Il18*$^{-/-}$, respectively; n≥7, P<0.01). Furthermore, cardiomyocytes were enlarged and disorganised with hyperchromatic nuclei in angiotensin II-treated WT mice, which were not observed in hearts from angiotensin II-treated IL-18$^{-/-}$ mice. Echo findings suggested that IL-18 deficiency increases LV myocardial performance index, thus increased global LV function.
Conclusion: IL-18 deficiency affords protection against cardiac remodelling during hypertension independent of an effect on blood pressure. These findings suggest that IL-18 signalling, intrinsic to the heart, is a crucial driver of hypertensive cardiac remodelling and a potential target for future therapies.

116 Prevention of heart failure by adeno-associated virus directed expression of neuregulin1beta1

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Heart failure (HF) is a leading cause of death worldwide, and effective treatments for HF are urgently required. A promising therapy undergoing clinical trial is Infusion of the growth factor Neuregulin-1 (NRG-1). NRG-1 activates growth factor receptors on cardiomyocytes (predominantly ErbB4, but also ErbB3) to confer protection. Clinically, NRG1 infusion therapy is limited because the high doses used can cause liver damage, while systemic delivery of a potent growth factor has the capacity to promote oncogenesis. Our hypothesis is that local, cardiomyocyte restricted expression of NRG-1, directed by adeno-associated viral vectors, will provide relief for heart failure but without these off-target issues. We designed and produced an adeno-associated virus (AAV) that instructs cardiomyocytes to express NRG-1-β1 (AAV-NRG1) and tested this virus in P1 neonates. Temporal vein injection of AAV-NRG1 in neonatal mice at P1 resulted in an increase in exogenous NRG-1-β1 expression at P9. This was accompanied by a profound increase in heart size and significant elevations in cardiac function (ejection fraction ~100%). We also assessed the ability of AAV-NRG1 application in the context of heart failure induced by ErbB4 deletion. We hypothesised removal of ErbB4 receptors from cardiomyocytes would abolish the pro-growth effect of AAV-NRG. Simultaneous expression of endogenous NRG1 in cardiomyocytes coincident with ErbB4 deletion rescued heart failure, however, cardiac enlargement is abrogated. We identify ErbB3 receptor upregulation as a potential mechanism of rescue. Together, these data highlight a proof of principle for a safer and restricted method of delivering NRG-1-β1 to cardiomyocytes in vivo. This approach clearly improves cardiac structure and function. Future experiments will examine the utility of AAV-NRG1 in other models of adult heart failure, including hypertension and aging.

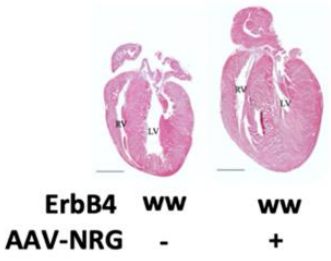

Figure: Enlargement of the heart with AAV-NRG

117 The search for a ligand for the pro-atherosclerotic orphan G protein-coupled receptor, GPR146

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Introduction. The pro-atherosclerotic orphan G protein-coupled receptor GPR146 presents a much-needed opportunity to manage atherosclerosis in treatment-refractory sub-populations such as those with familial hypercholesterolaemia. However, the pharmacology of GPR146 remains poorly understood. It has been proposed that C-peptide, the connecting peptide of proinsulin, is the endogenous ligand for GPR146[1], although these findings have not yet been replicated. Independent studies have now demonstrated that foetal bovine serum specifically activates GPR146[1,2] and further that the active component is contained within the fraction containing species of <3 kDa in size[3].
Aims. 1) To explore the constitutive signalling profile of GPR146. 2) To validate C-peptide as a ligand for GPR146. 3) To validate the proposed activation of GPR146 by serum.
Methods. CRE luciferase, SRE luciferase, NFAT-RE luciferase, and SRF-RE luciferase reporter gene assays were used to investigate the constitutive signalling profile of GPR146 through $G\alpha_s$, $G\alpha_{i/o}$, $G\alpha_{q/11}$, and $G\alpha_{12/13}$, respectively. To test the proposed ligands of GPR146, all possible canonical signalling pathways were tested using G protein reporter gene assays, NanoBiT β-arrestin recruitment assays, and YEN ERK signalling assays.
Results. No constitutive coupling to any G protein was detected. We did not find evidence that C-peptide or serum elicit specific signalling through GPR146 in any assay format investigated.
Discussion. Previous reports of C-peptide- and serum-induced activation of GPR146 were unable to be replicated. It is therefore unlikely that C-peptide is the endogenous ligand for GPR146. Given that serum is a complex biological mixture of variable composition, it is possible that the serum used in this study did not contain the active ligand. This study demonstrates the importance of independent validation of ligand receptor pairings.

[1]Yosten et al. 2013. J Endocrinol.
[2]Yu et al. 2019. Cell.
[3]Han et al. 2020. Cell Res.

118 Novel therapeutic agent to reverse atherosclerotic cardiovascular disease

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Atherosclerotic disease, characterised by development of plaques of fatty material in the inner wall of the arteries, contributes to 18 million deaths globally each year. Most of currently available medications only achieve risk factor reduction by lowering cholesterol, blood pressure, blood glucose levels and platelet adhesion; they do not remove plaques and are not able to treat advanced disease. We develop a first-in-class biologic candidate that shows, tantalizingly, an ability to reverse advanced atherosclerosis. Intravenous injection of this agent accumulates specifically in plaques and correlates with lipid-rich region in tunica media and plaque intima. The drug binding and target receptor expression are also conserved in human plaques. A short treatment in elderly mice with advanced plaque lesions potently reduces lipid-rich plaques, stabilises the lesions and significantly reduces plaque burden. The plaque size post-treatment was comparable to lesions in younger untreated mice. The treatment is safe; this drug does not elicit systemic and tissue toxicity even at doses 5-fold higher than the effective doses. In this presentation, I will discuss the translational pathway that we have planned to use this agent as a new treatment for atherosclerotic cardiovascular disease.

119 Gene expression analyses of Tas1R taste receptors in cardiometabolic disease

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Introduction. The sweet taste receptor (STR) is a family C G protein-coupled receptor responsible for cellular responses to sweet stimuli. The functional heterodimer, consisting of the TAS1R2 and TAS1R3 subunits, localises with the G protein α-gustducin in taste-sensory epithelium. It is commonly reported that these elements of the STR signaling system are present in cardiometabolic tissues, suggesting a role in nutrient sensing and metabolic regulation.
Aims. To use publicly available datasets to compare STR mRNA expression in human pancreas, intestine and adipose tissue, and to determine whether this expression is likely physiologically significant. Next, to identify diseases associated with the STR genes and examine changes in expression in diseased models. Finally, to examine co-expression of taste receptor genes and signaling partners in these same extraoral tissues.
Methods. Human gene expression data was mined from bulk tissue and single cell RNA-sequencing studies. Sequencing counts were extracted as transcripts per million RNA reads (TPM) for TAS1R2, TAS1R3, GNAT3 and control genes including: (1) marker genes ubiquitously expressed in the specific tissues tested, (2) other GPCRs with known physiological roles in the specific tissues tested, (3) other GPCRs with known expression outside the tissues of interest. Expression values of the STR were then compared to studies modelling diabetic tissue expression and rodent tissue expression to account for changes that may be observed in these conditions. An aggregate co-expression network from multiple tissues was then used to assess local and global gene set connectivity between taste-related genes and other functional GPCRs in the tissues of interest.
Results. Gene expression of STR signalling elements in human cardiometabolic tissue rarely exceeded 0.5 TPM, which was negligible when compared to physiologically active genes. This same result was observed in diseased tissues. In rodents, expression of the STR was marginally higher. Taste genes did not show significant co-expression in the extraoral tissues.
Discussion. We found scant evidence for physiologically-relevant STR gene expression levels in human cardiometabolic tissue, suggesting that the STR is unlikely to be a promising target for the treatment of cardiovascular and metabolic diseases.

120 Substances detected in poisoning and non-poisoning related suicides in Australia

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Introduction. Determining the relationship between drug use and suicide is complicated but can help to inform targeted suicide prevention strategies.
Aims. To identify the most common substances and substance classes detected at autopsy and their distribution in poisoning and non-poisoning related suicides.
Methods. We extracted data from the National Coronial Information System for suicides in Australia from 2013-2019. We classified cause of death as poisoning related if any type of poisoning was determined by the coroner to contribute to the cause of death. This included mixed causes of death such as drug toxicity combined with other methods. We extracted all substances detected as per the toxicology reports.
Results. Toxicology was performed on 13,675 deaths. From these, 3,403 (25%) were poisoning related. Prevalence Ratios (PR) for common medicine classes being detected in poisoning related suicides compared to non-poisoning related suicides were: antidepressants (PR 1.95 (95% Confidence Interval (CI) 1.80-2.11)), benzodiazepines (PR 2.61 (95%CI 2.41-2.83)), non-opioid analgesics (PR 2.45 (95% CI 2.25-2.68)) and opioids (PR 4.48 (95%CI 4.1-4.9)). Alcohol was equally prevalent in poisoning and non-poisoning related deaths (PR 1.05 (95%CI 0.96-1.14)), while amphetamines (PR 0.62 (95%CI 0.54-0.72)) and cannabinoids (PR 0.61 (95%CI 0.54-0.69)) were detected more often in non-poisoning related suicides.
Discussion. Both poisoning and non-poisoning related suicide deaths involved a high prevalence of psychotropic medicines or potential intoxication, which emphasises the association between indicators of poor mental health and suicide. Substances with a high involvement in poisoning should be prescribed cautiously, including antidepressants that are toxic in overdose, opioids, and potentially lethal combinations.

121 Unintentional poisoning in older adults: patterns in NSW Poisons Information Centre calls

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Introduction. Unintentional poisoning is defined as inadvertent exposure to substances with potentially harmful outcomes. Poisons Information Centres (PIC) provide risk assessment and management advice for poison exposures to the public and healthcare professionals. Health literacy, age-related changes, and polypharmacy makes medication management challenging in older adults. Moreover, older adults experience worse poisoning outcomes compared to other age groups (Gummin DD et al, 2021). To date, analysis of unintentional poisoning data is US-centric and focused on the paediatric population.
Aims. To explore the patterns of unintentional poisoning in older adults observed in NSW PIC call records.
Methods. A 6-month (January-June 2021) retrospective audit of calls to the NSW PIC involving older adults (≥70y) was conducted. Patient demographics, poisoning circumstances (error type, drugs involved) and outcomes were collected.
Results. 1395 Unintentional poisoning calls were audited. More exposures occurred in women (62%, n=867), at home (74%, n=1032), and were due to therapeutic error (71%, n=989). Patients were exposed to an average (SD) of 2±1.9 substances and 97% (n=1349) of patients used high-risk category drugs. Most patients were advised to monitor at the site of call (78%, n=1087). Of the 15% (n=214) of patients referred to hospital, cardiovascular drugs (38%, n=523), household products (19%, n=259) and centrally acting drugs (18%, n=253) were reported as being involved.
Discussion. This work describes unintentional poisonings in older Australians for the first time. Most presentations were asymptomatic and involved therapeutic errors (e.g. double dosing). These findings provide insight into the spectrum of unintentional poisoning exposures which could guide the development of medication safety interventions. Overall, emphasizing the PIC's role in pharmacovigilance and preventing unnecessary hospitalisations.

Gummin DD et al (2021) Clin Toxicol (Phila) 59:1282-1501

122 The impact of medicinal cannabis legalisation and re-scheduling on poisonings in Australia

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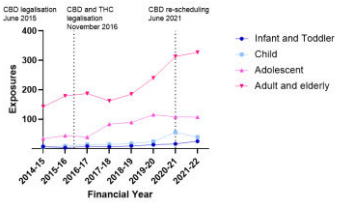

Introduction. The Therapeutic Goods Administration (TGA) has recently re-scheduled cannabis and tetrahydrocannabinols due to the increase in demand for medicinal cannabis. Re-scheduling alters access to cannabis, which could potentially have an impact on harm, including poisonings.
Aims. To evaluate the effect of medicinal cannabis legalisation and re-scheduling on poisonings.
Methods. Time-series analysis of calls regarding cannabis exposures to Australia's largest Poisons Information Centre (PIC), July 2014-June 2022. Joinpoint regression analysis was used to examine whether there were any significant changes in trend (changepoints) and calculate the average annual percent change (AAPC) in exposure calls.
Results. There were 2630 poisoning exposures to the NSW PIC over the study period. Of these cases, 82% (n=2149) were intentional exposures, and 18% (n=481) were unintentional. All age categories noted a rise in exposure calls (Figure). Most (66%, n=1735) were adults (20 years and over), followed by adolescents (15-19 years, 24%, n=619), children (5-14 years, 7%, n=178), and infants and toddlers (<5 years, 3%, n=87) (figure). Joinpoint analysis showed a significant increase in cannabis exposures, with an AAPC of 15.3% (95% CI: 12 to 18%, $P < 0.001$), 2014-15 to 2021-22, with no changepoints detected.
Discussion. There was a significant increase in cannabis exposures in the period after the legalisation. It is important that public health agencies consider applying harm minimisation approaches to limit the impact of cannabis legislation on acute poisonings, especially as legalisation of recreational cannabis continues to be debated.

123 Exposure to ginseng increases oxidative stress and membrane fluidity of ram spermatozoa

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Introduction. Korean ginseng is a common component of traditional herbal medicine, and is included in popular antioxidant supplements, including those marketed as 'fertility-boosting'. Previous studies have indicated that ginseng consumption may increase sperm motility, though there is little research elucidating its effects on other functional or metabolic parameters in sperm.
Aims. This study aimed to elucidate the biochemical changes that occur in ovine sperm after in vitro exposure to ginseng.
Methods. Sperm was exposed to 0, 0.1, 0.5, 1 or 5 mg/mL ginseng in vitro, At 0.5, 3 and 6 hours post-exposure, computer-assisted sperm analysis (CASA) and flow cytometry were used to assess motility, viability, acrosome reaction, membrane lipid disorder, mitochondrial superoxide production, intracellular reactive oxygen species (ROS) and DNA fragmentation.
Results. Despite no change to sperm viability, exposure to all ginseng concentrations significantly increased the production of mitochondrial superoxide across all time points (9.72%± 0.79% n=180 $p < 0.001$), although general intracellular reactive oxygen species (ROS) production was not altered. DNA damage was significantly increased across all time points in cells exposed to 0.5, 1 and 5 mg/mL (7.71% ± 0.39% n= 180 $p < 0.001$). All ginseng concentrations at all time points significantly increased membrane fluidity (19.3% ± 1.51% n = 180 $p < 0.001$).
Discussion. Despite the reported antioxidant activity of ginseng, the increase in mitochondrial superoxide production, and the increase in DNA damage suggests that exposure to these concentrations of ginseng increase oxidative stress in sperm. The higher membrane fluidity of treated sperm suggests potential oestrogenic activity of ginseng, as oestrogen can induce capacitation-like changes. Despite the popularity and perceived safety of herbal fertility supplements, this research indicates they should be used with caution until their effects are further elucidated.

124 Extracellular Vesicle derived biomarkers characterise physiological changes in cytochrome P450 activity

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Introduction. Cytochromes P450 (CYP) are the most clinically important family of drug metabolising enzymes. Understanding variability in CYP activity caused by inherent and environmental factors is critical to evaluating an individual's risk of altered drug exposure and hence requirement for dose adjustment. Recently attention has turned to plasma derived small extracellular vesicles (sEV) as a novel source of biomarkers to characterise differences in CYP activity. This is because EV are shed into the blood and contain cargo that is representative of their tissue of origin.
Aims. This study sought to characterise differences in EV derived CYP abundance associated with pregnancy and non-alcoholic fatty liver disease (NAFLD).
Methods. Liver-derived sEV were isolated from the plasma of pregnant females (n=9) and matched non-pregnant controls (n=3), and subjects with NAFLD (n=14) and matched healthy controls (n=14), using a novel two-step protocol. Liver sEV derived CYP3A4, CYP3A5 and CYP2D6 protein abundances were quantified across pregnancy trimesters (non-pregnant, T1, T2 and T3) and in subjects with different severity of NAFLD (simple steatosis and steatohepatitis; NASH) by liquid chromatography-mass spectrometry.
Results. Differences in CYP expression associated with pregnancy and NAFLD were consistent with reported differences in drug clearance and animal model data. By way of example, non-parametric analysis of liver sEV derived CYP abundance revealed significantly higher CYP3A4 (3.2-fold; $P = 0.003$) and CYP2D6 (3.7-fold; $P = 0.03$) protein expression in T3 versus non-pregnant females. Similarly, liver EV derived CYP3A4 protein abundance was 50% lower in subjects with NAFLD compared to matched healthy controls.
Discussion. Here we demonstrate for the first time that liver derived EV biomarkers recover the impact of two physiological states on CYP abundance and activity. This study builds on recent reports demonstrating that sEV derived biomarkers accurately describe the impact of induction based DDIs on CYP3A4 activity and supports the application of sEV derived markers as a mechanism to track changes in drug metabolising enzyme capacity.

125 Metabolic footprinting in a hollow-fibre infection model: ceftolozane-tazobactam *versus* *Pseudomonas aeruginosa*

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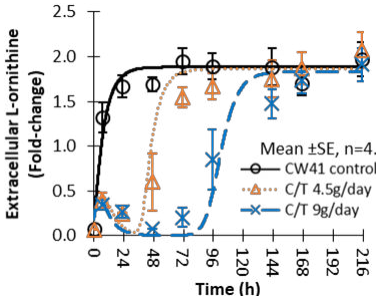
Introduction. Using extracellular metabolites in an *in vitro* PK/PD study like a hollow-fibre infection model (HFIM) could expedite the quantification of bacterial response to antibiotic exposure compared to traditional microbiological culturing protocols. Ceftolozane-tazobactam (C/T) is not yet approved for patients with cystic fibrosis (CF) and relies on off-label dosing regimens.
Aims. To mathematically model the relationship between bacterial response and extracellular metabolites in a HFIM.
Methods. A C/T-susceptible and multidrug-resistant hypermutable *Pseudomonas aeruginosa* CF clinical isolate, CW41, was challenged with C/T concentrations simulating continuous infusions of standard (4.5g/day) and high (9g/day) daily doses in the HFIM for 7-9 days (n=4). Ceftolozane concentrations were confirmed by LC-MS/MS. Total and resistant bacterial populations were quantified and mathematically modelled. Spent supernatant from HFIM was analyzed with untargeted LCMS-based metabolomics, and correlation analysis with bacterial data. Selected metabolites were co-modelled with their respective correlating bacterial population with a PK/PD-based transduction model.
Results. Both doses of C/T provided some killing, then failed with amplified resistance from 48-72h onwards. Secreted L-ornithine (Figure) and assimilated L-arginine highly correlated with the total bacterial population (0.82 and -0.79 respectively, p<0.0001). Ribose-5-phosphate, sedoheptulose-7-phosphate and trehalose-6-phosphate correlated with the resistant subpopulation (0.64, 0.64 and 0.67, respectively, p<0.0001), and were likely secreted as a result of resistant growth overcoming oxidative and osmotic stress induced by C/T exposure.



Discussion. Five extracellular metabolites were well described with mathematical modelling based on bacterial response. This proof-of-concept study suggests further exploration with other antibiotics and *P. aeruginosa* strains is warranted. Ceftolozane-tazobactam should be administered in combination with other antibiotics for CF patients, aligning with current CF treatment guidelines.

126 Accelerating inflammatory resolution to improve endothelial function and vascular health: targeting the non-canonical pathway for NO

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Introduction. Chronic cardiovascular diseases (CVD) are characterised by low-grade systemic inflammation in part due to reduced nitric oxide (NO) bioavailability that is secondary to endothelial dysfunction. Bioavailability of NO can be enhanced by activation of the non-canonical pathway of NO generation, through increased dietary inorganic nitrate consumption.
Aims. We sought to determine whether dietary inorganic nitrate might influence the inflammatory response in models of localised (cantharidin-induced blisters) and systemic inflammation (typhoid vaccine) in humans. Moreover, we assessed whether any effects on inflammatory pathways might impact upon systemic-inflammation induced endothelial dysfunction. Text to begin immediately following the heading and without additional line spacing. Do not bold or underline heading.
Methods. We conducted two clinical trials; Blister-NITRATE and Typhoid-NITRATE respectively to assess these issues.
Results. We show that dietary nitrate attenuates endothelial dysfunction following typhoid vaccine administration and accelerates resolution of cantharidin-induced blisters. Both phenomena are associated with an increased level of pro-resolving mediators consequent to monocyte phenotype switching to an anti-inflammatory phenotype. Moreover, we show that leukocytes of the monocyte lineage express XOR, that likely mediate localised nitrite reductase activity to elevate NO (and cGMP) to drive this process.
Discussion. Inorganic nitrate improves endothelial function in the setting of systemic inflammation. This effect is due to a dietary nitrate-induced pro-resolution effect resulting in an acceleration of the recovery response to an inflammatory trigger. We propose that this pro-resolution activity might be of potential therapeutic benefit in patients with established CVD.

127 Can we identify and correct aberrant NO signalling in clinical circumstances?

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Introduction: Over 30 years from the introduction of the term, "endothelial dysfunction" is not a fully defined or understood disorder. Although it is clear that the vascular endothelium secretes many homeostatic, generally vasodilator, autacoids, most attention remains focused on disorders of nitric oxide (NO) signalling, for example in association with atherogenesis. Furthermore, while there is wide awareness of potential impairment of NO generation, it may well be that the main defect in the NO signalling "cascade" is impairment of tissue responsiveness to NO ("NO resistance"), largely related to oxidative dysfunction of the NO "receptor" soluble guanylate cyclase (sGC).
Methods: Intracoronary injection of acetylcholine (ACh) represents the only commonly utilized means for identifying vascular endothelial dysfunction in the clinical setting. However, the ACh test is not widely utilized, and in general serves only to identify extreme cases of large coronary vessel spasm, whereas it is now clear that vasodilator impairment in small coronary arteries is also of great importance. Furthermore, an abnormal ACh test does not equate specifically to impairment of NO signalling. Furthermore, NO is also an important homeostatic autacoid in other tissues, such as circulating platelets, where it functions to prevent pathological platelet aggregation and resultant thrombus formation.
Results: Combined cardiovascular and platelet studies have shown that NO signalling is impaired at both the vascular and platelet levels in normal ageing and in many cardiovascular disease states, including myocardial ischaemia, heart failure, diabetes, atrial fibrillation and aortic valve stenosis. In all these cases, the predominant cause of impaired signalling is "NO resistance". In patients with angina pectoris, extent of NO resistance is an independent prognostic factor. We have shown that NO resistance may be aggravated, not only by sGC dysfunction, but also via impairment of the synergistic interactions between NO and other anti-aggregatory autacoids such as PGI_2, H_2S and Ang (1-7). Conversely, TakoTsubo ("broken heart") Syndrome, which occurs mainly in ageing women, is associated with supranormal responsiveness to NO, perhaps explaining the increased risk of hypotension and shock in this condition.
Conclusions: Normalisation of defective NO signalling represents an attractive therapeutic target in many forms of cardiovascular disease. Results of therapeutic interventions thus far will be presented.

128 Exploiting NO mechanisms to protect the heart in diabetes and heart failure – the path favouring HNO

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Introduction. The risk of fatal cardiovascular events is increased in patients with type 2 diabetes mellitus (T2DM). A major contributor to poor prognosis is impaired nitric oxide (NO•) signalling at the level of tissue responsiveness, termed NO• resistance.
Aims. To determine if T2DM promotes NO• resistance in the heart and vasculature and whether tissue responsiveness to nitroxyl (HNO) is affected.
Methods. At 8 weeks of age, male Sprague-Dawley rats commenced a high-fat diet. After 2 weeks, the rats received low-dose streptozotocin (two intraperitoneal injections, 35 mg/kg, over two consecutive days) and continued on the same diet. Twelve weeks later, isolated hearts were Langendorff-perfused to assess responses to the NO• donor diethylamine NONOate (DEA/NO) and the HNO donor Angeli's salt. Isolated mesenteric arteries were utilised to measure vascular responsiveness to the NO• donors sodium nitroprusside (SNP) and DEA/NO, and the HNO donor Angeli's salt.
Results. Inotropic, lusitropic and coronary vasodilator responses to DEA/NO were impaired in T2DM hearts, whereas responses to Angeli's salt were preserved or enhanced. Vasorelaxation to Angeli's salt was augmented in T2DM mesenteric arteries, which were hyporesponsive to the relaxant effects of SNP and DEA/NO.
Discussion. This is the first evidence that inotropic and lusitropic responses are preserved, and NO• resistance in the coronary and mesenteric vasculature is circumvented, by the HNO donor Angeli's salt in T2DM. These findings highlight the cardiovascular therapeutic potential of HNO donors, especially in emergencies such as acute ischaemia or heart failure.

129 NO mechanisms to protect the vasculature in stroke

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Introduction. Leptomeningeal collateral vessel flow is a strong predictor of ischaemic stroke outcome. Enhancing collateral flow with nitric oxide (NO) donors is an appealing therapeutic approach. Previous attempts to treat stroke patients with systemic NO donors, such as nitroglycerin (NG), have failed to show patient benefit, most likely due to off-target hypotension which paradoxically may limit collateral blood flow. We have shown that during experimental stroke collaterals have fluid shear stress that is 3-7 times higher (100 dyne/cm^2) than other blood vessels. This unique feature of collateral vessels may provide a way to selectively enhance collateral flow, using nanoparticle aggregates loaded with nitroglycerin (NG-NPAs), that only deliver NO to areas of high shear stress (≥ 100 dyne/cm^2).
Aims. 1. Investigate the effects of systemic "free" NG on blood pressure and collateral perfusion. 2.Determine if NG-NPAs can selectively enhance collateral perfusion and improve stroke outcome without causing hypotension.
Methods. Middle cerebral artery occlusion (MCAo, stroke) was induced for 70 min in male Spontaneously Hypertensive Rats. Changes in cerebral blood flow in the collateral-supplied ischaemic MCA territory were measured by laser speckle contrast imaging. Study 1: Animals were randomised to receive saline (control, n=6) or 4µg/kg/min, of NG (n=6), I.V, 25 minutes after MCAo. Study 2: Animals were randomised to receive blank-NPAs (B-NPA, n=7) or NG-NPAs (also delivering 4µg/kg/min of NG, n=7), I.V., 25 minutes after MCAo. Infarct volume was measured at 24 h.
Results. Study 1: 4µg/kg/min of free NG had no significant effect on collateral perfusion versus control at 40 minutes post-infusion ($p>0.9$), but significantly dropped blood pressure at 40 min post-infusion ($p=0.0065$). Study 2: NG-NPAs significantly increased collateral perfusion relative to B-NPAs at 40 minutes post-infusion ($p=0.026$), without reducing blood pressure ($p=0.99$). NG-NPAs significantly reduced infarct volume at 24 hours ($p=0.005$).
Discussion. Free nitroglycerin induced hypotension and was not an effective collateral enhancing treatment. This may explain the lack of benefit of systemic NG seen in recent clinical trials. However, we have shown that the same dose of NG, when packaged in shear activated NPAs, can selectively enhance collateral perfusion to penumbral tissue without inducing systemic side effects, which resulted in smaller infarcts in this model. Given the known importance of collateral flow, shear-activated NG-NPAs show great promise as a potential therapy for ischaemic stroke patients.

130 Toxicovigilance to identify opioid harms and guide prevention

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Opioid deaths are increasing worldwide but the epidemiology and substances involved varies considerably between jurisdictions. There has been a 50% increase in fatal poisonings in Australia in the past decade, and years of life lost from poisoning now outnumber the road toll. More than half of these deaths were opioid related, including from accidental overdose, recreational use, and deliberate self-poisonings. In the US, fentanyl (mostly illicitly manufactured) is responsible for the recent rise in overdose deaths in the US, with >71,000 deaths in 2021.
The changing nature of the opioid crisis in the past decade underscores need for accurate, timely data on opioid poisonings to guide effective response strategies and evaluate the efficacy of any strategies implemented. The timeliest data available for opioid toxicovigilance is from Poisons Information Centres (PIC). PIC data is coded by pharmacists and recorded at a substance and brand level, which has proved useful for opioid toxicovigilance in the past, e.g. assessing the impact on tamper-resistant oxycodone reformulation on poisonings, and the impact of codeine up-scheduling on poisonings with codeine and other opioids.
Linked data studies that combine pre-hospital, hospital and coronial data are less timely but provide a more complete picture of opioid poisoning. Linked studies reveal prevention opportunities: US patients who survived an opioid overdose were 130 times more likely to die from drug-related causes within the following 12 months.
A data-driven approach is needed to evaluate recent prevention strategies in Australia including real-time prescription monitoring and take-home naloxone.
This session will describe toxicovigilance activities aimed at identifying opioid harms, guiding prevention, and evaluating interventions. A variety of toxicovigilance studies will be presented using various data sources including pre-hospital care, poisons centre, hospital episodes and post-mortem toxicology/coronial data.

131 Improving opioid use for surgical patients

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Introduction. Opioid analgesics are commonly used in hospitals and are often patients first exposure to opioids. To promote appropriate opioid use in hospitals, the Australian Commission on Safety and Quality in Health Care developed the Opioid Analgesic Stewardship in Acute Pain Clinical Care Standard.
Aims. To discuss areas to improve opioid use for surgical patients described in the Standard.
Methods. Surgical patients' journey will be mapped and areas to improve opioid use will be discussed based on recent evidence developed at the University of Sydney. This includes opioid use before admission, during admission, after surgery and at discharge.
Results. Before surgery, chronic use of opioids has a limited role and are associated with increased postoperative pain, length of stay, healthcare cost and risk or persistent opioid use after surgery. Despite this, we identified chronic use of opioids before orthopaedic surgery occurs in 38% (162/430) of patients over five hospitals in NSW. On admission, patients can be assessed for their risk of opioid-related harm. Among 17,886 surgical patients who received opioid analgesics during their hospital stay, risk factors for general opioid-related adverse drug events included older age (Odds Ratio [OR] 1.02, 95% confidence interval [CI] 1.02–1.03) and multiple comorbidities. In terms of medications, both concurrent use of benzodiazepines (OR 1.54, 95% CI 1.35–1.76) and gabapentinoids (OR 1.70, 95% CI 1.48–1.96) were also associated with general ORADEs. After surgery, choice of opioids can affect patient outcomes. Analysis of 16,284 patients show extended-release opioid prescribing was also associated with increased incidence of opioid-related adverse events (OR 1.52, 95%CI 1.35–1.71); length of stay (RR 1.44, 95%CI 1.39–1.51); and 28-day re-admission (OR 1.26, 95%CI 1.12–1.41). After discharge, only 36% (24/66) patients had a documented opioid management plan in their discharge summary. In addition, 41% (27/66) of patients had more than 50% of opioids unused. Most patients (51.5%, 34/66) did not recall receiving any information on signs of opioid toxicity and interactions between opioids and alcohol.

132 Implementation of Take-Home-Naloxone in Community Pharmacies

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Introduction. Naloxone, an opioid antagonist, is a safe and effective antidote to opioid overdose, both when used in healthcare settings and when administered at home. Fatalities due to opioid overdose are preventable with the administration of naloxone, yet opioid-related deaths continue to increase. It appears, naloxone has reached only a small fraction of those in need. Trained service providers may not be contacted by opioid users for fears of arrest or they may arrive too late to resuscitate the individual. Community pharmacists are a promising outlet to increase the education and distribution of free naloxone to the diverse population in need.
Aims. To improve community pharmacists' intentions to discuss and provide take-home naloxone with patients and their peers.
Methods. Design-thinking methods were used to develop messages that mapped to the capability, opportunity and motivation (COM-B) model for pharmacists to discuss and provide take-home naloxone. Key messages were delivered as a short video (3 minute, 40 second) and infographic. Surveys, pre- and post- viewing the materials, were conducted.
Results. Dissemination of the video was a challenge with most participants (n=19/102) not seeing the video prior to viewing the embedded copy in the post-survey. The pre-survey mediation model accounted for 12.5% of the variance in discussing Naloxone, $F(4) = 3.46$, $p = .0110$. The post-survey mediation model accounted for 15.26% of the variance in discussing Naloxone, $F(4) = 4.37$, $p = .0027$. Capability, Opportunity, and Motivation each uniquely predicted Intentions in both surveys. Intentions did not predict discussing Naloxone over and above Intentions in either model.
Discussion. No single strategy will address the diverse multi-level barriers to pharmacists' discussing and dispensing take-home naloxone. However, a short theoretically informed video directly targeting identified barriers showed potential to increase antecedents to changing pharmacists' intentions at engaging in this important harm reduction intervention. The concept holds promise for other healthcare professionals and settings, such as emergency departments and general practices, where knowledge, attitudes and the provision of take-home naloxone could be enhanced.

133 The development of evidence-based opioid deprescribing guidelines

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Introduction. Overprescribing of prescription opioid analgesics is a major international public health problem. Current pain management guidelines provide advice regarding the initiation of opioid therapies, yet rarely address medication discontinuation.
Aims. To describe the development of the first international evidence-based deprescribing guideline for opioid analgesics, and discuss the processes and challenges of opioid deprescribing in clinical practice.
Methods. The guideline was developed in accordance with validated methodologies outlined by the National Health and Medical Research Council (NHMRC) and Bruyere Institute. A multidisciplinary guideline development group was assembled. Qualitative studies were conducted with healthcare professionals and opioid consumers to inform guideline scope and content. Evidence synthesis and appraisal was undertaken, with the certainty of evidence determined using Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.
Results. Three key clinical questions were generated; i) Does deprescribing of prescription opioids compared to continuation result in benefits or harms? ii) What is the evidence of how to deprescribe opioids? and iii) Which interventions are effective in deprescribing opioids? Six evidence-based recommendation and five consensus-based recommendations were developed. Evidence informing recommendations was deemed to be predominantly of low certainty. Extensive public consultation with key professional bodies, consumer organisations and State Health Departments assisted in refining the guideline content and format.
Conclusions. Evidence-based opioid deprescribing guidelines have the potential to optimise opioid use in clinical practice. There is a need to conduct usability testing of the developed opioid deprescribing guideline to optimise dissemination and implementation strategies and to ensure outputs are acceptable and useful for end-users.

134 Hunting Aldehyde-Trapping Drugs: Mechanistic Considerations and their Clinical Potential in ALD

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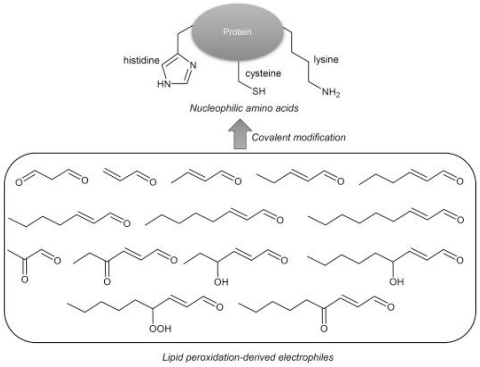
Free radical damage to unsaturated lipids releases a cocktail of oxidised fragments including many unsaturated aldehydes with strong electrophilic character (see image from Shibata and Uchida, 2019). Due to their ready reactions with cell proteins, toxic aldehydes amplify tissue injury in many diseases including various liver disorders afflicting heavy drinkers, a consequence of the oxidative stress accompanying chronic alcohol abuse. For example, the main urinary mercapturate of acrolein - a noxious 3-carbon aldehyde that is a key product of lipid peroxidation cascades - has emerged as a useful biomarker of acute alcoholic hepatitis (Vatsalya et al, 2019).
Knowledge of such pathological roles fuels a rising search for nucleophilic small molecules that trap toxic aldehydes within the body (May-Zhang et al. 2021). Unfortunately, however, progress in this field is hampered by a lack of suitable chemistries to achieve efficient trapping of diverse aldehydes at superior rates that "spare" the most vulnerable intracellular targets for these species. Thus although the hydrazino-based acrolein-trapper hydralazine has exhibited partial efficacy in a murine model of alcoholic liver disease (Chen et al., 2016), this drug remains subject to several liabilities that exemplify the challenges confronting this field of pharmaceutical innovation (Burcham, 2018). This talk will survey our recent work on the "joint toxicity" of complex mixtures of toxic aldehydes as well as the experimental strategy employed during our ongoing search for alternative trappers of such noxious species.



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135 P2X7 receptor antagonism inhibits acrolein-induced bladder damage: potential antidote for cyclophosphamide toxicity

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Introduction. Haemorrhagic bladder cystitis has been reported in 36% of patients undergoing chemotherapy with cyclophosphamide within 24 to 48 hours after treatment. Cyclophosphamide is metabolised in the liver to produce the metabolite acrolein, which is excreted into the urine, causing severe bladder cystitis. There is strong evidence between cystitis and bladder inflammation and the role of purinergic P2X7 receptors in the process of inflammation. Therefore, the question arises: is P2X7 antagonism a possible treatment for bladder cystitis? We, hence, aimed to determine whether the blockade of P2X7 receptors could prevent acrolein-induced urothelial damage.

Methods. An *ex vivo* model of bladder cystitis was established by perfusing acrolein (0.05%) into the whole porcine bladder. The effect of acrolein on the integrity of urothelial cells was explored using an *in vitro* model of urothelial barrier integrity. P2X7 receptor antagonist A804598 (10 nM) was used to determine whether inhibition of P2X7 receptors can protect against cystitis-induced damage to the urothelium in both *ex vivo* and *in vitro* models.

Results. Acrolein showed significant damage to the urothelium structure and tight junction proteins, and markedly diminished bladder contractile responses to acetylcholine. Acrolein also induced cell apoptosis in the mucosa layer in the *ex vivo* model and extreme damage to the urothelial barrier integrity in the *in vitro* model. An important finding of this study was the revelation of the role of P2X7 receptors in acrolein-induced urothelial inflammation and that the blockade of the P2X7 receptor by its antagonist remarkably protected the urothelium from this damage.

Conclusions. This study has provided strong evidence that the P2X7 receptor is involved in acrolein-induced bladder cystitis. Inhibition of P2X7 receptor activity could be a therapeutic target for the treatment of bladder inflammation. For instance, P2X7 antagonists could be co-administered with cyclophosphamide in patients undergoing chemotherapy, thereby protecting them against treatment-associated cystitis.

136 Does the truth lie within the gut? The role of the microbiome and probiotics in Parkinson's disease

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Introduction. Despite being recognised primarily as a motor disorder, gastrointestinal (GI) dysfunction is one of the first symptoms reported by individuals with Parkinson's disease (PD). This is hypothesised to result from a change in microbiota towards an inflammatory, dysbiotic composition. To date, there remains a limited number of studies that have reported an association between altered microbiota composition, GI symptoms, and PD, and it remains to be seen if this association exists within an Australian cohort. Furthermore, there are limited studies on the effect of probiotics in PD.
Methods. This study involved a multi-centre assessment of 167PD patients and 100 healthy-controls from St Vincent's Movement Disorders Clinic (Fitzroy, VIC), the Perron Institute Movement Disorders Clinic (Nedlands, WA), with a subset for the probiotic study. The Gastrointestinal Symptom Rating Scale (GSRS) was employed to measure the frequency and severity of GI-associated symptoms. Clinical and demographic measures, and the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) were undertaken on PD patients. Stool samples were analyzed using targeted sequencing of the V3-V4 regions of 16s rRNA genes.
Results. Results indicate that PD patients have significantly worse GI symptoms (e.g. acid reflux, decreased passage of stools and nausea/vomiting ($p < 0.05$)), when compared to healthy controls. Subsequently, the study identified that both relative abundance and diversity of microbial phyla/genera were significantly different in patients with PD when compared to healthy controls ($p<0.05$). Specifically, *Firmicutes*, *Proteobacteria* and *Verrucomicrobia* were all increased within PD. Reduced microbial diversity was significantly associated with greater disease and GI symptom severity.
Discussion. Consequently, this suggests that worse GI symptom presentation and severity in PD patients could be due to an altered microbiome composition and reduced diversity. Furthermore, as GI symptoms are one of the first to present, these results provide evidence for the use of the GSRS assessment to identify early symptoms in PD patients, and further explores the gut-brain connection in the progression and management of this disease

137 Getting to the guts of polyherbacy: the role of herbal interactions & cytotoxic development in at-risk organ models

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Introduction. Herbal polypharmacy (polyherbacy) is a common practice in traditional medicine. Polypharmacy is a well-documented concern with conventional medicines, however with the hundreds of potentially pharmacologically active constituents present in herbal products, polyherbacy can lead to unpredictable herb-herb interactions.
Aims. Organ tissues involved in the metabolism of herbal products are at risk of herbal interactions. Hepatotoxicity and nephrotoxicity are often investigated, but the effect of products on the gut epithelium is rarely investigated. This study sought to elucidate the impact on individual and combined herbal products on at-risk organ tissue models.
Methods. Caco2, HepG2 and BHK-21 cells were used as models of at-risk organs. Common herbal products and their common phytochemical were investigated: *Astragalus propinquus* (astragaloside IV – AST-IV), *Atractylodes macrocephala* (atractylenolide I – ATR-I) and *Psoralea corylifolia* (psoralen). MTT colorimetric assays were used to determine cell viability. AST-IV/ATR-I tested at 0-300µM, psoralen at 0-1000µM, herbal products at 0.1mg/ml-5mg/ml.
Results. Greater toxicity was observed to psoralen in BHK-21 cells (55%) compared to Caco2 (40%) and HepG2 cells (45%) (1000µM), while AST-IV and ATR-I showed minimal toxicity in all cell lines. AST-IV combined with previously non-toxic concentrations of psoralen decreased viability in HepG2 (21%) and BHK-21 cells (34%). Similar increases in toxicity were observed with combinations of ATR-I with psoralen, but only HepG2 cells were significant ($p<0.05$). Combinations of AST-IV (100 µM) with ATR-I showed little effect. *P. corylifolia* showed toxicity across all cell lines, with BHK-21 showing up to 82% viability loss at 5.0 mg/ml ($p<0.0001$). *A. propinquus* showed a similar pattern but was less toxic overall. *A. macrocephala* demonstrated toxicity at 3.0 mg/ml and 5.0 mg/ml in HepG2 and Caco2 cells ($p<0.05$). Combinations of *A. macrocephala* and *A. propinquus* showed no significant interactions or toxicity. *A. propinquus* showed additive interactions with *P. corylifolia* (0.1 mg/ml) in HepG2 cells and synergistic interactions in Caco2 cells at 5.0 mg/ml ($p<0.05$) but no significance in BHK-21 cells. *A. macrocephala* showed additive effects with *P. corylifolia* (0.1 mg/ml) in Caco2 cells, but synergistic interactions in BHK-21 cells at 3.0 mg/ml and 5.0 mg/ml ($p<0.05$).
Discussion. This study demonstrates the complicated nature of herbal interactions, indicating the diverse potential for localised and systemic toxicity to herbal products

138 An inquiring mind: Embedding a research culture in an undergraduate program

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Introduction. In 2017, Monash University launched a newly designed pharmacy Vertically Integrated Masters (VIM) program. One of the central components of the VIM was establishing a scaffolded research training program to support pharmacy graduate research competency development.
Aims. To evaluate the perceived impact of a pharmacy student scaffolded research training program.
Methods. Research skills teaching is scaffolded across the 5-year VIM to progress students from knowledge development to research skill application at increasing degrees of independence. Students complete a year-long internship in the final-year (i.e. interns) and are tasked to lead an individual research project relevant to their workplace. Interns in 2021 were asked to complete a voluntary anonymous survey to evaluate their experience completing the research training program, the impact on their research skills and any perceived barriers to research.
Results. In 2021, 183 interns completed the research training program with 55% (101/183) completing a project in a hospital setting and 45% (82/183) in a community pharmacy setting. Of the Interns who have completed the program, 52% (n=96/183) completed the survey. Of the survey respondents, 93% (n=89/96) agreed or strongly agreed that the program helped develop their research skills, 78% (n=75/96) felt confident to undertake further research, and 99% (95/96) selected that conducting research was important to pharmacy practice. Of the 83% (80/96) respondents experience at least one barrier to research, the most common barriers reported were lack of time to complete project at 64% (51/80) and lack of workplace support or direction at 41% (33/80). Of note, respondents were permitted to select more than one perceived barrier to research.
Discussion. The results of this study suggest that the scaffolded program had a perceived positive impact on intern research skill development. Variation in the degree of research mentorship received at the workplace may in part account for the reason why some interns reported a lack of confidence undertaking further research as “lack of workplace support” was a commonly perceived barrier. Training in research mentorship for workplaces is a potential area of growth for the program. This program may serve as a model for other institutions seeking to support pharmacy graduate research competency development.

139 Implementation of an innovative flipped-model and longitudinal experience to enhance research training

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Introduction. The attainment of fundamental research skills is imperative to advancing the pharmacy profession. Research training is an important component of student and postgraduate residency training; however, numerous barriers exist in operationalizing high-quality student or resident research training programs. Our institution has developed and implemented the flipped residency research model for postgraduate residency training and a longitudinal research pathway for pharmacy students.
Aims. To describe the design, implementation, and initial impact of the flipped residency research model and a pharmacy student research and scholarship training pathway.
Methods. The flipped residency research model modifies the research timeline to better align research activities with residents' abilities at specific time points during the year. The Research and Scholarship in Pharmacy (RASP) pathway was designed to create a longitudinal, selective pathway within a PharmD curriculum. Retrospective multi-methods analyses were used to evaluate the impact and perceived value from the residents and students.
Results. The flipped residency research model provided improvements in several areas pertaining to the research process, Including improved institutional review board efficiency and an increased publication rate. Residents who participated in the flipped residency research model self-reported increased comfort with study design, implementation, manuscript development and submission, and biostatistics. Fifty students completed the RASP pathway in the first two cohorts. Thirty-eight (76%) students presented an abstract derived from their project at a national meeting. The exit survey revealed positive student perceptions regarding the value and satisfaction of RASP. In the first cohort, 10 (40%) students published an original research manuscript within one year of graduation.
Discussion. The modified research timeline of the flipped residency research model better aligns research activities with resident experiences and abilities. The RASP pathway feasibly and effectively provided a mechanism for students to engage in a faculty-mentored longitudinal research experience within a PharmD curriculum that promoted skill development and opportunities for scholarship. Initial implementation of both programs demonstrated high rates of scholarly output and high value by residents and students.

140 Students as Reviewers: Using a Near Peer Review Process in World's first Pharmacy Student Research Journal

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Introduction. The Australian Pharmacy Students' Journal (APSJ), first established in January 2022, is a student-led journal. The APSJ provides the opportunity for students to experience the process of peer-reviewing.
Aim. To evaluate the student perception of a near-peer review process for a pharmacy student journal.
Method. Students and academics are invited to join a pool of reviewers for the APSJ by virtue of an expression of interest. Students must undergo the reviewer training to be eligible to undertake the role and are provided a "Reviewer Guide". Each article is reviewed by two student reviewers and one academic reviewer. In September 2022, student reviewers were invited to complete an anonymous online survey to evaluate their experience. Respondents were asked to rate elements of their experience across a 5-point Likert scale and were asked to respond to open-ended questions about attributes of the program and potential improvements.
Results. Between 04.07.2021 and 14.04.2022, 31 students have completed training and 18 have been reviewers. Of the student reviewers, 83 % (15/18) completed the survey, 53% (8/15) were from fourth year, 27% (4/15) were from Intern year, 20% (3/15) were from third year. Mean (SD) score perceptions (out of 5) were positively skewed when asked if the experience was valuable (4.29 +/- 1.16), supported research skill development (4.29 +/- 0.7), and enhanced peer review process understanding (4.57, +/- 0.62). Survey participants reported an average score (mean, SD) of 3.57 (+/- 0.9) (out of 5) when asked if they felt prepared for the role of reviewer. When asked what the student gained from the experience of the reviewer, the common themes were an improvement in research skills and insight into the peer review process. When asked what improvements the respondent would suggest for the process, the common themes were requests for exemplar reviews and further instruction about how to provide authors feedback.
Discussion. Student respondents who participated in the peer review process found the experience improved their research skills. However, less students felt prepared for this role suggesting a requirement to improve training. Student-led journals have had positive impacts on academic performance. However, this is the first time to our knowledge that the perceived impact of the student peer-review process has been investigated. The peer-review process is a potentially useful model to assist student research skill development.

141 Leveraging partnerships to drive innovation in research skills teaching and learning

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Background. Research and inquiry skills are crucial aspects of work in the healthcare and health science professions. Providing students with scaffolded, accessible and applicable experiences of research is essential to embedding research culture in the health professions.
Summary of presentation.
This presentation will describe two innovative approaches to research skills teaching and learning achieved through local and international partnerships. A Faculty Education Innovation grant funded a team of pharmacy and pharmaceutical science academics at Monash University to develop a teaching and learning tool using mind mapping to enhance undergraduate and postgraduate students understanding of research concepts. An international multidisciplinary collaboration supported by the Monash-Warwick Alliance co-created a suite of online training materials to assist students to develop knowledge in the theory and practice of quality improvement. Using different approaches, each project partnered with students in the development of the resources. Both collaborations produced flexible, asynchronous online learning resources during a time when the pandemic meant more traditional classroom learning was not always possible. At Monash University both resources have been embedded into the scaffolded research training program for pharmacists across the Vertically Integrated Masters and Masters of Clinical Pharmacy.
As well as showcasing the resources, this presentation will share the experiences and learnings of the teams to support others to successfully leverage partnerships to drive innovation in research skill teaching and learning for the healthcare and health science professions.

142 A community pharmacy osteoporosis screening service; an implementation science approach

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Introduction. Osteoporosis and poor bone health affects a significant proportion of the Australian population. Yet over 60% of Australians have misconceptions about it and a 50% don't take their osteoporosis medications as prescribed. Raising awareness of and screening for osteoporosis are part of the National Strategic Action Plan for Osteoporosis. Various public health interventions have been attempted to combat this increasingly prevalent condition with various degrees of efficacy. Implementation science approaches are used to reduce the gap between research and practice.
Aims. To describe the development and implementation of community pharmacy screening for osteoporosis and the barriers and facilitators in its implementation.
Methods. A pilot screening service was initially developed, informed through application of the literature and semi structured interviews with pharmacy stakeholders including patients, pharmacists, and pharmacy staff. A convenience sample of community pharmacies were then invited to implement the screening service via social media advertising and networks and training was provided. Stakeholder interviews were held throughout the implementation process. Several iterations of development were used, allowing for comparison between implementation strategies. The implementation process was documented and evaluated using the REAIM (reach, effectiveness, adoption, implementation, maintenance) framework.
Results. 16 community pharmacies were recruited and commenced a screening service. 191 pharmacy consumers (average of 11.9 people/pharmacy) were screened for osteoporosis during the study period (1 week in each pharmacy). Interviews were conducted with stakeholders throughout the project. Participants reported that osteoporosis was not a major disease that pharmacists often focused on, however, both patient and pharmacist participants felt like that it is important and that community pharmacies are suited towards screening. Most pharmacists reported time, remuneration, and COVID were major barriers to implementation.
Discussion. Consulting stakeholders is an important part of developing new pharmacy services to ensure an intervention's success. This study gathered insights into the current state of pharmacy knowledge and practice around osteoporosis and may assist future service development. More studies are underway to measure impact on outcomes.

143 Clinicians' Perspective of the Opioid Analgesic Stewardship in Acute Pain Clinical Care Standard

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Introduction. Opioid analgesics are high-risk medicines, widely used in hospitals to manage pain. To improve the use of opioids in Australia, The Australian Commission on Safety and Quality in Health Care released the first national Opioid Analgesic Stewardship in Acute Pain Clinical Care Standard.[1]
Aims. To explore clinicians' perspectives of the implementation of the Opioid Analgesic Stewardship in Acute Pain Clinical Care Standard to understand factors that may impact this process.
Methods. Qualitative one-on-one interviews were conducted with clinicians, including doctors, pharmacists, nurses, and patient safety officers. The interview guide was developed based on the Consolidated Framework of Implementation Research. Interview transcriptions were thematically analysed to identify common themes.
Results. In total, 30 clinicians were interviewed, including 6 doctors, 12 pharmacists, and 12 nurses from 21 sites across Australia. Themes identified included (i) attitude towards the Standard, (ii) evidence supporting the Standard, (iii) education on the Standard, (iv) organisational support and resources, as well as (v) impact of COVID-19. Clinician recommendations to improve implementation included benchmarking, collaboration across different health districts, and ancillary frameworks to the standard.
Discussion. Barriers to implement the standards exist at both the individual and system level. These include clinician attitude and knowledge of the standard, levels of organisational support and available resources, as well as increased pressure on the health system following the COVID-19 crisis. This study additionally identifies potential strategies to overcome these barriers including mandating the standards, clinician education, and increased investment of hospital leadership in the standards to improve implementation and provide additional resources.

[1]Australian Commission on Safety and Quality in Health Care (2022) Opioid Analgesic Stewardship in Acute Pain Clinical Care Standard – Acute care edition. Sydney, ACSQHC.

144 Persistence with oral anticoagulant therapy in people with atrial fibrillation: a cohort analysis of general practice data

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Introduction. Oral anticoagulants (OACs) are important to reduce the risk of ischaemic stroke in people with atrial fibrillation (AF). Although patients need to continue their OAC to achieve this benefit, little is known about persistence with anticoagulant therapy in Australia.
Aims. The study aimed to investigate the rate of OAC non-persistence in the first 12 months of use and its predictors in patients with AF, using national data from Australian general practices.
Methods. We analysed data obtained from the NPS MedicineWise dataset, MedicineInsight. We included patients with a recorded diagnosis of AF who newly initiated an OAC between 1 January 2013 and 30 December 2017. Persistence with therapy was defined as continued prescription of any OAC within 60 days after the exhaustion of the previous prescription. The follow-up period was 12 months post-initiation. Predictors were assessed using logistic regression.
Results. Of 16,075 patients (47.3% females) with a mean age of 74.6 ±10.2 years, 27.9% were initiated on warfarin, 10.3% dabigatran, 32.2% rivaroxaban, and 29.6% apixaban. Overall, 2,116 (13.2%; 95% confidence interval [CI] 12.6-13.7%) patients were potentially non-persistent within 12 months of initiation. The non-persistence rates for warfarin-, apixaban-, dabigatran- and rivaroxaban-users were 18.3% (95% CI 17.2-19.5%), 10.1% (95% CI 9.2-11.0%), 10.9% (95% CI 9.4-12.5%) and 12.2% (95% CI 11.4-13.2%), respectively. The rate of non-persistence with direct-acting OACs (11.2%) as a group was lower than for warfarin ($p < 0.001$). Factors that increase the risk of stroke (e.g., older age, hypertension, diabetes) were associated with better persistence, as was a higher CHA_2DS_2-VASc score and lower ORBIT bleeding risk score.
Discussion. Over 10% of patients were potentially non-persistent with OAC therapy within 12 months. Positively, persistence was higher for patients most at risk of stroke. It was also higher in those prescribed direct-acting OACs rather than warfarin, perhaps indicating their relative ease of use.

145 An investigation of mobile respiratory function testing in Western Australian communities

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Introduction. Lung function testing, such as spirometry, is an essential component in the diagnosis and appropriate management of chronic obstructive pulmonary disease (COPD) and asthma, although it may be difficult for regional residents to access. Many General Practitioner (GP) surgeries have spirometers but uptake and use is low. Alternative referral pathways are private respiratory laboratories, some of which offer mobile clinics.
Aim: To investigate the potential benefits of a mobile respiratory function testing service in Western Australia (WA).
Methods. Individuals >18 years who attended a mobile lung function testing clinic in 2021 in WA, at two metropolitan (Carine, Rockingham) and two regional (Narrogin, Busselton) sites were invited to complete a baseline and 6-8 week follow-up questionnaire.
Results. Questionnaires were completed by 59/74 (79.7%) respondents. Most were female (35/59; 59.3%); mean age was 62.5 ± 14.2 years. A history of asthma was reported in 50.9% (30/59), COPD in 18.6% (11/59) and both asthma and COPD in 13.6% (8/59). All 30 respondents with asthma had experienced asthma symptoms in the past 12 months; only eight (26.7%) had an Asthma Action Plan. At baseline, most (22/30; 73.3%) had Asthma Control Test (ACT) scores £19 (mean 16.6; range 8.0 – 25.0); at follow-up 16/31 (51.6%) had scores £19 (mean score 18.0; range 6.0 – 25.0). Following lung function testing, 13 respondents indicated they had COPD. Of the 11 diagnosed with COPD at baseline, the mean Clinical COPD Questionnaire (CCQ) and COPD Assessment Test (CAT) scores were greater at follow-up (CCQ: 1.9 vs 2.3; CAT: 10.3 vs 14.7), reflecting a worsening of disease. Most respondents (57/59; 96.6%) were satisfied with the lung function testing experience and would recommend the service to others (57/59; 96.6%).
Discussion. Although most participants had poorly controlled asthma, many perceived their asthma to be well-controlled. Greater awareness of the mobile lung function testing service is needed. Optimisation of treatment for lung disease requires correct diagnosis and where poorly managed, appropriate therapy should be reviewed and symptoms monitored. GPs should be educated on the importance of Asthma Action Plans to empower their patients to achieve better control of asthma symptoms and reduce the potential risk of hospitalisations.

146 Delirium, length of stay and antidepressant withdrawal in an intensive care unit

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Introduction. Antidepressant withdrawal can cause serious complications easily confused with delirium and other health concerns.
Aims. To determine if the prescribing and administration practices for antidepressants to invasively ventilated patients had a measurable impact on length of stay and diagnosis of delirium in an ICU.
Methods. This retrospective drug use evaluation study evaluated the prescribing and administration of antidepressants to invasively ventilated patients over one year at a four hundred and eighty-four-bed public district hospital. The doses were compared to the Australian guidelines, and the length of stay and delirium scores were calculated. All invasively ventilated patients in the year studied were divided into two groups; those prescribed antidepressants in the 30 days before admission (Group 1) and those not on antidepressants on admission (Group 2) to ICU.
Results. A total of 210 patients were included in the study, 74 in Group 1 (and 136 in Group 2. Of those in Group 1 only 6 (8%) had their antidepressant continued. Of the remainder 52 (70%) had their antidepressant stopped and 16 (22%) had it withheld. Patients not given their antidepressants experienced increased rates of delirium and increased lengths of stay (Table).
Discussion. The results suggest an area of potential improvement in antidepressant prescribing and administration. However, multiple confounding factors may explain these associations. Therefore, further study, with a larger sample size and more complex design, is required to fully determine if antidepressant withdrawal contributes to the delirium.

Antidepressants	Length of stay (days)	% with positive CAM ICU
Withheld	12.19	81%
Stopped	8.56	73%
Continued	5.67	67%
No Antidepressant	6.47	34%

147 Patient-led gout management: people with gout's perspectives on self-monitoring their urate

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Introduction. Despite access to safe and effective urate-lowering therapy, management of gout is suboptimal due to poor medication adherence and a failure to up-titrate therapy to attain target urate concentrations. Self-monitoring of urate using point-of-care devices may improve adherence to allopurinol and attainment of target urate concentrations.
Aims. To understand the perspectives and opinions of people with gout who have experience in self-monitoring of urate using point-of-care devices to inform gout management.
Methods. Semi-structured interviews (median 36 min 38 s) were conducted with people with gout (N = 30) across Australia. Participants self-monitored their urate (HumaSens2.0Plus) for 12 months. Interviews focused on device usage and how self-monitoring could impact their gout care. De-identified verbatim transcripts were thematically analysed.
Results. Participants found urate self-monitoring straightforward. They reported that self-monitoring urate affirmed the effectiveness of their medication. Participants were able to assess the effect of their behaviour (e.g., medication adherence and diet) on their urate control, with high urate concentrations triggering behaviour changes or discussions with their healthcare provider. Participants considered self-monitoring particularly useful for people with uncontrolled or recently diagnosed gout. Most participants wanted to continue self-monitoring, either at home or at a pharmacy. Rural participants considered self-monitoring efficient, reducing the need to travel for pathology collections.
Discussion. Patient-led self-monitoring of urate was perceived to reinforce the effectiveness of urate-lowering therapy, thereby encouraging adherence to allopurinol and facilitating shared-decision making with their healthcare professional. This model-of-care was reported to be convenient, particularly for people with gout living in rural regions, reducing travel requirements to access healthcare services. Further research is required to assess the cost-effectiveness and feasibility of implementation nationally.

148 Innovation and entrepreneurship – Are pharmacy students ready?

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Introduction. As the role of pharmacists continues to evolve and expand, a level of entrepreneurship is required to expand current pharmacy practice models and drive sustainable growth for the profession (Medina et al, 2013). While a strong clinical background is essential, it does not fully equip pharmacists with the skills or mindset to innovate and adapt to new challenges (Scahill et al, 2022). There are multiple gaps in the Australian healthcare system, in which pharmacists has the potential to contribute and improve.
Aims. To promote and evaluate pharmacy students' ability to develop healthcare business plans.
Methods. This is an observational study utilising quantitative and qualitative data.
Results. It was observed that a small proportion of students' proposals had decent merit and potential; some were creative but lacked logistics; and majority were restricted to a single dwelling community pharmacy. Despite encouragement to consider the wider sector of healthcare no students proposed a business plan outside the community pharmacy setting. Students were observed to be overwhelmed and required a large amount of mentoring for this task. Students feedback also indicated a lack of readiness to develop creative and innovative health service models.
Discussion. From our observation, pharmacy students require extensive support to step outside the traditional roles of pharmacist. With a rising demand for health service with innovation and entrepreneurship skills, greater inclusion of business content will be needed in the pharmacy curriculum. However, there is currently no consensus on best practice for entrepreneurship education in terms of curriculum content and methods of teaching (Sirelkhatim et al, 2015). If entrepreneurship is to be taught in pharmacy, further research is needed to evaluate the effectiveness of different approaches in delivering entrepreneurship education in pharmacy.

Medina MS, et al (2013) Am J Pharm Educ 77(8):162
Scahill SL, et al (2022) Curr Pharm Teach Learn 14(1): 5–12
Sirelkhatim F, et al (2015) Cog Business Manage. 2015;2(1):1052034

149 Core concepts in pharmacy: do they know what they need to know?

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Introduction. Over the past thirty years the identification of core concepts required for discipline-specific learning has helped to drive the development of focussed curricula. These initiatives have largely been driven by the recognition that students were graduating without a deep understanding of the fundamental knowledge expected for their discipline of study. Most recently a group of ASCEPT educators have developed core concepts for the discipline of pharmacology as a first step towards informing consistency in curriculum design (Santiago et al, 2021).
Aims. To capture what Pharmacy students believe to be fundamental 'big ideas' that all students studying Pharmacy should understand prior to becoming an intern Pharmacist.
Methods. A survey was developed to capture foundational science-related core concepts in two areas being (a) biomedical and pharmaceutical and (b) social/administrative, behavioural and clinical. Pharmacy students at Monash University and University of Canberra were independently surveyed over a period of one month in 2021. The questions answered using free text were thematically analysed by a minimum of two researchers.
Results. A total of 43 students completed the survey; they predominantly identified as female (72%) and most had completed at least three years of Pharmacy studies (77%). Students struggled to distinguish between core concepts (e.g. drug adherence), broad disciplines (e.g. pharmacology) and other essential skills, like drug calculations. Interestingly most students (74%) chose to skip over background preamble explaining core concepts, and the majority (83%) answered that their selection of core concepts was sourced from their own educational experiences.
Discussion. Students have opinions regarding what they believe is important in their Pharmacy studies however this is not always reflective of the core knowledge that educators are aiming for students to learn. Developing core concepts can help bridge the gap between what students think they need to know to be a practicing Pharmacist and what are fundamental and enduring ideas. The success of this task – as applied for Pharmacy curriculum - may be challenged by the many disciplinary areas underpinning Pharmacy education.

Santiago et al (2021) Pharmacol Res Perspect. 2021;9:e00894. https://doi.org/10.1002/prp2.894

150 Barriers and facilitators to implementing simulation into Pharmacy programs globally.

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Introduction. Simulation- based pharmacy education enhances student's knowledge, clinical skills and performance while promoting critical thinking. It provides an environment for students to learn patient care in a safe manner and thus the potential to decrease medication errors in practice. MyDispense is a simulation software developed by Monash University that has been utilised by over 200 institutions worldwide to educate pharmacy students. Despite this, little is known about the processes by which it is used to teach dispensing skills to students and how they use it to facilitate critical thinking in an authentic environment. Furthermore, gaps also exist about what barriers affect the uptake and utilisation of MyDispense, as well as reasons why MyDispense is or is not used.
Aims. The aim of this research was to investigate how dispensing is taught in pharmacy programs globally, and to identify the barriers and facilitators to implementing MyDispense.
Methods. A total of 18 interviews were conducted with selected educators from pharmacy schools worldwide, including 12 MyDispense users and 6 MyDispense non-user institutions. Two investigators conducted inductive analysis to generate key themes and subthemes to provide insight into the opinions, attitudes and experiences towards MyDispense and other simulation software used within pharmacy programs. Intercoder reliability was investigated and a Kappa coefficient of 0.72 indicated substantial agreement between both coders.
Results. Five overarching themes were identified: "dispensing and counselling"; "description of MyDispense use"; "barriers to MyDispense use"; "facilitators to use MyDispense" and "future use and suggested improvements".
Discussion. The initial outcomes of this project evaluated the awareness and utilisation of MyDispense by pharmacy programs globally. By addressing the barriers of use, promotion of the sharing of MyDispense cases can assist in creating more authentic assessments, as well as improving staff workload management. The outcomes of this research also facilitate the development of a framework for MyDispense implementation, which will streamline and improve the uptake of MyDispense within the faculty and by pharmacy school globally.

151 *Hepatitiscape™* - A Hepatitis-themed Virtual Escape Room Gamification in Pharmacy Education

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Introduction. Virtual learning tools have been needed to supplement face to face teaching in an era of blended and flexible learning arrangements. Escape rooms have been shown to be successful in exercising teamwork and promoting critical thinking in millennials, the new cohort of learners. There is limited research on escape room innovations in pharmacy education; none teaching Hepatitis and none that can be run interactively online. Authors designed *Hepatitiscape™* (an escape room testing Hepatitis knowledge through ten puzzles within three rooms to escape the virtual building).
Aim. To assess the effectiveness of the game-based learning using a new web-based interactive educational escape room (*Hepatitiscape™*) on knowledge gain.
Methods. A pre- and post- activity assessment was administered to measure students' knowledge gain on the topic of Hepatitis.
Results. A total of 418 students participated in this activity. A statistically significant improvement was seen in the knowledge score following implementation of the gaming activity (58.66% pre-intervention vs 72.05% post-intervention, $p < 0.05$).
Discussion. The virtual escape room game was an effective pedagogical approach to teach and reinforce clinical concepts of hepatitis among pharmacy students. Hepatitis is a specialised area and it can be difficult to find facilitators to run workshops. *Hepatitiscape™* can be run with minimal facilitation and off campus. With the evolving landscape of education and learner demographics, investment in technology- enhanced game-based learning is a promising trajectory to support students' growth in a learner-centered environment.

152 A science-themed escape room for teamwork and critical thinking skills development

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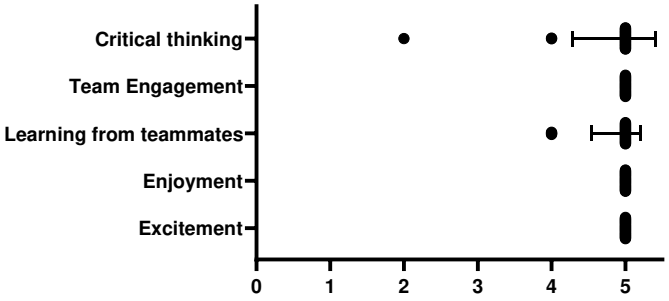

Introduction. The implementation of escape rooms is a novel active learning strategy within the higher education setting in various disciplines, including health sciences. Teaching soft skills like team dynamics, problem solving and critical thinking in content-heavy curriculum can be challenging. Escape rooms provide the opportunity for a group to work together as they solve puzzles within a limited time. The skills harnessed and developed within the game by participants are parallel to these soft skills (Taraldsen et al, 2022). The present study is a survey-based investigation where feedback was obtained from undergraduate biomedical or health science students following the completion of an on-campus physical escape room experience.
Methods. Undergraduate students for a biomedical science program were invited to participate in a 45-minute on-campus escape room game. Following the completion of the game, the participants completed a questionnaire that sought feedback in relation to three aspects: enjoyment of the game, soft skills development including teamwork and critical thinking and lastly, attitude towards games in general.
Results. Statements regarding the enjoyability, engagement and teamwork development within the game scored positively (refer to figure). A recurring positive theme in the feedback collected was that the participants found the activity fun and encouraged them to think critically.
Discussion. The present findings suggest that escape rooms can in a brief period, improve communication and teamwork skills and naturally comes with an element of fun, making the experience memorable and engaging.

Taraldsen L H et al (2022) Education Inquiry 13(2):169-184

153 Development and evaluation of a virtual privilege walk

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Introduction. Understanding the concept of privilege and recognising the existence of privilege in society and encouraging reflection on one's own privilege may improve empathy, an important skill for healthcare professionals to develop (McIntosh 2012). Privilege walks are one way to encourage self-reflection about privilege, but such activities may distress participants because of their identifiable nature. With this in mind, an online anonymous privilege walk was developed to encourage self-reflection of privilege in pharmacy students in a safe manner.
Aims. To evaluate a virtual privilege walk to encourage students to reflect on privilege, both their own privilege and as a concept in healthcare.
Methods. Statements from other privilege walks were analysed for clarity and transferability, and a list of 30 statements was developed and built into an online virtual privilege walk to allow students to confidentially see their walk results compared to the whole cohort. The virtual privilege walk and a reflective activity on privilege was undertaken by 186 first year pharmacy students. Before and after this activity, 78 students completed a 16 item diversity and oppression survey. This survey was designed to measure four factors: 1. Confidence in knowledge and understanding of diversity, 2. Awareness of diversity and oppression, 3. Opinions on pharmacy counselling and congruence between pharmacist and patient, and 4. Opinions on pharmacists' roles in promotion and support of diversity. Two way ANOVAs were used to determine any changes in the four factors pre and post activity.
Results. There was a significant increase in factors 1 ($F_{2,132} = 46.1$, $p < 0.0001$), 2 ($F_{14,924} = 29.1$, $p < 0.0001$) and 4 ($F_{1,264} = 56.7$, $p < 0.0001$), but a decrease in factor 3 ($F_{4,264} = 6.0$, $p = 0.0001$) post-activity compared with pre-activity.
Discussion. Confidence in knowledge and understanding of, awareness of and opinions on pharmacists' role in the support of diversity were all improved after students undertook and reflected on the privilege walk. Unexpectedly, more students thought pharmacy counselling is more effective if pharmacists and clients have the same gender, sexual identity or racial group post activity.
McIntosh (2012) Journal of Social Issues, 68(1):194—206

154 GPR84 antagonist, GLPG1205, reduces disease features in experimental severe asthma

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Introduction. Severe asthma is the major unmet clinical need in asthma management. Despite recent advances in biologics, many patients are unable to gain disease control and/or experience side effects, necessitating more effective therapies. Targeting GPR84, a medium-chain fatty acid receptor, with GLPG1205 (antagonist) improves lung function in patients with idiopathic pulmonary fibrosis, however, its application in severe asthma is untested.
Aim. To assess the effects of treatment with GLPG1205 in experimental severe asthma (Kim RY et al, 2017a, 2017b).
Methods. Mice (n=7-8/group) were administered ovalbumin (Ova) i.p. (day 0; or saline control), followed by intranasal Ova (days 12-13) to induce experimental asthma. Mice were then infected with Chlamydia muriduram (Cmu, day 14, 100 IFU; or SPG control) to induce experimental severe asthma. Mice were then re-challenged with Ova (days 33-34). Separate groups of mice were treated (days 32-34) with dexamethasone (DEX; 2mg/kg) to model inhaled steroid use or GLPG1205 (10mg/kg). Endpoint analysis (day 35) included in vivo invasive plethysmography to measure airway hyperresponsiveness to methacholine challenge, and airway inflammation measured in bronchoalveolar lavage.
Results. Ova induced airway hyperresponsiveness and increased airway inflammation ($14.7\pm1.4 \times 10^4$ cells/mL) compared to Sal/SPG controls ($2.1\pm0.2 \times 10^4$ cells/mL; $P<0.0001$) and was responsive to DEX treatment ($4.5\pm0.9 \times 10^4$ cells/mL; $P<0.0001$). Ova/Cmu-treated mice had increased airway hyperresponsiveness and inflammation ($16.6\pm1.8 \times 10^4$ cells/mL) compared to Sal/Cmu controls ($3.0\pm0.5 \times 10^4$ cells/mL; $P<0.01$), and DEX treatment had no effect ($18.9\pm4.1 \times 10^4$ cells/mL). Administration of GLPG1205 to Ova/Cmu-treated mice reduced steroid-insensitive airway hyperresponsiveness and inflammation compared to Ova/Cmu.
Discussion. Inhibiting GPR84 with GLPG1205 in experimental severe asthma reduces steroid-insensitive airway hyperresponsiveness and airway inflammation, warranting further exploration of its therapeutic use in severe asthma.

Kim RY et al (2017a) Am J Resp Crit Care Med 196:283-297
Kim RY et al (2017b) J Allergy Clin Immunol 139:519-532

155 Patient-specific methods to assess inhaled-toxicant susceptibility in fibrotic lung disease

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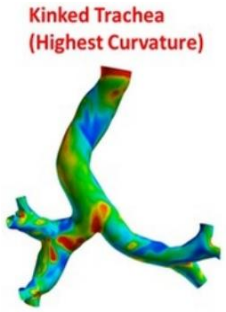
Introduction. In the pathogenesis of chronic lung diseases, including IPF, discrete areas of epithelial damage and repair appear in the respiratory tract mucosa and are thought to play a role in their initiation and exacerbation. These areas of perturbation may be due to the local effects of inhaled toxicants and activate underlying fibrotic processes. Previously, we developed mathematical simulations to predict focal areas of toxicant flux in a virtual 3-D model of an individual's large airway generations reconstructed from high-resolution CT scans.
Aims. To determine whether IPF disease severity is predictable from toxicant flux simulations or more simply from structural airway parameters.
Methods. Using patient CT scans, we performed three-dimensional simulations of reactive gas uptake in anatomically accurate models of the upper respiratory tract and quantified the patient-specific abnormalities with curvature and/or eccentricity parameters. For tissue analysis, patient lung sections were characterized by cell phenotype and extent of fibrosis for relevant correlation.



Results. Hotspot index of toxicant flux was related to structural parameters with higher values of hotspot index correlated with highly deformed proximal airways. Furthermore, it was possible to see correlations between these observations with ranks of pathological severity and fibrotic foci scores.
Discussion. These results demonstrate the relationships between geometric parameters quantifying clinically observed airway deformations and predicted sites of high toxicant uptake based on computational fluid dynamics. Our findings demonstrate that the extent of tracheal deformation varies across the different stages of IPF severity. We propose the evaluation of tracheal deformations and associated focal epithelial injuries as a predictor of risk for IPF exacerbations, clinical deterioration, and disease progression.

156 Vasodilator and anti-inflammatory effects of FPR agonist Cmpd17b in precision-cut lung slices.

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Introduction. Current treatments for pulmonary hypertension (PH) are limited to vasodilators that do not target inflammation or vascular remodelling. The small molecule formyl peptide receptor (FPR) agonist Cmpd17b, which has pro-dilator and anti-inflammatory bias at FPRs, dilates arteries and attenuates fibrosis in murine cardiac disease (Qin et al 2017) and vascular complications (Marshall et al 2020). Cmpd17b has yet to be tested in the context of PH.
Aims. To show that Cmpd17b elicits protective actions in the mouse pulmonary vasculature by 1) inducing vasodilation in precision-cut lung slices (PCLS) comparable to dilators currently used in therapy, (sildenafil and riociguat) and 2) inhibiting TNFα- or lipopolysaccharide- (LPS) mediated secretion of inflammatory cytokines. In addition, receptor dependence and mechanisms of FPR-mediated dilation were explored.
Methods. Using PCLS from 8-wk-old male C57BL/6J mice, intrapulmonary arteries were precontracted with 3μM 5HT, then dilator curves were performed. Cmpd17b-mediated relaxation was assessed in the presence of FPR antagonists, signalling inhibitors, and after TNFα or LPS treatment (24 or 72 hrs, also collected conditioned media for ELISA).
Results. Cmpd17b (n=9) elicited complete vasodilation with potency similar to riociguat but 5-fold greater than conventional FPR agonist Cmpd43 or sildenafil (all n=6) ($p<0.05$ *cf* Cmpd17b). Relaxation was inhibited by FPR1 antagonist (CsH 1μM), and maintained in the presence of inhibitors of sGC, eNOS or COX (ODQ, L-NAME, indomethacin, respectively). Cmpd17b maintained dilator efficacy and potency and inhibited secretion of pro-fibrotic and pro-inflammatory cytokines In TNFα- and LPS-treated PCLS (n=6, $p<0.05$).
Discussion. Cmpd17b-mediated vasodilation is mediated by FPR1, independent of guanylate cyclase and endothelial-derived relaxing factors, and maintained in inflamed lung tissue, where it exhibits additional anti-inflammatory effects. These findings support preclinical *in vivo* assessment of Cmpd17b as a novel dual-action therapy for PH.

1) Marshall et al (2020) Int J Mol Sci 21:4. 2) Qin C et al (2017) Nat Commun 8:14232

157 Casein kinase 1 delta inhibitor PF670462 inhibits inflammatory/fibrogenesis cytokines in airway epithelium

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Introduction. Casein kinase 1 delta (CK1δ) plays critical roles in multiple cellular functions, including vesicular trafficking, cell cycle progression, DNA damage repair, and circadian rhythm. CK1δ regulates circadian clock proteins period (PER) and BMAL1. Circadian variations impact on airway inflammation and treatment of asthma.
Aims. We aim to investigate whether CK1δ is involved in airway epithelial cytokine productions.
Methods. The level of immunoreactive CK1δ was evaluated in airway biopsies from non-asthmatic and asthmatic donors. A range of human airway epithelial cells, including human bronchial airway epithelial cell line BEAS-2B, alveolar epithelial cell line A549, primary human bronchial epithelial cell cultures from both infant and adult were used to measure inflammatory cytokine production induced by a variety of stimuli in the absence or presence of CK1δ inhibitor, PF670462.
Results. CK1δ immunoreactivity was distributed in the epithelium and sub-epithelium of airway tissues in airway biopsies from donors with and without asthma. CK1δ level was elevated in the airway biopsies of patients with severe asthma compared to those from control subjects. In BEAS-2B cells, PF670462 reduced both TNF-α and poly I:C induced GM-CSF, IL-8, and IL-6 levels. In A549 cells, PF670462 significantly inhibited IL-1α induced GM-CSF, and IL-6 levels. PF670462 inhibition of IL-1α induced IL-6 was observed in primary human bronchial epithelial cell cultures from infants. Similarly, PF670462 also inhibited IL-1α induced GM-CSF, IL-6, and IL-8 gene expression in freshly isolated adult human primary bronchial epithelial cells.
Discussion. We have shown that CK1δ level is elevated in asthma patients. Inhibition of CK1δ by PF670462 inhibits inflammatory cytokine production in different types of airway epithelial cells. These findings indicate that CK1δ may play a role in airway inflammation diseases, identifying CK1δ as a potential therapeutic target in respiratory diseases.

158 Pirfenidone is more effective than glucocorticosteroids in limiting influenza-A-viral infection and inflammation.

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Introduction & Aims. Patients with respiratory diseases are more susceptible to viral infection, often developing more severe and prolonged symptoms which often lead to deleterious effects such as lung function decline and irreversible disease progression. Emerging evidence suggests elevated transforming growth factor-beta (TGFb), seen in patients with respiratory diseases, likely plays a crucial immunosuppressive role to enhance viral infection. While glucocorticosteroids (GCS) effectively reduce inflammation, substantial evidence demonstrates their immunosuppressive effects. Pirfenidone (PFD) is an anti-fibrotic small molecule used in patients with pulmonary fibrosis to slow disease progression. Our recent studies have shown oral administration of PFD can reduce TGFb-enhanced viral infection in a mouse model. However, the use of oral PFD comes with unpleasant side effects, therefore the aim of this study was to determine if inhaled PFD could also reduce inflammation and disease severity and compare its effectiveness to that of GCS.
Methods. Transgenic C57Bl/6 mice with inducible lung-specific over-expression of TGFb were treated intranasally with vehicle (control), PFD (13.3 mg/kg) or GCS (1 mg/kg) daily, starting 2 days prior to infection with IAV (102 PFU, HKx31). Mice were culled at day 3 post infection, and lung tissue and bronchoalveolar lavage fluid (BALF) were collected for assessment of infection, inflammation, and immune responses.
Results. Daily administration of PFD, but not GCS, was able to reduce TGFb-enhanced viral load in lung homogenates ($p<0.05$), as measured by plaque assay. In BALF, the chemokine RANTES was reduced by both PFD and GCS, however IL-6, TNFa and KC were only reduced by PFD.
Conclusion. This study demonstrates that inhaled PFD was able to afford protection against TGFb-enhanced viral infection and inflammation more effectively than the current standard treatment, GCS. These promising findings offer the possibility of repurposing PFD to treat patients with respiratory disease during viral exacerbations, offering protection from worse disease outcomes.

159 Bronchodilation to FFA1/4 agonists is maintained in mouse allergic airways disease

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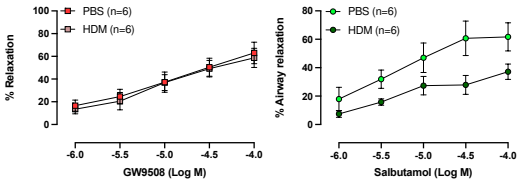
Introduction. Severe asthma reduces dilator responses to the β_2-adrenoceptor (β_2-AR) agonist salbutamol. Agonists of free fatty acid receptors 1 & 4 (FFA1 & FFA4) cause bronchodilation in precision cut lung slices (PCLS) from naive mice, but have not been tested in PCLS from a model of allergic airways disease.
Aims. To compare the efficacy of FFA1 and FFA4 agonists (GW9508, TUG-891 respectively) with salbutamol in a house dust mite (HDM) model of allergic airway disease.
Methods. On day 0, C57BL/6 females (6-8 weeks old, n=6-7 per group) were sensitised with HDM (100µg i.p). On day 14, mice were challenged with HDM (100µg i.n) and culled on day 15 for comparison with PBS controls. Anaesthetised mice were subjected to lung function testing via plethysmography to determine MCh-induced changes in airway resistance. PCLS were prepared for concentration-response curves using salbutamol, GW9508 and TUG-891. Receptor dependency was determined using selective antagonists (DC260126 for FFA1; AH7614 for FFA4).
Results. HDM induced inflammation and increased MCh-induced changes in airway resistance. Relaxation to GW9508, TUG-891 was comparable to salbutamol in PCLS from control mice. Pre-contraction to MCh (300nM) was increased in PCLS from HDM ($p<0.05$), with bronchodilator efficacy of GW9508 and TUG-891, but not salbutamol, maintained ($p<0.05$, Figure). GW9508 and TUG-891 efficacy were reduced by DC260126 and AH7614, consistent with their reported receptor selectivity.
Discussion. Evidence of inflammation, increased airway contraction and reduced efficacy of salbutamol in the HDM model is consistent with airway hyperresponsiveness and impaired β2-AR sensitivity in severe asthma. Airway relaxation to GW9508 and TUG-891 in this context, and confirmation of their receptor dependence, supports further pre-clinical evaluation of these novel receptor targets to overcome the limitations of current bronchodilator treatment for asthma.



160 A LASEREDD Focus: Lentiviral-Driven Directed Evolution of G Protein-Coupled Receptors in Human Cells for Drug Discovery.

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Developing selective G protein-coupled receptor (GPCR)-targeting drugs is a challenging area that has hindered GPCR research, target validation and drug discovery for many years. Compared to small molecules, antibodies can bind their targets over larger surfaces to achieve high target selectivity. Virtually no selective anti-GPCR antibodies, however, are currently available, which is a major hindrance to the field and limits our ability to treat diseases through GPCR-targeting antibody drugs. By far, the most significant barrier for antibody drug development (as well as small molecule development) is the challenge in expressing and purifying viable GPCR samples for immunization, panning and SAR determination. Existing methods to stabilise GPCRs are not generically applicable to improving GPCR expression, and often result in non-functional mutant GPCRs, leading to ineffective drug development. We have developed a novel and superior method called Lentiviral-Assisted Selection Enabling Receptor Engineering and Drug Discovery (LASEREDD). LASEREDD accelerates the preparation of GPCR samples for drug discovery by rapidly engineering high-expressing GPCR variants from diverse, minimally mutated gene libraries. The LASEREDD approach uses directed evolution in human cells and detailed structural and pharmacological evaluation to ensure our engineered GPCRs maintain their natural structure and function. These GPCR variants allow the preparation of: cell lines; virus-like particles; liposomes; and homogeneously purified protein samples with high GPCR protein content/activity, enabling biophysical and structural studies of challenging GPCRs, and facilitating antibody discovery and small molecule structure-based drug design. The application of LASEREDD to several challenging, peptide-activated, GPCRs will be presented, along with applications of LASEREDD-engineered GPCR variants.

161 Development of technologies for the targeted degradation of a GPCR

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Introduction**.** G protein-coupled receptors (GPCRs) are often targeted in the clinic by small molecule antagonists to inhibit their signalling processes in disease. While this approach has been successful, newer pharmacological modalities targeting GPCRs through different mechanisms may generate a greater therapeutic effect. One new modality is PROteolysis TArgeting Chimeras (PROTACs). PROTACs are heterobifunctional molecules that can bind the protein of interest with one pharmacophore, while simultaneously recruiting part of the ubiquitin proteasome to degrade that protein. A GPCR for which degradation would be therapeutically desirable is the β_2-adrenoceptor (β_2AR), as suppressing its signalling leads to more favourable outcomes in triple negative breast cancer. The dTAG-fusion protein system (Nabet et al, 2018), allows one to determine if a protein can be degraded by the cells' UPS, without having to first develop a degrader drug.
Aims. We set out to ascertain whether the β_2AR-dTAG fusion could be degraded by a dTAG-targeting small molecule. We next sought to determine whether an untagged β_2AR could be degraded by an intracellular bio-degrader.
Methods. Standard molecular biology techniques were used to generate a β_2AR-FKBP12^{F36V} "dTAG" C-terminal fusion protein as well as to generate an intracellular nanobody-based degrader. Western blots and luciferase reporter assays were used to assess protein degradation. A NanoBRET-based conformational biosensor based on EPAC was used to assess cAMP responses.
Results. The β_2AR-dTAG fusion protein can be degraded by a dTAG-binding small molecule PROTAC. We show that a novel intracellular nanobody-based degrader can also reduce the β_2ARs' functional effects.
Discussion. These experiments validate that the β_2AR is amenable to targeted protein degradation technology. Ultimately, these studies are the first steps towards developing targeted degradation tools and PROTACs for the β_2AR – a prototypical GPCR.

Nabet B et al (2018) Nature chem biol 14(5), 431-441.

162 Shining a light on localised signalling using a targeted optogenetic GPCR.

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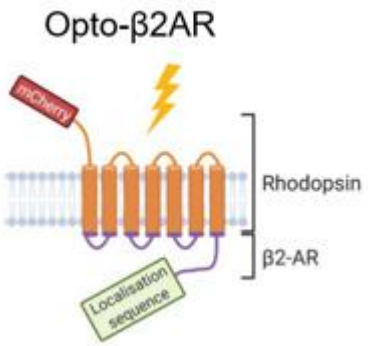
Introduction. The differential localisation of GPCRs at the plasma membrane or intracellular membranes results in location-specific production of second messengers that can confer unique downstream responses. To investigate the impact of intracellular location on GPCR signalling without using endocytic inhibitors or ligands with different permeability, we turned to optogenetic methods. Our approach utilised a rhodopsin β2-adrenoceptor (opto-β2AR) chimera that couples to canonical Gs-mediated signalling in response to light (Siuda et al., 2015).
Aims. Target opto-β2AR to intracellular membranes using novel location motifs and quantify light-mediated cAMP, ERK phosphorylation and gene expression.
Methods. Subcellular GPCR localisation was validated using confocal microscopy; receptor activation was quantified using signalling assays and a quantitative reverse transcription polymerase chain reaction (qRT-PCR) array.
Results. Opto-β2AR was successfully targeted to early endosomes, Golgi, nucleus and mitochondria where light activation differentially increased cAMP accumulation and ERK phosphorylation. Activation of the opto-β2AR at each intracellular location also conferred unique responses at the transcriptional level: 8 out of 84 genes assayed were significantly upregulated in response to signalling at one or more intracellular location, but not at the plasma membrane.
Discussion. Disease-relevant GPCR signalling can be location dependant: a greater understanding of signal compartmentalisation will challenge existing conceptions about plasma-membrane delimited signalling and encourage new strategies for GPCR-targeted drug discovery.



Siuda ER et al (2015) Nat Commun 6:8480-8492

163 Tumour Microenvironmental Features Direct Stem Cells Fate

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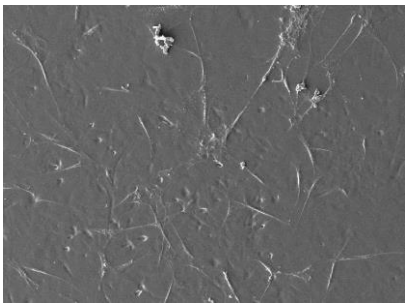
Introduction. The tumour comprising a heterogeneous microenvironment can influence tumour cell behaviour as well as different resident and recruited stroma cells. Mesenchymal stem cells are residing in different cancers and influence cancer cells and tumour microenvironment (TME).
Mesenchymal stem cells shape a part of the tumour stroma and have been reported to have a cancer supporting roles through different mechanisms[1]. The TME is an integral factor of malignancies in different cancers. In this study, we captured the TME breast cancer topographical features by imprinting method to test the effect of the TME on the MSCs.
Methods. To imprint the TME topographical features, the MDA-MB-231, and MDA-MB-468 cell lines (metastatic breast cells) was cultured on 6 well plates. After reaching the desired confluency (>90%), they were fixed by 4% glutaraldehyde. The polydimethylsiloxane (PDMS sylgard 184) polymer with the 10:1 w/w monomer to cross linker ratio was cast on the fixed cells to engineer the tumour cell membrane features as well as the TME topographical cues. The adipose derived MSCs were seeded on top of engineered substrate for 21 days.



Results. The TME topographical cues can enhance the integrin beta-3 gene expression and downregulate E-cadherin. Furthermore, the results of immunohistochemistry staining confirmed that it can enhance the protein expression of αSMA as the biomarker of myofibroblast cells and ki67 as the marker of cell proliferation[2]. Together, the tumour micro and nano topographical cues direct mesenchymal stroma cells to acquire tumour cell-like characteristics.

1. Shi, Y.; Du, L.; Lin, L.; Wang, Y. Tumour-associated mesenchymal stem/stromal cells: emerging therapeutic targets. *Nature reviews Drug discovery* 2017, *16*, 35-52.
2. Rudnick, J.A.; Kuperwasser, C. Stromal biomarkers in breast cancer development and progression. *Clinical & experimental metastasis* 2012, *29*, 663-672.

164 Repurposing of approved drugs targeting TGF-β for chemoresistant high-grade serous ovarian cancer

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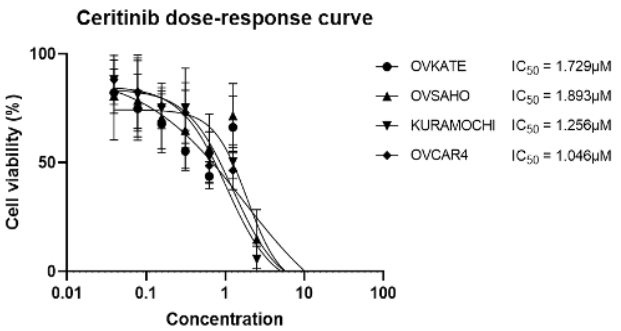

Introduction. High grade serous ovarian cancer (HGSOC) has low 5-year survival rate of 48%, due to chemotherapy resistance. Effective new therapies are required to improve the survival rate of HGSOC. TGF-β is a family of proteins associated with epithelial-mesenchymal transition and have been implicated in ovarian cancer progression and chemoresistance. Drugs that target TGF-β may have potential to be used to treat chemoresistant HGSOC and control tumour growth and progression. Drug repurposing is a strategy to identify new uses for approved drugs outside of their original indication, and ensure timely access to efficacious and cost-effective therapy for chemoresistant HGSOC.
Aims. To investigate potential of approved drugs targeting TGF-β to control cell growth of chemoresistant HGSOC
Methods. A ligand-based screening was performed by Cresset Discovery for approved drugs that bind to the TGF-β receptor complex and ligand. The drugs were shortlisted according to dosing, solubility, pharmacokinetics, and side effects. MTT assays were performed on eight molecularly-characterised HGSOC cell lines to obtain a dose-response curve of the shortlisted drugs.
Results. The IC_{50} of ceritinib, crizotinib, and teniposide are within range of the maximum plasma concentration for each drug (ceritinib 1.8µM; crizotinib 560nM; teniposide 61µM).
Discussion. Ceritinib, crizotinib, and teniposide have potential to be repurposed for treatment of chemoresistant HGSOC, as shown in preliminary *in vitro* studies.

165 Assessment of Store operated calcium entry (SOCE) in replicative and accelerated models of cellular ageing

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Introduction. Calcium (Ca^{2+}) homeostasis dysregulation has been linked to many age-related diseases such as Alzheimer's, Parkinson's disease, Huntington's disease and many more. SOCE is one of the major pathways involved in the regulation of Ca^{2+} homeostasis intracellularly and it has been also linked to many age-related disorders, however the role and regulation of SOCE in cellular ageing is not clear. In this study we developed a replicative and two accelerated models of cellular senescence using hydrogen peroxide (H2O2) and Mitomycin C (MMC). We then assessed the regulation of SOCE in these models.
Aims. A. To establish an accelerated model of ageing. B. To study the regulation of SOCE in the replicative and accelerated model of ageing.
Methods. To establish an accelerated model of ageing Human derived fibroblasts (HDF) were treated with various concentrations of H202 (50 µM, 100 µM, 150 µM and 300 µM for 24 hours) and MMC (50 nM, 100 nM, 200 nM, 400 nM and 600 nM for 48 hours). Subsequently, media was replaced with normal media, and cells were further cultured for five days. Senescence was confirmed by measuring senescence associated beta-galactosidase activity using the fluorometric Spiderβ-gal assay kit and high-content microscopy. SOCE regulation in the cellular ageing models was assessed by calcium influx assays using Fluo-4 calcium indicator.
Results. There was increased activity of senescence associated beta galactosidase in the H2O2 and MMC treated HDFs when compared to control. SOCE activity was downregulated in replicative ageing, however there was no difference in the SOCE activity in the H2O2/MMC induced cellular ageing.
Discussion. We have established an accelerated model of cellular ageing using H2O2 and MMC. We also show here that SOCE is downregulated in senescent cells compared to replicating cells, however there is no change in SOCE activity in the accelerated model of ageing.

166 Advancing allosterism and biased agonism to target the Adenosine A_1 receptor

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The adenosine A_1 G protein-coupled receptor (A_1R) is an attractive therapeutic target for a range of cardiovascular and neuronal disorders. However, it remains sub-optimally targeted due to high doses and the lack of highly subtype-selective ligands causing adverse effects (such as bradycardia, atrioventricular block, and hypotension). Emerging paradigms of A_1R pharmacology, including allostery and biased agonism, offer considerable clinical potential, presenting the opportunity to develop potent therapeutics with minimal on-target side effects. My research aims to understand the structural basis and the mechanism of allosteric modulation and biased agonism at the A_1R and to develop a computational approach to identify novel A_1R ligands. We have used a combined approach of mutagenesis, analytical pharmacology and molecular modelling (docking and molecular dynamics simulation) to identify molecular determinants of orthosteric ligand binding and activation, as well as allosteric modulation at the A_1R. Subsequent structure-function studies validated the first high-resolution A_1R structures in the inactive, active, allosteric modulator bound, and biased agonist bound conformations. Employing a high-throughput screening approach, we have elucidated the structure-activity relationship of a series of A_1R-biased agonists, identifying a high potency A_1R-biased agonist. We recently had three successful structure-based virtual ligand screening campaigns for novel orthosteric and allosteric ligands targeting A_1R. Specifically, we discovered first-in-class A_1R allosteric inhibitors, novel high-affinity A_1R antagonists, and novel A_1R allosteric enhancers. Currently, we are incorporating artificial intelligence deep learning models to assist our A_1R drug discovery pipeline. Collectively, findings from my research will assist in overcoming the challenges associated with the discovery, validation, and development of novel A_1R therapeutics with improved clinical efficacy for the treatment of major global health burdens.

167 Preclinical models to understand the risk of multiple concurrent medicines in old age: Where are we up to?

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Chronic medication use is common in older people to treat and manage chronic diseases. Older people with polypharmacy and multimorbidity are not adequately represented in clinical trials and there is minimal evidence on safety and efficacy of medications in this population. Observational studies indicate that polypharmacy (the use of 5 or more medications) and increasing Drug Burden Index (DBI: measure of total exposure to anticholinergic and sedative drugs) are associated with impaired physical and cognitive function, dependence in daily activities and increased frailty in older people. The mechanism behind this is probably multifactorial and poorly understood.

Preclinical models of clinically relevant drug exposures; particularly polypharmacy, in ageing would be useful tools to screen for and learn more about the mechanisms of drug induced adverse geriatric outcomes. This presentation will describe some of the important developments in this research. Preclinical functional and molecular mechanistic findings will be discussed.

168 Novel targets for the treatment of cigarette smoke-induced cognitive impairment in mice.

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Introduction. Chronic obstructive pulmonary disease (COPD) is a major health burden, that is currently the 3rd leading cause of death globally, with cigarette smoking being the leading causative factor. The “spill-over” of pulmonary inflammation and oxidative stress into the systemic circulation may reach the brain, leading to cognitive dysfunction, which impacts on quality of life and increases risk of death. Cessation of cigarette smoking can improve pulmonary and cognitive outcomes, however, its benefit on the underlying neuroinflammatory profile remains uncertain.
Aims. To investigate the neuroinflammatory profile relating to cigarette smoke exposure and cessation; define the benefits of antioxidants on these neuroinflammatory profiles.
Methods. Using our preclinical model of COPD, male BALB/c mice were exposed to cigarette smoke (9 cigarettes/day for 8 weeks) followed by 4 weeks of cigarette smoking cessation. Another cohort of cigarette smoke-exposed mice were co-administrated with a glutathione peroxidase mimetic, ebselen (10 mg/kg) or vehicle (5% CM-cellulose). We assessed both working (novel object recognition [NOR] test) and spatial (spontaneous Y-maze [sY-maze] test) memory as well as hippocampal microglial numbers, morphology (ionized calcium binding adaptor molecule-1 immunohistochemistry) and oxidative protein carbonylation.
Results. Cigarette smoke exposure increased lung inflammation and induced spatial and working memory impairments which were attributed to hippocampal microglial activation. Cigarette smoking cessation did not improve memory deficits or alter microglial activation. Prophylactic treatment with ebselen prevented the cigarette smoke-induced memory impairments, which was associated with restored synaptophysin expression without altering microglial activation.
Discussion. Chronic cigarette smoke exposure impairs hippocampal-dependent memory which was associated with neuroinflammation and oxidative stress. By inhibiting oxidative stress, ebselen ameliorated CS-induced memory loss via a microglial-independent mechanism. Future research into cigarette smoke induced microglial dysfunction is crucial to understand the mechanisms involved in COPD-induced memory loss.

201 Co-designing deprescribing guidelines' implementation into hospital for people living with dementia

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Introduction. As people living with dementia age, one or more of their medications, including acetylcholinesterase inhibitors (ChEI) or memantine, may become inappropriate resulting in more potential harm than possible benefit. The prevalence of inappropriate use of ChEIs/memantine calls for the need to regularly review to consider deprescribing (reducing/stopping) them.
Aims. As little remains known about the optimal strategies to implement ChEIs/memantine guidelines, we aimed to co-design, with hospital medical doctors and pharmacists, 'key elements' to facilitate their implementation in hospital clinical practice.
Methods. Using the persona-scenario method, we created personas for 4 groups of healthcare professionals (senior and junior medical doctors/pharmacists). Personas described a hypothetical healthcare professional's typical workday. Using a discussion guide developed with the Promoting Action on Research Implementation in Health Services framework, participants determined key elements by reflecting on how their 'persona' would become aware of the guideline, identify, and act (i.e., implement) deprescribing opportunities. A post-workshop survey was conducted to confirm the accuracy of the scenarios and the feasibility and effectiveness of the key elements proposed.
Results. We conducted 8 co-design workshops with 18 participants total to create scenarios that described how to implement the guidelines in practice. We extracted 144 key elements, 35 of which were contained in the scenarios and included in the survey. Key elements with the highest feasibility and efficacy were becoming aware of the guideline through handover documents, identifying patients during consultant led ward rounds and having an action plan for patients at discharge.
Discussion. Using the persona-scenario method enabled us to draw meaningful insights into key elements to facilitate the implementation of deprescribing guidelines for people living with dementia during hospital admission.

202 Cell division as a target in the development of new antimicrobial agents

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Introduction. *Acinetobacter baumannii* is a bacterial pathogen with high intrinsic antimicrobial resistance. Multidrug and extensively drug resistant strains of this pathogen are emerging, and new therapies are urgently needed. The bacterial cell division protein, FtsZ, is a promising drug target for the development of novel antimicrobials.
Aim. To examine the efficacy of cinnamaldehyde derivatives as antimicrobials against *A. baumannii* through FtsZ inhibition.
Methods. Methylbenzimidazolyl derivatives of cinnamaldehyde were synthesized. Microscopic analysis was performed to determine if the cinnamaldehyde analogs inhibited bacterial cell division. On-target activities were assessed through their effects on the polymerization and GTPase activity of purified FtsZ from *A. baumannii*. *In silico* docking was used to assess the compound binding site *in vivo* and *in vitro* toxicity assays were performed.
Results. The compounds displayed antimicrobial activity against *A. baumannii*. Bioactivity was significantly increased in the presence of a drug efflux pump inhibitor, suggesting that efflux contributes to intrinsic resistance against these agents. The compounds inhibited cell division as observed by the elongated phenotype and inhibited the polymerization and GTPase activity of the FtsZ protein. A di-chlorinated derivative was devoid of haemolytic activity and cytotoxicity against mammalian cells *in vitro*, as well as adverse activity in a nematode model *in vitro*.
Discussion. This is the first report of FtsZ-targeting compounds with activity against the critical priority pathogen *A. baumannii*. Halogenated methylbenzimidazolyl derivatives of cinnamaldehyde were found to be promising candidates for further development as antimicrobial agents.

203 Bridging the gap: using vignettes to teach cultural competence to pharmacy students

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Introduction. Cultural competence has been identified as a key focus area in the Accreditation Standards for Pharmacy Programs in Australia and New Zealand, where pharmacy graduates are expected to provide culturally safe care to patients from different cultural backgrounds. An interview study with RMIT pharmacy students revealed a lack of cultural competence teaching in the current pharmacy curriculum, where cultural competence knowledge acquisition in this cohort was mainly incidental rather than through the curriculum.
Aims. To address the gap in the curriculum through an interactive online cultural competence learning module.
Methods. An online cultural competence learning module was developed using a story telling approach. Due to COVID-19 travel and face-to-face contact restrictions an online approach suited both student and staff needs. The module entailed an introductory video that explained what cultural competence is, as well as three vignettes with patients from diverse cultural and religious backgrounds. The vignettes were interactive in nature as they were designed using HTML 5 package. Quizzes with automated feedback were embedded within the vignettes to allow students to reflect on their learning. The Transcultural Self-Efficacy Tool (TSET) was used pre- and post-module to evaluate the effectives of the module on cultural competence. Qualitative feedback was also collected from students.
Results. An overall improvement in the mean transcultural self-efficacy scores was observed in all the three domains: cognitive, practical and affective ($p<0.05$) using the TSET. Students appraised the module as being comprehensive, authentic and acknowledged that the module equipped them with skills requisite for health professionals such as pharmacists in dealing with cultural differences and serving culturally diverse populations.
Discussion. The design and implementation of the cultural competence module using a digital storytelling approach addressed the current gap in pharmacy curriculum and significantly enhanced cultural competence in pharmacy students. There is potential for the module to be adopted across different healthcare disciplines, to equip all healthcare students with cultural competence skills to meet the needs of our increasingly diverse populations.

204 Community pharmacists' acceptability of depression screening for older adults: A qualitative study

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Introduction: Approximately 10%-15% of older adults (≥65 years) experience late-life depression (LLD). LLD often goes undiagnosed and untreated and may negatively impact quality of life. Pharmacists are well-positioned to identify consumers at risk of LLD, thereby supporting the timely detection and treatment of LLD.
Aim: To explore community pharmacists' acceptability of pharmacist-delivered depression screening for older adults.
Methods: Community pharmacists were recruited through promotional emails from the Pharmaceutical Society of Australia and social media platforms. An interview guide was developed to explore pharmacists' perspectives on LLD screening services in community pharmacies. Semi-structured interviews explored pharmacists' attitudes towards potential roles in providing LLD screening services, factors affecting the effective implementation of such services in community pharmacies, and knowledge and awareness of LLD screening tools and support services. Inductive thematic analysis was used to analyse the data and identify key themes and subthemes. Each subtheme was categorised as either a barrier or facilitator and mapped to the Capability, Opportunity, Motivation-Behaviour (COM-B) model - a framework which suggests that behaviour change is impacted by these three constructs.
Results: Fifteen pharmacists were interviewed, 12 of which were female and 11 of which practiced in a metropolitan area. Four key themes were identified: Training Needs, Environmental Factors, Pharmacists' Roles, and Organisational Support. Sixteen subthemes were mapped to the COM-B constructs, whereby five subthemes were mapped to Capability, eight to Opportunity and three to Motivation. Barriers to LLD screening in community pharmacies included lack of time, privacy, and remuneration, while facilitators included training, pharmacists' accessibility, and rapport with consumers.
Discussion: Community pharmacists found pharmacist-delivered LLD screening to be an acceptable service. However, the development of appropriate referral and remuneration pathways, and pharmacist-specific guidelines, is warranted. The findings of this study may facilitate the development of pharmacist-delivered depression screening services for older adults, thereby potentially contributing to the timely identification and treatment of LLD.

205 Attitudes of rheumatoid arthritis patients towards Disease Modifying Antirheumatic Drug deprescribing

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Introduction. People living with rheumatoid arthritis (RA) may be taking one or more medications that they no longer need. Current literature states the prevalence of polypharmacy in RA is 67.9%. However, there is little evidence about polypharmacy in RA and even less on how patients with RA feel about deprescribing.
Aims. To determine the attitudes and beliefs regarding Disease Modifying Anti-Rheumatic Drug (DMARD) use and RA patients' willingness to have their medications deprescribed.
Methods. A cross sectional study of RA patients was conducted using a self-administrated survey adapted for people living with RA from the validated revised Patients' Attitudes Towards Deprescribing (rPATD) questionnaire. Participant characteristics such as the number of medications, disease activity and time since diagnosis were also collected. Descriptive analyses were used to analyse and interpret data.
Results. To date, we have recruited 40 RA participants; 57.5% were female and the median age was 66.5 years (interquartile range, IQR 54.75-75.25). The median number of medications was 9 (IQR 6-12.25), including 3 RA specific medications. Median years since diagnosis was 11 (IQR 5-14). The majority of RA patients (80%) agreed they would be willing to stop one of their RA medicines if their rheumatologist said it was possible and 55.6% reported that they have not had a bad experience ceasing a medication in the past. Additionally, over half of patients (53.8%) believed they spend a lot of money on their RA medications.
Discussion. Most RA patients are willing to have one or more of their DMARDs deprescribed if their rheumatologist supports it, highlighting the importance of discussing deprescribing with RA patients. However, further research is needed to develop tools and solutions to identify and address opportunities for deprescribing in RA patients.

206 Sedative burden in hospitalised patients taking at least one antipsychotic medication

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Introduction. Sedation is a common adverse effect of antipsychotics. Although there is only limited evidence supporting the effectiveness of using multiple antipsychotics and in combination with other psychotropic medications, it remains common in clinical practice. The use of multiple medications with sedating properties can exacerbate central nervous system depression, and multiple risks are associated with a higher sedative burden.
Aims. To investigate the changes in the sedative burden between admission and discharge among patients taking at least one antipsychotic medication before hospitalisation.
Methods. This retrospective observational study utilised existing inpatient data from three South Australian public hospitals between 1 January to 31 December 2019. Patients' sedative burden before admission and on discharge were quantified by the sedative component of the drug burden index (Sed-DBI) and the sedative load model (SLM).
Results. No significant differences were found in the Sed-DBI score and sedative load between admission and discharge in the total study population (n=711). However, significant differences were observed for patients admitted to acute mental health units (n=407) (DBI score: $p<0.0001$; sedative load: $p= 0.018$). Lower pre-admission DBI score, younger age, male gender, a longer length of hospitalisation, and a greater mean number of medications predicted an increase in DBI scores, while a lower pre-admission sedative load, male gender, and a greater mean number of medications predicted an increase in sedative load at discharge.
Discussion. The findings of our study identified patients at a higher risk of being discharged with a significantly higher sedative burden. Future research could focus on patients admitted to acute mental health units, and explore the risks associated with the increased sedative burden in patients on discharge.

207 Patient Reported Experiences Following Implementation of the DBI Intervention Bundle in Hospital

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Introduction. The Drug Burden Index (DBI), which measures a patient's exposure to anticholinergic and sedative medications, is commonly associated with adverse outcomes. A DBI intervention bundle was implemented in the Electronic Medical Records, supported by a stewardship pharmacist to facilitate medication review in hospital.
Aims. Following integration of the DBI intervention bundle, to explore patients' and carers' preferences and experiences of medication management in hospital, their attitudes towards deprescribing and goals of care.
Methods. Eligible patients and their carers were invited to complete self-administered questionnaires and a structured interview within 24 hours of planned discharge. Patients aged ≥65 years admitted for ≥48hours to Aged Care, General Medicine, Rehabilitation, Orthopaedics or Cardiology at two acute Australian hospitals, or their carers, were eligible. Questionnaire and interview results were summarised using descriptive statistics.
Results. A total of 28 participants completed the questionnaires and interviews in the first three weeks of data collection. The majority of participants (85%) reported they would like to be involved in making decisions about in-hospital medication changes, with patient reported experiences shown in the Table. Most (82%) would be willing to stop one or more regular medications if told it were possible by their doctor. The most commonly reported goals of care (n=26) were maintaining good health and preventing illness (54%), optimising functional independence (50%) and symptom control (46%).
Discussion. Preliminary findings suggest that most patients / carers want to be involved in decisions about their medicines and more than half feel sufficiently informed and involved. They could articulate a wide range of goals, which could be used to inform medication management in hospitals.

Patient Reported Experience (n= total number of respondents overall)	%
Told rationale behind medication changes (n=25)	64%
Given opportunity to ask questions (n=25)	68%
Sufficiently involved in medication reduction/ cessation (n=12)	58%
Sufficiently informed about medication reduction / cessation (n=13)	62%
Sufficiently involved in medication increase / initiation (n=16)	56%
Sufficiently informed about medication increase / initiation (n=16)	63%

208 Sleep Health Management in Residential Aged Care Facilities

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Introduction. In humans, sleep is essential for the maintenance of several neurobiological processes such as memory consolidation, mood and metabolic regulation. It is known that sleep patterns vary with age and are affected by multiple factors. While non-pharmacological strategies are generally considered first-line for managing sleep disturbances, sedatives are excessively and inappropriately used in the older population.
Aims. This study aimed to explore the management of sleep health in residential aged care facilities (RACFs) by nurse professionals and to identify the key factors that impact provision of optimal sleep health care.
Method. An inductive thematic qualitative research method was employed to analyse the data collected from semi-structured interviews with registered nurses working in RACFs.
Results. Seventeen interviews were conducted, and the data yielded three themes: 1) the nurses' observations and knowledge of sleep health, 2) the strategies employed in RACFs for the management of sleep disturbances, 3) the organizational barriers to evidence-based sleep health management.
Discussion. Nurse participants reported the use of both non-pharmacological and pharmacological interventions. Sedatives were commonly prescribed due to their fast action and accessibility despite the guidelines indicating their use in later stages. Although benzodiazepines are known for their many side effects, such as drowsiness and oversedation, temazepam was the most commonly administered drug. Sleep in RACFs was affected by several factors such as aging and comorbidities (e.g., dementia, pain, anxiety). However, there were also many modifiable factors that negatively impacted sleep management in RACFs. These include staffing ratios, nursing duties, medication side effects and lack of training and involvement of allied health professionals. This study highlighted the importance of involving a multidisciplinary team and the urge to develop guidelines and training programs for healthcare professionals to improve sleep health management in RACFs.

209 Impact of partnered pharmacist medication charting on potentially inappropriate medication use

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Introduction. With the aim of improving the quality use of medicines and enhancing interdisciplinary collaboration, a partnered pharmacist medication charting (PPMC) model was trialled in the emergency department (ED) of a tertiary hospital.
Aims. To evaluate the impact of PPMC on potentially inappropriate medication (PIM) use.
Methods. A controlled study compared PPMC to two comparison groups among older people (≥ 65 years) presenting to ED. In the PPMC group, pharmacists initially obtained the best-possible medication history (BPMH) and collaborated with medical officers to co-develop treatment plans and chart medications. The early BPMH group included BPMH taking by pharmacists, followed by traditional medication charting by medical officers. The usual care group followed the traditional charting approach by medical officers, without a pharmacist-collected BPMH. Using Beers criteria, PIM use was assessed at ED presentation (i.e. at baseline), ED departure, and hospital discharge. Between-group comparisons used the Kruskal-Wallis test with Dunn's post-hoc test. Within-group comparisons (on ED departure/hospital discharge vs at baseline) used the Friedman rank sum test with a pairwise Wilcoxon rank-sum post-hoc test or Cochran's Q test with Dunn's post-hoc test, as appropriate.
Results. The use of at least one PIM on ED departure was significantly lower for the PPMC group than for the comparison groups (p=0.040). The results were also significant for the median number of PIMs per patient (p=0.036) and PIMs per prescribed medication (p=0.029) on ED departure. However, outcomes at hospital discharge were not statistically different. PIM use on ED departure or hospital discharge did not differ from baseline within the comparison groups.
Discussion. PIM use on leaving ED, but not at hospital discharge, was significantly reduced with PPMC.

210 Carboplatin dose optimisation in the infant cancer patient

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Introduction. Therapeutic drug monitoring (TDM) facilitates evidence-based dosing decisions from an individual's measured drug exposure. This approach to treatment is particularly valuable in infants, as there is high variability associated with AUC due to marked differences in developmental physiology. Carboplatin TDM is well established in the UK, as there is a clearly defined relationship between AUC and efficacy/toxicity, therefore carboplatin is dosed to achieve a desired AUC. For an AUC of 5.2mg/ml.min, doses of 4.4mg/kg (<5kg) or 6.6mg/kg (5-10kg) are administered in infants (Barnett *et al* 2021). If 5.2mg/ml.min is well tolerated then an AUC of 7.8mg/ml.min can be targeted to improve clinical outcome.
Aims. To determine the most optimal body-weight based doses to achieve AUCs of 5.2 and 7.8mg/ml.min in infants. Methods. Real time carboplatin TDM was performed across multiple cycles in 90 patients, ≤10kg. Samples taken on day 1 were analysed on day 2, allowing dose intervention on day 3, based on AUC and CL values determined by Bayesian modelling (Barnett et al 2021). AUC and CL values measured across 165 occasions were utilised to assess variability of current dosing, determine dose required to achieve a target AUC and to predict change in AUC using the modified dose. Dosing regimens were assessed using the percent of target AUC achieved under standard and modified dosing that were within 10% (desirable) or 25% (acceptable) of the target.
Results. High variability in carboplatin dosing (3.3-12.2mg/kg) and exposure (46-167% of target AUC) was observed in infants. For patients <5kg, 4.4mg/kg dosing was not sufficient to achieve a target of 5.2mg/ml.min, with only 48% of patients within the 25% target AUC acceptance limits. In contrast, 6.6mg/kg in patients 5-10kg resulted in a higher proportion within the 25% target window (74%). The required carboplatin daily dose was not significantly different between infants <5kg and 5-10kg, with a dose of 6mg/kg identified as an appropriate regimen for all patients ≤10kg. Additionally, a carboplatin dose of 9mg/kg was required to obtain a target AUC of 7.8mg/ml.min.
Discussion. A more appropriate body-weight carboplatin dosing approach has been identified for infants. Although TDM is still the gold standard approach to ensure patients achieve target exposures, the adoption of these modified doses will benefit treatment centres without routine access to carboplatin monitoring.
Barnett *et al* (2021) *Br J Clin Pharmacol* 87:256–262

211 Feasibility of routine Therapeutic Drug Monitoring for 5-Fluorouracil

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Introduction. In 2019 the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) produced recommendations for the monitoring of 5-Fluorouracil with a target AUC range of 20-30 mg/L*h. However, the monitoring of 5-Fluorouracil is not practiced routinely in Australia, even though approximately two thirds of patients are dosed incorrectly.
Aims. We set out to determine the feasibility of providing a routine TDM service for 5-Fluorouracil.
Methods. We conducted a feasibility study of patients receiving infusions of 5-Fluorouracil greater than 24 hours. Plasma samples were sent to the Clinical Pharmacology Laboratory at the University of Newcastle where they were analysed for 5-Fluorouracil using a validated LC-MSMS. The results of the 5-Fluorouracil analysis were returned to the referring oncologist who then decided whether to adjust the dose of 5-Fluorouracil given to the patient.
Results. The study recruited 38 patients receiving 5-Fluorouracil infusions, which ranged in age from 33 to 77 years. There were 23 males and 15 females. Of the 38 patients 36 received a 46 hour infusion while 2 received a 96 hour infusion. Only 36% (13/36) of patients were within the 5-Fluorouracil therapeutic range consistent with previous studies. Only 1 patient had an AUC greater than 30, while 61% (22/36) of patients had an AUC less than 20. On a second round of monitoring 4/12 achieved an AUC between 20-30, a further 2/4 achieved the target after 3 rounds of TDM and 2 reached the target after 4 and 5 rounds of TDM. Median time to provide results of the clinician was 5 days from collection of the sample with a range of 2 to 9 days.
Discussion. Only 36% of patients achieved the therapeutic 5-Fluorouracil AUC of 20-30 with standard treatment, this was increased to 58% after clinicians decided to increase the dose of 5-Fluorouracil after performing TDM. We have shown that routine TDM of 5-Fluorouracil is feasible with a sample turnaround time of under a week providing oncologist with sufficient time to adjust 5-Fluorouracil dose if desired.
Beumer J (2019) Clin Pharm Therapeutics 105 598-613

212 Phase 1a/1b trial of a tight junction regulator (IMU-856) for coeliac disease

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Introduction. IMU-856 is an orally available and systemically acting small molecule modulator that targets an undisclosed epigenetic regulator. Preclinical studies show that IMU-856 restores barrier function and regenerates intestinal architecture while maintaining immunocompetency in the gastrointestinal tract.
Aims. To determine the safety, tolerability, and pharmacokinetics of IMU-856 in healthy volunteers.
Methods. Healthy volunteers received single ascending doses (10 to 160 mg) or multiple ascending doses (40 mg to 160 mg once daily for 14 days) of IMU-856 or placebo. Safety and tolerability were assessed by physical examination, clinical laboratory tests, vital signs, and 12-lead electrocardiograms. The concentration of IMU-856 in plasma was measured using a validated LC-MS method and pharmacokinetic parameters were estimated using non-compartmental analysis.
Results. IMU-856 showed near linear pharmacokinetics following single ascending (n=33) and multiple ascending (n= 22) doses, with minimal accumulation (C_{max} and AUC_{inf} increased ~1.5-fold after 14 days). The T_{max} was between 2 to 5 hours and the terminal t½ of IMU-856 ranged from 14-20 hours. Steady-state plasma concentrations of IMU-856 were reached after ~4 days. Most related treatment-emergent adverse events were mild in severity, with no dose-dependency. There were no clinically important findings relative to safety and tolerability.
Discussion. IMU-856 was safe and well-tolerated with a benign adverse effect profile in healthy volunteers. The pharmacokinetics of IMU-856 allow once-daily dosing. The ongoing phase 1b will provide initial data for IMU-856 in patients with well-controlled celiac disease during periods of gluten-free diet and gluten challenge.

213 Is Cannabidiol a Clinically Relevant Anti-Cancer Drug?

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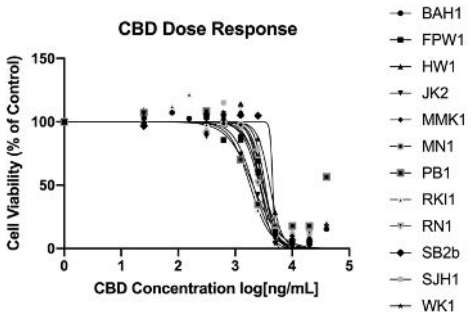
Introduction: Whilst pre-clinical reports have demonstrated the anticancer properties of cannabidiol (CBD), a non-intoxicating constituent of the cannabis plant, clinical evidence remains unclear.
Aim: To assess whether *in vitro* CBD concentrations are clinically relevant.
Method: 12 patient-derived glioblastoma cell lines (11 primary and 1 recurrent) were incubated with various concentrations of CBD for 72 hours, and cell viability measured in triplicate repeats.
Results: The half maximal inhibitory concentration (IC50) was determined by Prism to be on average 2,945 ng/mL (2,863 to 3,029 95% CI), with little variation across the 12 glioblastoma cell lines.



Discussion: Patients in a clinical trial treated with an oral dose of CBD either: placebo, 200mg, 400mg, or 800mg - producing a steady state CBD blood plasma concentration of 0, 10, 22, and 63ng/mL respectively[1]. From this and our CBD IC50 data, a dose of 40,000mg or 40g of oral CBD would be required to cause toxicity to glioblastoma tumour cells. A CBD study in rhesus monkeys, reported a median lethal dose (LD50) of 212 mg/kg for intravenous injection[2] – which would be equivalent to 12,000mg or 12g of CBD in a 60kg human.
Conclusion: The CBD dose required to reach glioblastoma IC50 plasma concentrations in humans, likely exceeds the LD50.

(1) Freeman TP et al. Lancet Psychiatry (2020). (2) Rosenkrantz et al. Toxicol Appl Pharmacol (1981).

214 Drug Burden Index Intervention Bundle for medication review: patient and clinician experiences

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Introduction. The Drug Burden Index (DBI) measures a person's total exposure to anticholinergic and sedative drugs. We piloted an intervention bundle including the DBI embedded in the hospital Electronic Medical Records, clinician deprescribing guides, consumer leaflets and a Stewardship Program to facilitate medication review and deprescribing.
Aims. Following implementation of the bundle, to explore i) hospital clinician experiences of using the bundle and ii) patient, carer and General Practitioner's (GP's) experiences of in-hospital medication review and deprescribing.
Methods. Semi-structured interviews were conducted with hospital clinicians, patients and carers at an Australian tertiary referral hospital. Doctors or pharmacists in Aged Care or General Medicine services were eligible. Patients aged≥75 years with high DBI (DBI≥1) in the target services, and their carers were eligible. Surveys were distributed to consenting patients' GPs. Survey responses were summarised using descriptive statistics. Qualitative interview data was thematically analysed. Clinician interviews were mapped to domains from the Human Organisation Technology-fit Framework. Patient interviews were mapped to the National Health Service Patient Experience Framework.
Results. Eight clinicians completed the interviews and mainly reported themes around the subdomain of system use. Seven patients and two carers completed the interviews and mainly reported themes around information, communication and education. Four GPs completed the survey. Clinicians reported that the bundle supported in-hospital communication such as facilitating medication review during ward rounds but reported challenges such as heavy workload, with suggestions to further integrate the bundle into existing workflows. Most patients with deprescribing reported feeling better or no different. Patients, carers and all surveyed GPs described poor communication from hospital clinicians regarding in-hospital medication changes and rationale behind changes.
Discussion. The DBI intervention bundle was well-accepted by hospital clinicians but requires further integration into existing workflows for sustainability. Future studies should aim to facilitate communication of in-hospital medication review and rationale behind medication changes with all stakeholders involved in medication management.

215 An LC-MSMS assay of Cannabidivarin and metabolites

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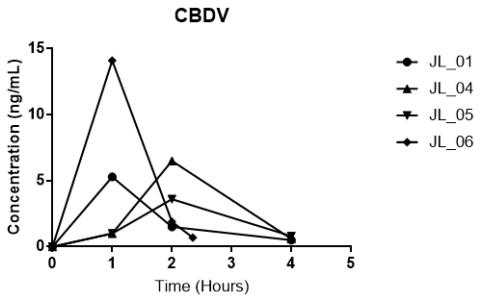
Introduction. Cannabivarin (CBDV) is a propyl analogue of Cannabidiol and expresses efficacy in seizure-reduction in pre-clinical models of epilepsy. To investigate the pharmacokinetics of CBDV in a trial of RETT syndrome, an assay needs to be developed.
Aims. To develop and validate an LC-MSMS assay of CBDV and metabolites: 6-hydroxy-CBDV, 7-hydroxy-CBDV, 7-carboxy-CBDV in human plasma.Methods. CBDV and metabolites were extracted from plasma by addition of 0.1% formic acid in acetonitrile and deuterated standards and injected onto a Shimadzu 8060 Triple quadrupole LCMSMS using a Restek Raptor ARC-18 column and binary gradient with mobile phases 0.1% formic acid in water, and acetonitrile.
Results. Method validation followed FDA bioanalytical method guidelines. The analytical range was validated from the limit of quantitation of 0.5ng/mL to 50ng/mL for 6-hydroxy-CBDV, 7-hydroxy-CBDV, and CBDV, and 50ng/mL to 5000ng/mL for 7-COOH-CBDV. Intra-batch imprecision for all compounds was 6.7-11.4% and inter-batch was 6.9-13.8%. Accuracy for all compounds was between 86 – 113 % and matrix effects were accounted for by internal standards. PK was analysed for five children to generate AUC's and calculate C-max at approximately 2 hours. Values were within analytical range, except one 7-Carboxy-CBDV trough value at 15 months of 11,109ng/mL.



Discussion. A method was successfully developed and validated to assay patient samples to ascertain PK of CBDV and metabolites in human plasma.
Hurley E et al(2022) Epilepsia, 63:7 pp 1736-1747

216 Amnion Epithelial Cell Therapy Reduces Vascular injury and Cognitive Impairment after Hypertension and Stroke

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Introduction. Hypertension is a major risk factor for stroke and cognitive impairment. Current therapies for hypertension and ischaemic stroke can effectively reduce blood pressure or restore blood flow but they do not target underlying mechanisms. Cell therapy has great therapeutic potential for many conditions as, unlike single pharmacological agents, cells can deliver multiple mediators which could more effectively target complex disease mechanisms. Human amnion epithelial cells (hAECs) have many properties (eg. anti-inflammatory, anti-fibrotic and immunologically inert) that make them attractive candidates for a cell-based therapy for cardiovascular diseases.
Aims. To test the potential of hAECs to treat hypertension and stroke induced vascular and brain injury.
Methods. Male C57Bl6 mice (8-12 weeks) were administered vehicle (saline) or angiotensin II (0.7 mg/kg/d) for 14 d via a subcutaneous osmotic minipump. After minipump implantation, a subset of mice were injected with 10^6 of hAECs intravenously. Systolic blood pressure was measured using tail-cuff; inflammation was assessed using flow cytometry and markers of fibrosis using quantitative PCR. In a separate cohort of mice stroke was targeted to the pre-frontal cortex (PFC) using the photothrombotic method. A subset of mice were injected with 10^6 of hAECs intravenously 1 day after stroke. Cognitive function was assessed using the Barnes maze or novel object recognition test (NORT).
Results. Treatment with hAECs limited the development of hypertension by angiotensin II (185⍰5 mmHg vs 165⍰4 mmHg; n=9-11, P<0.05), as well as hypertension-induced aortic inflammation and expression of *Col1a1* and *Col5a1*. Hypertensive mice had impaired working memory, which was restored with hAEC treatment. Twenty-eight days after stroke, mice exhibited impaired learning and cognitive flexibility as assessed in the Barnes maze (~50% increase in time taken to locate and enter the escape hole). hAEC therapy ameliorated the impaited learning and cognitive flexibility.
Discussion. Intravenous administration of hAECs blunted angiotensin II-induced hypertension, aortic inflammation, markers of fibrosis and cognitive impairment. hAEC therapy also improved post-stroke cognitive impairment. This study suggests that hAECs or their cellular products could be explored as treatments hypertension or stroke.

217 Antihypertensive effects of neurosteroid ganaxolone in two rodent models

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Introduction. Ganaxolone (GNX) is a synthetic form of allopregnanolone, an allosteric modulator of GABA A receptors ($GABA_AR$). In male hypertensive mice (BPH/2J), allopregnanolone reduced BP and restored $GABA_AR$ d-subunit mRNA in the hypothalamus and medial amygdala (MeAm), suggesting that a lack of tonic inhibition in the forebrain mediates hypertension in this model. Yet, GNX's antihypertensive therapeutic potential has to be established.
Aims. To determine the antihypertensive effects of GNX in BPH/2J and in spontaneously hypertensive rats (SHR).
Methods. Hypertensive and normotensive animals were implanted with telemetry probes to measure cardiovascular parameters. The cardiovascular response to stressors and pentolinium were measured before and 2 weeks after treatment with GNX or vehicle. δ-$GABA_AR$ mRNA expression (qPCR) and protein levels (IHC) were also measured.
Results. Compared to pre-treatment, BP was selectively reduced in GNX-treated hypertensive strains (-9 to 11 mmHg; $P<0.001$), in both males and females, while no difference was observed in vehicle-treated nor normotensive animals. The pressor response to stressors was exaggerated in hypertensive compared to normotensive rodents ($P<0.01$), as well as the depressor response to ganglion blockade ($P<0.01$). Female BPH/2J treated with GNX had a reduced pressor response to stress compared to pre-treatment (-40%, $P<0.05$) and a decreased depressor response to pentolinium (-32%, $P=0.02$). Similarly, GNX-treated male BPH/2J had a reduced pressor response to stress (-20 to 38%, $P<0.001$), but no change in depressor response to pentolinium. The cardiovascular response to stress and pentolinium in rats was not changed by GNX treatment. In the hypothalamus, δ-$GABA_AR$ mRNA expression was lower in BPH/2J than in normotensive BPN/3J, and GNX treatment restored levels like BPN/3J. In rats, while δ-$GABA_AR$ mRNA expression was unaffected by the strain or treatment, δ-$GABA_AR$ protein level was higher in the MeAm and hypothalamus of SHR treated with GNX compared to vehicle-treated animals ($P<0.005$).
Discussion. GNX is a promising antihypertensive strategy as we showed a consistent and potent BP reduction in 2 different models of hypertension, males and females. However, it is still unclear if GNX effects are dependent on SNS activity, they may be related to the increase of the $GABA_AR$ δ-subunit protein expression and activity.

218 The citrus bioflavonoid hesperidin reverses metabolic and hepatic abnormalities in metabolic syndrome.

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Introduction. Metabolic syndrome (MetS) is a cluster of metabolic abnormalities (i.e. hypertension, obesity, dyslipidemia, hyperglycemia and hyperinsulinemia) that affects 1 in 4 people. MetS increases cardiovascular risk and all-cause mortality. Inflammation is a major cause of end-organ damage in MetS, suggesting that anti-inflammatory molecules could benefit MetS patients. Hesperidin, a potent citrus bioflavonoid, has well-established anti-inflammatory properties, but its effects in the setting of metabolic syndrome, particularly on the liver are unclear.
Aims. To determine the optimal dose of hesperidin required to improve circulating and hepatic inflammation, and glycaemic control in mice with MetS.
Methods. Male C57BL6 mice were fed a high-fat salt sugar diet (HFSS; fat content = 43% kcal and drinking water with 0.9% saline and 10% high fructose corn syrup) from 5 weeks of age to induce metabolic syndrome. Following 6 weeks of the diet, mice were randomly allocated to receive daily high or low doses of hesperidin (70 or 280 mg/kg, respectively) or placebo for 12 weeks. Mice fed a normal control diet (NCD) receiving placebo were used as healthy controls. Physiological parameters were measured weekly and fortnightly. At end point, blood and livers were collected and immune cell populations were characterized using flow cytometry.
Results. HFSS significantly ($P<0.05$) increased weight gain, fasted blood glucose, plasma insulin and blood cholesterol (specifically high-density lipoprotein, HDL). Hesperidin treatment had no effect on weight gain or blood glucose, however, high dose hesperidin significantly reduced plasma insulin and low-dose hesperidin significantly reduced HDL, Total hepatic immune cell counts were reduced in HFSS mice, specifically CD4+ T cells. Interestingly, high dose hesperidin significantly increased total hepatic immune cells. Specifically, myeloid-derived (CD11b+) and CD8+ T cells that were significantly increased in high-dose hesperidin-treated mice, but not CD4+ T cells. Low dose hesperidin had no effect on any of the hepatic immune cell populations.
Discussion. Hesperidin improved glycaemic and lipid control in MetS. Surprisingly, MetS was associated with a reduction in hepatic leukocytes. High dose hesperidin treatment reversed this abnormality, but via varying leukocyte subsets. Further analyses (qPCR and histology) are currently underway to further explore these mechanisms of action.

219 The role of endothelial angiotensin II receptors in the release of nitric oxide

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Introduction. The renin-angiotensin-aldosterone system (RAAS) plays a major role in the cardiovascular system, including blood pressure regulation. The principal mediator of is angiotensin II (AngII), is known to act through two receptors, type 1 (AT1R) and type 2 (AT2R). AT1R has been thoroughly studied and acts to stimulate vasoconstriction, however, the role of AT2R in response to AngII remains undefined.
Aims. To investigate whether AT2Rs and/or nitric oxide (NO) influence AngII-mediated vasoconstriction in rat small mesenteric arteries (RMA).
Methods. Third order mesenteric arteries (200-300 µm) were isolated from male Wistar rats. Receptor expression was assessed using whole RMAs imaged *en face* for immunolabel. Vasoconstriction in response to AngII (10 pmol/L – 10 nmol/L) was measured using wire myography in the presence of either AT1R, AT2R or NO synthase (NOS) blockade with losartan (1 µmol/L), PD123319 (1 µmol/L) or L-NAME (100 µmol/L), respectively. Responses are presented as percentage of 45 mM K+ vasoconstriction. All data are shown as the mean±SEM, and subjected to two-way ANOVA with repeated measures (Greisser-Greenhouse correction) and Bonferroni multiple comparisons.
Results. Expression of AT1R was found within both vascular endothelial (VEC) and smooth muscle cells (VSMC), whereas AT2R was restricted to VECs. AngII stimulated concentration-dependent vasoconstriction in RMA (E_{max} 48.2±6.6%; EC_{50} 7.8 nM; n=28). Block of AT1R abolished vasoconstriction to AngII (E_{max} 1.0±0.3%, $p<0.05$; n=14). In contrast, AT2R block augmented vasoconstriction to AngII (E_{max} 102.6±23.6%; EC_{50} 1.7 nM; n=6). The influence of the endothelium was investigated in denuded arteries, where AngII vasoconstriction was markedly augmented (E_{max} 194.2±25.6% $p<0.05$; EC_{50} 1.7 nM; n=8), and was now not further increased during block of AT2Rs (E_{max}135.9±12.9%; EC_{50} 1.2 nM; n=5). Similarly, block of NOS with L-NAME augmented contraction to AngII (to that seen in denuded arteries; E_{max} 178.6 ± 23.2% $p<0.05$; EC_{50} 2.5 nM; n=21), and block with L-NAME was not further increased during block of AT2Rs (E_{max} 194.4 ± 29.2%; EC_{50} 0.8 nM; n=6), effectively removing the influence of the endothelium.
Discussion. Together these results demonstrate that both VEC AT1R and AT2R suppress VSM AT1R-mediated vasoconstriction by releasing NO from the endothelium.

220 Effects of Human Amnion Epithelial Cells In Experimental Chronic Stroke

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Introduction. Treatment with human amnion epithelial cells (hAECs) is neuroprotective within 90 min of experimental stroke. However, the broader therapeutic window is not yet defined.
Aims. To investigate the therapeutic window of hAECs therapy during chronic stroke in aged mice.
Methods. Male (n=46) and female (n=58) C57BL/6 mice (12-16 months) were subjected to photothrombotic stroke in the left M1 cortex. Mice were treated with saline or hAECs (1x106 i.v.) at day 1, day 7 or both days 14 and 35 post-stroke. Cylinder tests were performed prior to stroke and treatments, and after weeks 5 and 8 to assess motor asymmetry. Mice were euthanised at 8 weeks for infarct analysis.
Results. Preliminary data showed that mice treated with hAECs at day 1 following stroke recovered at a faster rate than those treated with saline (P=0.04, linear mixed analysis), with a tendency for a smaller infarct at 8 weeks (p=0.06). Treatment with hAECs at day 7 following stroke appeared to promote recovery in females (P=0.08, linear mixed model analysis). By contrast, treatment with hAECs on days 14 and 35 following stroke had no effect on motor impairment in either sex as assessed at 8 weeks. Thus, systemic treatment of aged mice at 1 day (but not from 14 days) after stroke can promote motor recovery. Treatment of females with hAECs as late as 7 days following stroke may be beneficial for long-term functional recovery.
Discussion. Ongoing studies are examining effects of hAECs therapy in males within 7 days of stroke.

221 Unravelling the intracellular signalling pathways in CGRP-induced vasorelaxation in rat coronary arteries

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Introduction. Calcitonin gene-related peptide (CGRP) may play an important role in modulating coronary microvasculature resistance and is known to be cardioprotective. However, despite its clinical importance, the precise signalling pathways underlying vasodilation are yet to be elucidated in these vessels.
Aims. To establish the role of endothelial cells (ECs) and smooth muscle cells (SMCs) and the signalling pathways activated during CGRP-induced vasorelaxation in the coronary microvasculature.
Methods. Coronary septal arteries were isolated from male Wistar rats and mounted in the wire or pressure myograph at 37°C and left to develop myogenic tone. ECs were removed with a hair and confirmed by <10% relaxation to 1 µmol/L ACh. Arteries were pre-incubated with inhibitors for 15 minutes prior to CGRP application. For EC Ca^{2+} imaging, ECs were selectively loaded with Oregon Green BAPTA and Ca^{2+} activity was recorded using a linescan confocal microscope. EC Ca^{2+} activity was analysed using Imaris. Data were analysed using either parametric two-way ANOVA with Sidak's multiple comparisons or paired t-test, or non-parametrically using Mann-Whitney with multiple comparisons followed with Bonferroni-Dunn correction. $p < 0.05$ was considered statistically significant.
Results. CGRP (1 pmol/L–10 nmol/L) caused a concentration-dependent relaxation (EC_{50} 50 pmol/L, n=6) that was right-shifted by the nitric oxide synthase inhibitor, L-NAME (100 µmol/L, EC_{50} 1.4 nmol/L, n=6), and removal of the endothelium (EC_{50} 1.6 nmol/L, n=14). The Gbg-subunit inhibitor, gallein (100 µmol/L), also significantly attenuated vasorelaxation to CGRP (EC_{50} 50 nmol/L, n=5). No global increase in EC intracellular Ca^{2+} was observed (F/F0 = 0.98±0.05, n=5) following CGRP application in ECs loaded with Ca^{2+} indicator, but it was observed in response to ACh (F/F0 = 1.28±0.02, n=5).
Discussion. This study indicates that the most potent CGRP-induced vasorelaxation in rat septal arteries is EC-dependent. EC dysfunction in the coronary microvasculature underlies several pathological conditions and results in the reduced bioavailability of nitric oxide; therefore, this could attenuate the vasodilator action of CGRP on coronary vessels in these patients. Interestingly, it appears that CGRP-induced nitric oxide release relies on a Ca^{2+}-independent pathway. Furthermore, these data suggest that both the EC-dependent and -independent components to CGRP vasorelaxation occur via a Gbg-mediated signaling pathway in rat coronary arteries.

222 Bias profile and efficacy-driven selectivity of xanomeline at the muscarinic acetylcholine receptor family

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Introduction. Activation of the M_4 muscarinic acetylcholine receptor (mAChR) has emerged as a promising approach for the treatment of schizophrenia, with anticipated outcomes beyond those provided by current antipsychotic medications. The progress of xanomeline in Phase III clinical trials is a promising unprecedented step towards better treatment options [1]. Xanomeline is an efficacy-driven selective muscarinic agonist, meaning it binds to M_1-M_5 mAChRs with identical affinity, but signals more strongly at specific subtypes, in particular the M_4 mAChR, compared to all others. Is the signal preference of xanomeline at the M_4 mAChR shared across the multiple cellular responses available to it, and what is the structural basis for the efficacy-driven selectivity of xanomeline?
Aims. We aimed to i) assess the signalling profile of xanomeline at the M_4 mAChR across a wide range of signalling events, and ii) elucidate its mechanism of efficacy-driven selectivity at the mAChR family.
Methods. We used a combination of analytical pharmacology, computational biology, biochemistry and chemistry.
Results. Xanomeline displays a significant biased signalling profile at the M_4 mAChR compared to the endogenous agonist, ACh [2], that is not conserved at the M_2 mAChR. Additionally, xanomeline's binding pose, similar across mAChRs in their inactive states, differs significantly between mAChRs in their active states. Such difference between M_4 mAChR versus other subtypes is predominantly driven by the position of the extracellular loop 2 directing the orientation of the aliphatic tail of xanomeline in the binding pocket, influencing its signalling strength depending on the receptor subtype.
Discussion. With its successful progress to Phase III, xanomeline may become the first novel class of drug for the treatment of schizophrenia in almost 50 years. Elucidation of the mechanism of efficacy-driven selectivity of xanomeline at the mAChR family will assist in guiding the rational design of future efficacy-driven selective drugs for other receptors.

[1] https://clinicaltrials.gov/ct2/show/NCT04659161.
[2] McDonald JK et al. (2022) ACS Chem Neurosci. 12, 3112–3123

223 Investigating the pharmacological relationship between GPR161 and spexin-1

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Introduction. GPR161 is a Family A orphan G protein-coupled receptor (GPCR) localised to a highly specialised structure of the cell, primary cilium, and involved in the negative regulation of the Sonic Hedgehog signalling pathway. Loss of GPR161 in zebrafish results in aberrant cardiac looping and in mice can lead to lumbar-sacral spina bifida, congenital cataracts and embryonic lethality. Recently, spexin-1, a 14-amino acid neuropeptide, was proposed to be a putative ligand for GPR161 (Foster et al, 2019), however, this has not yet been fully validated.
Aims. To investigate the pairing of GPR161 to the endogenous peptide, spexin-1.
Methods. RNA expression data was sourced from the Human Protein Atlas and Genotype-Tissue Expression project across 19 healthy, human tissues. Proximal interactions between GPR161 and downstream effector molecules such as G alpha (Gα) proteins and β-arrestins, and downstream extracellular signal-regulated kinases (ERK) activation were quantified using bioluminescence resonance energy transfer (BRET) assays while changes in distal second messenger levels were measured using the cyclic AMP response element (CRE) reporter gene assay, upon spexin-1 treatment. Appropriate positive controls were established for all assay systems in each individual experiment.
Results. GPR161 appears to show constitutive activity through the Gαs signalling pathway consistent with previous reports in the literature. Compared to control, no concentration-dependent change in Gα protein activation (via Gαs, Gαi1, Gαi2 or Gαi3), β-arrestin2 recruitment or ERK1/2 activation was observed for spexin-1 at GPR161. Expression of GPR161 was shown in HEK293 cells using enhanced yellow fluorescent protein (eYFP) and FLAG-tagged constructs.
Discussion. These preliminary results indicate that spexin-1 likely does not activate GPR161, despite there being some overlap in RNA expression of the two genes.

Foster SR et al (2019) Cell 179:895-908.e821

224 Characterisation of Casein Kinase 1 Delta transcript variants in breast cancer tumourigenesis

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Introduction. Casein Kinase 1 Delta (CK1δ) is a conserved serine/threonine protein kinase with three splice variants (CK1δ1/2/3) that are highly expressed in metastatic and primary breast tumour cells and involved in cellular processes, such as circadian rhythm and inflammation. When CK1δ is knocked down or pharmacologically inhibited, breast tumour cell invasiveness and tumorigenicity is suppressed in cell lines and in orthotopic xenograft models (Bar et al., 2018). CK1δ splice variants present attractive molecular targets for the development of novel therapeutics.
Aims. To explore the role of CK1δ transcript variant expression and function in human breast tumour cell lines.
Methods. MDA-MB-231.NI parent and CSNK1D shRNA knockdown cells were incubated with 3 μM of CK1δ/ε inhibitor PF670462 for 48h. Cells were imaged using fluorescence microscopy for immunoreactive CK1δ. CK1δ protein expression was measured with western blot and CSNK1D/E mRNA are measured by RT-qPCR. IL-1α (30 pM) induced IL-6 and IL-11 cytokine levels and mRNA are measured by immunoassay and RT-qPCR.
Results. Knockdown of CK1δ variants display counter-regulation and/or compensation through increased CSNK1E expression. Knockdown of CK1δ2 results in significant increase of CK1δ1 ($n=3;P<0.05$). Inhibition of CK1δ/ε with PF670462 (3 μM) significantly increases immunoreactive CK1δ in MDA-231 cells ($n=3;P<0.0003,P<0.05$). Knockdown of both CK1δ1/2 prevents this increase. Partial counter-regulatory increase is observed when only CK1δ2 is knocked down. PF670462 attenuated fibrogenic cytokine levels, IL-6 and IL-11, following 30 pM IL-1α stimulation ($n=3$; $P<0.05$).
Discussion. CK1δ, and its transcript variants, have complex co-regulatory pathways with potential substrate redundancy and preferential expression. CK1δ can inactivate itself through autophosphorylation which suggests tightly regulated mRNA. Cytokine attenuation by PF670462 indicates potential to modulate the metastatic precursor, tumour fibrosis. These results present promising evidence for potential transcript variant specific influence on tumourigenic behaviour and the therapeutic potential of their inhibition.
Bar et al (2018) Silencing of casein kinase 1 delta reduces migration and metastasis of triple negative breast cancer cells. *Oncotarget*, *9*(56), 30821-30836. doi:10.18632/oncotarget.25738

225 Gs priming of non-Gs protein activation and signalling at the glucagon-likepeptide-1 receptor

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Introduction. The glucagon-like peptide-1 receptor (GLP-1R) is a class B1 G protein-coupled receptor (GPCR) and a very important therapeutic target for the treatment of type-2 diabetes and obesity. The GLP-1R preferentially couples Gs when activated by endogenous peptide agonists, leading to the production of cAMP, however the GLP-1R also couples to other G protein subtypes including Gq, which results in the release of intracellular calcium. However, it remains unclear how the GLP-1R can pleiotropically couple to more than one class of G protein, and the contribution of individual transducers to integrated cellular responses.
Aims. This study aimed to explore the contribution of Gs and Gq to downstream signalling and to gain mechanistic insight into how the receptor can couple to both classes of G protein in response to peptide and non-peptide ligands.
Methods. cAMP production and calcium mobilisation were measured in response to increasing concentrations of ligand in wild-type (WT) and CRISPR-Cas9 HEK cells lacking either endogenous Gs (ΔGs) or Gq/11(ΔGq/11) proteins. The effect of Gs on heterotrimeric Gq protein activation was monitored in HEK ΔGs cells using TRUPATH. All cell lines stably expressed the GLP-1R at similar levels. The agonists assessed include GLP-1 (the endogenous ligand), Peptide-19 (dual incretin receptor peptide), exendin-4 (4FDA approved GLP-1R agonist) and PF 06882961 (small molecule ligand).
Results. All agonists promoted cAMP production in HEK WT and HEK ΔGq/11 cells, but responses were abolished in HEK ΔGs cells. Furthermore, while Gq/11 was essential for calcium mobilisation, with responses abolished in HEK ΔGq/11 cells, calcium responses were also heavily impaired in HEK ΔGs cells. Restoration of Gs expression in HEK ΔGs cells rescued GLP-1R mediated calcium response. Further experiments revealed Gs overexpression increased the dissociation of the Gq or G11 heterotrimer (using TRUPATH) in both HEK ΔGs cells and cells lacking all G proteins.
Discussion. Our data corroborate known findings implicating Gs and Gq as the main G proteins that mediate cAMP production and calcium signalling, respectively, downstream of GLP-1R activation. Our data also reveals that Gs is required for GLP-1R calcium signalling that results from the ability of Gs to enhance GLP-1R-mediated activation of Gq and G11 proteins. We therefore propose that Gs primes the GLP-1R into its active conformation for subsequent coupling and activation of Gq/11.

226 Investigating the atypical DRY motif of the potential lipid-lowering orphan receptor GPR146

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Introduction. GPR146 is an orphan G protein-coupled receptor (GPCR) recently linked to atherogenesis through promoting increased total serum cholesterol. It is thought act via a novel hepatic mechanism that increases very low-density lipoprotein (VLDL) secretion, and therefore may be inhibited by pharmacological agents to achieve lipid-lowering effects (Yu et al., 2019). However, the development of GPR146-targeted drugs is hampered by unknowns surrounding its function. We noted an atypical Asp-Arg-Tyr sequence in the DRY motif, which is known to regulate receptor expression and signalling. GPR146 is one of only two known receptors where arginine is substituted for a histidine, possibly presenting implications for its cellular behaviour and trafficking.
Aim. This study aims to investigate cell surface expression and constitutive signalling profiles of wild-type GPR146 and two DRY motif mutants (H3.50R, H3.50Y), where the histidine at position 3.50 is replaced either by the canonical arginine or a tyrosine residue identified in rodent orthologs.
Results. GPR146 constructs were transiently transfected into HEK293 cells and expression profile analysed by immunoblot. Whole-cell GPR146 expression did not significantly differ between DRY motif variants, and discrete receptor populations could be produced upon deglycosylation. All three variants displayed similar plasma membrane expression profiles in biotinylation pull-down studies. While previous studies have suggested coupling of GPR146 to the Gαs pathway, we report no constitutive activity of any DRY mutant through a downstream CRE-luciferase reporter assay.
Discussion. As whole-cell expression of GPR146 is equivalent across wild-type, H3.50R, and H3.50Y variants, the atypical motif is unlikely to influence receptor translation and maturation. Similarly, membrane expression is observable and broadly consistent among the constructs, suggesting that the DRY mutants examined do not influence receptor trafficking to the cell surface. However, further investigation may be warranted to confirm if this behaviour is conserved in native cell types. Finally, while GPR146 mutations did not affect constitutive Gαs GPR146 signalling, other pathways remain to be explored.

Yu, H. et al. (2019). Cell 179(6) 1276-1288.e1214.

227 Fine-tuning glutamate receptor activity with allosteric inhibitors for neurodegenerative and psychiatric disorders

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Introduction. The major excitatory neurotransmitter glutamate acts via ionotropic and metabotropic glutamate receptors (mGlu). Allosteric inhibitors binding to alternate sites at the mGlu5 subtype are promising therapeutic strategies for neurodegenerative and psychiatric disorders. Allosteric inhibitors offer the potential to fine-tune receptor activity as well as greater subtype selectivity compared to competitive counterparts. Historically, discovery programs have classified allosteric inhibitors based on effects on canonical signalling responses alone. We have recently identified novel mGlu5 signalling fingerprints and a new role in cellular metabolism, which we hypothesise may be linked to differential preclinical profiles of structurally diverse allosteric inhibitors.
Aims. To profile diverse mGlu5 allosteric inhibitors at multiple measures of mGlu5 activity, linking molecular pharmacological properties to preclinical and clinical effects.
Methods. Using a combination of recombinant cells expressing human or rat mGlu5 as well as primary brain cell cultures, we profiled structurally diverse mGlu5 allosteric inhibitors for modulation of orthosteric agonist stimulation of different signalling responses. Rigorous analytical methods were applied to quantify allosteric inhibitor cooperativity and affinity using second messenger assays and range of compartmentalised kinase biosensors to measure: IP1, intracellular Ca2+, extracellular signal regulated kinases and AMP-activated protein kinase.
Results. We show mGlu5 signals to AMPK, a previously unappreciated connection between mGlu5 activity and cellular metabolism. By employing compartmentalised biosensors, we found structurally diverse mGlu5 allosteric inhibitors differentially influenced spatio-temporal mGlu5 activity. Probe dependence was evident for allosteric inhibition of glutamate versus quisqualate, which has implications for translating to primary brain cell cultures and in vivo effects.
Discussion. Ultimately, this work is providing an enriched understanding of the molecular properties of diverse allosteric inhibitors with varied preclinical and clinical effects. By unveiling previously unappreciated bias and kinetic profiles for mGlu5 allosteric inhibitors, this work has the potential to inform future, rational, drug discovery efforts.

228 Phosphodiesterase (PDE) Inhibitors as novel drugs for the treatment of respiratory diseases

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Asthma and COPD are respiratory diseases with significant unmet needs with current treatments being the use of inhaled bronchodilators (β2 agonists and muscarinic receptor antagonists), along with inhaled glucocorticosteroids as anti-inflammtory drugs. Another pharmacological approach to treating asthma and COPD is the inhibition of the PDE family of enzymes as another class of drugs still used in the treatment of respiratory diseases are the xanthine seg theophylline, that are non-selective PDE inhibitors. However, they have fallen out of favour in many parts of the world with the advent of inhaled drugs as they have a narrow therapeutic window. However, PDE4 is now recognised as the predominant PDE isoform in most inflammatory cells considered of importance in the pathogenesis of asthma and COPD, whilst PDE3 is understood to be the predominant PDE in airway smooth muscle. Inhibition of PDE3 induces airway smooth muscle relaxation and inhibition of PDE4 inhibits the activation of inflammatory cells. This has led to the development of a number of PDE 4 inhibitors being developed and the orally active PDE4 inhibitor roflumilast is now approved as an anti-inflammatory drug to reduce exacerbations, but is restricted to "add on therapy" for the treatment of patients with severe COPD on top of standard of care as this drug also has a very narrow therapeutic window which limits it's wider use.
To try and improve the therapeutic window, a number of inhaled PDE4 inhibitors have been developed, but to date they have shown only modest clinical benefit with a number of molecules being dropped from development, except Tanimilast (CHF6001) that is still undergoing clinical trials as a treatment for asthma and COPD (1). Ensifentrine is an inhaled drug exhibiting both PDE3 and PDE4 inhibition in the same molecule that has both bronchodilator and anti-inflammatory activity. This "first in class" "bifunctional" drug has been demonstrated to cause significant bronchodilator activity in patients with asthma or COPD (2). In addition, bronchodilator doses of ensifentrine inhibits LPS-induced recruitment of inflammatory cells into the lungs of healthy volunteers confirming its anti-inflammatory effects (2). Recently ensifentrine has successfully completed a Phase 3 trial in patients with COPD that have shown a very significant reduction in exacerbations (3). Importantly, use of this "bifunctional" drug has not been associated with any significant gastrointestinal or cardiovascular side effects and ensefentrine shows promise as a future treatment strategy for patients with asthma or COPD (2,3).

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2. Franciosi et al. Lancet Respiratory Medicine. 1: 714-727 (2013)
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229 Influenza A virus infection in pregnancy: acute and chronic manifestations beyond the lung

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Seasonal epidemics and pandemics to viruses such as influenza A virus (IAV), respiratory synctitial virus and SARS-CoV-2 result in significant mortality and morbidity. Respiratory viral infections are considered to cause a broad spectrum of disease including localised upper respiratory tract disease or in more severe cases a manifestation of a lower respiratory tract disease culminating in pneumonia. However, in some individuals a severe widespread systemic disseminated disease can also ensue resulting in cardiovascular complications. This has been demonstrated in high risk cohorts in particular pregnant women. Pregnancy is a heightened state of immunosuppression whereby the immune system increases tolerance to foetal antigens to ensure successful pregnancy. However, this state raises the risk of severe disease to viral infections.
Here, I will present pre-clinical evidence to put forward the hypothesis that influenza A virus infection in pregnancy triggers a "Vascular Storm" event resulting in inflammation in the cardiovascular system, placenta and foetus. The vascular storm is not an acute event but rather it represents an initial trigger or 'hit' of a delayed sequelae of phenotypic changes that occur in the cardiorespiratory system in both women and their offspring.
The 3 key questions to be discussed are:
1. What are the mechanisms driving the vascular storm by IAV in pregnancy?
2. What are the anatomical sites of the vascular storm?
3. Does the vascular storm affect the long term respiratory and cardiovascular health of women and their offspring?
Finally, I will discuss i) therapeutic strategies for modulating the virus-dependent vascular storm and ii) why better clinical management of gestational influenza and women's health post-partum is necessary to prevent future cardiovascular complications.

Liong S et al. (2020) PNAS, 117 (40) 24964-24973.
Oseghale, Liong et al, (2022) PLoS Pathogens, https://doi.org/10.1371/journal.ppat.1010703.

230 Challenging the inhibitory/excitatory paradigm: Increased GABAergic inhibition can lead to epilepsy

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Introduction. Patients with developmental and epileptic encephalopathies (DEE) can present with variants in genes that code for $GABA_A$ receptors. Historically, these variants are presumed to cause loss-of-function receptors leading to reduced neuronal GABAergic activity. Yet, patients with $GABA_A$ receptor variants have diverse clinical phenotypes and many are refractory to treatment despite the availability of drugs that enhance GABAergic activity. Aims. To evaluate the function of *GABRB3* or *GABRD* missense variants identified from patients with DEE. Methods. Two-electrode voltage clamp methods were used to assess the function of 44 pathogenic *GABRB3* and 6 pathogenic *GABRD* missense variants. Phenotype/genotype analysis was used to determine patient phenotype correlations. Results. We show that variants segregate into gain-of-function and loss-of-function groups. Respective patients display distinct clinical phenotypes. The *GABRB3* gain-of-function cohort (n = 27 patients) presented with a younger age of seizure onset, higher risk of severe intellectual disability, focal seizures at onset, hypotonia, and lower likelihood of seizure freedom in response to treatment. Febrile seizures at onset are exclusive to the loss-of-function cohort (n = 47 patients) (1). Of the *GABRD* cohort, 5 patients displayed a gain-of-function variant and these patients suffered from generalized epilepsy and various degrees of learning difficulties or intellectual disability, whereas the one patient with a loss-of-function variant had autism spectrum disorder, normal cognition and no seizure history (2). Discussion. Overall, patients with *GABRB3* and *GABAD* variants that increase GABAergic activity have more severe developmental and epileptic encephalopathies. This paradoxical finding challenges our current understanding of the GABAergic system in epilepsy and how patients should be treated.

1. Absalom et al 2022, Nat Commun, 13(1):1822
2. Ahring et al 2022, Brain, 145(4):1299-1309

231 Innovative Approaches to Resolve Inflammation in the Heart and Vasculature

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Active resolution of inflammation is essential to facilitate tissue healing and repair, failure to resolve inflammation may thus lead to chronic inflammation, dysregulated cellular homeostasis and adverse tissue remodelling in cardiovascular diseases. We and others have identified a group of pro-resolving G-protein-coupled receptors, such as formyl peptide receptors, central to disease progression. As the master switch to promote the resolution of inflammation, pro-resolving G-protein-coupled receptors thus represent an attractive "druggable" target. This presentation explores the therapeutic innovation and molecular mechanisms of targeting this group of receptors to resolve inflammation in cardiovascular diseases. Importantly, we have identified an efficacious prototype molecule improves the resolution of inflammation, limits tissue inflammation and remodelling, and preserves cardiac and vascular function, in preclinical models of cardiovascular diseases. Thus, "fine-tuning" FPRs may be a viable therapeutic strategy to minimise end-stage organ remodelling and failure that contributes to the progression of cardiovascular diseases.

232 Preclinical models to understand the risk of polypharmacy in old age.

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The use of chronic medications are common in older people. Older people that are taken polypharmacy (use of 5 or more drugs) for multi-morbidity, are hardly included in clinical trials to establish efficacy and safety. Clinical observational studies have found associations with polypharmacy and impaired physical function in older people. Preclinical models can be used to screen for adverse geriatric outcomes.

This presentation will cover our advancements in the development and use of preclinical models to understand the risk of polypharmacy in age. We will (1) explore whether chronic use of therapeutics, in monotherapy or polypharmacy, impair translatable functional outcomes in ageing and whether deprescribing can reverse these outcomes, (2) probe our data set to identify factors that determine severity of response, and (3) discuss our current mechanistic findings.

233 Pharmacoepidemiological research methods and findings to inform deprescribing practice

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Laboratory research has produced critical pharmacological and other evidence to guide deprescribing in patients. Randomized trials are another principal source of evidence about how to conduct deprescribing and the effects of deprescribing on outcomes. However, many deprescribing questions cannot be answered with laboratory studies or trials. When laboratory studies and trials are too expensive, unethical, impractical, or untimely, pharmacoepidemiological (observational) studies are necessary. Pharmacoepidemiological studies can provide new information about how deprescribing is occurring and the effects thereof to guide practice. The objectives of this session are to: 1) explain the roles of pharmacoepidemiology in generating evidence for deprescribing practice; 2) identify key challenges and opportunities when using pharmacoepidemiological approaches; and 3) discuss key applications using data from around the world that further elucidate the roles, challenges, and opportunities for pharmacoepidemiological research conducted to inform deprescribing practice. Particular attention will be paid to innovative methodological best practices and advances, such as target trial emulation, that have enabled the conduct of high-quality observational studies of medication discontinuation and dose reduction.

234 Deprescribing trials: Challenges and pitfalls

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The process of planning, conduction and reporting a deprescribing trial (DT) are characterised by specific challenges and pitfalls in contrast to trials investigating the effect (or efficacy) of a drug or pharmaceutical intervention. Given the hypothesis, that a certain drug (or several drugs) may not be beneficial for the individual patients, important questions are: what (single drug or different drug classes), where (setting and active participants) and who (patient population). To consider in all DT are the risks i) for the patients and ii) the complexity of the process.

Single drug (or one drug class) desprescribing trials, e.g. proton pump inhibitors, can be performed in hospitals, in ambulatory care and nursing homes. The advantage of such a study is that physicians may focus on one drug only and can be supported by nurses, pharmacists or electronic tools. However, with regard to risks, every pharmacological aspect of the drug must be considered, e.g. rebound effects or withdrawal effects. General “reductions of polypharmacy” are more complex trials, where deprescribing physicians need support to consider all possible options in one patient and probably more than one visit. A number of large-scale deprescribing trials were not successful, most likely due to the complexity of the process, even with electronic decision support (e.g. SENATOR, Sönnichsen et al). In hospitals different healthcare providers are available at one time and a process of deprescribing can be implemented. However, interprofessional cooperation represents a major challenge where physicians may not accept suggestions from pharmacists. And: even after successful deprescribing in-hospital, the effect may not last after discharge. Similar situations may arise in nursing homes. A large number of nursing home residents may suffer from dementia or receive palliative care. In such patients deprescribing may be easier to perform than in community dwelling older patients, where e.g. withdrawal of a statin can be more hazardous. Particularly in this setting patient and caregiver envolvement may play the biggest role and the process requires communication skills and careful evaluation of patient’s expectations, i.e. in family conferences.

Cochrane Special Collection: Achieving sustainable healthcare through deprescribing of unnecessary medications. https://www.cochrane.org/news/special-collection-achieving-sustainable-healthcare-through-deprescribing-unnecessary

235 Co-design with consumers and clinicians to develop research priorities and deprescribing interventions

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This presentation will discuss three examples of co-design with consumers and clinicians to support implementation of deprescribing and medicine optimisation in practice.

Achieving quality use of medicines in people living with dementia is a global patient safety challenge. In the past, research questions have been primarily determined by drug companies or researchers, with little involvement of consumers and clinicians. We used the James Lind Alliance Priority Setting Partnership method to identify the Top 10 unanswered quality use of medicines questions for people living with dementia, as determined by consumers (people living with dementia, carers, family/friends) and clinicians. First, a national qualitative survey and interviews asked consumers and clinicians (n=151 and 77 respectively) what questions they have about medicine use in people living with dementia. These responses were summarised (conventional content analysis) into 68 unique summary questions, which were then cross-checked with the published literature to determine if they had already been answered. A second survey (171 consumers and 67 clinicians) followed by an online workshop with consumers and clinicians (n=17) was conducted to prioritise the unanswered questions. The highest priority questions concerned shared decision making, clinician knowledge and skills, transitions of care and deprescribing. Targeting future research efforts towards these priorities will ensure research funds are being directed to the most urgent areas of need in practice.

Co-design methods have also been used to develop interventions and resources. We used a persona-scenario co-design method to determine key elements required to implement deprescribing guidelines in the hospital setting. Key elements with the highest feasibility and efficacy were becoming aware of the guideline through handover documents, identifying patients during consultant led ward rounds and having an action plan for patients at discharge. We also developed a consult patient decision aid and action plan for deprescribing cholinesterase inhibitors using co-design principles to maximise comprehensibility and usefulness for practice.

Involvement of consumers and clinicians in research and use of co-design supports responsible use of research funds by ensuring that research aligns with the needs of the community and maximising the likelihood of success and adoption of research findings into practice.

236 Delayed drug hypersensitivity reactions: Clinical presentations, immune mechanisms, and common culprits.

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Drug hypersensitivity reactions, or drug allergies, are idiosyncratic adverse drug reactions which are commonly reported by patients. Hypersensitivity reactions can be broadly classified as acute or delayed, correlating with the mechanism by which they occur. Delayed drug hypersensitivity reactions include a diverse group of clinical phenotypes where T cell activation is often involved. The interaction between T-cell receptors (TCR) and human leukocyte antigen (HLA) molecules, which present antigen to TCR, therefore, is one of the key immunological processes involved in these reactions. Clinically, while these reactions can affect other specific other organs, i.e. drug induced liver injury (DILI), they often involve the skin with varying clinical severity, both with and without systemic symptoms. The most severe of these reactions are termed SCARs, or severe cutaneous adverse reactions, which includes acute generalised eczematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) spectrum. These conditions, while rare, are associated with high morbidity and mortality, and can present significant clinical challenges in their diagnosis, acute management as well as the identification of the culprit. Reducing the risk of these events, were possible, is a key aspect in their overall management.

This talk will give a broad overview of some key clinical presentations, introduce immune pathways by which these reactions occur as well as discuss common drug associations of delayed drug hypersensitivity.

237 Mechanisms of drug hypersensitivity and HLA.

Andrew Gibson[1]. Institute for Immunology and Infectious Diseases (IIID), Murdoch University[1], Perth, WA, Australia.

Introduction. Delayed hypersensitivity reactions are associated with drug-reactive cytotoxic CD8+ T cells, up to 50% mortality, and predisposition by HLA alleles specific to drug, reaction, and ethnic population. In 2002, our group reported the breakthrough discovery association between HLA-B*57:01 and predisposition to abacavir-hypersensitivity, driving implementation of preventative screening into clinic, and we continue to discover novel HLA associations for high utility drugs, including HLA-A*32:01 with vancomycin-hypersensitivity in Europeans. However, the incomplete positive predictive value and low carriage of many HLA-risk alleles combined with the high cost of sequence-based typing has limited clinical implementation of screening across drugs and populations. Moreover, as the cellular immunopathogenesis at the acute site of tissue damage remains undefined, there remain no targeted treatments, and as HLA discovery remains dependant on genetic association study and large ethnicity-matched control cohorts, minority populations remain at risk. Importantly, while HLA is critical to immunopathogenesis and CD8+ T-cell activation, the risk HLA-interacting epitope and T-cell receptor (TCR) have remained undefined. However, drug-induced oligoclonal TCR expansion is recently reported in the affected tissue of patients. Provision of the full length TCR by single-cell sequencing enables opportunity for synthetic expression into in vitro co-culture to functionally confirm HLA- and drug-restriction for individual patients from populations where risk remains undefined.
Methods and results. Using affected tissue samples of patients, 10x 5' single-cell RNA-TCR-CITE-sequencing, and a TCR reporter assay, we show that different dominant TCRαβ in the skin of different patients are expressed on the same transcriptome-defined populations of cytotoxic CD8+ T-cells, providing signatures towards the development of targeted diagnostics and treatments. Moreover, we validate oxypurinol (drug metabolite) and ethnicity-unreported risk HLA(-B*58:01)-restriction of a dominant TCR in blister from an African American patient with allopurinol-hypersensitivity. Finally, we designed HLA allele-specific PCR-based screening tools for HLA-A*32:01 and B*35 to provide rapid (<3 hours), robust (100% sensitivity), and economically-viable (<$10AUD) implementation strategies.
Discussion. Utilising acute tissue samples from the Australasian-registry of severe cutaneous adverse reactions (AUS-SCAR), these methodologies provide avenues to define novel drug- and HLA-restriction using the drug-expanded TCR(s) and implement cost-effective HLA-prevention and -diagnostic strategies for diverse Australian populations.

238 Current and new technological advances to study HLA and drug interactions

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HLA risk alleles are associated with predisposition to $CD8^+$ T cell-mediated delayed drug hypersensitivity reactions, and drug-expanded T cell receptors (TCR)s have recently been identified in the affected tissue of patients. However, our understanding of the HLA-TCR-interacting epitope(s) remains undefined and is further impeded by complex antigenic mechanisms of drug-induced activation, including the formation of drug protein-derived peptides or indirect drug-HLA interaction driving an altered immunogenic repertoire of HLA-loaded self-peptides. A commonly used and robust method to assess TCR-peptide-HLA interactions is the Jurkat TCR reporter assay which utilizes an artificial TCR transfected into the Jurkat E6.1 cell line together with CD8 alpha and a reporter gene, typically NFAT-driven luciferase or GFP. These T cells are then co-cultured with matched peptide- and/or drug-pulsed single HLA Class I allele antigen-presenting cells and TCR activation is measured by reporter gene activity. An exciting new advancement in the comprehensive profiling of TCR-HLA interactions is T-Scan. T-scan provides a readout of antigens productively recognized by TCRs presented by the correct HLA allele leading to functional TCR signalling. In this assay, epitope discovery cells (EDCs) containing a granzyme B reporter gene are infected with sub-pools of lentiviral peptide libraries that cover the entire virome or human peptidome and then pulsed with the drug of interest. EDCs are co-cultured with primary $CD8^+$ T cells expressing the artificial TCR of interest and EDCs that have been targeted for killing through the cytolytic activity of functionally activated T cells are sorted by granzyme B reporter activity. Next-generation sequencing allows for the identification of the exact peptide sequence responsible for the cytotoxic TCR-peptide-drug-HLA interaction. This unbiased peptidome scanning approach to identity and functionally validate all cognate epitopes driving risk HLA-TCR-restricted reactions provides an opportunity to confirm the risk HLA allele in patients and populations where risk remains unreported, as well as providing pivotal information regarding the structural interactions between HLA, TCR, drug, and self-epitopes to inform HLA cross-reactivities and safe future drug design.

239 HLA Pharmacogenomics in our region, stronger guidance for pre-emptive HLA testing needed

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Human leukocyte antigen (HLA) alleles associated with clinical phenotypes most often manifest as Severe Cutaneous Adverse Reactions (SCARs) or Drug-Induced Liver Injury (DILI), and cause significant morbidity and mortality. Their incidence is very low in many, but not all populations, especially in the diverse genetic ancestry of Australia and our region. More than 30 drugs have been associated with HLA variants and these Immune-Mediated Adverse Drug Reactions (IM-ADRs). Advocates for clear testing indications are challenged by critical association differences between phenotype and HLA variants. Firstly, the frequencies of the variants show very large geographical differences, for example the carriage rate for *HLA-B*15:02* carbamazepine Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) is 15% in South East Asians and <0.1% in Europeans. Additionally, the SCAR phenotype can manifest differently, for example as SJS/TEN in Han Chinese (*HLA-B*13:01*) and as Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) in Aboriginal Australians (*HLA-B*56:02*) (Somogyi et al 2019). For DILI, the *HLA-DRB1*15:01* amoxicillin-clavulanate carriage rate ranges from about 10% in Europeans to 50% in Papua New Guineans, however, the incidence of DILI is low. Carbamazepine and allopurinol are candidates for expanded testing with strong evidence for phenotype association. Critics highlight the lack of confirmatory studies - mainly due to low patient numbers and restricted HLA genotyping. In contrast to TGA, FDA has strong recommendations and warnings for genetic testing before prescribing. Recent funding from Australian Genomics is for Australian indicator development. An unusual case report of statin-associated necrotizing myopathy and *HLA-DRB1*14:08* in an Aboriginal Australian will be presented.

Karnes JH et al (2019) Annu Rev Pharmacol Toxicol 59: 463-86
Somogyi AA et al (2019) Brit J Clin Pharmacol 85: 2163-69

240 High-Potential Candidate Medicines for Preeclampsia and Preterm Birth: Analysis of Maternal Medicines in the Drug Development Pipeline and Target Product Profile Matching

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Introduction. The maternal "drug-drought" is a significant barrier to reducing maternal and neonatal mortality. Target product profiles (TPPs) are an important tool for driving new product development by specifying upfront characteristics that new products should take. Currently, TPPs for maternal medicines do not exist.
Aims. To develop TPPs for two key maternal conditions (preeclamspia and preterm birth) and systematically rank candidate maternal medicines under development from 2000-2021 against TPPs, to identify the products with high potential to improve maternal and newborn outcomes.
Methods. We used multiple methods, including in-depth interviews and an online international survey involving stakeholders with diverse expertise to develop four new TPPs. Candidate medicines in clinical development were ranked against pre-specified criteria based on TPPs (including efficacy, safety, administration and stability). Each candidate was classified as high, medium or low potential based on quantification of matching to the TPP criteria.
Results. We performed 44 stakeholder interviews and received 92 survey responses. Survey results showed a high level of agreement across most TPP variables (preeclampsia 89% agreement; preterm birth 98% agreement). Of the 87 candidates in development for preeclampsia, seven were high potential (*Prevention*: esomeprazole, L-arginine, chloroquine, vitamin D and metformin; *Treatment*: sulfasalazine and metformin). Of the 71 candidates in development for preterm birth/labour, ten were high potential (*Prevention*: Omega-3 fatty acid, aspirin, vaginal and oral progesterone, L-arginine, and selenium; *Treatment*: nicorandil, isosorbide dinitrate, nicardipine and celecoxib).
Discussion. We have developed a novel method for ranking the potential of obstetric medicines in clinical development against TPPs. Prioritising R&D funding for candidate medicines that match the TPP criteria can drive development of medicines that will address the needs of women and providers, particularly in LMICs.

241 Inhaled oxytocin development for prevention of postpartum haemorrhage in low-resource settings

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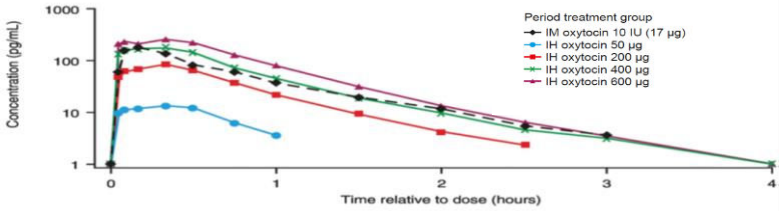
Introduction. Postpartum haemorrhage (PPH) is the most common direct cause of maternal mortality globally, accounting for an estimated 60,000 deaths per year, overwhelmingly in the poorest countries of the world. The World Health Organisation recommends every woman received an injection of 10 IU of oxytocin immediately after childbirth to reduce the incidence of PPH.
Aims. To develop a low cost, simple to use heat stable inhaled oxytocin for use in childbirth where access to high quality injectable oxytocin is not possible.
Methods. Spray drying methods were used to engineer particles for delivery into the alveolar region of the lung. Aerosolisation performance was characterised with Next Generation Impactors. Formulation stability was assessed following standard ICH guidelines. Preclinical pharmacokinetics and pharmacodynamics were characterised in a postpartum sheep model. Phase I clinical trials were conducted in healthy human volunteers to confirm safety and pharmacokinetics.
Results. A heat stable, dry powder formulation suitable for inhalation was developed with a shelf-life of over three years. Oxytocin was rapidly absorbed into the systemic circulation following administration to sheep lungs and uterine smooth muscle contractility was observed, similar to the response induced by intramuscular injection. Administration to healthy female volunteer subjects demonstrated that inhaled delivery was safe and well tolerated.
Discussion. The results confirm that inhaled delivery of a dry powder containing oxytocin may be an alternative route of administration to prevent PPH. This could overcome barriers to access in low-resource settings such as the need for cold-chain storage and administration by a highly trained healthcare worker.



242 Spermatogenic targets for male contraception

Brendan J. Houston[1], Anne E. O'Connor[1], D. Jo Merriner[1], Amy Luan[1], Don. F Conrad[2], Moira K. O'Bryan[1]. School of BioSciences and Bio21 Institute, The University of Melbourne[1], VIC, Australia. Oregon National Primate Research Centre, Oregon Health and Science University[2], OR, USA.

Despite an overwhelming need, and the potential, for a reversible male contraceptive to improve the reproductive health of men AND women worldwide, male contraception is an exceptionally overlooked area. No ingestible or injectable drugs that reliably inhibit sperm function are currently available, meaning there has been no significant advancement in male-targeted modes of contraception in several decades.
We have identified a suite of testis enriched genes affected by high confidence genetic variants in infertile men. Deletion of each of these three genes in mice results in male infertility with a common defect in sperm mitochondrial dysfunction and abnormal sperm motility. No associated health burden was observed, thus presenting each as a strong target for contraceptive development.
The absence of one gene, predicted to be a sperm-specific energy protein, does not affect the total number of motile sperm. However, loss of this gene prevents the whipping motion of the sperm tail at the midpiece, where mitochondria reside. Consequently, these sperm cannot swim well under viscous conditions that are reflective of the environment at the site of fertilisation in the upper regions of the female reproductive tract (oviduct). Another two genes are essential for normal numbers of motile sperm and appear to play roles in the development and function of mitochondria in the sperm tail.
Further research is being done to further understand gene function and generate assays to measure protein activity of these targets, with a major goal of screening large compound libraries to identify specific and reliable targeting compounds.

243 Cryo-EM structure of the human P2X1-purinoceptor for use in male contraception

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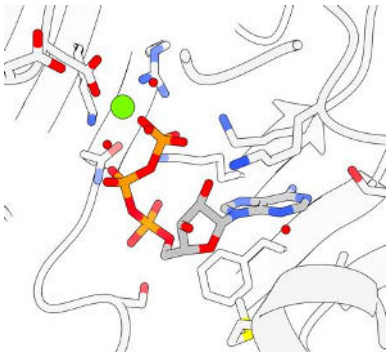
The search for a male contraceptive has been a challenging area of medical research for decades. Most strategies have focused on using hormonal or spermatogenic mechanisms that stop the production of functional sperm. These strategies can have problematic side effects, including loss of male characteristics and libido and long-term effects on fertility. Our previous research using a dual genetic knockout mouse model has identified the α_{1A}-adrenergic G protein-coupled receptor and the P2X1-purinoceptor ligand-gated ion channel as novel targets for a non-hormonal male contraceptive (White et al., 2013). Further development of this potential male contraceptive is hampered by a lack of drug-like P2X1-purinoceptor antagonists, partly due to the need for structural information on the human P2X1-purinoceptor.



Here we have used cryogenic electron microscopy (cryo-EM) to determine the first high resolution (<2 Å) structure of the human P2X1-purinoceptor bound to the endogenous ligand ATP and uncovered the key molecular interactions at the ATP-binding site. Our work has developed the framework for determining structures of the P2X1-purinoceptor in different conformational states (apo, antagonist bound) and will pave the way for the development of new P2X1-purinoceptor antagonists.

White CW et al (2013) 110 (51) 20825-20830 PNAS doi: 10.1073/pnas.1318624110

244 Potential factors that can affect the performance of undergraduate pharmacy research students: a descriptive study

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Aims. This descriptive study aimed to examine whether student past coursework performance, student or research supervisor characteristics, and the type of research project are related to the overall academic performance of a pharmacy student completing an honours research program.
Methods. Data on undergraduate honours students who completed a Bachelor of Pharmacy degree at The University of Sydney, Sydney, Australia, between Jan 2015 and Dec 2020 was collected. This included socio-demographic characteristics, type of project undertaken, and academic outputs. Data was also collected on each supervisor's academic role, level of experience, research area, and where they completed their PhD. Descriptive statistics were used to analyse the study cohort and linear regression and unpaired t-tail analyses were conducted using SPSS software.
Results. Of the 130 students included in this study, 67% were female, 60% were domestic and 40% international students. Across the five year study period, each student was supervised by one of 48 individual academics who were a mix of early- (31%), mid-career (29%), and experienced researchers (40%) for pharmaceutical science (50%), clinical (45%), and education (5%) projects. Just less than half (49%) of students published one peer-reviewed journal article. Female students outperformed male students ($p = 0.031$) with female students also twice as likely (15%) to receive a university medal eligible mark compared with men (7.0%). Similarly, domestic students were twice as likely (15%) when compared with international students (7.7%) to receive a university medal eligible mark. Students who undertook a pharmaceutical science-based project outperformed education-based project students ($p = 0.0235$). Students who had published at least one peer-reviewed journal article outperformed those who had not published ($p = 0.0014$).
Discussion. Factors that affected honours performance were student gender, residential status, type of project undertaken, and there was a correlation between whether a student had published a peer-reviewed journal article and their performance.

245 Work-readiness of final year pharmacy students in undergraduate and graduate-entry programs

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Introduction. Work-readiness is a set of competencies and attributes possessed by a prospective employee that are favourable to an employer. The Deakin University Work Readiness Scale (WRS) (Caballero et al, 2011) describes four factors that are important determinants of work-readiness of an individual: personal characteristics, organisational acumen, work competence, and social intelligence. The Australian Pharmacy Council's accreditation standards define "fitness-to-practise" and also describe readiness-to-practise "from a competency perspective (including knowledge, skills, behaviours and attitudes), and the capacity to undertake professional practice safely from the perspective of wellbeing and impairment". As pharmacy curricula are developed around these standards, it is expected that after completing their degrees, graduates should be entry-level pharmacist work-ready.

Aims. To compare indicators of entry-level pharmacist work-readiness between final year students enrolled in 4-year undergraduate B.Pharm and 2-year accelerated graduate-entry M.Pharm programs.
Methods. This study undertook a mixed methods approach. Quantitative analysis of performance on similar competency-based assessments in the "Professional Practice" unit of study was carried out. Qualitative analysis in the form of focus groups was also carried out to explore student perceptions of their own work-readiness.
Results. Quantitative analysis showed no significant differences in performance criteria between B.Pharm and M.Pharm that could not be accounted for. The focus groups showed that students in both programs had high levels of confidence and self-perceived competence, exhibiting no major differences in the emerging themes. The main factors affecting these perceptions were clinical placements, simulation-based learning and assessment, work-experience, and focus on community pharmacy. Overall, there were no differences in the indicators of work-readiness analysed in this study between the two programs.
Discussion. The results of this study suggest that both the undergraduate and graduate-entry programs equally prepare students for entry-level pharmacist work-readiness.

Caballero CL et al (2011) J Teach Learn Grad Employability, 2:41-54

246 Improving the effectiveness of workplace-based assessment for Intern Pharmacists

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Introduction. Assessment determines a health practitioner's readiness for independent practice. For intern pharmacists, transition to pharmacist registration includes the successful completion of a period of supervised practice, when preceptors are responsible for making decisions about an intern's practice based on observation and assessment of performance in the workplace. Currently, there is no nationally consistent approach to workplace-based assessment (WBA) of intern pharmacists.
Aims. The Australian Pharmacy Council (APC) received funding from the Pharmacy Board of Australia to develop WBA tools. The objectives were to i) develop an initial suite of tools; ii) seek feedback from stakeholders; and iii) pilot their use in community and hospital settings.
Methods. The project resulted in three types of tools; Entrustable Professional Activities (EPAs), Case Based Discussions (CbD) and In Training Assessment (ITA) activities covering six areas of focus. The tools were developed through a consultative process overseen by education experts (technical working group) and a project governance group, the latter comprising members of the Pharmacy Board and the APC. The technical working group agreed on the tools to develop based on an available Intern Year Assessment Blueprint and these were then drafted by a consultant. APC held three consultative forums and a pilot study to gather feedback from intern pharmacists (n=10) and preceptors (n=15) in community (n=8) and hospital (n=17) settings.
Results. Feedback gathered demonstrated that the proposed tools were feasible, acceptable, and useful. Future direction will involve further evaluation of the tools in diverse practice settings.
Discussion. Trends in health professional education driven by adoption of competency-based approaches are bringing greater scrutiny to workplace-based assessment methods and processes. These tools form an initial toolkit for use in the supervised practice period, providing stronger evidence about intern pharmacist readiness to progress to independent practice.

247 Professional hierarchies and status: Considerations for educational design of inter-professional student experiences.

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Introduction. Trust and respect are essential for high-performing teams to perform individual and team-based roles to maintain safe and effective medication management practices. Challenges to status due to professional boundaries and hierarchy can influence team dynamics and performance. How these dynamic interactions play out in students learning about power and status before entering the workforce is limited.
Aims. We aimed to investigate how teamwork occurs and impacts outcomes using a design principle of equal status in newly formed inter-professional teams of pre-registration students.
Methods. In 2022, we delivered an inter-professional medication safety micro-curriculum in medical, pharmacy and nursing students (n=650 students, teams of 4-6 students) to prepare students on team-based approaches for quality use of medicines and safe medicines practice. The micro-curriculum design was informed by Allport's Inter-group contact theory to aid successful development of inter-group attitudes and behaviours. We chose to equalise status in each team by placing more experienced final year undergraduate pharmacy and postgraduate nursing students with early clinical stage postgraduate medical students. Included in the post-teaching self-rated questionnaires was an open-ended question on appropriateness of team composition and status within members. Thematic qualitative analysis and coding by degree program was conducted and linkages to communication and team performance investigated.
Results and Discussion. Of 658 students participating in the research study (response rate= 99%), 542 comments on team dynamics were received. 98% students agreed that team composition was appropriate to complete the task. However, perception of equal status was only reported by 50% of students. Degree program was not associated with either perception of equal status or professional dominance. Thematic analysis of open text suggests that unequal numbers of students from each profession in a team and perceived professional hierarchy might explain perceptions of inequality. Professional hierarchies are evident in students and should be considered to in designing team activities.

248 Can brief whiteboard videos improve healthcare providers' knowledge and self-efficacy to deprescribe?

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Introduction. Whiteboard videos are gaining popularity as a teaching tool, however, their ability to increase healthcare providers' knowledge or self-efficacy for deprescribing remains unknown.
Aims. To evaluate changes in healthcare providers' knowledge and self-efficacy for deprescribing after watching four 3-minute whiteboard videos: "Why deprescribe?", sedatives, proton-pump inhibitors (PPIs), and opioids.
Methods. Whiteboard videos were created in English and French based on a literature review of deprescribing and founded on domains of behaviour change according to the therapeutic domains framework. Videos addressed deprescribing barriers, engaging patients, effective alternative treatment options and how to taper. Healthcare providers were recruited via social media and convenience sampling. Knowledge and self-efficacy were ascertained using multiple choice questions and a self-efficacy scale (0-10) respectively. A McNemar's test was used to assess mean differences in the proportion of respondents identified as having high self-efficacy (≥70%). Mean change in knowledge score for each video was assessed with paired t-tests.
Results. Pre and post-questionnaires were completed by 368 participants, of whom 82,3% (n=303) were women and 59% (n=217) watched the video in English. After watching the "why deprescribe?" video, 27.8% more participants were "very confident" in deprescribing. There was a significant increase in self-efficacy for engaging patients, starting alternatives and tapering for sedatives, PPIs and opioids. Knowledge about each medication class significantly increased. The majority of participants stated they gained new knowledge and skills, 90.4%, 94.3% and 86.0% and most had increased motivation to deprescribe, 93.0%, 96.6% and 90.7% for sedatives, PPIs and opioids, respectively.
Discussion: Theory-based brief educational whiteboard videos increased health care providers' knowledge and self-efficacy for deprescribing sedative-hypnotics, PPIs and opioids. Each video increased health care providers' motivation to deprescribe.

249 Cultivating interprofessional education for nursing and pharmacy students: a pilot study

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Introduction. Nursing staff and pharmacists have opportunities to collaborate around medication in hospitals, and with the expansion to include pharmacists located in aged care facilities, the importance of collaboration between nursing staff and pharmacists regarding dose administration and potential dosage form modification cannot be underestimated (McDerby et al., 2020). Interprofessional education (IPE) embedded in the curriculum of nursing and pharmacy programs has been limited to date at RMIT. It was recognised that there was a need to implement additional IPE activities to foster collaboration between pharmacy and nursing students, and to strengthen knowledge on dosage form modification across different clinical settings for both disciplines.
Aims. To evaluate student perceptions of a simulation IPE activity in undergraduate nursing and pharmacy students.
Methods. Nursing students participated in an immersive simulated exercise where patients required medications for which there were barriers to administration. Pharmacy students were also present in the simulated health environment, observing the work of the student nurses and to provide advice regarding medication administration to the nursing students. Both nursing and pharmacy students were invited to complete a survey regarding the experience at the end of the simulation exercise and pharmacy students completed a reflection.
Results. Survey results indicated a very high satisfaction regarding the exercise for both pharmacy and nursing students. Analysis of pharmacy student reflections also indicated apprehension regarding their preparedness to contribute to the exercise, enjoyment in participation, their understanding of the value of collaboration between the two groups of students and also recognition of their need to be more prepared for such situations.
Discussion. The interprofessional learning opportunity was viewed as valuable by both nursing and pharmacy students. Further research is required to formally evaluate the impact of simulation IPE on knowledge, skills and attitudes of pharmacy and nursing students towards IPE and dosage form modification.

McDerby, NC et al. (2020) Australasian Journal on Ageing 39:e466-e471.

250 Evaluating Collective Impact Theory as a Catalyst for Implementing Population-Level Evidence-Based Deprescribing.

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Introduction. Collective Impact Theory (CI) consists of five conditions, common agenda, shared measurement, continuous communication, mutually reinforcing activities, and backbone support. CI was used to underpin the SaferMedsNL deprescribing initiative in Newfoundland and Labrador, Canada, (NL) because CI is an emerging theory for facilitating key stakeholder engagement to bring about behaviour change at a population level. It remains unknown if CI can facilitate the implementation of evidence-based deprescribing interventions at a population level.
Aims. To identify which of the five conditions of CI stakeholders considered to have been met, and explore the contexts that supported or restricted CI in the SaferMedsNL deprescribing initiative across NL.
Methods. Representatives of stakeholder groups involved with SaferMedsNL (doctors, pharmacists, nurses and their representative associations along with patient advocates and policymakers) were invited to semi-structured interviews. One-on-one telephone interviews (60-90 minutes) based on 17 overarching questions were conducted, transcribed verbatim and thematically analysed.
Results. Of 18 invitees, 13 consented to be interviewed. Three conditions were completely met: common agenda (a need to reduce potentially inappropriate sedatives and proton pump inhibitors), shared measurement (prevalence of medications from pharmacy claims), and continuous communication (minimum quarterly meetings). Two conditions were partly met: mutually reinforcing activities and the role of backbone support. Contexts that restricted collective impact included political contexts, professional association goals, and lack of clarity on who was responsible for developing the mutually reinforcing activities. Contexts that supported collective impact included, government will and funding, formalisation of interdisciplinary collaborations and the personnel in the backbone organisation.
Discussion. Stakeholders agreed that CI was an appropriate catalyst for bringing together diverse stakeholders, facilitating a shift away from the isolated impact of siloed interventions. Contexts including political lobbying and lack of clarification between stakeholders proved to be challenging. The backbone organisation was vital to success.

251 Deprescribing heart failure medications in older people: a systematic review and meta-analysis.

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Introduction. Optimisation of heart failure (HF) medications in frail older people requires a complex balance of the benefits and risks of medications with disease progression and co-morbidities. The safety of deprescribing is unclear.
Aims. To determine the feasibility and safety of reducing or ceasing HF medications in older people and evaluate these outcomes by frailty status.
Methods. A systematic search of electronic databases (CENTRAL, MEDLINE, Embase, Ageline, CINAHL, IPA, PyschInfo) and registries was conducted according to PRISMA 2020 checklist. Eligible studies included randomised controlled trials (RCTs) and observational studies of people aged ≥50 years, diagnosed with HF and reported ceased or reduced dose of HF medications. Two reviewers independently screened all studies, validated extracted data, and assessed risk of bias (RoB2, ROBINS-I) and certainty of evidence (GRADE). If heterogeneity (Higgins I^2) was not substantial (I^2<60%), a meta-analysis was conducted on the proportion of participants whose HF medications were ceased or dose-reduced, not re-started; mortality, hospitalisation; adverse drug withdrawal effects (ADWE); and frailty status.
Results. Five RCTs (480 participants) and 22 observational studies (412,988 participants) across six drug classes were included. No study reported frailty status. Only three studies reported low risk of bias. RCTs reported successful reduced dose of an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-renin blocker (ARB) in 64% of participants; and successful cessation of digoxin and diuretics in 52% and 53% respectively. Of these participants in the intervention group, 100%, 100 % and 76% did not re-start the deprescribed medication within 12-26 weeks. Moderate certainty showed decreased mortality from reduced dose of an ACEI/ARB (n=56) (Risk Ratio [RR] 0.64, 95%CI 0.30-1.64). There was high certainty that ceasing digoxin (n=178) reduced mortality (RR 0.30, 95%CI 0.03-2.83) but increased the risk of hospitalisation (RR 5.48, 95%CI 1.26-23.80). Overall, the most frequently reported ADWE was worsening HF and occurred in 20%-75% of participants within 5-232 weeks of deprescribing.
Discussion. Over 50% of older people with HF could cease digoxin or reduce the dose of an ACEI/ARB, but this was associated with increased risk of hospitalisation and worsening HF. Evidence is needed to support deprescribing in HF.

252 Willingness of people living with cognitive impairment and their caregivers to deprescribe

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Introduction. People living with cognitive impairment commonly take multiple medications including potentially inappropriate medications (PIMs) which puts them at risk of medication related harms.
Aims. To explore willingness to deprescribe of people living with cognitive impairment (dementia or mild cognitive impairment) and multiple chronic conditions and assess the relationship with patient characteristics and beliefs.
Methods. Cross-sectional study using results from the revised Patients' Attitudes Towards Deprescribing questionnaire (rPATDcog) collected as baseline data in the OPTIMIZE study, a pragmatic, cluster-randomized trial educating patients and clinicians about deprescribing. Eligible participants were 65+, diagnosed with dementia or mild cognitive impairment, and prescribed at least 5 long term medications.
Results. The questionnaire was mailed to 1,409 intervention patients and 553 (39%) were returned and included in analysis. Participants had a mean age of 80.1 (standard deviation 7.4) and 52.4% were female. 78.5% (431/549) of participants said that they would be willing to have one of their medications stopped if their doctor said it was possible. Willingness to deprescribe was negatively associated with getting stressed when changes are made and with previously having a bad experience with stopping a medication ($p< 0.001$ for both). A higher proportion of those on one or more PIMs, compared to no PIMs, reported having a bad experience when stopping a medication in the past (29.5% vs 13.6%; $p<0.001$) and being stressed when changes are made to their medications (22.6% vs 11.7%; $p=0.01$).
Discussion. Most people living with cognitive impairment are willing to deprescribe. Addressing previous bad experiences with stopping a medication and stress when changes are made to medications may be key points to discuss during deprescribing conversations.

253 The association between medication discharge counselling and readmission to hospital

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Introduction. Patients are often prescribed new medications during a hospital stay. Medication counselling is vital to ensure appropriate medication use after hospital discharge. However, its impact on clinical outcomes remains inconclusive.
Aims. To investigate the association between the completeness of new medication counselling during discharge and readmission to hospital.
Methods. A cross-sectional study of adult patients admitted to NSW hospitals in 2019 was conducted. The sample included participants who completed the Adult Admitted Patient Survey 2019 and were prescribed a new medication. The primary exposure was the completeness of medication discharge counselling provided to patients, including (i) explanation of the purpose of the medication, (ii) explanation of medication side effects, and (iii) patient involvement in the decision to use the medication. The outcomes were 30-day readmission to hospital or presentation to Emergency Department (ED). Multilevel mixed methods regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the associations above, after adjusting for demographics, health conditions, and patients' experience with health staff.
Results. A total of 8341 patients (mean age 59.2 years, 52.6% female) were included in the analytic sample. 85% of the patients had the purpose of the medication explained thoroughly, 57% had medication side effects explained fully, and 64% felt completely involved in the decisions to use the medication. Patients who were thoroughly explained the purpose of their medication had a lower odds of 30-day readmission to hospital (OR 0.58, 95%CI 0.44-0.77) and ED visits (OR 0.69, 95%CI 0.53-0.89).
Discussion. Many patients did not receive proper counselling on new medications at discharge from hospital. Those who received complete medication counselling were less likely to be readmitted. These data suggest that accurate medication counselling may reduce hospital readmission, which could potentially improve patient outcomes and reduce the burden on the healthcare system.

254 Prevalence of frailty among long-term care residents living with dementia and its association with medication use: a retrospective cross-sectional study

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Introduction. Frailty is an important geriatric syndrome affecting many older adults. The prevalence of frailty among people with dementia in long-term care facilities (LTCFs) and its impact on medication use is unknown.
Aims. To estimate the prevalence of frailty among people living with dementia in LTCFs and explore differences in medication use according to frailty status.
Methods. A cross-sectional retrospective analysis of data obtained from residential medication management reviews performed by accredited pharmacists in 343 LTCFs in Australia from January to December 2019 was performed. Pharmacists captured comorbidity data for each resident using the ICD-10 codes. Individuals with dementia were identified using ICD-10 codes. Frailty was assessed using a modified 36-item frailty index applied to the ICD-10 comorbidity codes for residents. Polypharmacy was defined as the concurrent use of ≥ 9 regular or "as needed" medications and potentially inappropriate medications (PIMs) were identified according to the updated Beers Criteria 2019. Logistical regression was used to determine the likelihood of exposure to polypharmacy and PIMs according to frailty status.
Results. Among 5076 residents, 80% (n=4062) were frail, 20% (n=1014) were non-frail with a median age of 86 years (interquartile range 81.0-91.0), and 43.5% were males. Polypharmacy was present in 70.2% of frail and 44.1% of non-frail individuals, while 83.8% of the frail group were exposed to PIMs compared to 79.5% of the non-frail. Frail individuals displayed higher likelihood of exposure to polypharmacy (adjusted odds ratio [AOR]: 2.67; 95% Confidence interval [CI]:2.29-3.11), and PIMs (AOR: 1.18, 95% CI: 0.98-1.42).
Discussion. Frailty, polypharmacy, and PIMs exposure are highly prevalent among people with dementia in LTCFs. Future studies should systematically document frailty and design and test interventions to improve medication use in this complex patient population.

255 Effectiveness of bisphosphonates versus denosumab following hip fracture in people with dementia

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Introduction. The relative effectiveness of bisphosphonates and denosumab, which are both first-line antiresorptive medications post hip-fracture, is not well understood in people with dementia.
Aims. We investigated the risk of recurrent fractures, recurrent hip fractures and death in people prescribed bisphosphonates or denosumab following hip fracture, including in people with dementia.
Methods. Parallel population-based cohort studies were conducted in Australia, Hong Kong, Taiwan and the United Kingdom. Patients ≥50 years prescribed a bisphosphonate or denosumab within 60 days of discharge following their first hip fracture were included. Cox proportional hazards regression with competing risks, adjusted with inverse probability of treatment weights was used to estimate subdistribution hazard ratios (sHRs) with 95% confidence intervals (CIs) for treatment outcomes. Subgroup analyses were conducted for people with dementia. Results were combined using random effects meta-analyses.
Results. 18,292 people were prescribed bisphosphonates and 8,560 denosumab. In meta-analyses, bisphosphonates versus denosumab were associated with similar rates of recurrent hip fractures, (sHR 1.13; 95%CI 0.76-1.69), and mortality, (sHR 0.99; 95%CI 0.94-1.04), but higher rates of any recurrent fractures, (sHR 1.16; 95%CI 1.11-1.21). People with dementia also exhibited statistically non-significant trends towards higher rates of recurrent fractures, (sHR 1.30; 95%CI 0.74-2.29), with bisphosphonates versus denosumab.
Discussion. Bisphosphonate users had higher rates of recurrent fractures than denosumab users, but similar rates of recurrent hip fractures and death. Results were similar in people with dementia, suggesting that guidelines on first-line anti-resorptive therapy post hip fracture may be generalizable to people with dementia.

256 Targeting inflammasome-dependent neuroinflammation in vascular dementia

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Introduction. Vascular dementia (VaD) is the second leading cause of dementia worldwide after Alzheimer's disease (AD). VaD is associated with chronic cerebral hypoperfusion, and its prevalence increases steeply with age. Currently, no specific treatments for VaD exist due to incomplete understanding of the underlying pathophysiology. Early detection of VaD is vital for developing disease-modifying therapies, but this is challenging without blood-based biomarkers.
Aims. To overcome shortcomings in preclinical VaD research, our team has built a basic science research program to uncover molecular mechanisms that drive white matter lesions and cognitive impairment in VaD. Our aim is to identify translatable preclinical targets and therapies to treat VaD, and novel biomarkers for early diagnosis of VaD in humans.
Methods. Toward this goal, we have employed a most promising animal model of VaD, chronic cerebral hypoperfusion induced by bilateral common carotid artery stenosis (BCAS) and established a genetics-based molecular framework and identified cellular signalling pathways that play a prominent role in the pathophysiology of VaD in both young and old animals.
Results. We demonstrated that activation of the Absent In Melanoma 2 (AIM2) inflammasome contributes to both brain pathology and cognitive impairment in VaD. We also demonstrated the tissue- and cell-specific presence of Nucleotide-binding oligomerization domain, Leucine rich Repeat and Pyrin domain containing Proteins (NLRP)1, NLRP3 and NLR Family CARD Domain Containing 4 (NLRC4) inflammasomes in the VaD brain, suggesting an involvement of other inflammasome complexes. Crucially, this evidence from the mouse model of VaD is consistent with findings in autopsied brains of VaD patients.
Discussion. We have demonstrated that activation of the inflammasome substantially contributes to the pathophysiology of chronic cerebral hypoperfusion-induced brain injury and may therefore represent a promising therapeutic target for attenuating cognitive impairment in VaD.

257 Changes to the blood-brain barrier proteome in a mouse model of glioblastoma

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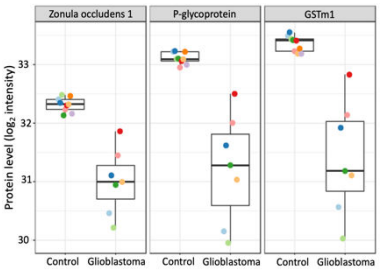
Introduction. Glioblastoma is a form of brain cancer with a 95% fatality rate over the first 3 years after diagnosis (Korja et al, 2019). For a drug to access the tumour, it must first cross the blood-brain barrier (BBB). In order to more effectively traffic potential therapeutics into the tumour, a thorough assessment of drug transporter and metabolising enzyme levels at the BBB in glioblastoma is essential.



Aims. To compare the proteome of brain endothelial cells (BECs) isolated from mouse brains with or without a glioblastoma.

Methods. Adult female C57BL/6 mice were anaesthetised with ketamine/xylazine (ip, 100/10 mg/kg) and administered an orthotopic intracranial injection of mouse GL261 glioma cells or vehicle (n=7-9). After tumour growth (29 days), mice were humanely killed under inhaled isoflurane anaesthesia. Brains were sampled and CD45+/CD45- endothelial cells isolated using magnetic bead separation. Liquid chromatography tandem mass spectrometry-based quantitative proteomics was used to compare BEC protein levels between groups.

Results. BECs from mice with a glioblastoma exhibited lower levels of proteins that control the permeability of water-soluble compounds (zonula occludens-1, 2.5-fold, $p<0.001$; Fig 1) and lipid soluble compounds (P-glycoprotein, 3.7-fold; breast cancer resistance protein, 2.5-fold; glutathione-s-transferase m1 3.9-fold; $p<0.001$; Fig. 1) into the brain, compared to controls. In addition, BECs isolated from the glioblastoma brain had a 6.1-fold higher ($p<10^{-6}$) level of a trafficking protein known to be present at the luminal plasma membrane of BECs. This may represent a novel target that could be exploited to increase the delivery of chemotherapeutics across the BBB in glioblastoma.

Discussion. Results will assist in the identification of drug subtypes that are likely to have high permeability from blood into the glioblastoma site. Chemotherapeutics can be designed or modified to exploit trafficking pathways highly expressed at the glioblastoma BBB to determine whether this can enhance brain penetration and treatment efficacy.

Korja M et al (2019) Neuro-oncology 21:370-379.

258 Rigorous pharmacological characterisation of metabotropic glutamate receptor 1

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Introduction. Metabotropic glutamate receptor 1 ($mGlu_1$) is a G protein coupled receptor that is highly expressed in the CNS, playing a key role in important neurobiological processes (Gregory et al, 2020). As such, $mGlu_1$ dysfunction is implicated in numerous neurological disorders. Allosteric modulators, compounds binding to sites distinct to that of glutamate to fine-tune $mGlu_1$ activity, are a promising therapeutic approach for targeting $mGlu_1$. However, current drug discovery fails to consider pleiotropic $mGlu_1$ signalling and the complexities of allosteric modulation. As a result, little is known about how chemically divergent modulators differentially affect $mGlu_1$ function.

Aims. To assess the properties of known, putative and novel positive (PAMs) and negative (NAMs) $mGlu_1$ allosteric modulators across multiple signalling endpoints, to better understand $mGlu_1$ receptor function and pharmacology.

Methods. Allosteric modulators were tested for modulatory effects on multiple orthosteric ligands across multiple signalling pathways (calcium mobilisation, IP_1 accumulation, extracellular signal regulated kinases (ERK) and AMP-activated protein kinase (AMPK) activation) in HEK293A cells stably expressing human $mGlu_1$. Pharmacological parameters were derived using operational models of agonism and allosterism.

Results. Chemically distinct $mGlu_1$ PAMs and NAMs displayed differential pharmacology at human $mGlu_1$. Modulatory effects were dependent on the orthosteric agonist, as well as the equilibrium state of each assay. A previously characterised $mGlu_5$ selective NAM was found to have activity at $mGlu_1$, whereas a proposed $mGlu_1$ NAM was found to exert it effects via non-selective mechanisms. For the first time, we report $mGlu_1$ mediated activation of AMPK.

Discussion. Most $mGlu_1$ allosteric drug discovery relies on a single measure of ligand activity against one orthosteric agonist. Our data highlight the importance of rigorous characterisation of $mGlu_1$ allosteric pharmacology, to avoid translational problems arising from unappreciated pharmacological properties. In addition, we reveal $mGlu_1$-AMPK signalling, revealing a novel pathway of interest in treating $mGlu_1$ related neurological disorders.

Gregory KJ., Goudet C (2020) Pharmacol Rev 73:521-69

259 Desensitising Properties of Gain-of-function *GABRB3* variants influence the severity of DEE

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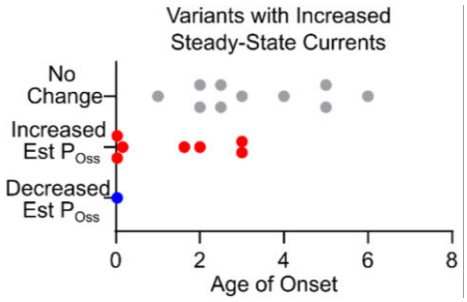
Developmental and epileptic encephalopathies (DEE) are characterised by seizures beginning in childhood. Many are associated with genetic variants in the *GABRB3* gene, that encodes for the β3 subunit of $GABA_A$ receptors ($GABA_AR$). These variants can alter GABA sensitivity resulting in either a gain (GoF) or loss of receptor function (LoF). A recent genotype/phenotype correlation study of DEE-causing *GABRB3* variants determined that patients with GoF variants have a distinct and more severe clinical phenotype than those with LoF variants (1). It is unclear whether receptor desensitisation contributes to the severity of the patient phenotype.
Aim: To determine how $GABA_AR$ desensitisation influences the severity of patient phenotype.
Method: 20 GoF and 5 LoF variants were expressed in *Xenopus oocytes* as singly mutated concatenated receptors. Current decay rates, steady-state currents (Est. Po(ss, max)) and maximum open probability (Est. Pomax) were measured using two-voltage clamp electrophysiology. Data were compared with non-parametric ANOVA and Dunn's posthoc test. Comparisons were restricted to data from variants measured on a single day.
Result: GoF variants that increased the current decay typically had an older onset (age of onset > 4 months), meaning receptors were more desensitised than wild-type (WT). However, the most severely affected patients (age < 2 months) with GoF variants had, in general, a significant increase in Est. Po(ss,max) compared to WT, meaning receptors were less desensitised. Whilst GoF variants did not alter the Est. Pomax, all 5 LoF variants had a significantly lower Est. Pomax ($p < 0.05$).
Conclusion: Variants that resulted in receptors with reduced desensitisation and increased GABA sensitivity are likely to exacerbate the severity of patient phenotype.



1. Absalom NL et al Nat Commun. 2022;13(1):1822.

260 Adenosine receptor modulators for the treatment of chronic pain

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Introduction. Neuropathic pain, one of the most intense types of chronic pain, is caused by malfunction of the nervous system and involves persistent changes in pain signalling. We have shown that there is an increase in endogenous adenosine in the spinal cord in chronic pain states, which is accompanied by increased sensitivity of adenosine A1 receptors in the spinal dorsal horn. These adaptations produce anti-nociceptive activity that can be further enhanced using allosteric modulators or biased agonists of the adenosine receptor. Aims. The aims of this study were to 1) identify the analgesic mechanisms of two adenosine A1R modulators, the allosteric modulator MIPS521 and the biased agonist BnOCPA at the cellular and neuronal circuit level in rodent and primate, and 2) determine their analgesic efficacy and potential for adverse effects in rodent models of neuropathic pain. Methods. A partial nerve ligation (PNL) or sham surgery was performed to injure the left sciatic nerve of adult Sprague-Dawley rats. We used patch-clamp electrophysiology to measure changes in nociceptive synaptic input and intrinsic activity of spinal nociceptive neurons to understand the analgesic mechanism of A1R modulators at a circuit level. Paw withdrawal threshold (PWT) was used to assess the effects of MIPS521 and BnOCPA on mechanical allodynia and conditioned place preference to assess effects on spontaneous pain. Results. Data showed that both compounds reduced nociceptive synaptic input in rodent and primate spinal cord slices and a reduction in spontaneous and intrinsic activity. Both compounds reduced pain behaviour in rodent models of neuropathic pain with no adverse effects. Discussion. This study provides evidence that modulation of the adenosine A1 receptor is an effective strategy to treat neuropathic pain. Interesting, the activity of both compounds, discriminate between receptors in nociceptive pathways and A1R in off-target tissues, through different mechanisms. This study reveals new possibilities for the development of novel therapeutics that target adenosine signalling in pain pathways.

Wall MJ et al (2022) Nat Commun. 13(1):4150.
Draper-Joyce CJ et al (2021) Nature. 597:571-576.

261 Bacteria and Neuron Interactions in the Bladder

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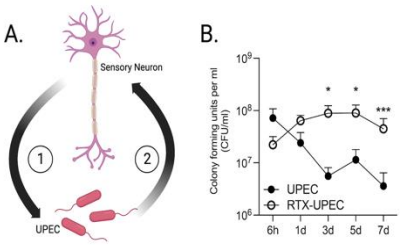
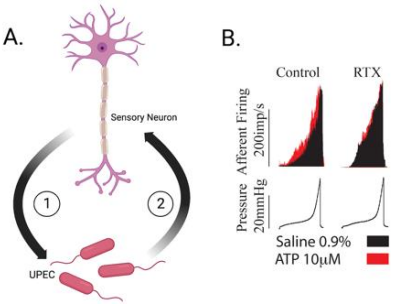
Introduction: Urinary tract infections (UTIs) caused by uropathogenic *Escherichia coli* (UPEC) are one of the most common bacterial infections in the world. Whilst UTI's are often resolved with antibiotic treatment, individuals that have peripheral neuropathy, such as with diabetes, multiple sclerosis, or following spinal cord injury are significantly more susceptible to persistent and recurrent UTIs (rUTIs). As a result, altered bladder sensory nerve signalling is hypothesised to be a mechanism underlying susceptibility to UTI infection. However, the interactions between bladder-innervating sensory nerves and UPEC (Figure 1A) are unknown.

Aims: Determine the effect of 1) neuropeptides (NPs) on UPEC growth, 2) UPEC constituents on bladder sensory neuron activity, 3) bladder sensory neuron depletion on UPEC infection severity.



Methods: 1) UPEC was grown in the presence of Substance P, CGRP and Neurokinin A. Bacterial growth was measured by optical density and colony count at 1, 2, 4, 6 and 8 hours. 2) Mouse bladder-innervating dorsal root ganglia (DRG) neuron responses to live and heat-killed UPEC were measured via calcium imaging. 3) *in vivo* bladder infection with $4x10^7$ UPEC was performed in control mice (N=5) and in mice following bladder nerve denervation using resiniferatoxin (RTX) (N=5). Weight loss and urine UPEC count was measured at 6hours, 1-, 3-, 5-, and 7-days post infection. Bladder inflammation was determined by histology at day 7 post infection.

Results: 1) No NPs affected UPEC growth compared to controls ($p>0.05$). 2) Both live and heat killed bacteria activated a sub-population (<10%) of bladder innervating DRG). 3) Neuron depletion with RTX led to higher urine UPEC count (*$p<0.05$) (Figure 1B) and increased clinical scores (mean + SEM, $p<0.05$) but had no effect on weight loss ($p>0.05$). Blood in urine was greatly evident in RTX treated mice compared to UPEC only mice.



Discussion: While common NPs released from bladder sensory neurons do not directly affect UPEC growth, depletion of neurons using RTX significantly impaired UPEC clearance and worsened UTI symptoms in mice. This could indicate an alternative indirect effect of neurons on UPEC clearance. Further investigation into interactions between bladder immune cells and neurons could potentially address this knowledge gap.

262 Oral nanotherapeutic formulations of GLP-1 agonist Liraglutide

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Introduction. Reformulation of injectable medications to make them orally bioavailable is a critical area of research with the aim to improve patient compliance and quality of life. Glucagon-like peptide 1 (GLP-1) agonists are anti-diabetic medication used to treat type 2 diabetes, obesity, and chronic weight management. Currently liraglutide is not orally bioavailable and must be given via subcutaneous injection. GLP-1 agonists also demonstrate almost excessive action on the pancreas.

Aims. This study aimed to develop and demonstrate a Ag2S quantum dot and chitosan-glucose encapsulating polymer-based nanotechnology for oral liraglutide delivery in high fat diet or age induced metabolic impairment.

Methods and Results. Pharmacokinetic data demonstrated 50% of oral liraglutide localization to the pancreas and minimal expression in the liver and gut. ICP-MS demonstrated co-delivery of QDs to the pancreas. Pharmacodynamics studies highlighted that liraglutide were effective at reducing blood glucose in a dose dependent manner. In 16-week high fat diet (HFD) fed and aged (24 months) mice, 4-week treatment with oral and injected liraglutide improved metabolic parameters (insulin resistance, fasting and fed insulin and glucose regulation). Injectable liraglutide alone promoted weight loss in HFD fed mice, while both oral and injectable promoted reduced food intake.

Discussion. These studies demonstrate the broad application of our nanotechnology for non-liver acting medications and highlight an organic platform for oral drug delivery.

263 Multiplexed physiological perfusion systems for optimising the predictive value of drug screening

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Introduction. Nutrient availability in the tumor microenvironment has a crucial impact on cellular processes, metabolism and anti-cancer drug responses. However, the vast majority of current *in vitro* biomedical studies are conducted in unphysiological circumstances, with supra-physiological levels of nutrients in a non-flowing culture environment. This static setting distorts the metabolism in cancer models and may impair the predictive value of the micro-physiological systems such as organoid and tissue slices. We aim to create a more physiologically relevant microenvironment to better emulate the *in vivo* process and improve the predictive value of current culture systems.
Methods. In our study, a medium with human plasma-like components and concentrations (Melbourne Medium, MM) was developed and supplied at a constant flow by taking advantage of a multiplexed superfusion system to provide continuous medium supply and therefore prevent nutrient depletion. We compared the human lung adenocarcinoma epithelial A549 cells cultured in MM and conventional medium (CM) under flow or static conditions measuring the cell viability, cell junction formation, metabolism and chemo-therapeutic response.
Results. Our culture system profoundly increased the survival of A549 cells when compared to conventional culture and maintained the viability above 95% after 5 days culture. Additionally, A549 cells displayed a more EMT-like phenotype with tight junction disruption. Importantly, metabolomic profiling validated the culture system by showing maintenance of the physiological nature of the culture media, while simultaneously preventing the accumulation of certain metabolic waste products. Furthermore, the potency of chemotherapy paclitaxel was strongly influenced by the culture media, as A549 cells were less sensitive to paclitaxel in static MM compared to CM. Thus, CM may overestimate paclitaxel potency and Emax especially in static (non-flowing) conditions.
Discussion. Our more physiologically relevant culture system provides a baseline with which to achieve a better emulation of the (patho)physiological microenvironment, and may further improve the predictive value of cancer therapeutic screening.

Cantor JR et al (2017) Cell 169: 258-272

264 Bacteriophage nanobots

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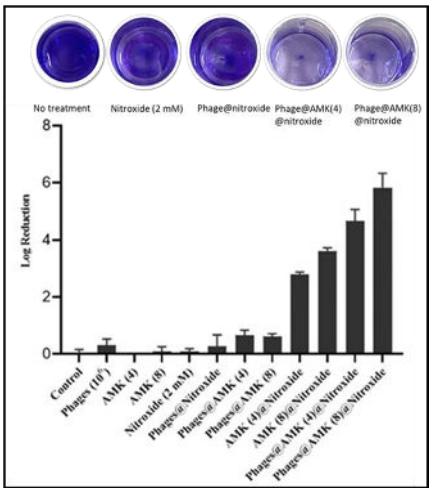
Introduction. Currently, there are no effective solutions to the inexorable rise of antimicrobial resistance. This global challenge has increased interest in the use of obligate viral predators of bacteria, bacteriophages (phages), as an alternative strategy.
Aims. The present project developed phage-drug conjugates as phage nanobots to prevent and/or treat bacterial infections, including those caused by antimicrobial-resistant pathogens.
Methods. The present project developed conjugates comprising a phage and one or more types of active agent conjugated by a patented linker.[1] Bacteriophages are employed as an antimicrobial agent as well as a drug carrier system for selectively delivering ligated payloads to a target cell.
Results. The combination of an antibiofilm agent, amikacin and bacteriophage showed a significant effect on *P. aeruginosa* biofilms, reducing bacterial viability of biofilm cultures by more than 5 logs
Discussion. The key innovation is the smart functional linker with stimuli-responsive features which release of payloads at the infection site. The key expertise is in the correct choice of phages and payloads for specific clinical applications.This allows for controlled and site-specific delivery of the active agent, minimising off-target toxicity and maximising concentration at site.



[1]Duong, H.T.T., Iredell, J.R., and Huang, H. "Phage-drug conjugate", filed 29 November 2021.

265 Systematic review of intravenous drug compatibility in neonatal intensive care setting

D Thisuri N De Silva[1], Brioni Moore[1], Tobias Strunk[2], Michael Petrovski[3], Vanessa Varis[4], Kevin Chai[5], Leo Ng[6], Kevin T Batty[1], Curtin Medical School, Curtin University[1], Perth, WA, Australia; Neonatal Directorate, King Edward Memorial Hospital for Women[2], Subiaco, WA, Australia; Pharmacy Department, King Edward Memorial Hospital for Women[3], Subiaco, WA, Australia; University Library, Curtin University[4], Perth, WA, Australia; School of Population Health, Curtin University[5], Perth, WA, Australia; Curtin School of Allied Health, Curtin University[6], Perth, WA, Australia.

Introduction. Patients in Neonatal Intensive Care Units (NICUs) often receive simultaneous administration of IV drugs via three-way connectors (Y-site). Incompatibility data are summarised in authoritative references and clinical guidelines; however, the methods and source data may not be relevant to the NICU setting. A systematic review would facilitate compilation and evaluation of the scientific evidence regarding physicochemical drug compatibility.
Aim. To conduct a systematic review of physicochemical compatibility of IV drugs used in neonatal settings.
Methods. The 'SPIDER' systematic review model was used to formulate the research question. The search strategy included a predetermined list of NICU drugs prepared by a clinical expert panel. The retrieved results were deduplicated and entered into 'Research Screener' (https://researchscreener.com), a semi-automated, machine-learning tool for abstract screening and further study selection. The selected articles were then subjected to full-text reading to include in the review, based on pre-determined inclusion criteria, prior to formal data extraction.
Results. After deduplication of the database search results (n=42814), 25597 articles were available for screening. Two reviewers used Research Screener to screen up to 2600 articles in cycles of 50. Overall, 323 references were selected for full text reading and 117 met the inclusion criteria for the systematic review (Y-site compatibility). The majority (70%) had only evaluated physical compatibility, 2% evaluated chemical compatibility only, and 28% evaluated both physical and chemical compatibility of selected IV drug combinations. Physical compatibility has been evaluated by both visual and subvisual methods. HPLC is the most widely used technique to assess chemical compatibility.
Discussion. Combined physicochemical compatibility data provides a more comprehensive evaluation of IV drug compatibility but has been reported in <30% of published literature. Research Screener enabled the reviewers to screen 10% of a large search database to select the eligible studies for systematic review. We conclude there should be a focus on physicochemical compatibility studies to support clinical decisions in vulnerable patient groups.

266 Effect on dissolution time after cutting a slow-release tablet formulation – Panadol-Osteo®

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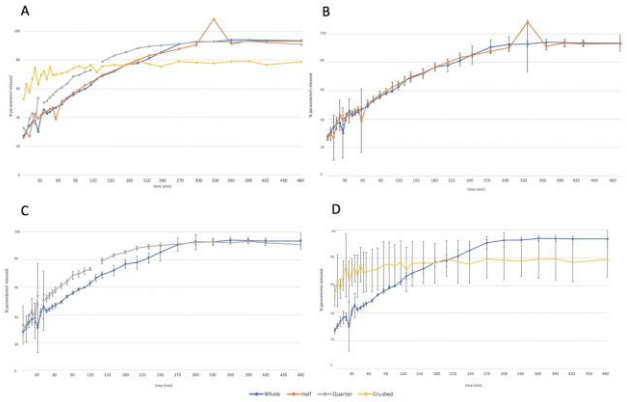
Introduction. Current standard practice will often recommend not to cut or crush slow released oral tablets. However, personalised medicine practice will sometime require tablets to be modified to meet a patient's need, such as swallowing difficulty or reduced dose. (McGillicuddy et al. 2015)
Aims. Compare the dissolution and drug release profile of slow-release paracetamol tablet (Panadol Osteo®) before and after modification.
Methods. Panadol Osteo® dissolution test was performed using USP standard (USP 39), paracetamol concentration was determined at 243 nm using Nanodrop™ spectrophotometry.



Results. The study shown that cutting-in-half Panadol Osteo® tablets do not cause significant changes in dissolution and its drug release profile (Graph B), a minor increase in dissolution rate is observed when the tablet is cut into quarters (Graph C), but it would lose the slow-release profile when the table are crushed (Graph D)
Discussion. Many pharmaceutical formulations can be used to design slow-release tablets. Our study show that some slow-release methods, such as multi-layered formulation, will allow some modification to meet individuals' need. The multi-layered formulation is used by more than half of all slow-release products current available in Australia. Therefore, many other slow-release tablets maybe able to be modified, but confirmation test by dissolution and drug release studies are needed for each product prior to clinical application.

McGillicuddy A, et al. (2015) Eur J Clin Pharmacol 72(2):141-151.
United States Pharmacopeia and National Formulary (USP 39-NF 34). U.S. Pharmacopeial Convention: Rockville; 2016.

267 Development of a novel pH-buffered alginate gel for resistant wound infections

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Introduction. A cutaneous wound is the consequence of a tissue injury that exposes the underlying dermal tissue to pathogen invasion which often results in development of clinical infection. Wound reepithelialisation is a critical step in tissue regeneration and restoration of intact skin barriers during wound healing. A natural response to tissue injury includes a slightly acidic skin environment to prevent pathogen colonisation and changes in wound pH environment have been documented to affect the healing outcomes, however, several contradicting studies show different wound healing outcomes in response to pH changes. To identify the best pH for treating infected and non-infected wounds, novel topical pH-buffered gels were developed maintaining an acidic and alkaline wound pH environment.
Aims. To develop a novel pH-buffering formulation that maintains the wound pH acidic or alkaline following cutaneous tissue injury to promote healing in infected and non-infected wounds.
Methods. Acid and alkaline buffered gels (pH 4.5 and 7.5 respectively) were prepared using a combination of organic and inorganic acids in Milli Q water and buffered to the desired pH using a pre-standardised 1N sodium hydroxide (NaOH) solution. Xanthan gum was used as a gel base. The acid-buffering capacity of the gels was evaluated against 1N NaOH and artificial wound fluid (AWF) at different wound pH. The healing ability of the gels was determined using *in vitro* wound scratch assay and investigated for *in vitro* antibacterial activity against resistant Gram-positive and Gram-negative bacterial strains. The cell viability and rheological properties were also evaluated.
Results. Our results showed that the acid-buffered gels promote healing at pH 4.5 while alkaline-buffered gel inhibits cellular responses required for healing. The *in-vitro* antibacterial studies demonstrated inhibition for both Gram-positive and Gram-negative bacteria. The cell viability assay revealed no potential toxicity against skin cells at the antibacterial concentrations.
Discussion. Collectively, the developed pH-buffered gel indicates the potential positive role of acidic pH on cellular responses mediating tissue regeneration. Future studies are required to evaluate the antimicrobial and healing-promoting effects of the acid-buffered gel in preclinical models of wound infection.

268 Health and medication-related goals of care in Home Medicine Reviews: A secondary analysis of the Goal-directed Medication review Electronic Decision Support System (G-MEDSS)© cluster-randomised clinical trial

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Introduction. Inclusion of health and medication-related goals of care within medication reviews may improve quality of life and reduce adverse events.[1] The Goal-directed Medication review Electronic Decision Support System (G-MEDSS)© allows healthcare practitioners conducting medication reviews to align recommendations to the person's goals and preferences.
Aims. To conduct a secondary analysis of individuals receiving the Home Medicines Review (HMR) service within the G-MEDSS cluster-randomised clinical trial (RCT) to categorise and describe health and medication-related goals included within HMR reports to general practitioners, and where and how goals were integrated into HMR reports.
Methods. HMR reports were collected from consultant pharmacists enrolled in the intervention (G-MEDSS + HMR) and comparison (HMR alone) groups during the Australian national cluster-RCT.[3] Goals of care were identified as health-related, medication-related or both. The Taxonomy of Patient-Centred Goals[2] was adapted to describe the health and medication-related goals documented within the HMR reports.
Results. HMRs were collected at baseline (n=88 intervention, n=112 comparison) from 53 consultant pharmacists enrolled in the study. Preliminary findings have identified a wide range of health-related (e.g. improving quality of life) and medication-related (e.g. taking less medications, avoiding side effects) goal domains, and goals were often interwoven with medication recommendations. Many medication-related goals of care were specific to medication classes (e.g. insomnia management with SSRIs) and health-related goals were mostly included in the general patient summary/introduction.
Discussion. Health and medication-related goals of care are often reported within HMR reports. Further analysis will compare the goals of care captured by G-MEDSS with the health and medication-related goals documented by consultant pharmacists within the HMR reports, to further inform the importance of including goals within HMR.
1) Verdoorn S et al. (2019) PLoS Med 16(5): e1002798. 2) Kouladjian O'Donnell L et al. (2020) BMC Geriatr 20, 51. 3) Bogardus ST et al. (1998) J Gen Intern Med 13(10):675-80.

300 Exploring cardiac GPCRs for effective fibrosis treatment

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Introduction. Pathological fibrosis in the myocardium causes cardiac remodelling leading to heart failure and serves as a converging point for almost all heart diseases. There remains unmet therapeutic need to treat cardiac fibrosis in order to reduce heart failure progression. The second messenger cAMP, commonly modulated downstream of G protein-coupled receptor (GPCR) activation, has been shown to inhibit cardiac fibrosis may be harnessed as a good therapeutic target in heart failure.
Aim. This study was conducted to evaluate GPCR modulation of cAMP signaling in adult human ventricular cardiac fibroblasts (NHCF-V) in the presence or absence of the pro-fibrotic mediator, transforming growth factor beta 1 (TGF-β1).
Methods. This study evaluated 11 candidate GPCRs, selected based on gene expression in both human cardiac fibroblasts (The Human Protein Atlas) and human cardiac organoid. GPCR-mediated cAMP accumulation in NHCF-V was evaluated with LANCE cAMP assay. NHCF-Vs were treated with 1 µM forskolin and then exposed to agonists of selected GPCRs for 30 min in the absence or presence of 48 hr TGF-β1 (10 ng/mL) pre-treatment. Nonlinear regression in GraphPad Prism 9.3.1 was used to quantify the potency (pEC50) of the agonists. Data are presented as mean ± SEM.
Results. Increased cAMP accumulation was observed in NHCF-V upon stimulation with 5'-N- ethylcarboxamidoadenosine (pEC50 = 7.2 ± 0.6; + TGFβ-1 pEC50 = 6.9 ± 0.4), isoprenaline (pEC50 = 8.1 ± 0.8; + TGFβ-1 pEC50 = 8.3 ± 1.0), beta calcitonin gene-related peptide (pEC50: not determined) and histamine (pEC50: not determined), effects predicted to be mediated by the A_{2B} receptor, β_2-adrenoceptor, calcitonin receptor-like receptor and H_2 receptor, respectively. A reduction in cAMP accumulation was observed upon stimulation with ozanimod (pEC50: not determined) and spexin-1 (pEC50 = 9.1 ± 0.3; + TGFβ-1 pEC50 = 9.4 ± 1.1), effects predicted to be mediated by $S1P_1$ receptor and G protein-coupled receptor 161, respectively.
Discussion. These findings have quantified GPCR-mediated modulation of cAMP accumulation, a pathway pertinent to fibrosis, in human cardiac fibroblast in the absence and presence of the profibrotic cytokine TGF-β1.

301 Preventing urate-lowering therapy induced gout flares: a systematic review and network meta-analysis

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Introduction. Urate-lowering therapy (ULT) initiation may precipitate a transient rise in flares. However, evidence for the comparative rate of flares for different ULT therapies and drugs used to prevent flares (prophylaxis) is limited.
Aims. To examine: (1) flare risk post initiation or escalation of different ULTs; (2) change in flare risk with and without prophylaxis; (3) adverse event (AEs) rate associated with prophylaxis; and (4) the optimal duration of prophylaxis.
Methods. We searched Medline, Embase, Web of Science, Cochrane databases and clinical trial registries for clinical trials investigating adults with gout initiating or escalating ULT, from inception to Nov 2021. Frequentist random-effect network meta-analyses were performed and reported risk ratios (RR) with 95% confidence intervals (95% CIs). We assessed bias using the Revised Cochrane risk-of-bias tool. The study is registered with PROSPERO, CRD42020178479.
Results. We identified 3775 records, of which 29 publications (27 trials) were included. Comparative to placebo plus prophylaxis, the RR of flares ranged from 1.08 [95% CI 0.87-1.33] for febuxostat 40mg plus prophylaxis to 2.65 [95% CI 1.58-4.45] for febuxostat 80mg plus lesinurad 400mg plus prophylaxis. Due to a low level of reporting of flares per prophylactic drug in trials that did not randomise prophylaxis, comparisons of flare risk between prophylactic drugs were limited to trials where prophylaxis was randomised. ULT plus prophylaxis was associated with a lower RR of flares compared to ULT alone (0.35 [95% CI 0.25-0.50] rilonacept 160mg, 0.43 [95% CI 0.31-0.60] rilonacept 80mg and 0.50 [95% CI 0.35-0.72] colchicine). Rilonacept was associated with greater treatment related AEs relative to ULT alone. Most studies were assessed as a high risk of bias, with 4 (14%) of 28 studies and 2 (18%) of 11 studies rated as low risk of bias for flares and AEs, respectively.
Discussion. The risk of ULT-induced flares varied depending on the ULT drug and dosing strategy. Colchicine and rilonacept significantly reduced the incidence of flares, but the evidence for nonsteroidal anti-inflammatory drugs and corticosteroids was limited. Additionally, there was limited data on the harms and optimal duration of prophylaxis.

302 The influence of soluble microenvironment on tumour cell cytotoxicity of chemotherapeutics

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Introduction. There have been increasing concerns about the contrasting hypernutritional composition of conventional cell culture medium (CM) with that of the human physiological microenvironment. Melbourne medium (MM) is a plasma-like physiological medium developed by our group.
Aims. To compare the drug efficacy of breast cancer drugs in MM and CM, and to use proteomics to study protein expression differences in pathways relevant to drug mechanisms.
Methods. A systematic search for launched and discontinued breast cancer drugs was conducted using Cortellis Drug Discovery Intelligence database. Acridine orange and ethidium bromide (AO/EB) staining was used in combination with Operetta high content imaging microscope to conduct automated viable and non-viable cell numeration. The protein expression differences in MDA-MB-231 and MCF7 cells in MM vs. CM were established by global proteomics.
Results. A total of 230 discontinued drugs and 54 launched drugs were identified after the Cortellis search. The drug list was refined to 12 drugs for testing efficacy. Of the 12 drugs, paclitaxel, docetaxel and ispinesib showed differences in effectiveness in MDA-MB-231 cell line between MM and CM groups. The potency of these drugs was higher in CM compared to MM. Four out of 12 drugs also showed differences in potency in MCF-7 cell line between MM and CM groups. Global proteomics analysis indicated that 1317 and 794 proteins were differentially expressed between MM and CM in MDA-MB-231 and MCF-7 cells, respectively.
Discussion. The effectiveness of breast cancer drugs was greatly influenced by the microenvironment in which the drugs were tested. Ispinesib, a KIF11 inhibitor that failed in phase II clinical trial, showed reduced effectiveness on tumour cells in MM, a finding that if available during the preclinical evaluation may have arrested its further development.

303 Adding a Dimension to Biomechanical Cues Underlying IPF

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Introduction. Idiopathic Pulmonary Fibrosis (IPF) is a progressive disease in which the lung parenchyma undergoes irreversible remodelling. Remodelling propagates from fibrotic foci, regions characterized by excess deposition of extracellular matrix (ECM) driven by activated myofibroblasts. The myofibroblast fibrogenic activity is driven both by biomechanical and biochemical cues. We have demonstrated that modulating the stiffness of the matrix microenvironment can revert the myofibroblast to a phenotype that appears 'afibrogenic.'
Aims. The present study seeks to reveal signalling pathways altered by the stiffness and dimensionality of the microenvironment in order to explain the 'afibrogenic' nature of fibroblasts cultured in the soft microenvironment.
Methods. Pulmonary fibroblasts were cultured either in a 2D stiff (conventional monolayer) or 3D soft (spheroid) microenvironment and the phenotypes engendered by these settings were characterized by a multi-omics approach, complemented with measurements of conventional fibrotic markers. To ascertain the extent to which fibroblasts in the soft microenvironment remain 'afibrogenic,' fibroblast spheroids will also be maintained for up to 28 days.
Results. Compared to fibroblasts cultured as a stiff 2D monolayer, fibroblasts cultured in the 3D soft microenvironment showed striking downregulation of actin cytoskeleton and stress fiber proteins, multiple subtypes of fibrillar collagen and connective tissue growth factor and upregulation of lipofibroblast markers such as perilipin 2. Additionally, fibroblasts in the soft, spheroid microenvironment showed altered signalling pathways, evidenced by a marked increase in the production of interleukins 6, 8 and 11, and remodelled signalling by TGF-b, one of the best characterised fibrogens, which caused notable increases in myofibroblast activation for cells in the 2D stiff microenvironment.
Discussion. This study highlights fibroblast sensitivity to the mechanical microenvironment; that acute exposure to a soft environment causes dedifferentiation from the myofibroblast to a phenotype with resistance to TGF-b-induced myofibroblast activation. Our ongoing long-term spheroid culturing will subsequently allow us to determine the persistence of the 'afibrogenic' phenotype.

304 Effects of acute and chronic trimethylamine-N-oxide and simulated diabetes in cardiac myoblasts

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Introduction: Trimethylamine-N-oxide is a gut metabolite receiving considerable attention for its proposed involvement in cardiovascular disease (CVD). However, whether elevated TMAO reported in cardio-metabolic disorders reflects causal involvement, or a secondary or biomarker role in disease, remains to be elucidated. The cardiovascular, metabolic and energetic effects of TMAO warrant study in models of disease.
Aims: To characterise the effects of TMAO on cell viability and death, mitochondrial respiration, and gene expression in cardiomyoblasts under control conditions and in simulated diabetes mellitus (SDM).
Methods: H9c2 cardiomyblasts were maintained under control (5 mM glucose, 0 mM palmitate, 0 mM insulin) or SDM conditions (25 mM glucose, 100 µM palmitate, 100 nM insulin) and incubated with 10 or 100 µM TMAO for 1 or 72 hrs (acute and chronic exposures). Cells were also grown for 1, 5, and 10 hrs with and without similar TMAO concentrations under control conditions. Cell viability and death were assessed via an MTT assay and extracellular protein (LDH) release, with mitochondrial respiration detailed using an Oroboros Oxygraph-2k system. Changes in myoblast gene expression were also assessed at the 1 and 72 hr time points via quantitative real-time PCR.
Results: Simulated diabetes alone worsened cell viability and death, and significantly reduced mitochondrial respiration. In contrast, acute exposure to 10-100 µM TMAO did not influence viability, death or respiration (in healthy or SDM cells). However, mitochondrial respiration in both healthy and SDM cells was significantly repressed by more prolonged incubation with 100 µM TMAO. Expression of genes related to mitochondrial fission processes were reduced with SDM but unaltered by TMAO.
Discussion: *In vitro* studies indicate that while diabetic conditions detrimentally impacts cardiomyoblast viability and death, TMAO fails to influence these measures (in healthy or SDM cells). However, mitochondrial respiration is reduced during prolonged exposure to TMAO, an effect exaggerated by SDM. These findings provide some support for a potentially causal role for TMAO in cardio-metabolic disease, though further investigation is needed to further test such effects and unmask underlying molecular mechanisms.

305 Sex differences in risk of diabetes-associated cardiovascular events with SGLT2i versus GLP-1Ras

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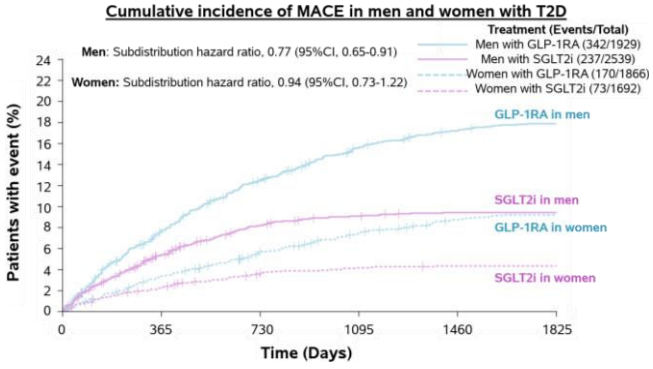
Introduction. Despite known sex differences in diabetes-induced cardiovascular disease, pharmacological treatment recommendations are independent of sex. Sodium glucose co-transporter-2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP-1RAs) reduce major adverse cardiovascular events (MACE) in people with type 2 diabetes (T2D), however their potential sex-specific effects remain unknown.
Aims. The objective was to test the hypothesis that sex-specific differences in patient MACE outcomes are evident in SGLT2i vs. GLP-1RA-prescribed T2D Australians.
Methods. This population-based cohort study included men and women with T2D (≥30 years), discharged from a Victorian hospital between 2013 and 2017, and dispensed an SGLT2i or GLP-1 RA within 60 days of discharge (n=8026, 44.3% women). Using Cox proportional hazards regression with Fine and Gray competing risks, subdistribution hazard ratios (sHR) with 95% confidence intervals (CI) were estimated for MACE, its individual components, and mortality in a follow-up to mid-2018. Analyses were conducted for all men and women, further stratified by age and baseline heart failure (HF) status.
Results. In a median follow-up time of 756 days, SGLT2i (n=4231) vs. GLP-1RAs (n=3795), reduced the rate of MACE in men (sHR 0·75; 95%CI 0·64-0·89), but not women (figure). SGLT2i reduced MACE rates in men (sHR 0·64; 95%CI 0·47-0·87) and women (sHR 0·48; 95%CI 0·29-0·81) ≥65 years, and in men with baseline HF (sHR 0·45; 95%CI 0·28-0·73).
Discussion. SGLT2i, relative to GLP-1RAs, demonstrate favourable effects for the reduction of MACE among Australian men, including older men, and men with baseline HF.
Analogous benefit in women is only evident in older females.



306 Never waste a good crisis: The changing face of pharmacy practice

Fei Sim[1]. Faculty of Health Sciences, Curtain University[1], Perth, WA, Australia

Events in the past three years experienced in Australia, including the pandemic and natural disasters, have created challenges but also opportunities for pharmacy practice. Whilst public health emergencies are major threats to the healthcare system, they have positioned pharmacists to be essential primary healthcare providers. During these crises, pharmacists demonstrated agility, responsiveness, and reliability. Pharmacists have proven, yet again, our value as primary healthcare providers and medicine experts. Pharmacy services across practice settings during these difficult times have enabled Australians to continue to have timely access to medicines and continued care for a range of acute and chronic health conditions. Pharmacist-led vaccination service is only one of the many examples of professional services with demonstrable positive impact. This session aims to provide an overview of the impact of the pandemic and other public health crises on the scope of pharmacist services, and how these circumstances contribute to a paradigm shift in pharmacy practice. The lessons learned are critical consideration as our profession prepare for the current and emerging workforce to better meet the needs of Australians and our healthcare system. The opportunities these crises provide should be leveraged as the profession advocate for sustainability and remuneration of these roles. Contemporary pharmacist roles should also be considered by education providers and professional bodies as part of workforce planning. In sum, never waste a good crisis.

307 Human cardiac organoids as microphysiological systems to study peptide receptor function

Simon R Foster[1,2], Janice D Reid[1] Mary Lor[1], Rebecca L Fitzsimmons[1], Richard J Mills[1], James E Hudson[1]. QIMR Berghofer Medical Research Institute[1], Brisbane, QLD, Australia. Dept of Pharmacol[2], Biomedicine Discovery Institute, Monash University, Clayton, VIC.

Introduction. G protein-coupled receptors are central regulators in cardiovascular biology that are targets of frontline therapies for hypertension and heart failure. However, the cardiovascular roles for a small fraction of the GPCR family are known and the downstream signalling networks are poorly characterised. Human cardiac organoids (hCO) constitute microphysiological systems to enable receptor function studies & accelerate cardiovascular drug discovery.
Aims. To characterise peptide-dependent function in human cardiac organoids.
Methods. Multi-cellular human pluripotent stem cell-derived cardiac organoids (hCO) represent a controlled model for exploring intracellular and paracrine signalling in human heart tissue (Mills et al, 2017, 2021). RNA-seq data from human heart tissue and hCO were analysed for GPCR expression. A panel of peptide GPCR ligands were screened in hCO to profile their impact on contractile force, rate and kinetics. Analyses of hCO functional parameters were performed using custom Matlab scripts. Peptides were characterised in subsequent concentration-response studies.
Results. Analyses of hCO and human heart tissue revealed robust expression of 73 receptors (>5 CPM), including classical cardiovascular receptors and orphan GPCRs. We observed peptide-mediated effects on multiple cardiac parameters. For example, endothelin-1 increased the force and rate of hCO contraction (50 and 45%, respectively; $P<0.0001$ vs unstimulated control). These responses were concentration-dependent (EC_{50} of 7 nM for force; 7.5 nM for rate). In addition, peptide-dependent effects were mediated via less well-characterised cardiac receptors, including a 15% increase in activation time for neuropeptide Y ($P<0.0001$ vs unstimulated control).
Discussion. We have shown that our hCO platform can be used to dissect peptide GPCR-driven changes on specific cardiac functional parameters. We are currently using global phosphoproteomics and transcriptomics approaches to explore the downstream signalling networks to determine the signalling mechanisms that underpin these responses.

Mills R et al (2021) Cell. 184(8):2167-2182.e22.
Mills R et al (2017) Proc Natl Acad Sci U S A. 114(40):E8372-e8381.

308 Nociceptive detection using a cell-based microfluidic platform

Yingkai Wei[1,2], Ziqiu Tong[1,2], Wendy Imlach[3], Nicholas Veldhuis[4], Dusan Matusica[5] and Nicolas H. Voelcker[1,2,6,7]. Drug Delivery Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University[1], Melbourne, VIC, Australia; Australian Research Council Centre for Personalized Therapeutic Technologies[2], Melbourne, VIC, Australia; Monash Biomedical Discovery Institute and Department of Physiology, Monash University[3], Melbourne, VIC, Australia; Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Monash University[4], Melbourne, VIC, Australia; Pain and Sensory Cell Biology Laboratory, Flinders Health and Medical Research Institute[5], Adelaide, SA, Australia; Commonwealth Scientific and Industrial Research Organization (CSIRO)[6], Melbourne, VIC, Australia; Melbourne Centre for Nanofabrication[7], Melbourne, VIC, Australia;

Introduction. The absence of quantitative pain detection tools and the lack of appropriate nociceptive cell models for drug development has significantly impacted the diagnosis and treatment of chronic pain. The research presented demonstrates a novel approach towards nociceptive assessment and offers a potential new model for screening of novel analgesic drugs. The platform showed a sensitive, unbiased method for detection of nociceptive mediators using only microliter volumes of complex biological fluids.
Aims. The research presented focuses on the development and validation of a cell-based microfluidic biosensor for nociceptive detection.

309 Multiplexed Superfusion System for Cell Culture: from Prototype to Product

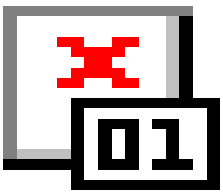
Bryan Gao[1,2], Alastair G Stewart [1,2]. ARC Centre for Personalised Therapeutics Technologies, University of Melbourne[1], Parkville, VIC, Australia; Department of Biochemistry and Pharmacology, University of Melbourne[2], Parkville, VIC, Australia.

Introduction. The artificiality of non-physiological static culture conditions engenders higher rates of false-positive and false-negative results that pose unnecessary and costly risks and uncertainties across the entire biomedical research field. We have prototyped a continuous flow system compatible with conventional practices and protocols with greatly enhanced throughput to achieve physiological emulation in cell culture.

Aims. We intend to work with our industrial partner for commercialisation of the flow system. Specifically, we aim to 1. Conduct relevant market analysis, 2. Validate the product usability in industrial environments, and 3. Develop a minimum viable product.

Methods. While providing essential perfusion capability in 12 and 24 well-plates, the product development focused on quality improvement in user-friendliness, product robustness, and compatibility to scaled manufacturing. Market analysis was primarily through secondary research focusing on industrial background and competition landscape.

Results. Device modularity for custom throughput, compatibility to scaled-fabrication, and innovation in (micro)fluidic interconnections for user-experience have been addressed. Market analysis suggested a 3-nested commercialization pathway consisting of Product (i.e., pump) – System (i.e., perfusion) – Service (i.e., toxicology assays) for progressively specialized markets.

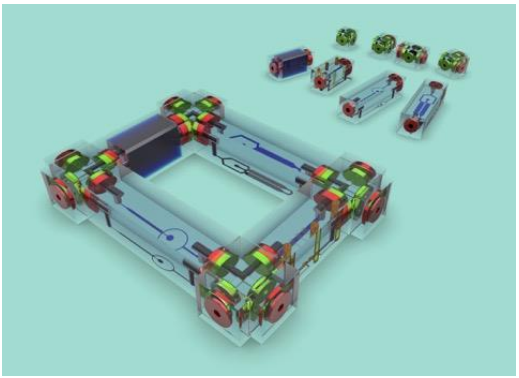


Discussion. Our suite of perfusion technologies provides a much-needed improvement in physiological emulation to support the predictive value of *in vitro* biomedical and biological research.

310 Scalable models for disease modelling and drug testing: the next generation of human-on-chips

Yi-Chin Toh[1-3], Centre for Biomedical Technologies[1], Centre for Microbiome Research[2], School of Mechanical, Medical & Process Engineering[3], Queensland University of Technology, Brisbane City, QLD, Australia

Introduction. New generation of therapeutics, including immunotherapy, microbes, and vaccines act through complex biological processes, often involving multiple organ systems in the human body. Traditional 2D cell cultures and animal testing models cannot meet with this new demand. This has catapulted the rapid advancement of human microphysiological systems (MPS) or popularly known as organoid- or organs-on-chips to better predict the efficacy and side effects of these new classes of therapeutics. A major challenge is how to mimic complex cellular microenvironment and physiological processes while fulfilling the needs of the intended application, such as having sufficient throughput, operational simplicity, and quantitative readouts, so that they will be practical for deployment in routine drug testing and biological experimentation.



Methods. A design approach is used to integrate cells, biomaterials and micro-technologies such as microfluidics and microarrays into MPS systems so that we can mimic biological complexity while considering manufacturing and automation constraints. Assay readouts to measure drug responses should also be considered during the design of the MPS.

Results & Discussion. To date, my lab has successfully engineered human-relevant testing models in various formats. These included a micropatterned human stem cell model to model embryonic neurodevelopment defects as well as compartmentalised microfluidic arrays and modular microfluidic systems to emulate systemic multi-organ interactions involved in drug-induced adverse skin reactions, and microbial-liver interactions.

311 Why are changes needed in drug dosing for infectious diseases?

Sam Salman[1,2,3] Clinical Pharmacology and Toxicology Unit, PathWest, WA, Australia[1], Medical School, University of Western Australia, Perth, WA, Australia[2], Immunology, Fiona Stanley Hospital, WA, Australia.[3]

The dose regimens presented at time of registration often do not reflect the optimal use of a drug, particularly as time passes. This is true for many anti-microbial agents where a growing literature identifying sources of variability that affect the required dose regimen for an individual to treat the infection, while also avoiding toxicity. These include variability across patients including age, size, organ function, and severity of illness which each can influence the expected pharmacokinetic profile. Variability in microbes also need to be considered to ensure adequate cure. When these sources of variability are measurable, and their effect quantifiable, they can be considered at the initiation of dosing. Despite the growing knowledge base not all potential sources of variability can be accounted for prior to treatment. Information collected after the initiation of treatment, such as drug concentrations, microbial resistance, and clinical response, is needed to further characterise and achieve treatment targets.

This talk will explore a range of patient, microbe and other factors that explore why ongoing changes, and further research efforts, are needed in dosing of antimicrobial agents.

312 How can preclinical studies be used for establishing drug concentration targets?

Fekade B Sime[1]; UQ Centre for Clinical Research, The University of Queensland, Brisbane, QLD, Australia

The development drug-exposure-response relationship for antimicrobials requires a unique approach as compared to most other drug classes. Antimicrobials are not required to act on the host physiological system to illicit their therapeutic effect, rather should be selective in acting on the pathogen that causes the infection without affecting the host physiology. Therefore, the desired pharmacological action (or effect) of antimicrobials does not manifest in any direct therapeutic alteration of the physiology of the host. There is often no clear objective clinical endpoint measurable from physiological changes that can be used to titrate the dose for the required effect. The clinical endpoints are rather subjective often described as microbiological cure, resolution of infection or clinical cure. It is therefore extremely challenging, if not impossible, to derive drug-exposure-response relationship from clinical studies to enalbe establish drug concentration targets for antimicrobials. The use of pre-clinical research tools, including both in vitro infection models and animal infection models, is critical in describing exposure-response relationships to derive exposure targets that can be used to guide dosing. This presentation will summarise the utility of pre-clinical infection models in establishing drug concentration targets that can be used for optimisation of dosing regimens both during drug development as well as during clinical use as part of routine therapeutic drug monitoring program.

313 Developing pharmacokinetic models for clinical care; how can we make them useful?

Cornelia B Landersdorfer[1]. Monash Institute of Pharmaceutical Sciences, Monash University (Parkville Campus)[1], Melbourne, VIC, Australia.

Traditionally, an empirical 'one-size-fits-all' approach has been applied to antibiotic dosing. This approach has been increasingly ineffective and may lead to suboptimal antibiotic exposures, risking treatment failure, emergence of resistance and/or toxicity, particularly for compounds with a narrow therapeutic window. Additionally, even at a given daily dose, the shape of the antibiotic exposure profile can substantially influence treatment outcomes.
Mathematical models that characterise the population pharmacokinetics and interpatient variability of antibiotics are valuable to predict the dosing regimens required to achieve targeted exposure profiles. In order to make pharmacokinetic models useful for the application in clinical care it is critical that they have been robustly evaluated, including on their predictive performance and precision of parameter estimates. Patient groups at high risk of mortality from an infection, including the critically ill and those requiring kidney support, often display different pharmacokinetics (e.g. augmented renal clearance or alterations in volume of distribution) compared with the general patient population. It is thus important that pharmacokinetic models for use in clinical care are based on data from the target patient population to maximise efficacy and minimise toxicity and resistance for successful treatment outcome. Models that include the impact of patient covariates which affect the antibiotic exposure profiles and can be determined as part of clinical care, used in combination with therapeutic drug monitoring, enable personalised antibiotic dosing, for example through adaptive feedback control algorithms.
Population pharmacokinetic models are ideally suited to be linked with mechanism-based pharmacodynamic models that describe the time-course of bacterial response and are typically developed based on preclinical studies. Ultimately, such pharmacokinetic/pharmacodynamic models are envisaged to enable model-informed precision dosing for the selection of optimised antibiotic treatment regimens based on the characteristics of the patient and their infecting bacteria.

314 Ahead of the Curve with Vancomycin in Children

Tony Lai[1,2,3]. Department of Pharmacy, The Children's Hospital at Westmad[1], Westmead, NSW, Australia; School of Pharmacy, University of Sydney[2], Sydney, NSW, Australia.

Introduction. Vancomycin Area Under the Concentration (AUC) therapeutic drug monitoring (TDM) is recommended by consensus guidelines for methicillin-resistant staphylococcus aureus (MRSA) infections (Rybak et al. 2020). However, despite the evidence supporting this approach, Australian hospitals' uptake in clinical practice is poor due to practical barriers and gaps in clinical expertise.
Aims. To describe a real-life example of implementing Vancomycin AUC TDM with Bayesian Forecasting (BF) software in a tertiary paediatric referral hospital
Methods. The senior antimicrobial stewardship pharmacist implemented vancomycin AUC TDM with BF using DoseMeRx™ by 1. Creating a business case, 2. Engaging key stakeholders, 3. Developing a new vancomycin local guideline and TDM service delivery model, and 4. Evaluating and refining the implementation with Quality Improvement methodology (Reed 2016) using acute kidney injury (AKI) as a key performance indicator for success. AUC TDM with BF started on August 2021 to November 2022, and vancomycin-induced AKI was compared to a matched cohort from July 2018 to July 2021 when trough-based TDM was used.
Results. One hundred seventy-three patients prescribed vancomycin had AUC TDM with BF from Aug 2021 to November 2022. The incidence of Vancomycin-induced AKI decreased from 3% to 0.01% compared to the period before AUC TDM was implemented. In addition, 12 patients during the trough-based TDM period required dialysis and intensive care, and no patients required dialysis or intensive care from vancomycin-induced AKI in the AUC TDM with BF period.
Discussion. Implementing quality improvement methodologies is feasible to change routine care from trough-based TDM to AUC TDM with BF for vancomycin.

Rybak, M. J., et al (2020). Clinical Infectious Diseases 71(6): 1361-1364.
Reed JE, Card AJ. (2016) BMJ Quality & Safety. 25(3):147-52.

315. Lost in Translation? Insights from drug repurposing for COVID

Craig R Rayner[1,2]. Certara[1], Princeton NJ, USA; Faculty of Pharmacy and Pharmaceutical Sciences, Monash University[2], Melbourne, VIC, Australia.

Repurposing is an important strategy in general for developing medicines. However in the midst of a health emergency it presents formidable challenges for all stakeholders- manufacturers, medicines regulators, policy recommending agencies, public health officials and procurers. In this presentation examples of the application of translational science, quantitative and clinical pharmacology, adaptive clinical trials, epidemiological modelling and quantitative integration of real world evidence to support decision making in the COVID-19 pandemic will be presented.

316. The valley of death – why Australia failed to develop clinically effective drugs in COVID-19

Jennifer H Martin, Chair, Clinical Pharmacology, University of Newcastle NSW

Introduction. The issue of taking drugs from laboratory into clinical trials or clinical practice can be long, expensive, and arduous. As seen during COVID-19 where there was additional urgency together with a lack of funding, little clinical pharmacology input into choice and dose, and potted engagement with multidisciplinary skillsets, Australia spent a lot of funds on medicines and vaccine trials that never made it to clinical practice. For a country that has such a strong medical research platform, there has to be deep assessment of where it went wrong and how experts in drug development including pharmacology and toxicology can ensure that there is better collaboration and stronger medicines leadership subsequently.

317 Australian Program for Drug Repurposing for Treatment Resistant Ovarian Cancer

Nikola A Bowden[1]. School of Medicine and Public Health, University of Newcastle and Hunter Medical Research Institute[1], Callaghan, NSW, Australia

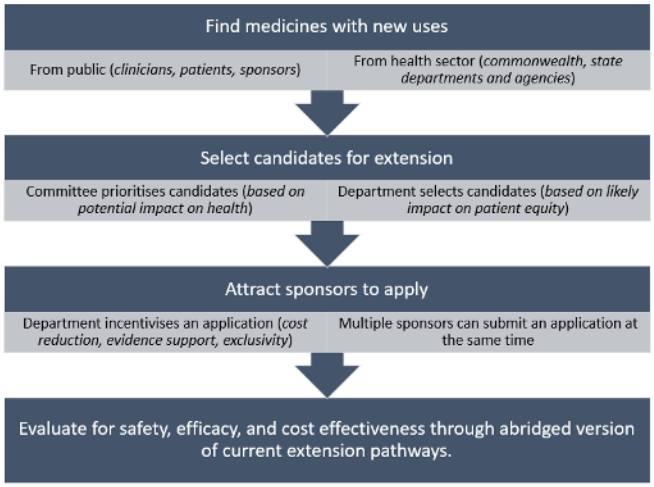
Introduction. High grade serous (HGS) ovarian cancer, the most common subtype of ovarian cancer, has a poor 5-year survival rate due to disease recurrence and resistance to current therapies. Effective new therapies are urgently required. Ongoing efforts to find new drug targets are continuing, but traditional drug development requires approximately 12-16 years processing time and investment of USD$1-2 billion to achieve market approval. This lengthy development pipeline, while necessary for identifying innovative treatments, is not the only option for providing patients with timely access to efficacious, cost-effective therapy. Drug repurposing is a method for identifying new uses for approved or investigational drugs that are outside the scope of the original intended or approved medical use. The development of repurposed drugs is attractive because therapeutic advances and new drug options for ovarian cancer patients has been far slower than expected. We are undertaking one of the most ambitious approaches to developing new ovarian cancer treatments ever undertaken by establishing the Australian program for drug repurposing for treatment resistant ovarian cancer.
Aims. To examine the British Pharmacopeia, currently the most globally comprehensive pharmacology database, for Federal Drug Administration (FDA) and European Medicines Agency (EMA) approved drugs that bind to well-defined targets specific to treatment-resistant HGS ovarian cancer.
Methods. Targets for drug repurposing screens are identified using artificial intelligence platforms. Over the 5-years of this program we will screen 20 drug targets/biological pathways, using an established drug repurposing pipeline to permit this degree of screening at scale. Consumer, clinician and scientific input is gathered at each step of the pipeline and health research economic analysis conducted on all repurposed drug candidates.
Discussion. The Australian program for drug repurposing for treatment resistant ovarian cancer is rapidly delivering data to support the development of clinical trial concepts for the use of repurposed drugs specific for treatment resistant ovarian cancer. The drug repurposing pipeline can be adapted for us for any known drug target for any disease or condition.

318 Repurposing medicines in Australia

Nick Henderson[1], Department of Health and Aged Care, Health Products Regulation Group, Canberra, ACT, Australia

Introduction: Off-label usage of medicines can lead to inequitable access to medicines for patients due to medico-legal concerns, and because the treatment may not be subsidised and therefore not affordable. A model (see figure below) to repurpose medicines is currently being developed to allow already registered on-patent and off-patent medicines to be repurposed in Australia.

Discussion: Through consultation, the Department has received broad support for this initiative from consumers and the pharmaceutical industry in Australia. Applications for new uses of registered medicines will be encouraged from the public and the health care sector. In attracting sponsors to apply to register, repurposing candidates may receive a range of viability incentives. In this model, sponsors will remain liable for post-market pharmacovigilance. The TGA's focus is finalising practicalities for potential implementation, subject to decisions of government.



319 A perspective on "knowledge" curricula – what do pharmacists need to know?

Timothy F Chen, Sydney Pharmacy School, Faculty of Medicine and Health, The University of Sydney.

The practice of pharmacy is underpinned by a firm knowledge, understanding, and application of basic pharmaceutical sciences to practice. Within broader university structures, a school of pharmacy may be a standalone faculty; or embedded in a broader health faculty; or embedded in a broader science and or engineering faculty, amongst other options. In many ways, the position of the school of pharmacy within the university structure may reflect the curriculum on offer. Irrespective of this, pharmacy curricula have always had to contend with content dense specialised disciplines, and their underpinning sciences, including pharmacology, pharmaceutical chemistry, and pharmaceutics, amongst others. A challenge for contemporary pharmacy curricula is the depth and breadth of content of the basic pharmaceutical sciences included in curricula, and how this content is integrated and applied to the practice of pharmacy. Necessarily, with limited time, decisions on whether to include or exclude specific content from the programme must be made. Consideration of the overall goals and specific learning objectives of the pharmacy programme may help in making such decisions. There is no easy answer to what pharmacology content can (safely) be omitted from pharmacy curricula, but consideration of whether the content can be applied to practice or could be applied to practice may help. This presentation will attempt to address this complex matter. Better and smarter integration of pharmacological content to practice-based learning and teaching may be a starting point, acknowledging that this may be rather restrictive, and that implementation of specific (innovative) pharmacological approaches to practice is an entirely separate challenge.

320 Student learning: Context matters

P.K. Rangachari. B.Hsc. (Hons) Program, Dept. Medicine, McMaster University, Hamilton ON, Canada

What students SHOULD learn can be decided on by Committees but what they DO is far less certain. The WHAT of learning is usually categorized as knowledge, skills and attitudes. Of these, knowledge is discipline specific and can be framed as content objectives; skills are more generic and attitudes most general. Core concepts in different disciplines including pharmacology have been carefully considered and defined. Attitudes change little and are often bypassed, skills can be tested, much emphasis is focused on knowledge, though more often usual assessments really gauge information. What students learn is difficult to gauge.
Wine growers talk in terms of terroir, a complex interplay of climate, soil, and grapes. In much the same way the quality and flavour of learning depends on resources, local conditions, selection of students, numbers, teacher training and their attitudes. The experiences in different countries with the pandemic have been stark reminders of how quickly expectations can stumble. Careful ongoing monitoring is crucial. Teachers should give students an opportunity to express their opinions on an ongoing basis, rather than distributing questionnaires as an end of term ritual. Blind adherence to evidence-based information may not help. Approaches successful in one locale do not necessarily transfer well. Context trumps aspirations.

321 Core Concepts of Pharmacology Education: an international collaboration for the benefit of all pharmacology students and educators

Clare Guilding, School of Medicine, Newcastle University, Newcastle Upon Tyne, UK

The International Union of Basic and Clinical Pharmacology Education Section (IUPHAR-Ed) is a dynamic global community of educators in basic, clinical and translational fields of pharmacology. We develop initiatives to actively promote access to educational materials, collaboratively develop new resources, discuss matters related to pharmacology education, and have recently restructured the section to oversee three main initiatives

1. The Pharmacology Education Project: https://www.pharmacologyeducation.org/
2. The Core Concepts of Pharmacology Education Project: https://coreconceptspharmacology.org/
3. Pharmacology Education meetings and networking events including the WCP2023 Education Satellite Symposium

IUPHAR-Ed endorsed and adopted the Core Concepts of Pharmacology Education project in 2022[1]. The project aims to transform pharmacology education by coming to agreement about the fundamental ideas that all pharmacology graduates should remember, understand and apply years after they graduate. Over 250 pharmacology educators from 22 countries have contributed to the project so far, which firstly identified 25 core concepts. Through a combination of online meetings, asynchronous work and a hybrid meeting in Italy, we then defined these core concepts and developed sub-concepts. The process of defining core concepts and developing sub-concepts with an international group whose expertise spans a wide diversity of healthcare, allied healthcare and basic science disciplines, was challenging for certain concepts such as drug elimination, half-life and potency.

1. Core Concepts of Pharmacology, International Core Concepts of Pharmacology Education Project 2022, Accessed 30th September 2022. Available from: https://coreconceptspharmacology.org/

322 Core Concepts, concept inventories and pedagogical content knowledge – a path to an evidence-based, concept driven curriculum

Paul J. White, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Vic Australia

The discipline of pharmacology and the profession of pharmacy both lack an agreed set of concepts that all students should understand and apply. A group of ASCEPT pharmacology educators recently developed and unpacked a list of core concepts (White et al, 2021; Santiago et al., 2021) as a pilot study. An international initiative recently identified the globally relevant core concepts of our discipline. These 25 core concepts of pharmacology education will allow educators and students to focus on the concepts that experts in the field believe are the most critical for students taking a foundational pharmacology module. The next phase of this work involves unpacking the core concepts, developing educator resources to teach the concepts, and producing a *concept inventory* – an assessment to test attainment of the concepts.

White, P. J., et al. (2021). Identifying the core concepts of pharmacology education. *Pharmacology research & perspectives*, *9*(4), e00836.
Santiago, M. et al., (2021). Defining and unpacking the core concepts of pharmacology education. *Pharmacology research & perspectives*, *9*(6), e00894.