apsa
Australasian Pharmaceutical Science Association

ASCEPT

APSA-ASCEPT
JOINT SCIENTIFIC MEETING
5–8 DECEMBER 2017
BRISBANE CONVENTION & EXHIBITION CENTRE

Program

Optimising medicines for optimal patient outcomes

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Download the meeting app
Event code: apsa-ascept

Tuesday 5 December 2017

09:00 – 18:00 **Registration desk open**
Boulevard foyer, Brisbane Convention & Exhibition Centre

10:00 start

ASCEPT Board meeting (10:00 – 12:30)
Room: Arbour Boardroom

Council of Pharmacy Schools meeting (10:00 – 12:30)
Room: Meeting room B3

Pharmacogenomics Workshop (10:00 – 12:00)
Room: Meeting room B2
Chair: Prof Andrew Somogyi

Thiopurine pharmacogenetics: From classic simplicity to modern complexity
Dr John Duley, The University of Queensland

Research and education programs facilitating evidence-based clinical implementation of pharmacogenomics and precision medicine in Australia
Assoc Prof Liz Milward, The University of Newcastle

Student/ECR short presentations

Pharmacogenomics SIG AGM

Workshop: Careers and Early Stage Biomedical Translation (10:00 – 16:45)
Room: Meeting room B1

Supported by Accelerating Australia, Supported by MTPConnect

10:00 – 12:30
Overview of the life sciences industry from an Australian Perspective
Dr Phil Kearney, Merck Sharp & Dohme Australia and Prof Daniel Hoyer, The University of Melbourne

Transformational stage of the industry resulting in opportunities for biomedical entrepreneurs

What is a biomedical entrepreneur?
Prof Maree Smith, The University of Queensland and Prof Darren Kelly, The University of Melbourne

12:30 – 13:15 Lunch

13:15 – 16:45
What is happening in our biomedical translation ecosystem?
Assoc Prof Kevin Pfleger, Harry Perkins Institute of Medical Research and University of Western Australia

Facilitated and interactive workshop to identify the main hurdles for biomedical translation in Australia from the perspective of participants

Clinical Pharmacology Workshop (13:30 – 16:45)
Room: Meeting room B3

Clinical Pharmacology SIG AGM

Clin Pharm Noir — A case-based, interactive workshop on forensic toxicology

Can the living help the deceased?
Assoc Prof Darren Roberts, NSW Poisons Information Centre, Sydney Children's Hospital Network, Westmead

The final consult
Prof Nick Buckley, The University of Sydney

Poisoning through the ages
Prof Ian Whyte, Calvary Mater Newcastle

Education Forum (12:30 – 16:45)
Room: Meeting room B2

ASCEPT Education Forum AGM

Engaging students in the digital world
Dr Kirsten Staff and Dr Sheridan Gentili, University of South Australia

Preparing educators to deal with the challenges of an ever-changing higher education environment
Assoc Prof Lesley Lluka, The University of Queensland and Assoc Prof Shane Bullock, Monash University

17:00 – 18:00 **Conference opening and Japanese Pharmacological Society keynote address**
Room: Boulevard Auditorium
Chair: Prof Dom Geraghty
Use of "extended clearance concept" in new drug discovery and development; prediction of the effect of drug-drug interaction and pharmacogenomics on PK/PD/TD of drugs - 100
Prof Yuichi Sugiyama, Sugiyama Laboratory, RIKEN Innovation Center, Japan

18:00 – 19:30 **Welcome reception**
Boulevard foyer, Brisbane Convention & Exhibition Centre

Social media policy

Meeting attendees must gain approval from a speaker or poster presenter prior to quoting or publishing that individual's specific scientific result on any forum including social media.

We respectfully ask that if you attend a presentation where a presenter has communicated that they do not wish to have their presentation commented on in the social media environment that you adhere to this request.

If you are presenting preliminary or unpublished data, and do not wish the results to be broadcast, please use the following logo with your presentation asking the audience to refrain from posting your material. It should appear on the title slide or poster, and if you like, any slides you do not want posted or commented on, so that your audience recognises your request.

Wednesday 6 December 2017

07:30 – 18:00	**Registration desk open** Boulevard foyer, Brisbane Convention & Exhibition Centre			
08:30 – 09:30	**APSA lecture** **Room:** Boulevard Auditorium **Chair:** Dr Joe Nicolazzo **Reflections and connections on a pharmacokinetic journey – 101** Prof Kevin Batty, School of Pharmacy, Curtin University			
09:30 – 10:20	**Morning tea with exhibitors** **Poster presentations:** Cardiovascular, Clinical Pharmacology, Drug Discovery, Toxicology, Pharmaceutical Science Supported by JPA			**APSA Council meeting** **Room:** Meeting room B1
10:25 – 12:30	**Symposium 1:** Cannabinoids for patients: Getting the pharmacology right first time Supported by Queensland Government	**Symposium 2:** Novel aspects of drug metabolising enzymes - structure, function and regulation	**Symposium 3:** Mice, modelling and post-marketing surveillance to inform medication efficacy and safety	**Symposium 4:** Optimising teaching to enhance student outcomes
	Room: Boulevard Auditorium	**Room:** Meeting room B3	**Room:** Meeting room B2	**Room:** Meeting room B1
	Chair: Prof Jennifer Martin	**Chairs:** Prof Ross McKinnon and Prof Peter Mackenzie	**Chairs:** Dr Danijela Gnjidic and Assoc Prof Simon Bell	**Chairs:** Dr Lynette Fernandes and Dr Greg Maynard
10:25 – 10:50	**Understanding cannabinoid clinical pharmacology in order to drive clinical studies – 102** Dr Catherine Lucas, University of Newcastle	**Cytochrome P450 structure - function: Insights from molecular dynamics simulations – 107** Prof John Miners and Dr Pramod Nair, Flinders University	**Preclinical models to understand the risks of single and multiple concurrent medicines in old age – 112** Dr John Mach, Kolling Institute of Medical Research; The University of Sydney	**Introducing a large-scale research project for undergraduate students – 117** Assoc Prof Susan Rowland, The University of Queensland
10:50 – 11:15	**Cannabinoids for patients: Comparative efficacy and toxicity in a paediatric setting – 103** Prof Noel Cranswick, Melbourne University	**CYP2J2 over-expression in breast cancer cells drives tumourigenesis and anti-cancer drug resistance – 108** Prof Michael Murray, The University of Sydney	**Application of pharmacometric modelling for studying drug effects – 113** Prof Carl Kirkpatrick, Monash University	**Peer assessment to develop critical analysis and self-reflection in large undergraduate cohorts – 118** Dr Rosa McCarty, The University of Melbourne
11:15 – 11:40	**High quality human cannabinoid analytics to drive clinical studies – 104** Dr Peter Galettis, University of Newcastle	**Regulation and function of UGTs in cancer – 109** Dr Robyn Meech, Flinders University	**Novel approaches in pharmacoepidemiological studies to communicate benefits and risk of medicines – 114** Dr Danijela Gnjidic, The University of Sydney	**Development of interprofessional communication skills for interprofessional collaboration – 119** Dr Karen Luetsch, The University of Queensland
11:40 – 12:05	**Pharmacokinetic analysis of vaporized cannabinoids through inhalation – 105** Dr Zheng Liu, University of Newcastle	**Arylamine N-acetyltransferase-1: Drug metabolism and more – 110** Dr Neville Butcher, The University of Queensland	**Pharmacoepidemiological studies to inform medication safety in older adults with chronic diseases and dementia – 115** Assoc Prof Simon Bell, Monash University	**Student perspectives on peer assessment, feedback and team work – 120** Mr Jayden Kelly and Mr Mohammdali Taher, Monash University
12:05 – 12:30	**Pharmaceutical aspects of cannabis – 106** Assoc Prof Jennifer Schneider, University of Newcastle	**Sulfotransferase: Structure, function and protein-protein interactions – 111** Prof Rodney Minchin, The University of Queensland	**Changing guideline recommendations on the pharmacological management of back pain – 116** Assoc Prof Christine Lin, The George Institute for Global Health	**Panel discussion**
12:30 – 13:25	**Lunch with exhibitors** **Poster presentations:** Cardiovascular, Clinical Pharmacology, Drug Discovery, Toxicology, Pharmaceutical Science			
	Drug Disposition and Response SIG meeting	**Pharmacoepidemiology SIG meeting**	**APSA AGM (12:45 – 14:00)** (please take lunch into room with you)	
	Room: Meeting room B3	**Room:** Meeting room B2	**Room:** Meeting room B1	

13:30 – 15:30	**Oral presentations 1: Drug Discovery/ Pharmaceutical Science** Supported by THE UNIVERSITY OF PHARMACOLOGY	**Oral presentations 2: Cardiovascular**	**ASCEPT Gillian Shenfield Early Educator Award**	
	Room: Boulevard Auditorium	**Room:** Meeting room B3	**Room:** Meeting room B2	
	Chair: Dr Lauren May	**Chair:** Dr Tracey Gaspari	**Chair:** Dr Lynette Fernandes	
13:30 – 13:45	**Quantification of metformin in human serum by hydrophilic interaction liquid chromatography - mass spectrometry – 121** Dr Ahmed Abdalla, University of South Australia	**Cardiomyocyte ErbB4 receptors are essential for cardiac hypertrophy and growth of neonatal mice, and contribute to maintenance of cardiac function in adult hearts – 129** Dr Melissa Reichelt, The University of Queensland	**Developing a new unit in a new curriculum – 137** Dr Betty Exintaris, Monash University	
13:45 – 14:00	**ORAI1 calcium channels in cell death during mammary gland involution – 122** Dr Felicity Davis, The University of Queensland	**Comparing the anti-fibrotic effects of emerging treatments: Serelaxin and the IRAP inhibitor, HFI-419 to a clinically-used angiotensin receptor blocker and ACE inhibitor in a high salt-induced mouse model of kidney disease – 130** Mr Matthew Shen, Monash University	**Oral presentations 3: Pharmacoepidemiology** **Room:** Meeting room B2 **Chair:** Prof Andrew McLachlan	**Oral presentations 4: Cancer theme** **Room:** Meeting room B1 **Chair:** Prof Alan Boddy
14:00 – 14:15	**Pre-clinical pharmacokinetic development of the hypoxia-activated cytotoxin SN36506 – 123** Dr Matthew Bull, The University of Auckland, New Zealand	**Role of TRPC3 in endothelium-dependent vasodilation of rat mesenteric arteries – 131** Dr Sarah Wright, University of New South Wales	**What are the predictors of persistent prescription opioid analgesic use for non-cancer pain in Australia? – 138** Mrs Samanta Lalic, Monash University	**Population pharmacokinetics of carboplatin, etoposide and melphalan (CEM) in children with high-risk neuroblastoma – 144** Dr Janna Duong, The University of Sydney
14:15 – 14:30	**A new high-throughput approach for investigating GPCR internalisation in real-time – 124** Dr Simon Foster, University of Copenhagen, Denmark	**Targeting IRAP: A novel treatment to stabilise existing abdominal aortic aneurysms – 132** Mr Kaki Fan, Monash University	**Development of comorbidities in men with prostate cancer treated with androgen deprivation therapy: An Australian population-based cohort study – 139** Ms Huah Shin Ng, University of South Australia	**The novel fatty acid epoxide analogue CTU targets the mitochondrion and depletes cardiolipin to promote killing of MDA-MB-231 breast cancer cells – 145** Mr Hassan Choucair, The University of Sydney
14:30 – 14:45	**CSKSSDYQC peptide conjugated N-trimethyl chitosan enhance the oral bioavailability of gemcitabine by targeting goblet cells – 125** Assoc Prof Jingyuan Wen, University of Auckland, New Zealand	**Inhibition of the transient receptor potential melastatin 7 (TRPM7) channel-kinase improves cardiac function in an *ex vivo* model of ischaemia/ reperfusion injury – 133** Dr Tamara Paravicini, RMIT University	**Antithrombotic prescribing for patients with a history of atrial fibrillation: An analysis using MedicineInsight data – 140** Dr Daniel Taylor, NPS MedicineWise	**The potential of MK2 inhibitors in glioblastoma therapy – 146** Assoc Prof Lenka Munoz, The University of Sydney
14:45 – 15:00	**Nicotine-loaded chitosan nanoparticulate dry powder inhaler formulation for its activity – 126** Dr Nazrul Islam, Queensland University of Technology	**Functional regulation of bitter taste receptors by beta2-adrenergic and M2 muscarinic acetylcholine receptors – 134** Mr Jilai Zhao, The University of Queensland	**Questions from Australian public and health professionals on medication use in breastfeeding: Comparative call analysis of two national medicines call centres – 141** Dr Treasure McGuire, The University of Queensland	**Induction of apoptosis in triple negative breast cancer cells by selenium derivatives – 147** Ms Jackmil Puthoor Jogy, University of Otago, New Zealand

15:00 – 15:15	**Monitoring NanoBRET ligand binding to endogenous adenosine A_{2B} receptors – 127** Dr Elizabeth Johnstone, Harry Perkins Institute of Medical Research	**Defining the progression of diabetic cardiomyopathu in a mouse model of type 1 diabetes – 135** Dr Miles De Blasio, Baker Heart & Diabetes institute	**Prevalence of potentially inappropriate medication use in older inpatients with and without cognitive impairment: A systematic review – 142** Mr Mitchell Redston, The University of Sydney	**The effect of curcumin on in vitro metabolism and predicted *in vivo* exposure of imatinib – 148** Mr Jeffry Adiwidjaja, The University of Sydney
15:15 – 15:30	**Dual action calcium sensing receptor modulator, calhex231, unmasks novel mode-switching mechanism – 128** Dr Karen Gregory, Monash University	**Systemic and cardiac-selective targeting of histone deacetylase 4 (HDAC4) to limit diabetic cardiomyopathy – 136** Mr Andrew Willis, Monash University	**Health professionals' and researchers' opinions on conducting clinical deprescribing trials – 143** Mr Alexander Clough, The University of Sydney	**Triterpenoid micellar nanoparticles for the treatment of glioblastoma: Potential inhibition of the PI3K/Akt signaling – 149** Dr Rebecca Roubin, The University of Sydney
15:30 – 15:55	**Afternoon tea with exhibitors**			**Cardiovascular SIG meeting** **Room:** Meeting room B3
16:00 – 18:00	**Oral presentations 5: Pharmacy Practice**	**Oral presentations 6: Drug Disposition and Response/Pharmaceutical Science** Supported by TECAN.	**Oral presentations 7: Urogenital and Gastrointestinal** Supported by astellas Leading Light for Life	**Oral presentations 8: Neuro- and Behavioural Pharmacology**
	Room: Boulevard Auditorium	**Room:** Meeting room B3	**Room:** Meeting room B2	**Room:** Meeting room B1
	Chair: Dr Petra Czarniak	**Chair:** Dr Andrew Crowe	**Chair:** Dr Michael Winder	**Chair:** Assoc Prof Marie Odile-Parat
16:00 – 16:15	**Predictors of adverse drug reaction-related hospitalisation in Southwest Ethiopia: A prospective cross-sectional study – 150** Mr Mulugeta Angamo, University of Tasmania	**Troches or orally dissolving tablets for delivery of pilocarpine in treatment of xerostomia (dry mouth)? – 158** Mrs Rose Estafanos, The University of Queensland	**Pulsed magnetic stimulation for persistent post-prostatectomy stress urinary incontinence: A pilot study – 166** Dr Renly Lim, University of South Australia	**Morphine dosing affects development of antinociceptive tolerance and motor behavior – 174** Mr Alok Kumar Paul, University of Tasmania
16:15 – 16:30	**Investigating the impact of Universal Healthcare Coverage on the practice of Indonesian Community Pharmacy: A qualitative study – 151** Mr Andi Hermansyah, The University of Sydney	**Lipophilic salts of small molecule kinase inhibitors for increased oral bioavailability using lipid formulations – 159** Dr Leigh Ford, Monash University	**Pharmacological effects of a jungle ginger on rat prostatic smooth muscle – 167** Ms Nguok Ngie Eunice Su, Monash University	**Increased osmotic pressure promotes glioblastoma invasiveness – 175** Miss Wenjun Pu, The University of Queensland
16:30 – 16:45	**Home Medicines Reviews - exploring accredited pharmacists' work processes – 152** Ms Marea Patounas, Queensland University of Technology	**Triglyceride-mimetic prodrugs of testosterone significantly enhance lymphatic transport and oral bioavailability – 160** Dr Tim Quach, Monash University	**Post-hospital changes in medication regimen complexity and potentially inappropriate medication use in older adults with chronic kidney disease – 168** Mr Wubshet Tesfaye, University of Tasmania	**Discovering methyllycaconitine analogues specific for $\alpha_4\beta_2$ over α7 nAChR subtypes – 176** Prof Mary Chebib, The University of Sydney
16:45 – 17:00	**Adoption of the Ohio Emergency Department opioid prescribing guidelines – 153** Dr Jonathan Penm, The University of Sydney	**Characterising and predicting the *in vivo* kinetics of therapeutic mesenchymal stem cells and their secretome – 161** Dr Haolu Wang, The University of Queensland	**Effect of Rho-kinase inhibitors on contractility of porcine corpus cavernosum – 169** Miss Amelia Jack, Bond University	**Inhibition of $\alpha_5\beta_1$ with the clinically validated small peptide ATN-161 is neuroprotective and functionally restorative in experimental stroke – 177** Ms Danielle Edwards, University of Kentucky, USA

17:00 – 17:15	**Pharmacy in the community: The potential of role extension – 154** Dr Caroline Morris, University of Otago, New Zealand	**Permeation of quercetin through the human epidermis – 162** Dr Azadeh Alinaghi, University of South Australia	**The effects of aging on polarization in collagen sandwich-cultured hepatocytes – 170** Miss Sun Woo Kang, Anzac Research Institute	**Morphine regulates cellular migration and invasion by modifying the circulating proteolytic profile in mice – 178** Miss Nan Xie, The University of Queensland
17:15 – 17:30	**Just rubbish? Examining the concerns and attitudes of pharmacists to pharmaceuticals entering the environment – 155** Mrs Judith Singleton, Queensland University of Technology	**Evaluation of optimised piperacillin plus tobramycin combination dosage regimens against *Pseudomonas aeruginosa* (Pa) for patients with altered pharmacokinetics *via* the hollow fibre infection model and mechanism-based modelling – 163** Mr Rajbharan Yadav, Monash University	**Human 5-HT_3AC receptors are subtly different to 5-HT_3A receptors – 171** Prof Helen Irving, La Trobe University	**Stress induced analgesia is reduced in neuropathic pain states – 179** Mr Nicholas Atwal, The University of Sydney
17:30 – 17:45	**Adherence to lipid lowering medications for secondary prevention of stroke – 156** Mrs Judith Coombes, The University of Queensland; Princess Alexandra Hospital	**CMF-019, the first G protein biased small molecule apelin agonist, is a vasodilator and positive inotrope *in vivo* – 164** Mr Cai Read, University of Cambridge, UK	**Characterization of Na_v channels in colon-innervating dorsal root ganglion neurons in mice – 172** Ms Andelain Erickson, The University of Adelaide	**Phytocannabinoid actions in an animal model of neuropathic pain – 180** Miss Jessica Falon, The University of Sydney
17:45 – 18:00	**Cost-effectiveness of pharmacist management of hypertension – 157** Prof Carlo Marra, University of Otago, New Zealand	**Polymer precipitation inhibitors can maintain drug supersaturation and increase in vivo absorption from lipid-based formulations – 165** Ms Estelle Suys, Monash University	**Histamine receptor (Hrh) subtypes mediate bladder afferent sensitivity in mice – 173** Ms Ashlee Caldwell, The University of Adelaide	**Nesfatin-1 suppresses feeding and induces emesis in *Suncus murinus* (House Musk Shrew) – 181** Dr Sze Wa Chan, Caritas Institute of Higher Education, Hong Kong
19:30	**AAPS student dinner**			
	The Plough Inn, 29 Stanley St, South Brisbane			

Thursday 7 December 2017

08:00 – 17:00	**Registration desk open** Boulevard foyer, Brisbane Convention & Exhibition Centre			
08:30 – 09:30	**British Pharmacological Society keynote address** **Room:** Boulevard Auditorium **Chair:** Prof Dom Geraghty **Innovations in clinical pharmacology education – 200** Dr Clare Guilding, Newcastle University Medicine Malaysia, Malaysia			
09:30 – 10:25	**Morning tea with exhibitors** **Poster presentations:** Drug Disposition and Response, Inflammation/Respiratory, Neuro- and Behavioural Pharmacology, Pharmacoepidemiology, Pharmacogenomics, Urogenital and Gastrointestinal, Pharmacy Practice, Education			
10:30 – 12:30	**Symposium 5:** Why is polypharmacy increasing in aged care facilities and what can we do about it? **Room:** Boulevard Auditorium **Chair:** Ms Natali Jokanovic	**Symposium 6:** New strategies to treat chronic inflammatory diseases Supported by RMIT UNIVERSITY **Room:** Meeting room B3 **Chairs:** Assoc Prof Ross Vlahos and Prof Emilio Badoer	**Symposium 7:** Novel targets for the treatment of pain Supported by The University Of Queensland AUSTRALIA | IMB Institute for Molecular Bioscience **Room:** Meeting room B2 **Chairs:** Prof Richard Lewis and Assoc Prof Irina Vetter	**Symposium 8:** Improving biomolecule behaviour **Room:** Meeting room B1 **Chair:** Prof Rodney Minchin
10:30 – 11:00	**Increasing polypharmacy in aged care facilities: Trends, problems and solutions – 201** Ms Natali Jokanovic, Monash University	**Adipokines, cardiovascular function and brain inflammation – 205** Prof Emilio Badoer, RMIT University	**Decoding spinal cord circuits to find novel targets for chronic pain – 209** Dr Wendy Imlach, Monash University	**CESTEM-1 clinical trials: Using dynamin inhibitors to reverse resistance to monoclonal antibody therapy – 213** Dr Fiona Simpson, The University of Queensland
11:00 – 11:30	**How is Canada addressing the increasing burden of polypharmacy? – 202** Dr Justin Turner, University of Montreal, Canada	**Mineralocorticoid and estrogen receptors: Novel therapeutic targets in cardiovascular disease and stroke? – 206** Prof Chris Sobey, Latrobe University	**Nav1.7 as a target for pain treatment: Therapeutic challenges and opportunities – 210** Dr Sulayman Dib-Hajj, Yale University, USA	**i-bodies against the chemokine receptor CXCR4 with novel pharmacology – 214** Dr Michael Foley, La Trobe University
11:30 – 12:00	**Integrating prescribing and dispensing data across primary care, hospitals and aged care: The MedView Project – 203** Mr David Freemantle, Fred IT Group	**The paradox of Z-drugs in motor recovery after stroke – 207** Prof Mary Collins, The University of Sydney	**GPCRs and ion channels: The cause of and solution to chronic visceral pain? – 211** Assoc Prof Stuart Brierley, Flinders University; SAHMRI	**Antibody-polymer-drug conjugates for biomedical applications – 215** Dr Charlotte Williams, Commonwealth Scientific and Industrial Research Organisation (CSIRO)
12:00 – 12:30	**Application of a structured approach to simplify medication regimens in residential aged care – 204** Dr Janet Sluggett, Monash University	**Targeting oxidant-dependent pathways to treat cognitive dysfunction in chronic obstructive pulmonary disease – 208** Assoc Prof Ross Vlahos, RMIT University	**Mechanosensors and pain – 212** Dr Kate Poole, University of New South Wales	**Downsizing disulfide-rich bioactive peptides – 216** Dr Richard Clark, The University of Queensland
12:30 – 13:25	**Lunch with exhibitors** **Poster presentations:** Drug Disposition and Response, Inflammation/Respiratory, Neuro- and Behavioural Pharmacology, Pharmacoepidemiology, Pharmacogenomics, Urogenital and Gastrointestinal, Pharmacy Practice, Education		Supported by CPS Inc. Council of Pharmacy Schools: Australia & New Zealand	**Toxicology SIG meeting** **Room:** Meeting room B1

13:30 – 15:30	Oral presentations 9: Garth McQueen student oral prize	Oral presentations 10: Clinical Pharmacology Supported by Therapeutic Guidelines	Oral presentations 11: Pharmacy Practice	Oral presentations 12: Respiratory/Toxicology
	Room: Boulevard Auditorium	**Room:** Meeting room B3	**Room:** Meeting room B2	**Room:** Meeting room B1
	Chair: Dr Tina Hinton	**Chair:** Assoc Prof Matt Doogue	**Chair:** Dr Carl Schneider	**Chairs:** Emeritus Prof Roy Goldie and Dr Ian Musgrave
13:30 – 13:45	**Gene delivery targeting cardiac O-GlcNAc modification limits diabetic cardiomyopathy – 217** Mr Darnel Prakoso, The Baker Heart and Diabetes, The University of Melbourne	**Microdosed cocktail of apixaban, edoxaban and rivaroxaban can predict drug interaction with therapeutic doses – 225** Prof Gerd Mikus, University Hospital Heidelberg, Germany	**Identifying clinical pharmacist patient prioritisation criteria – 233** Mrs Nazanin Falconer, The University of Queensland	**Vale Domenico (Dom) Spina** Emeritus Prof Roy Goldie, Flinders University
13:45 – 14:00	**The safety of metformin in haemodiafiltration – 218** Miss Felicity Smith, University of New South Wales; St Vincent's Hospital	**The influence of ABCG2 genotype on allopurinol dose predictions – 226** Dr Daniel Wright, University of Otago, New Zealand	**Evaluation of a quantitative approach for analysis of semi-structured pharmacy consumer interviews – 234** Mr Ardalan Mirzaei, The University of Sydney	**IRAK3 modulates NFκB through its guanylate cyclase activity – 241** Ms Lubna Freihat, Monash University
14:00 – 14:15	**Neuronal calcium sensor-1 (NCS-1) in the regulation of calcium homeostasis and cell death in MDA-MB-231 basal breast cancer cells – 219** Miss Alice Bong, The University of Queensland	**Late onset rise of 6-MMP metabolites in inflammatory bowel disease patients on azathioprine or mercaptopurine – 227** Prof Murray Barclay, Christchurch Hospital, New Zealand	**Response of community pharmacy staff to a request for an antibiotic product without a valid prescription: A simulated client study in Sri Lanka – 235** Mr Shukry Zawahir, The University of Sydney	**Intranasal delivery of the TLR7 agonist, imiquimod, protects against influenza A virus-induced morbidity in mice – 242** Mr Jonathan Erlich, RMIT University
14:15 – 14:30	**The relationship between busulphan AUC and the incidence of sinusoidal obstruction syndrome in haematopoietic stem cell transplants – 220** Mr Parth Upadhyay, The University of Sydney	**Minimising the functional burden of medications in older inpatients: Implementation of the Drug Burden Index – 228** Ms Rayan Nahas, Royal North Shore Hospital	**What Is Polypharmacy Exactly (WIPE) – 236** Ms Nashwa Masnoon, University of South Australia	**A novel endosomal NOX2 oxidase inhibitor protects against high pathogenicity influenza A virus-induced disease – 243** Ms Eunice To, RMIT University
14:30 – 14:45	**An investigation of the vascular effects of Sailuotong, a standardised Chinese herbal formula, for vascular dementia – 221** Miss Seungyeon Yeon, Western Sydney University; The Science of Integrative Medicine (NICM)	**A stimulation study to assess the possible contribution of measurement error in quetiapine depression trials – 229** Ms Jia Ning Careen Tan, The University of Queensland	**Psychotropic medicines use in Residents And Culture: Influencing Clinical Excellence (PRACTICE) tool: A development and content validation study – 237** Miss Mouna Sawan, The University of Sydney	**Localisation of polymyxin in human alveolar epithelial cells – 244** Mr Maizbha Uddin Ahmed, Monash University
14:45 – 15:00	**The Medication Regimen Simplification Guide for Residential Aged CarE (MRS GRACE): A novel tool to optimise medication regimens for residents of aged care facilities. – 222** Ms Esa Chen, Monash University	**A multicentre open-label pharmacokinetic-pharmacodynamic study of febuxostat in patients with chronic gout – 230** Mr Bishoy Kamel, University of New South Wales; St Vincent's Hospital	**"Good prescribing is a bit like good driving; everybody thinks they're a good driver." An exploratory study on the barriers and facilitators to using quality prescribing indicators (QPIs) in general practice – 238** Dr Li Shean Toh, University of Tasmania	**Pharmacological characterisation of small molecule C5aR1 inhibitors in primary human macrophages – 245** Ms Xaria Li, The University of Queensland

15:00 – 15:15	**Behavioural, pharmacologic and histologic characterisation of a rat model of mechanical low back pain – 223** Mr Thomas Park, The University of Queensland	**The safety and pharmacokinetics of metformin in heart failure – 231** Mrs Gina Chowdhury, University of New South Wales; St Vincent's Hospital	**Contextualised medication information is critical to treatment uptake and adherence among people living with HIV – 239** Dr Amary Mey, Griffith University	**Getting under the skin – why receptor fluid choice is crucial in *in vitro* skin permeation tests – 246** Dr Ana Macedo, University of South Australia
15:15 – 15:30	**Understanding the physiological role of endogenous allosteric modulators in the muscarinic acetylcholine receptors – 224** Ms Ee Von Moo, Monash University	**Vignettes from hospital-level electronic prescribing data – 232** Dr Paul Chin, Canterbury District Health Board, New Zealand	**A study on usual Residential Medication Management Review (RMMR) practice – 240** Mrs Leila Shafiee Hanjani, The University of Queensland	**Can an educational intervention lead to a sustained reduction in gastric lavage for poisoning admissions? – 247** Dr Jacques Raubenheimer, The University of Sydney
15:30 – 15:55	**Afternoon tea with exhibitors**			**Respiratory & Inflammation SIG meeting** **Room:** Meeting room B1
16:00 – 17:00	**ASCEPT Rand Medal Lecture**			
	Room: Boulevard Auditorium			
	Chair: Prof Dom Geraghty			
	Optimising medicines for optimal patient outcomes? Perhaps we need more comparative ineffectiveness research! – 248 Prof Nicholas Buckley, Sydney Medical School, The University of Sydney			
17:00 – 18:00	**ASCEPT AGM**			
	Room: Boulevard Auditorium			
19:00 – 23:00	**Meeting dinner**			
	Boulevard Room, Brisbane Convention & Exhibition Centre			

Friday 8 December 2017

08:00 – 15:45	**Registration desk open**			
	Boulevard foyer, Brisbane Convention & Exhibition Centre			
08:30 – 09:30	**APSA Medal Oration**			
	Room: Boulevard Auditorium			
	Chair: Prof Andrew McLachlan			
	Colloids, carriers and collaborations: A pathway to enhanced drug delivery – 300 Prof Chris Porter, Monash Institute of Pharmaceutical Sciences (MIPS), Monash University			
09:30 – 10:25	**Morning tea with exhibitors**			
10:30 – 12:30	**Symposium 9:** Certara New Investigator Award Sponsored by CERTARA	**Symposium 10:** The blood-brain barrier: A regulator of CNS drug access and disease progression Sponsored by GENESEARCH eFREEZER	**Symposium 11:** The ethics of selling or recommending complementary medicines Sponsored by Griffith UNIVERSITY, QUALITY USE OF MEDICINES NETWORK QUM	**Symposium 12:** APSA Early Career Researchers
	Room: Boulevard Auditorium	**Room:** Meeting room B3	**Room:** Meeting room B2	**Room:** Meeting room B1
	Chair: Prof Carl Kirkpatrick	**Chair:** Dr Joe Nicolazzo	**Chair:** Dr Jasmina Fejzić	**Chair:** Prof Kevin Batty
10:30 – 11:00	**The use of oral anticoagulants in people with dementia – 301** Dr Jenni Ilomaki, Monash University	**BBB permeability of molecularly-targeted anti-tumor agents: necessary for effective treatment of brain tumors – 305** Prof William Elmquist, University of Minnesota, USA	**Complementary medicines, health professional responsibilities and trust – 309** Prof Eleanor Milligan, Griffith University	**How to reliably measure customers' perceptions of service quality in community pharmacy – 313** Dr Stephen Carter, The University of Sydney
11:00 – 11:30	**Strategies for precision use of targeted anti-cancer medicines – 302** Dr Andrew Rowland, Flinders University	**Clearance of beta-amyloid is facilitated by apolipoprotein E (apoE) and circulating high-density lipoproteins (HDL) in bioengineered human vessels – 306** Prof Cheryl Wellington, University of British Columbia, Canada	**What are the potential harms of complementary medicines? – 310** Dr Geraldine Moses, Mater Hospital; The University of Queensland	**The safety of transdermal fentanyl initiation in Australian clinical practice – 314** Dr Natasa Gisev, University of New South Wales
11:30 – 12:00	**Big data: Driving innovation for geriatric pharmacoepidemiology and pharmacovigilance research – 303** Dr Prasad Nishtala, University of Otago, New Zealand	**HIV infection and Alzheimer's disease: The integral role of the blood-brain barrier – 307** Prof Michal Toborek, University of Miami, USA	**Selling complementary medicines and the new Code of Ethics for Pharmacists – 311** Dr Adam La Caze, The University of Queensland	**Personalized microneedle eye patches by 3D printing to treat peri-orbital wrinkles with a small peptide – 315** Dr Lifeng Kang, The University of Sydney
12:00 – 12:30	**Developing the next generation of analgesics – 304** Dr Jennifer Deuis, The University of Queensland	**The cerebral vascular basement membrane: A target for Alzheimer's disease and stroke – 308** Prof Gregory Bix, University of Kentucky, USA	**Regulating complementary medicines and pharmacy practice – 312** Assoc Prof Laetitia Hattingh, Griffith University	**The provision of enhanced and extended services in Western Australian community pharmacies – 316** Dr Petra Czarniak, Curtin University
12:30 – 13:25	**Lunch with exhibitors and ASCEPT student poster finalists presentation**			
	Workshop: MedicineInsight – Big data to support health research and practice, NPS MedicineWise (please take lunch into room with you)			NPS MEDICINEWISE
	Room: Meeting room B1			

13:30 – 15:00	Oral presentations 13: Drug Discovery / Pharmaceutical Science Supported by MONASH University Institute of Pharmaceutical Sciences	Oral presentations 14: Clinical trainees	Oral presentations 15: Pharmacogenomics	Oral presentations 16: Education
	Room: Boulevard Auditorium	**Room:** Meeting room B3	**Room:** Meeting room B2	**Room:** Meeting room B1
	Chair: Dr Karen Gregory	**Chair:** Dr Paul Chin	**Chairs:** Assoc Prof Nuala Helsby and Dr Marina Junqueira Santiago	**Chair:** Assoc Prof Elizabeth Davis
13:30 – 13:45	**Reversal of age related pseudocapillarization utilising vascular endothelial growth factor related, nitric oxide dependent drug treatments on *in vitro* liver sinusoidal endothelial cells – 317** Dr Nicholas Hunt, Anzac Research Institute, The University of Sydney	**A randomised controlled trial of patient information leaflets as a medication counselling tool – 323** Dr Richard McNeill, Canterbury District Health Board, New Zealand	**No significant effect of *CYP3A, ABCB1, POR* and *NR1I2* polymorphisms on acute rejection and nephrotoxicity in the first 3 months post kidney transplantation in patients receiving tacrolimus – 329** Ms Rong Hu, The University of Adelaide	**Best possible medication history gamification – development and pilot study – 335** Dr Paulina Stehlik, Bond University
13:45 – 14:00	**Cell-specific and biased signalling of a peptide mimetic and small molecule at the relaxin receptor RXFP1 – 318** Dr Martina Kocan, Florey Institute of Neuroscience and Mental Health	**"Therapy induced" Takotsubo Cardiomyopathy: Does it matter? – 324** Dr Gao Jing Ong, Queen Elizabeth Hospital	**HLA-B status leading to potential severe adverse drug reactions in Aboriginal Australians – 330** Prof Andrew Somogyi, University of Adelaide	**Engaging students in learning outcomes and career relevance through a multi-dimensional, interactive map – MyCourseMap – 336** Assoc Prof Lisa Tee, Curtin University
14:00 – 14:15	**Investigation of the insulin mimetic effect of *Teucrium polium in vitro* – 319** Dr Rima Caccetta, Curtin University	**A physiological based pharmacokinetic model to guide dosing of ivacaftor in the presence of pharmacoenhancers – 325** Dr Angela Rowland, Flinders Medical Centre	**Potential simple and multifactorial drug and gene interactions of tricyclic antidepressants in older Australians – 331** Mr Mohitosh Biswas, The University of Newcastle	**"Visual thinking strategies" in early pharmacy undergraduate education can support the development of professional communication and cultural competencies – 337** Dr Trudi Aspden, University of Auckland, New Zealand
14:15 – 14:30	**Measuring ligand-binding in endosomes: A signalling platform for pain transmission – 320** Dr Nicholas Veldhuis, Monash University	**Evaluation of the role and impact of brain computed tomography scans in the assessment of clinically diagnosed overdose cases and an attempt to formulate a procedural framework – 326** Dr Emma Tay, St Vincent's Hospital	**Signalling modification by Single Nucleotide Polymorphisms in the third intracellular loop of the mu-opioid receptor – 332** Dr Marina Junqueira Santiago, Macquarie University	**Experiences developing a pharmacology online careers portal: Evaluating impact on student career awareness – 338** Dr Barbara Kemp-Harper, Monash University
14:30 – 14:45	**Mutations in the NPxxY motif stabilise different conformational states of the α_{1B}- and β_2-adrenoceptors – 321** Dr Lotten Ragnarsson, The University of Queensland	**Real-time review of electronic prescribing of restricted antimicrobials - a pilot of a new antimicrobial stewardship initiative for Christchurch Hospital – 327** Dr Niall Hamilton, Canterbury District Health Board, New Zealand	***ABCB1* pharmacogenetics in Papua New Guinea HIV/AIDS patients and association with efavirenz CNS/Psychiatric adverse effects – 333** Miss Helena Van Schalkwyk, University of Adelaide	**Exploring the use of a novel computer-based interactive pharmacy simulation program in university and professional pharmacy practice education – 339** Dr Kenneth Lee, University of Tasmania
14:45 – 15:00	**Drug delivery to the intestinal lymphatics enhances the immunosuppressant effects of mycophenolic acid in mice – 322** Mrs Ruby Panakkal Kochappan, Monash University	**Thyroid immune-related adverse events following PD-1 inhibitors for cancer: Characteristics and associations – 328** Dr Frida Djukiadmodjo, Austin Health	**Interleukin genetics and not *COMT* or *OPRM1* may affect risk of persistent pain following total knee arthroplasty – 334** Dr Daniel Barratt, University of Adelaide	**The journey of a prescription: An interprofessional education simulation of the patient and prescription flow through prescriber and dispenser – 340** Dr James Green, University of Otago, New Zealand
15:00 – 15:15	**Comfort break**			
15:15 – 15:45	**Awards and meeting close**			
	Room: Boulevard Auditorium			
	Chairs: Dr Joseph Nicolazzo and Prof Carl Kirkpatrick			

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Wednesday 6 December, 09:30 – 10:20 and 12:30 – 13:25

Drug Discovery

417	**New drug formulation for combating antibiotic resistance** Hien Duong, The University of Sydney
418	**Angiotensin II receptor type 1 transactivation of EGFR via TRIO-dependent mechanisms** Liz Johnstone, University of Western Australia
419	**Smad2 linker region: A central integrating point for GPCR mediated transactivation of tyrosine and serine/ threonine kinase receptors** Danielle Kamato, The University of Queensland
420	**Reversal of age related pseudocapillarization using direct actin & lipid raft disruptor drugs on in vitro liver sinusoidal endothelial cells** Glen Lockwood, Centre for Education and Research on Ageing
421	**The rational design of self-adjuvanting subunit vaccines by site-specific conjugation of protein antigens with Toll like receptor ligands** Zhenghui Xu, The University of Queensland
422	**The novel fatty acid epoxide analogue CTU targets the mitochondrion and depletes cardiolipin to promote killing of MDA-MB-231 breast cancer cells** Hassan Choucair, The University of Sydney
423	**Anti-proliferative activity of novel ω-3 epoxy fatty acid analogues in MDA-MB-231 triple negative human breast cancer cells** Yassir Al-Zubaidi, The University of Sydney
424	**Assessment of taste 1 receptor allosteric ligands for activity at metabotropic glutamate receptors** Amy NY Chen, Monash University
425	**Small molecule inhibitors of Amyloid β and α Synuclein (αSA53T) protein aggregation** Sukanya Das, The University of Adelaide
426	**Bias in fluorescence-based voltage-gated sodium channel assays** Jennifer Deuis, The University of Queensland
427	**Nrf2 activators in medicinal plants of the Australian Aboriginal Dharawal people** Karthik Dhananjayan, Western Sydney University
428	**Phosphatase and tensin homolog (PTEN) silencing suppresses Ca2+ responses in MDA-MB-231 breast cancer cells** Trinh Hua, The University of Queensland
429	**Comparison of analgesic and constipation profile of two G-protein biased endomorphin-2 analogue after intracerebroventricular administration in rats** Mohammad Zafar Imam, The University of Queensland
430	**Structure-based virtual screening for the rapid discovery of selective butyrylcholinesterase inhibitors** Jared Miles, The University of Queensland
431	**Natural product honokiol reduces Aβ42-induced toxicity in Caenorhabditis elegans, Aβ42 fibrillation, cholinesterase activity, DPPH radicals, and chelates iron(II)** Jared Miles, The University of Queensland
432	**Development and optimisation of a FLIPR high-throughput cAMP assay to screen for Gαi mediated GPCR modulators** Michael Morgan, The University of Queensland
433	**Development of a BRET based assay for AT1R-EGFR transactivation: evidence for functional heteromers** Shannon O'Brien, The University of Queensland
434	**Consequences of pharmacological inhibition of store-operated calcium entry on calcium signalling in MDA-MB-468 breast cancer cells** Greta Poo, The University of Queensland
435	**The sweet taste receptor: A novel target for drug discovery?** Susan Tan, University of New South Wales
436	**Assessment of calcium responses induced by the transient receptor potential cation channel subfamily V member 4 (TRPV4) activator GSK1016790A in MDA-MB-468 breast cancer cells using automated epifluorescence microscopy** Zara Wagner, The University of Queensland
437	**PAR1 and PAR2 open TRPV4 with conserved signalling pathways** Owen Woodman, RMIT University
438	**Neuronal calcium sensor-1 (NCS-1) in the regulation of calcium homeostasis and cell death in MDA-MB-231 basal breast cancer cells** Alice Bong, The University of Queensland
439	**Understanding the physiological role of endogenous allosteric modulators in the muscarinic acetylcholine receptors** Ee Von Moo, Monash University

Cardiovascular

457	**Bleeding-related admissions in patients with atrial fibrillation receiving antithrombotic therapy: Results from the Tasmanian Atrial Fibrillation (TAF) study** Endalkahcew Admassie Alamneh, University of Tasmania
458	**Epicatechin's cardiovascular protective effects are mediated via opioid receptors and nitric oxide** Andrew Fenning, Central Queensland University
459	**Exploiting E3-ubiquitin ligase mediated protein degradation pathways as new therapeutic target strategies for cardiovascular disease and beyond** Ingrid Gelissen, The University of Sydney

460	**Nattokinase: A promising alternative in prevention and treatment of cardiovascular diseases** Yiguang Lin, University of Technology Sydney
461	**Gaps in anticoagulation knowledge in patients with atrial fibrillation** Kehinde Obamiro, University of Tasmania
462	**Phosphoinositide 3-kinase p110alpha gene delivery limits cardiac remodelling and inflammation in a pre-clinical model of type 2 diabetes** Darnel Prakoso, Baker Heart and Diabetes Institute
463	**Targeting Annexin-A1 to treat diabetic cardiomyopathy** Jesse Walsh, Baker Heart and Diabetes Institute
464	**β-IIe5-Angiotensin II as a novel treatment for cardiac fibrosis** Yan Wang, Monash University
465	**Functional regulation of bitter taste receptors (T2Rs) by B2-adrenergic and M2 muscarinic acetylcholine receptor** Jilai Zhao, The University of Queensland
466	**Gene therapy targeting the hexosamine biosynthesis pathway (HBP) attenuates markers of diabetic cardiomyopathy in a mouse model of type-2 diabetes (T2D)** Charles Cohen, Monash University
467	**Blood pressure lowering post-stroke; a review of the evidence supporting recommendations of draft Clinical Guidelines for Stroke Management 2017** Fahmida Ilyas, SA Health
468	**Resveratrol shows neuronal and vascular-protective effects in older, obese, streptozotocin-induced diabetic rats** Jordon Irwin, Central Queensland University
469	**The microRNA miR-124 inhibits vascular smooth muscle cell proliferation by targeting S100 calcium-binding protein A4 (S100A4)** Hyun Kook, Chonnam National University Medical School
470	**The role of phospholipase A2 in the cardiovascular effects of Pseudechis australis snake venom** Amna Mazeh, The University of Melbourne
471	**Endotoxin tolerance-like response in human abdominal aortic aneurysm (AAA) macrophages** Lara Meital, University of The Sunshine Coast
472	**β3-adrenergic receptors in the rat cremaster muscle artery** Samantha Saunders, University of New South Wales
473	**The association between short sleep duration and BMI in Australian Indigenous children** Joseph Tucci, La Trobe University
474	**Vascular effects of Australian brownsnake venoms (*Pseudonaja spp.*): The role of secretory phospholipase A2** Nhi T Vuong, The University of Melbourne
475	**Delineating the signal transduction pathways by which relaxin mediates its anti-fibrotic actions in human cardiac fibroblasts** Chao Wang, Monash University
476	**Targeting IRAP: A novel treatment to stabilise existing abdominal aortic aneurysms** Kaki Fan, Monash University
477	**Comparing the anti-fibrotic effects of emerging treatments: Serelaxin and the IRAP inhibitor, HFI-419 to a clinically-used angiotensin receptor blocker and ACE inhibitor in a high salt-induced mouse model of kidney disease** Matthew Shen, Monash University
478	**Systemic and cardiac-selective targeting of histone deacetylase 4 (HDAC4) to limit diabetic cardiomyopathy** Andrew Willis, Baker Heart and Diabetes Institute
479	**Role of TRPC3 in endothelium-dependent vasodilation of rat mesenteric arteries** Sarah Wright, University of New South Wales
480	**An investigation of the vascular effects of Sailuotong, a standardised Chinese herbal formula, for vascular dementia** Seungyeon Yeon, Western Sydney University / The Science of Integrative Medicine (NICM)

Clinical Pharmacology

491	**Therapeutic drug monitoring of voriconazole** Kanka Chaudhri, University of New South Wales / St Vincent's Hospital
492	**Antithrombotic drug-drug interaction alerts in MedChart** Amanda Crawford, University of Otago
493	**Prescribing based on the effective dose 50 (ED50)** Simon Dimmitt, University of Western Australia
494	**'Mrs Have-A-Chat': Pilot study showing that following up an "AdherenceCheck" every two weeks for 9 months improves the management of medicines in the older-aged living in a rental retirement village** Sheila Doggrell, Queensland University of Technology
495	**Making adverse drug reactions visible** Matthew Doogue, University of Otago
496	**Severe cutaneous adverse reactions and the (in)accuracy of medicines information sources** Marie-Claire Morahan, Canterbury District Health Board
497	**Peri-operative medication dosing in obese elective surgical patients: A systematic review of clinical studies** Zahid Hussain, University of Tasmania

498	**Audit of individual patient use applications for high cost medicines at a tertiary hospital** Joshua Inglis, Royal Adelaide Hospital
499	**Cannabinoid toxicity post human intraperitoneal injection** Catherine Lucas, University of Newcastle
500	**Clinical relevance of drug-drug interaction alerts** Sylvain Meslin, University of New South Wales / St Vincent's Hospital
501	**A chiral UHPLC-MS/MS method to investigate the pharmacokinetics of enantiomeric ketorolac in human plasma Suzanne Parker, The** University of Queensland
501.1	**A suite of LC-MSMS assays to investigate the pharmacokinetics of meropenem in critically ill patients receiving renal replacement therapy** Suzanne Parker, The University of Queensland
502	**Current antimicrobial stewardship (AMS) practices in the Australian community pharmacies** Tasneem Rizvi, University of Tasmania
503	**Inappropriate drug prescribing in elderly hospitalised patients with falls and fractures** Natalia Soerjadi, The Canberra Hospital
504	**A time and motion study of phlebotomists' work** Sophie Stocker, St Vincent's Hospital
505	**Impact of deprescribing interventions in older hospitalised patients on prescribing and clinical outcomes: a systematic review of randomised trials** Janani Thillainadesan, Royal North Shore Hospital
506	**A multicentre open-label pharmacokinetic-pharmacodynamic study of febuxostat in patients with chronic gout** Bishoy Kamel, University of New South Wales / St Vincent's Hospital
507	**A stimulation study to assess the possible contribution of measurement error in quetiapine depression trials** Jia Ning Careen Tan, The University of Queensland
508	**The perceived impact of medicines, foods and substances taken by mother on their breastfed baby** Hilai Ahmadzai, Curtin University
509	**The effect of deprescribing after chronic polypharmacy on locomotor activity and cognition in a preclinical model** Swathi Ekambareshwar, The University of Sydney
510	**A simple, sensitive and rapid LC-MS/MS method for the simultaneous measurement of anthracyclines, cyclophosphamide and taxanes in breast cancer patient samples** Peter Galettis, University of Newcastle
511	**Relationship between plasma dolutegravir concentration and cause of anti- HIV therapy discontinuation** Mari Kato, National Hospital Organization Nagoya Medical Center
512	**Preclinical models to understand the risks of single and multiple concurrent medicines in old age** John Mach, Kolling Institute/ The University of Sydney/ Royal North Shore Hospital
513	**Prevalence and prediction of adverse drug reactions in older inpatients with hyperpolypharmacy** Rayan Nahas, Royal North Shore Hospital
514	**Pharmacometrics to address weaknesses in Australian medical countermeasure product development** Thomas Polasek, d3 Medicine, A Certara Company
515	**Intravesical mitomycin C enhances spontaneous phasic contractile activity in the murine bladder** Eliza West, Bond University
516	**The influence of perioperative opioids on cancer metastasis** Nan Xie, The University of Queensland
517	**Simultaneous determination of adalimumab and infliximab in human serum by liquid chromatography/tandem mass spectrometry** Mei Zhang, University of Otago
518	**Ibuprofen in Infants younger than 6 months: What is the efficacy and safety profile?** Victoria Ziesenitz, University of Basel Children's Hospital
519	**The safety and pharmacokinetics of metformin in heart failure** Gina Chowdhury, University of New South Wales / St Vincent's Hospital Sydney
520	**The safety of Metformin in Haemodiafiltration** Felicity Smith, University of New South Wales / St Vincent's Hospital Sydney
521	**Discharge summaries: An untapped resource for optimising Adverse Drug Reaction identification** Frida Djukiadmodjo, Austin Health

Toxicology

555	**Inhibition of human Cav3.2 channels by synthetic cannabinoid MDMB-CHMICA in vitro** Chris Bladen, Macquarie University
556	**Potential role of herb-herb interactions in hepatotoxicity** Susan Britza, University of Adelaide
557	**QSAR models define molecular initiating events for multiple AOPs** Davy Guan, The University of Sydney
558	**Functional evaluations of synephrine and octopamine - stimulants in pre-workout supplements** Andy Koh, Bond University

Pharmaceutical Science

563	**Chemical profile and anti-cancer potency of *Dendrobium* species from China and Australia** I Gusti Md Gde Surya C. Trapika, The University of Sydney
564	**Olfactory targeted mucoadhesive microparticles for enhanced brain uptake of phenytoin** Sasi Bhushan Yarragudi, University of Otago
565	**Synthesis and characterization of a smart inulin hydrogel system for colon targeted drug delivery** Franklin Afinjuomo, University of South Australia
566	**Induction of localised vasodilation and hyperpermeability using a novel nitric oxide donor nanoparticle** Houman Alimoradi, University of Otago
567	**Scarring in horses – is there a way to objectively quantify an equine scar?** Selena Boyd, The University of Queensland
568	**Prediction of skin permeation based on solute properties using machine learning and statistical tools** Hanumanth Srikanth Cheruvu, The University of Queensland
569	**Quality of levofloxacin tablets: In vitro dissolution testing and content evaluation** Ensieh Izadi, University of Tasmania
570	**Evaluation of PLGA nanoparticles (NPs) uptake using Caco-2 cell monolayers** Danhui (Cathy) Li, University of Auckland
571	**Human NAT1 regulates invasion of MDA-MB-231 breast cancer cells by modulating the expression of MMPs** Pengcheng Li, The University of Queensland
572	**Effect of N-acetyltransferase 1 on the sensitivity of chemotherapeutics in breast cancer** Courtney Mcaleese, The University of Queensland
573	**An investigation of sodium fusidate and recombinant cytochrome p450 enzymes inhibition in-vitro** John Mishriky, RMIT University
574	**Physiologically-based IVIVC compared with conventional IVIVC for predicting *in vivo* pharmacokinetics of crushed paracetamol mixed with thickened fluids for swallowing disorders** Chandramouli Radhakrishnan, 4am Software
575	**Release of somatostatin monomers from self-assembled hydrogels** Uma Rai, RMIT University
576	**L-arginine protects skeletal muscle against statin-induced myopathy** Kimberly Ryan, Central Queensland University
577	**Intrinsic dissolution study of aspirin** Dorothy Saville, University of Otago
578	**Effect of storage on release from enteric coated diclofenac tablets** Dorothy Saville, University of Otago
579	**Drug content and in vitro dissolution of ciprofloxacin tablets: Comparison and Evaluation** Deepali Sharma, University of Tasmania
580	**Removal of interstitial hyaluronan with recombinant human hyaluronidase (rHuPH20) influences the systemic and lymphatic uptake of a monoclonal antibody in rats** Ian Styles, Monash University
581	**Preparation of viable and metabolically active epidermal membrane** Krishna Chaitanya Telaprolu, The University of Queensland
582	**Arylamine N-acetyltransferase 1 regulates cancer cell survival via modulation of pyruvate dehydrogenase** Lili Wang, The University of Queensland
583	**Biomedical applications of water-soluble pillar[n]arenes** Nial Wheate, The University of Sydney
584	**Distribution of therapeutic proteins into thoracic lymph after intravenous administration is protein size-dependent and primarily occurs within the liver and mesentery** Preeti Yadav, Monash University

Thursday 7 December, 09:30 – 10:20 and 12:30 – 13:25

Pharmacoepidemiology

400	**Trends in anticoagulant use among people with dementia in Australia** Jenni Ilomaki, Monash University
401	**Mapping medication burden, prescribing and dispensing patterns within community dwelling elderly clients of community pharmacies** Lauren Corre, University of South Australia
402	**Use of medicines with sedative or anticholinergic properties and medicine-induced deterioration in older people: An intermediary pathway to frailty** Renly Lim, University of South Australia
404	**Health professionals' and researchers' opinions on conducting clinical deprescribing trials** Alexander Clough, The University of Sydney
405	**Prevalence of potentially inappropriate medication use in older inpatients with and without cognitive impairment: A systematic review** Mitchell Redston, The University of Sydney
406	**Exercise and weight loss supplements: Understanding the risks** Robin Bell, University of Newcastle
407	**SGLT2 inhibitors and diabetic ketoacidosis - review of PI's and comparison with Endocrinology position statement** Genevieve Gabb, SA Health
408	**Health literacy and uptake of osteoporosis medications in a population-based sample of Australian women** Sarah Hosking, Monash University
409	**SGLT-2 inhibitors and diabetic ketoacidosis - review of CMI and comparison with Endocrinology position statement** Fahmida Ilyas, SA Health
410	**Evaluation of bortezomib use in Queensland public hospitals for the treatment of multiple myeloma** Crystal Loke, The University of Queensland
411	**What do women want to know about menopausal symptoms management: An Australian medicines call centre analysis** Rifani Bhakti Natari, The University of Queensland
412	**Patterns of oral anticoagulant use in people with and without dementia: A systematic review** Taliesin Ryan-Atwood, Monash University
413	**Consumer information gaps and concerns regarding opioid analgesics and anxiolytic/hypnotic/sedative medicines** Kudrat Sidhu, The University of Queensland
414	**The Medication Regimen Simplification Guide for Residential Aged CarE (MRS GRACE): A novel tool to optimise medication regimens for residents of aged care facilities** Esa Chen, Monash University
415	**What are the predictors of persistent prescription opioid analgesic use for non-cancer pain in Australia?** Samanta Lalic, Monash University
416	**Anovulatory infertility in Australia: A retrospective analysis of medicine use and health outcomes** Mohammed Altaf, The University of Queensland

Education

440	**Experiences in defining Entrustable Professional Activities to drive the learning of undergraduate pharmacy students** Hesham Al-Sallami, University of Otago
441	**Older people as university-based instructors to improve empathy and attitudes toward older people among first-year pharmacy students** Simon Bell, Monash University
442	**A digital portfolio: Learning gains and efficiencies for placements in new BPharm programme** Lynne Bye, University of Auckland
443	**Education for vancomycin – what works?** Jane Carland, University of New South Wales/St Vincent's Hospital Sydney
444	**Creating a labelling standard for compounded medicines – a learning task requiring higher order thinking skills** Stephen Carter, The University of Sydney
445	**Nursing students are more reliant on ongoing assessment scores to succeed in pharmacology than paramedic or optometry students** Sheila Doggrell, Queensland University of Technology
446	**Do pharmacy students have different personal characteristics than other students?** James Green, University of Otago
447	**Student engagement in learning: Learning space matters** James Blanchflower, The University of Sydney
448	**Pilot study of a clinical pharmacology exam for medical students prior to hospital internship in Newcastle** Catherine Lucas, University of Newcastle
449	**Evaluation of a new integrated Master of Pharmacy curriculum** Rebecca Roubin, The University of Sydney
450	**Development of a program wide pharmaceutical compounding strategy using the scaffold learning approach to improve student learning outcomes** Vijay Suppiah, University of South Australia
451	**Gamification to enhance learning of difficult concept in Pharmacology** Lisa BG Tee, Curtin University

452	**Improving student engagement: Utilising a wet pain practical** Waltraud (Trudie) Binder, University of New South Wales
453	**Demonstrating the ability to prescribe medicines: A multi-professional view** Lynda Cardiff, Queensland University of Technology
454	**Does attending lectures matter when lecture recordings are available? Results for a preliminary study of nursing students in pharmacology** Sheila Doggrell, Queensland University of Technology
455	**Implementation of a consistent and structured approach to small class workshops: A case study in pharmacy education at Monash University** Nilushi Karunaratne, Monash University
456	**Practicing pharmacists' preferences for skills taught in an undergraduate pharmacy program** Carlo Marra, University of Otago
456.1	**Developing a new unit in a new curriculum** Betty Exintaris, Monash University

Pharmacogenomics

481	**Clinically actionable CYP450 pharmacogenotypes relevant to analgesics used for alleviating rheumatoid arthritis pain in community-dwelling older Australians** Thilani Dias, University of Newcastle
482	**Cytochrome interactions between lumacaftor and ivacaftor undergoing Orkambi cystic fibrosis therapy** Elena Schneider, Monash University
483	**The role of efflux transporters in the transfer of drugs from mother to breastfed infant via breastmilk** Hilai Ahmadzai, Curtin University
484	**Silencing ABCC2 transporter gene enhances oxaliplatin chemo-sensitivity in colorectal cancer cells** Riya Biswas, Auckland University of Technology
485	**Raised urinary excretion of thymine following an oral load is a marker for severe fluoropyrimidine toxicity** John Duley, The University of Queensland
486	**The ethics of direct-to-consumer pharmacogenomic screening in primary care** Suzanne Harvey, The University of Queensland
487	**Therapeutic drug safety, important to 'Close the Gap' for Aboriginal and Torres Strait Islanders: An illustrative case of phenytoin hypersensitivity syndrome** Fahmida Ilyas, SA Health
488	**Physiologically based pharmacokinetic modelling of atomoxetine in the different CYP2D6 genotypes** Seok-Yong Lee, Sungkyunkwan University
489	**No significant effect of CYP3A, ABCB1, POR and NR1I2 polymorphisms on acute rejection and nephrotoxicity in the first 3 months post kidney transplantation in patients receiving tacrolimus** Rong Hu, The University of Adelaide
490	**ABCB1 pharmacogenetics in Papua New Guinea HIV/AIDS patients and association with efavirenz CNS/Psychiatric adverse effects** Helena Van Schalkwyk, The University of Adelaide

Neuro- and Behavioural Pharmacology

522	**GLP-1-induced anorectic and emetic responses are mediated via exendin (9-39)-sensitive mechanisms in Suncus murinus** Sze Wa Chan, Caritas Institute of Higher Education
523	**Polyphenol reversal of amyloid-induced neurite dysfunction** Mirabel Alonge, University of Adelaide
524	**Endosomal trafficking kinetics of orexin receptors as measured by BRET trafficking assay** Natasha Dale, Harry Perkins Institute of Medical Research
525	**Splicing regulation and function of cytosolic sulfotransferase: SULT4A1** Misgana Idris, The University of Queensland
526	**Diverse approaches to understand functional pharmacology- examples of the serotonin 5-HT1B and 5-HT2A receptors** Amber Ko, Eurofins Pharma Discovery Services
527	**Statins exhibit diverse effects on behaviour and brain cytokine levels in an in vivo model of LPS-induced neuroinflammation** Amelia McFarland, Griffith University
528	**The role of caveolae in glioblastoma invasiveness** Wenjun Pu, The University of Queensland
529	**Air on a G-String: Guanine as a biological stress sensor in relation to depression and neurological disorders** Tim Shaw, The Peter Doherty Institute
530	**Behavioural, pharmacologic and histologic characterisation of a rat model of mechanical low back pain** Thomas Park, The University of Queensland
531	**Morphine dosing affects development of antinociceptive tolerance and motor behaviour** Alok Kumar Paul, University of Tasmania

Drug Disposition and Response

532	**Pharmacokinetics and metabolism of dabrafenib and trametinib in BRAF V600E/K metastatic melanoma** Hannah Yejin Kim, The University of Sydney
533	**Optimisation of a meropenem plus tobramycin combination dosage regimen against hypermutable and non-hypermutable Pseudomonas aeruginosa via the hollow-fibre infection model and mechanism-based modelling** Rajbharan Yadav, Monash University
534	**Evaluation of optimised piperacillin plus tobramycin combination dosage regimens against Pseudomonas aeruginosa (Pa) for patients with altered pharmacokinetics via the hollow fibre infection model and mechanism-based modelling** Rajbharan Yadav, Monash University
535	**High-throughput assay for simultaneous quantification of the plasma concentrations of Omeprazole, Dextromethorphan, Midazolam, Losartan and their metabolites using liquid chromatography/tandem mass spectrometry (LC-MS/MS)** Santosh KS Adiraju, The University of Queensland
536	**The influence of sampling time on estimated tobramycin exposure in cystic fibrosis patients** Yanhua Gao, The University of Queensland
537	**Tumour expression of copper transporters in colorectal cancer patients** Johnson Liu, University of New South Wales
538	**Investigating the optimal initial dose of gentamicin in paediatric oncology patients considering efficacy and reduction in renal function** Carolina Llanos, The University of Queensland
539	**Interaction of mangosteen extract and alpha mangostin with metformin in diabetic rats: PK/PD studies** Lucy Sasongko, Institut Teknologi Bandung
540	**Early prediction of chemotherapy efficacy in liver cancer cells by specific ROS levels** Haotian Yang, The University of Queensland
541	**Drug delivery to the intestinal lymphatics enhances the immunosuppressant effects of mycophenolic acid in mice** Ruby Panakkal Kochappan, Monash University
542	**Polymer precipitation inhibitors can maintain drug supersaturation and increase in vivo absorption from lipid-based formulations** Estelle Suys, Monash University

Urogenital and Gastrointestinal

543	**The effects of aging on polarization in collagen sandwich-cultured hepatocytes** Sun Woo Kang, Anzac Research Institute
544	**Tachykinin NK2 receptor expression in the human colon; an insight into the influence of gender, age and disease** Stelina Drimousis, University of New South Wales
545	**Antibiotic guidelines for Urinary Tract Infections (UTI) and hospital length of stay** Poh Loh, Royal Perth Hospital
546	**Age-related variations in porcine bladder responses to clinical antimuscarinics** Christian Moro, Bond University
547	**Histamine receptors as regulators of urothelial and detrusor contractile activity** Christian Moro, Bond University
548	**β-adrenoceptors in the urinary bladder vasculature** Donna Sellers, Bond University
549	**Ethanol as an intravesical vehicle: Effects on bladder function** Katrina Smith, Bond University
550	**Prazosin but not tamsulosin sensitises PC-3 and LNCaP prostate cancer cells to docetaxel** Briohny Spencer, Griffith University
551	**Purinergic P2X7 receptor antagonist A804598 reduces the damage induced by acrolein in ex-vivo porcine bladders** Zhinoos Taidi, University of New South Wales
552	**Histamine receptor (Hrh) subtypes mediate bladder afferent sensitivity in mice** Ashlee Caldwell, University of Adelaide
553	**Characterization of Nav channels in colon-innervating dorsal root ganglion neurons in mice** Andelain Erickson, The University of Adelaide
554	**Pharmacological effects of a jungle ginger on rat prostatic smooth muscle** Nguok Ngie Eunice Su, Monash University

Inflammation/respiratory

559	**The immunomodulation of dynorphin 3-14 on lipopolysaccharide-activated toll-like receptor 4 signalling pathway** Peter Cabot, The University of Queensland
560	**Intranasal delivery of the TLR7 agonist, imiquimod, protects against influenza A virus-induced morbidity in mice** Jonathan Erlich, RMIT University
561	**IRAK3 modulates NFκB through its guanylate cyclase activity** Lubna Freihat, Monash University
562	**Pharmacological characterisation of small molecule C5aR1 inhibitors in primary human macrophages** Xaria Li, The University of Queensland

Pharmacy Practice

585	**Drug use evaluation of levetiracetam at a tertiary teaching hospital** Oksana Burford, Curtin University
586	**Hospital pharmacists' and patients' views about what constitutes effective pharmacist-patient communication** Bernadette Chevalier, The University of Queensland
587	**Improving community pharmacy management of non-prescription medicine requests with mystery shopping and feedback** Jack Collins, The University of Sydney
588	**Surgical antibiotic prophylaxis use and infection prevalence in breast surgery procedures in a major teaching hospital in Western Australia** Petra Czarniak, Curtin University
589	**Psychometric testing of scales measuring perinatal depression literacy and comfort with providing perinatal depression care** Sarira El-Den, The University of Sydney
590	**Communication between community pharmacies and prescribers in New Zealand** James Green, University of Otago
591	**Medicine use in early childhood: Which vaccines, branded or generic medicines do parents of children five and under choose?** James Green, University of Otago
592	**What is the attitude of Australian pharmacists to the use of medicines for assisted dying at end-of life?** Tony Hall, Queensland University of Technology
593	**Health professionals' opinion of a brief email format for answering medicine information enquiries** Ann Roslyn Hutton, Christchurch Hospital
594	**Pharmacy and the ethical dilemma of Physician Assisted Suicide (PAS): A systematic review** Sami Isaac, The University of Sydney
595	**Common co-morbidities and polypharmacy in elderly patients in a South Australian tertiary healthcare hospital** Muhammad Khan, The University of Queensland
596	**Weight loss product usage and advice in community pharmacies in North Queensland** Gillian Knott, James Cook University
597	**Factors associated with pharmacists' perceptions of working conditions in Canada** Carlo Marra, University of Otago
598	**What Is Polypharmacy Exactly (WIPE)** Nashwa Masnoon, University of South Australia, Royal Adelaide Hospital
599	**Do Australian pharmacists feel prepared to respond to local disasters and emergencies?** Elizabeth McCourt, Queensland University of Technology
600	**Over-the-counter medicines: The complexity of decision-making for pharmacy students** Sara McMillan, Griffith University
601	**Insights into consumer use, storage and disposal of unwanted and expired medicines** Fiona Kelly, Griffith University
602	**Non-prescription sales of antimicrobials in developing countries: A systematic review** Fatima Sakeena, The University of Sydney
603	**Principlism: An approach for determining ethical responsibilities of pharmacists when selling complementary medicines** Amber Salman Popattia, The University of Queensland
604	**Implementation of the Goal-directed Medication review Electronic Decision Support System (G-MEDSS)** Mouna Sawan, The University of Sydney
605	**Pharmacist perceptions of psychotropic monitoring in Australian aged care facilities** Carl Schneider, The University of Sydney
606	**Do pharmacists fit in the disaster health management team puzzle?** Judith Singleton, Queensland University of Technology
607	**How do health professionals perceive medicinal cannabis? Results of a systematic review** Judith Singleton, Queensland University of Technology
608	**Community pharmacists' perception of their role in primary mental health care** Mary Wong, University of Otago
609	**Electronic prescribing of insulin with Medications Management, Anaesthetics & Research Support (MARS)** Hua Bing Yong, Princess Alexandra Hospital
610	**Prevalence of potentially inappropriate medicine use in older Australians living in residential aged care facilities** Hosam Bony, University of South Australia
611	**Comparison of the management of medicines in the older-aged living in different leasehold retirement villages** Sheila Doggrell, Queensland University of Technology
612	**Tablet crushers: The investigation of powder loss using different sizes and brands of atorvastatin tablets** Mitchell Everlyn, The University of Queensland
613	**Study of the 'Hospital Formularies' of different level hospitals based on the 'WHO - Essential Medicines List'** Bharatkumar Gajjar, Pramukhswami Medical College
614	**How does perceived cost influence pharmacy patronage? A scoping review.** Bethany Grew, The University of Sydney
615	**Improving outcomes in type 2 diabetes patients using a pharmacist diabetes intervention tool** Laetitia Hattingh, Griffith University
616	**Complementary and alternative medicine (CAM) use in cancer patients commencing new chemotherapy** Karly Huber, Griffith University

617	**Are pharmacists' estimates of medication adherence related to HbA1c levels in people with type 2 diabetes?** Mangesh Kharjul, Otago University
618	**Developing a screening tool to identify people with swallowing difficulties of solid oral medicines** Esther Lau, Queensland University of Technology
619	**Dose administration aids - how useful do patients think they are?** Esther Lau, Queensland University of Technology
620	**Factors influencing non-adherence among people living with chronic health conditions in Australia** Amary Mey, Griffith University
621	**Medication information and supply behaviours in elite athletes** Lily Ngu, University of Western Australia
622	**Healthcare and pharmacy service provision for Pakistani migrants residing in developed countries: A systematic review** Ahsan Saleem, The University of Queensland
623	**Piloting a novel observational technique for the administration of medicines to children in paediatric wards** Jose Manuel Serrano Santos, Queensland University of Technology
624	**Evaluation of antimicrobial use in a tertiary care hospital by using specific indicators: A prospective, observational study** Siavash Shahbazi Nia, Al-ameen College of Pharmacy
625	**Does medication increase the risk of infection burden in residential aged care?** Mohammad Shohel, Curtin University
626	**Measuring menopause symptoms: A scoping review of existing tools** Joy Spark, University of New England
627	**Completeness of controlled drug prescribing in regional NSW** Joy Spark, University of New England
628	**Tablet crusher comparisons: Usability testing by people with and without limited hand function** Kathryn Steadman, The University of Queensland
629	**Management of non-healing mouth ulcer presentations in community pharmacies** Brigitte Janse van Rensburg, The University of Queensland
630	**Chronic disease, medications and lifestyle: Perceptions from a regional Victorian Indigenous Community** Joseph Tucci, La Trobe University
631	**Perceptions of credible drug information sources for Indigenous people attending a regional Aboriginal Health Service** Joseph Tucci, La Trobe University

100 Use of "extended clearance concept" in new drug discovery and development; Prediction of the effect of drug-drug interaction and pharmacogenomics on PK/PD/TD of drugs

Yuichi Sugiyama, Sugiyama Laboratory, RIKEN, Yokohama, Japan

In this presentation, I will summarize the significant role played by drug transporters in drug disposition, focusing particularly on their roles in the PK/PD/TD of drugs. Even when drugs ultimately undergo metabolism and/or biliary excretion in the liver, their elimination rate is sometimes determined by the hepatic uptake rate mediated by uptake transporters. Elucidation of the rate-determining process is therefore critical for predicting their hepatic clearance, and their systemic and regional exposures. I will show you how to understand the so-called "Extended clearance concept (ECC)" that includes the passive transport and transporter-mediated membrane transport and enzyme-mediated metabolism processes and to investigate the effect of changes in transporter (influx, efflux) function and metabolizing enzyme function on the pharmacokinetics of drugs in the blood and the liver and, ultimately, the pharmacological and/or toxicological effects (1-2). The use of transporter function offers the possibility of delivering a drug to the target organ, avoiding distribution to other organs (thereby reducing the chance of toxic side-effects), controlling the elimination process, and/or improving oral bioavailability. For drugs, the target molecule of which is inside the cells, the efflux transporter is the determinant for their pharmacological effect or adverse reactions even though it had negligible impact on the plasma concentrations. Development of probe substrates applicable to the PET imaging will elucidate the quantitative relationship between the transport activities and drug response. Drug transporters are also important for the disposition of endogenous and food derived compounds.

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2) Yoshida K, Maeda K, Sugiyama Y. Hepatic and Intestinal Drug Transporters: Prediction of Pharmacokinetic Effects Caused by Drug-Drug Interactions and Genetic Polymorphisms. Annu Rev Pharmacol Toxicol. 53: 581-612 (2013)

101 Reflections and connections on a pharmacokinetic journey

Kevin T Batty, School of Pharmacy, Curtin University, Perth, WA, Australia

Introduction: The rich Australian landscape of pharmaceutical and pharmacological sciences is populated by generous researchers who assist students and academics along the path of innovation and scientific discovery.
Aim: This presentation describes a journey of antimalarial and antimicrobial pharmacokinetic research, highlighting research collaborations and reflecting on an individual's contribution to the team. The shared purpose has been to improve the treatment of infectious diseases, especially in vulnerable populations.
Discourse: The artemisinin antimalarial drugs were emerging as important therapeutic agents in the 1990s. However, there was a paucity of pharmacokinetic (PK) data at the time and analytical techniques were problematic. Enthused by the prospect of a research project which the supervisors deemed plausible, the journey began. In the fullness of time, aided by advice and support from numerous experts in their field, our contributions included PK data for artesunate and its active metabolite, dihydroartemisinin, in Vietnamese patients, and evidence that artesunate was a prodrug.
A subsequent phase of research for the next generation of doctoral students focussed on a murine malaria model for pharmacokinetic-pharmacodynamic (PKPD) and toxicokinetic investigations. New collaborations included expertise in PKPD modelling, to optimise the use of rich data in sophisticated models.
Entering the classroom, PowerPoint and clinical pharmacokinetics have replaced chalk, blackboards and differential calculus. The PK jargon includes feathering, well stirred models and fu. We focus on competent mathematical skills, an understanding of the principles and applying PK knowledge in the context of optimising patient outcomes.
Now it is the era of sparse sampling, pharmacometricians, microvolume blood samples and liquid chromatography-mass spectrometry (LCMS) analysis. Our foray into dried blood spot assays has been based on the goal to minimise invasive blood samples and extend the scope of PK studies in field settings where laboratory equipment is non-existent. Blood volumes are <50 µL and dried on paper cards, compared to 2-3 mL samples for centrifugation and separation of plasma for frozen storage. The enticing prospect of PK studies in remote settings and paediatric or neonatal populations is accompanied by a new paradigm in assay validation and biopharmaceutical science, and the privilege of collaborating with highly committed researchers whose mission is to improve patient care.

102 Understanding cannabinoid clinical pharmacology in order to drive clinical studies

Catherine J Lucas[1], Jennifer Schneider[2], Peter Galettis[1], Jennifer H Martin[1], [1]Discipline of Clinical Pharmacology, University of Newcastle, Newcastle, NSW, Australia; [2]School of Biomedical Sciences and Pharmacy, University of Newcastle, Newcastle, NSW, Australia

Introduction: Interest in the medicinal uses of cannabinoids is increasing. There is, however, a current lack of good quality evidence pertaining to the complex pharmacology and physiological effects of exogenous cannabinoids in humans, administered either as extracts or the whole plant. Understanding of basic pharmaceutics, pharmacokinetics and pharmacodynamics for different parts of the cannabis plant is essential to guide safe dosing and reduce toxicity.
Aims: To outline the key pharmacological knowledge required to guide further exploration of the efficacy and toxicity of different cannabinoids and formulations in blinded, placebo-controlled studies.
Discussion: There is a need for pharmacological knowledge on the difference of the whole plant compared with numerous different individual chemicals, many of which are known to contribute to the pharmacological and toxicological properties of cannabis. Varying levels of these compounds may produce different physiological effects. Omission of animal studies limits knowledge of toxicity and median lethal dose pivotal to guiding dosing in early phase human studies. The absorption of cannabinoids differs with route of administration and bioavailability is variable with all modes of administration. Diet, microbiome, pharmacogenetics, body composition and other unknown patient factors influence absorption, metabolism and elimination. Cannabinoids may accumulate in tissues, with variable release from lipid storage compartments. Metabolism is predominantly hepatic (but also occurs in extra-hepatic tissues) and as such, there is significant potential for drug-drug interactions. Important active metabolites of Δ^9-tetrahydrocannabinol and cannabidiol can have pharmacodynamic effects. Understanding the clinical pharmacology of cannabinoids is critical for maximising therapeutic effects and minimising negative side effects and for regulatory support to enable human use.

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103 Cannabinoids for patients: Comparative efficacy and toxicity in paediatric setting

Noel E Cranswick, Department of Pharmacology, University of Melbourne, Parkville, VIC, Australia

The off-label use of cannabis products in children has rapidly increased over the last few years in Australia, mostly for the treatment of drug-resistant epilepsy. Up until recently, many children have received extemporaneously produced products from back-yard operations. Many of these products have been produced illegally and are of unknown quality with no specific safety information available. Until recently, all of the experience in the use of cannabinoids was anecdotal with emotive reports of vast improvement in severely affected children. There are now some data from randomised trials with some evidence of efficacy but significant side-effects associated with the use of cannabinol (CBD) in Dravet syndrome and Lennox-Gastaut syndrome. Mostly as the result of political processes, there is increasing use of CBD in Australian children who sufer from a variety of drug-resistant epilepsy syndromes. The details of the access schemes and available products varying from State to State. The Victorian experience, in an open-label access scheme, is that the apparent rate of improvement and side-effects is similar to that reported in the clinical trials. There is evidence of a specific and highly clinically relevant drug interaction between CBD and clobazam resulting in an increased rate of adverse events as well as some improvement in seizure control. Further studies are needed to better define the role of CBD in the treatment of children with drug-resistant epilepsy before it can recommended in routine clinical practice.

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104 High quality human cannabinoid analytics to drive clinical studies

Peter Galettis[1,2,3], [1]Discipline of Clinical Pharmacology, University of Newcastle, [2]Callaghan NSW, Hunter Medical Research Institute, New Lambton Heights NSW, [3]Australian Centre for Cannabinoid Clinical and Research Excellence (ACRE)

There is increasing interest in the use of cannabis for medicinal purposes. However the term medicinal cannabis refers to a number of different products, including Cannabis Flos, Cannabis Oils and THC or CBD extracts from plants. In order to know the characteristics of the products being administered to patients in clinical studies, it is firstly important to have a clear indication of which cannabinoids and the relative amounts of each cannabinoid that are present in these materials. This requires development of reliable and robust analytical techniques capable of both separating each of the different cannabinoids and also determining the concentrations of each cannabinoid present. Once the cannabinoids and the amount present in a particular product is known, it is then possible to develop analytical methods for the determination of cannabinoids in human plasma or other biological fluid samples obtained when these products are administered in a clinical trial. The two main active cannabinoids in cannabis are currently considered to be THC and CBD. Once either THC or CBD enter the body they are then metabolised significantly to a number of metabolites with the main ones being hydroxyl THC, carboxy THC and the carboxy THC glucuronide as well as the equivalents for CBD. However, in the cannabis plant these compounds are present predominantly in the carboxylated form (THCA and CBDA) and require decarboxylation to be converted to THC and CBD. This is usually achieved by heating the plant material either by smoking or some form of vaporisation. This presentation will discuss a number of issues involved in developing analytical methods for a complex material such as cannabis. It will also discuss factors to be considered in developing analytical methods for measuring cannabinoids and their metabolites in biological fluid.

105 Pharmacokinetic analysis of vaporized cannabinoids through inhalation

Zheng Liu[1,2], Noel Cranswick[2], Jennifer Martin[1], [1]School of Medicine and Public Health, University of Newcastle, Callaghan, NSW, Australia, [2]Clinical Pharmacology, Department of Medicine, The Royal Children's Hospital Melbourne, Australia

Medicinal cannabinoids have gained significant attention recently, due to potential benefits in therapeutic applications. The most important two components for clinical use are Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD). There is currently little high quality evidence however people have used these therapies to treat a wide variety of symptoms such as distress, pain relief and anxiety. Developing high quality evidence requires knowledge about the pharmacology, prior to undertaking clinical trials. Pharmacology of these therapies are complex as they are lipophilic and patients often use a mix of oral, intravenous, and pulmonary routes. In the absence of clinical trial and pharmacology data for all routes, indications, and population groups, population modelling is required to help predict dosing. We have developed several preliminary modeling projects to understand the pharmacology of cannabinoid therapies used in the clinical trial setting here in Australia. In this presentation we discuss the issues regarding dosing in these studies and the methods used. This work has enabled the pharmacokinetic models for THC and CBD to be developed and the relevant parameter values estimated. The resultant pharmacokinetic information revealed will help clinicians understand the pharmacokinetic information of cannabinoids. Specifically, the developed pharmacokinetic models can be used to forecast concentration profiles of the drug under many different dosing regimens and assess the drug accumulation in a multiple-dose setting. This provides the good opportunity for dosing optimization and improve decision making in future clinical trials.

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106 Pharmaceutical Aspects of Cannabis

Jennifer J Schneider, School of Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan, NSW, Australia

According to recorded history, Cannabis has been used as a medicine for thousands of years with different parts of this plant being administered topically, orally or smoked for pharmacological effect. Use of cannabis in Western Medicine was reported in the 19th and 20th century and its use began to wane in the 1940s-largely due to the availability of other medicines and the impact of government legislation. In the last decade, there has been a resurgence in interest in the medicinal use of cannabis for treating different conditions. This rise in popularity has seen many different forms of cannabis become available. These include "medibles" (edible forms of marijuana), home grown products and pharmaceutical grade formulations. While modern pharmaceutical dosage forms generally consist of a single drug or a combination of two or three drugs for which specific dosage form testing criteria are clearly defined in pharmacopoeias, the re-emergence of cannabis for therapeutic use has taken us back to a time when tinctures and extracts made up most of the entries in pharmacopoeias. The complexity of working with plant extracts instead of a single drug entity presents challenges in ensuring patients receive consistent doses of the extracted material, that different extracts contain the same ingredients, that formulations maintain potency on storage and there is reproducible bioavailability of the medicinal agents. This presentation will explore the pharmaceutical aspects of cannabis and cannabinoid products including formulations, routes of delivery, stability and factors influencing bioavailability.

107 Cytochrome P450 structure-function: Insights from molecular dynamics simulations

Pramod C Nair[1,2], Ross A McKinnon[2], John O Miners[1,2], [1]Department of Clinical Pharmacology, [2]Flinders Centre for Innovation in Cancer, Flinders University, Adelaide, SA

Cytochrome P450 (CYP) enzymes from families 1, 2 and 3 play an essential role in the metabolic clearance and detoxification of a myriad of drugs and non-drug xenobiotics. Although experimental techniques such as X-ray crystallography have provided valuable information relating to CYP structure-function, the structures elucidated by X-ray crystallography are static and data are limited in terms of the thermodynamics of binding and understanding the flexibility of CYP enzyme active sites. We have utilized Molecular Dynamics Simulations (MDS) to model the thermodynamics and flexibility of CYP2C9 in order to elucidate the importance of protein plasticity in substrate binding. CYP2C9 primarily metabolises weakly acidic drugs (e.g. NSAIDs, phenytoin, S-warfarin), but also has the capacity to metabolise some basic drugs (e.g. amitriptyline). Initial studies demonstrated that simulation times of 100 ns and longer were necessary to adequately model the conformational flexibility of CYP2C9. Distance mapping between the Cα atoms of substrate recognition sites (SRSs) and the heme Fe atom (as the reference point) of the CYP2C9 catalytic site shows SRS1 (B-C loop, which lies between helices B and C) and SRS3 (helix G) as the most flexible regions of this enzyme. On the other hand, the least malleable regions were SRS2 and SRS4. The structural flexibility of SRS1 and SRS3 facilitates the binding of diverse ligands of different molecular shape and size. MD simulations further demonstrated that the binding of acidic (carboxylic acids) and basic (amines) drugs to CYP2C9 occurs by subtle conformational readjustment of amino acids within the active site. The binding of acidic substrates within the CYP2C9 active site is mediated mainly via a combination of H-bonding (Arg-108) and aromatic hydrophobic (Phe-114 and Phe-476) interactions. By comparison, the basic substrates predominantly bind within the CYP2C9 active site via aromatic hydrophobic (Phe-114 and Phe-476) interactions. MDS additionally provides insights into the mechanisms of drug-drug interactions, for example the heterotropic activation of flurbiprofen by dapsone. Binding of dapsone induces a conformational change in the B-C loop of CYP2C9 allowing formation of a salt-bridge between Arg-105 and the sulfone group of dapsone. This positioning of dapsone in turn stabilises the binding of flurbiprofen (via pi-pi interactions) and 'tightens' the active site, resulting in a more favourable orientation of flurbiprofen for catalysis with an increase in maximal velocity (and hence intrinsic clearance).

108 CYP2J2 over-expression in breast cancer cells drives tumourigenesis and anti-cancer drug resistance

Michael Murray[1], Nenad Petrovic[2], Peter I Mackenzie[3], Sarah E Allison[1], [1]Department of Pharmacology, University of Sydney[1], Sydney, NSW, [2]School of Pharmacy and Medical Science, University of South Australia, Adelaide, SA, [3]Clinical Pharmacology, Flinders University[3], Bedford Park, SA

Introduction: Cytochrome P450 2J2 (CYP2J2) is over-expressed in many human cancers and generates tumourigenic epoxyeicosatrienoic acids (EETs) from arachidonic acid, but the underlying mechanisms are unclear.
Aims: We have addressed the mechanisms by which EETs regulate tumourigenesis in human breast-derived cell lines.
Methods: MDA-MB-468 breast cancer cells were stably transfected with human CYP2J2 (MDA-2J2 cells) and Affymetrix microarray profiling was undertaken. Cell viability was assessed using MTT reduction and ATP formation, apoptosis using caspase-3 activity, cell migration using a 3D-matrigel droplet assay, and reactive oxygen species (ROS) using 2',7'-dichlorofluorescin diacetate and flow cytometry. Gene expression was evaluated using RT-PCR and protein expression by western immunoblotting. Gene silencing was undertaken using specific siRNAs.
Results: The proliferative and migratory capacities of MDA-2J2 cells were enhanced over MDA-CTL. 182 genes were differentially expressed in MDA-2J2 cells relative to control (MDA-CTL) cells (log-fold ≥ 2). From pathway analysis bone morphogenetic protein receptor 1B (BMPR1B) and aldehyde dehydrogenase 1A1 (ALDH1A1) were two genes of interest that were upregulated and functional in MDA-2J2 cells. Addition of the BMPR1B ligand BMP2 stimulated the migration of MDA-2J2 cells, but not MDA-CTL cells, from matrigel droplets. Cell killing by the major breast cancer drug paclitaxel was impaired in MDA-2J2 cells compared to MDA-CTL. Basal and paclitaxel-activated ROS content was lower, and the paclitaxel-mediated formation of protein adducts by reactive aldehydes derived from lipid peroxidation was attenuated in MDA-2J2 cells. Silencing of ALDH1A1 restored the sensitivity of MDA-2J2 cells to paclitaxel and formation of ROS to levels comparable with MDA-CTL. Doxorubicin, sorafenib and staurosporine also promoted ROS-mediated cell death that was attenuated in MDA-2J2 cells and was reversed by ALDH1A1 gene silencing.
Discussion: Over-expression of CYP2J2 in MDA-2J2 cells activates the expression of BMPR1B, which promotes migration, and ALDH1A1, which modulates ROS production by anti-cancer agents and diminishes their efficacy. Novel approaches to target BMPR1B and ALDH1A1 may inhibit migration and drug resistance in breast cancers that over-express CYP2J2.

109 Regulation and function of UGTs in cancer

Robyn Meech[1,2], Dong Gui Hu[1], Apichaya Chanawong[1], Lu Lu[1], Ross A McKinnon[1,2], and Peter I Mackenzie[1], [1]Department of Clinical Pharmacology, Flinders University. [2] Flinders Centre for Innovation in Cancer, Flinders University, Bedford Park, SA, Australia

Introduction: UDP Glucuronosyltransferases play critical roles in the elimination of numerous therapeutic drugs as well as endogenous lipophilic molecules such as steroid hormones. UGTs are often regulated by ligands that are also UGT-substrates, thus generating regulatory loops through which small molecules control their own metabolism. There is evidence that UGT activity influences the progression of steroid-dependent cancers (breast and prostate) via glucuronidation of growth-promoting steroids. In addition UGTs conjugate several steroidal anti-cancer drugs and cytotoxic anti-cancer drugs, and this may influence therapy response and the acquisition of drug resistance.
Aims: To understand the mechanisms of local regulation of UGTs in cancer cells by steroids and by various classes of anti-cancer drugs, and how this regulation may influence cancer cell growth and response to therapy.
Methods: A suite of gene regulation analysis tools is used to understand how multiple UGTs are regulated in cancer cells by steroids, steroidal anti-cancer drugs, and cytotoxic anti-cancer drugs. We also examine how UGT overexpression or ablation affects cancer cell growth and drug resistance.
Results: Results of studies in two areas are presented. 1. We show the mechanisms by which UGT2B15 and UGT2B17 are induced in breast cancer by natural steroids and by the selective estrogen receptor modulators Tamoxifen and the aromatase inhibitor Exemestane. We present data on the effects of loss and gain of UGT2B15/17 function in breast cancer cells. 2. We show the mechanisms of UGT induction by cytotoxic anti-cancer drugs in cancer cells, and also provide evidence that UGT expression can be constitutively elevated in cancer stem cells. We present data on the effects of loss and gain of UGT function on cancer cell drug response/drug resistance.
Discussion: Our studies indicate that UGT expression and regulation may be an important variable in cancer progression and drug resistance. Opportunities to modulate UGTs for therapeutic benefit in cancer will be discussed.

110 Arylamine N-acetyltransferase-1: Drug metabolism and more

Neville J Butcher, Lili Wang, Peng cheng Li, Rodney F Minchin, School of Biomedical Sciences, University of Queensland, Brisbane, QLD, Australia

The arylamine N-acetyltransferases (NATs; EC 2.3.1.5) are a family of highly conserved phase II xenobiotic-metabolising enzymes that are found in both prokaryotes and eukaryotes. In humans, there are two functional enzymes, NAT1 and NAT2. Both NAT genes are genetically polymorphic, which, combined with post-transcriptional regulation, results in highly variable NAT enzyme activities, both between and within individuals. Although this variability in NAT enzyme activity affects the susceptibility of individuals to drug toxicity and various cancers, there is a growing body of evidence that suggests the NAT1 isozyme has an important physiological role in the cell in addition to xenobiotic metabolism. NAT1 is a ubiquitously expressed protein and is also found in all immortalised cancer cell lines tested to date, albeit at very different levels. We, and others, have used various strategies to manipulate NAT1 expression/activity in human cancer cell lines in order to investigate its role in cancer cell biology. Several different phenotypes have been observed, including changes in cancer cell metabolism, growth and survival, gene expression, invasion, and sensitivity to chemotherapeutics. The exact molecular mechanism/s linking NAT1 to these phenotypes is yet to be determined, but appears to involve changes in the acetylome. Using CRISPR-generated NAT1 knock-out cell models, we have identified changes in the lysine acetylation of several important proteins, including p53, sirtuins 1 and 2, and ACSS2. Although NAT1 is unable to acetylate proteins itself, we have recently discovered that it interacts with the acetyltransferase p300/CBP and can modulate its activity. We hypothesise that NAT1 is a key regulator of p300/CBP acetyltransferase activity.

111 Sulfotransferase: Structure, function and protein-protein interactions

Rodney F Minchin, Misgana Idris and Neville J Butcher, School of Biomedical Sciences, University of Queensland, Brisbane, QLD, Australia

The cytosolic sulfotransferases (SULTs) are responsible for the sulfonation of numerous endogenous hormones and neurotransmitters as well as therapeutic agents and environmental toxins. Variability in sulfotransferase activities has been linked to catecholamine toxicity, adverse drug reactions, drug therapy failure, and cancer susceptibility. In humans, there are 4 SULT families (SULT1, SULT2, SULT4 and SULT6). The SULT4 family comprises a single member SULT4A1, which has been referred to as a 'sulfotransferase-like protein" because it retains many of the features of the other SULTs but does not appear to be catalytically active. Nevertheless, recent SULT4A1 knockout studies in mice show a severe phenotype indicative of its biological importance. All human sulfotransferases have a dimerisation motif that regulates enzyme activity as well as protein stability. The formation of heterodimers provides an additional mechanism by which a cell can regulate sulfotransferase function. This will be demonstrated with several human sulfotransferase examples.
SULT1A3, which has only emerged since the great apes separated from other species, is required for neurotransmitter metabolism in several organs such as the GI tract and the brain. SULT1A3 efficiently metabolises dopamine and can influence its toxicity in neuronal cells *in vitro*[1]. The gene for the protein resides in a region of chromosomal instability so multiple copies can be demonstrated in humans. Importantly, there is an association between copy number variation and risk of developing neurodegenerative diseases such as Alzheimer's and early onset Parkinson's[2]. Our more recent data show that SULT4A1 is an important regulator of SULT1A1 and SULT1A3 by heterodimerisation that targets the proteins for degradation via autophagy. This finding may explain the severe phenotypes reported in SULT4A1 knockout animals.

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112 Preclinical models to understand the risks of single and multiple concurrent medicines in old age

John Mach[1,2,3], Caitlin Logan[1,3], Doug Drak[1,3], Gizem Gemikonakli[1,3], Swathi Ekambareshwar[1,3], Jennifer Debenham[1,3], Alice E Kane[3,4], Susan Howlett[4], Rafael de Cabo[5], David G Le Couteur[3,6]& Sarah N Hilmer[1,2,3], [1]Kolling Institute, Sydney, NSW [2]Royal North Shore Hosp, Sydney, NSW, [3]University of Sydney, Sydney, NSW, [4]Dalhousie University, Halifax, Canada, [5]National Institute on Aging, National Institute of Health, Maryland, USA, [6]Concord Hospital, Sydney, NSW

Introduction: Chronic medication use is common in older people. Older people, particularly those with polypharmacy (use ≥ 5 drugs) for multi-morbidity, are rarely included in clinical trials to determine efficacy and safety. Observational studies indicate polypharmacy and increasing Drug Burden Index (DBI: measures total anticholinergic and sedative medication exposure) are associated with impaired physical function in older people. Preclinical models of clinically relevant drug exposures in ageing would be useful to screen for adverse geriatric outcomes prior to marketing.
Aim: To develop a preclinical mouse model to determine whether chronic use of therapeutic drugs (monotherapy or polypharmacy) and/or increasing DBI exposure impair translatable functional outcomes in ageing.
Methods: From 12 months of age, male C57BL/6 mice were fed control diet or feed/water containing therapeutic doses of study drug(s). We tested regimens of five drugs that had Zero DBI (simvastatin, metoprolol, omeprazole, paracetamol, irbesartan), Low DBI (simvastatin, metoprolol, omeprazole, paracetamol, citalopram), High DBI (simvastatin, metoprolol, oxybutynin, oxycodone, citalopram) and single drugs from the High DBI regimen as monotherapy. Functional tests are performed every 3 months throughout life. Power calculations estimate that a sample size of 10-12 per group is required to detect changes in functional measures with treatment.
Results: For the subgroup of animals with data currently available after 6 months of treatment (age 15 and 18 months), compared to control, measures of spontaneous activity in the open field (distance and midzone entries), grip strength (wire hang), nesting scores and frailty score were reduced in the Low DBI, High DBI and citalopram groups (n=25-40, $p<0.05$). Compared to control, muscle endurance (rotarod) was significantly reduced in Low DBI and citalopram after 6 months of treatment (n=25-40, $p<0.05$).
Discussion: We have developed a preclinical model that can detect impaired functional outcomes following chronic treatment with polypharmacy regimens or monotherapy in ageing mice. These methods can be applied to determine and understand mechanisms and reversibility of the risks of medicines to global health outcomes in old age.

113 Application of pharmacometric modelling for studying drug effects

Carl M Kirkpatrick, Centre for Medicine Use and Safety, Monash University, Melbourne, VIC

What was once a nicety in drug development and at times considered an “academic” practice, the application of quantitative clinical pharmacology (pharmacometrics) has now become a fundamental in the armamentarium of pharmaceutical industry for the development of a medicine. Indeed, the application of pharmacometrics can now be witnessed from the very early stages of drug development through to post-marketing surveillance of a new medicine. This presentation highlights some of the pharmacometric approaches across in-vitro, pre-clinical and clinical stages of drug development to enhance drug development programs. In particular, how this approach is utilised to make key go/no go decisions and posology.

114 Novel approaches in pharmacoepidemiological studies to communicate benefits and risks of medicines

Danijela Gnjidic, Faculty of Pharmacy, University of Sydney, Sydney, NSW, Australia

Introduction: Assessing outcomes from medicines in people with multi-morbidity, polypharmacy and dementia is difficult as measures of clinical significance are rarely employed in clinical trials and applying the clinical trial evidence to 'real-world patients' with drug-drug, and disease-drug interactions is often challenging.
Methods: Recent efforts have been focused on employing novel pharmaco-epidemiologic methods to tackle the complex systems and networks that drive medication utilisation.
Results: In our study of community-dwelling men, using multi-state modelling method, we found that increasing medication burden was associated with transition to frailty states, namely from robust to frail state and subsequent increased risk of mortality in older people. Moreover, efforts have been made to quantify complex patterns of multimorbidity and polypharmacy in older adults using novel analysis such as Association Rule and Frequent-set analysis. In our study, using the Association Rule methodology we found several morbidity clusters. In relation to polypharmacy exposure, Frequent-set analysis showed that medication combinations differed according to geriatric syndrome status.
Discussion: Pharmacoepidemiology and pharmacovigilance data on medication utilisation and drug safety has a major influence on prescribing for older people.

115 Pharmacoepidemiological studies to inform medication safety in older adults with chronic diseases and dementia

Simon Bell, Centre for Medicine Use and Safety, Monash University, Melbourne, VIC, Australia

Randomised controlled trials (RCTs) are the 'gold standard' for investigating medicine efficacy but often exclude vulnerable population groups such as people with dementia, frailty and multimorbidity. Recent advances in the availability of electronic medical records, development of clinical registries and administrative claims data offer the potential to better understand and optimise medicine use in these vulnerable population groups. Observational studies conducted using these data sources are useful for detecting longer-term health outcomes and rare adverse events not able to be detected in RCTs. International consensus research priorities generated at the recent Optimising Geriatric Pharmacotherapy through Pharmacoepidemiology Network (OPPEN) in Stockholm will be presented. These priorities will be summarised under the themes of quality of medication use, vulnerable patient groups; multimorbidity and polypharmacy, person-centred practice and research, deprescribing, methodologies, variability in medication use, and national and international comparative research. Australian and international examples will be presented to demonstrate how observational studies can help improve the limited evidence base to inform prescribing for vulnerable population groups. Results of this pharmacoepidemiological research will assist clinicians better understand the benefits and risks of strict adherence to disease-specific clinical practice guidelines in people with dementia, frailty and multimorbidity.

116 Changing guideline recommendations on the pharmacological management of back pain

Christine Lin, Musculoskeletal Health Sydney, Sydney School of Public Health, The University of Sydney, Sydney, NSW, Australia

Introduction: Low back pain is a prevalent condition that causes the highest disease burden globally in terms of disability. Sciatica is a severe form of back pain that is characterised by radiating leg pain caused by lumbar nerve root compromise. To treat acute low back pain, the drug paracetamol has been universally endorsed by international clinical guidelines as a first line treatment, while the drug pregabalin is recommended for neuropathic pain conditions and commonly used to treat sciatica. However, there has been no direct evidence on the efficacy and safety of paracetamol or pregabalin in low back pain or sciatica.
Aims: To investigate the efficacy and safety of paracetamol in patients with acute low back pain and pregabalin in patients with sciatica.
Methods: Two double-blinded, randomised controlled trials were conducted. In the PACE Study, 1652 patients with acute low back pain were randomised to receive either paracetamol or placebo for up to 4 weeks and followed up at regular time points for 3 months. The primary outcome was time to recovery from pain, and secondary outcomes included pain intensity and disability. We also collected safety outcomes. In the PRECISE Study, 209 patients with sciatica were randomised to receive either pregabalin or placebo for up to 8 weeks and followed up at regular time points for 1 year. The primary outcome was leg pain intensity measured at 8 weeks. Secondary outcomes included pain at 1 year and disability at 8 weeks and 1 year. We also collected safety outcomes.
Results: In PACE, there was no difference in the time to recovery between those who took paracetamol or placebo, and no difference in all secondary outcomes and adverse events. In PRECISE, there was no difference in leg pain intensity at 8 weeks between those who took pregabalin or placebo, and no difference in all secondary outcomes at all time points. More people in the pregabalin group reported an adverse event (n = 68 versus 43 in the placebo group, p = 0.002); the most common adverse event was dizziness.
Discussion: Paracetamol is no more effective than placebo for acute low back pain. Pregabalin is no more effective than placebo for sciatica and is associated with more adverse events. These findings challenge the guideline recommendations supporting their use.

117 Introducing a large-scale research project for undergraduate students

Susan L Rowland, Institute for Teaching and Learning Innovation *and* School of Chemistry and Molecular Biosciences, The University of Queensland, St Lucia, QLD, Australia

The idea of conducting a research project with hundreds of undergraduate student researchers is both exciting and challenging for the implementers. We recently completed an OLT-funded project in which we worked with multiple educators around Australia to develop, deliver, and evaluate large-scale undergraduate research projects (LUREs) in their science and health-related classes.

After the implementations we spoke to the staff about their work, and about the things that both supported and challenged their endeavours. The current literature in this area focuses on the academic experience of impementing a LURE. We spoke with academics, but we also expanded our circle of enquiry by speaking to the laboratory technicians, the para-academics, and teaching assistants who were involved in the projects. This is the first study in which these staff members are given a voice as implementers of LUREs.

Our results gave us some surprising insights into what makes a LURE work, and the differences in challenges and pay-offs for the various implementer groups. In this talk I will share our findings, which will be of interest to academics, administrators, teaching assistants, and support staff who have a stake in LUREs.

118 Peer assessment to develop critical analysis and self-reflection in large undergraduate cohorts

Rosa C McCarty, Michael J Lew" Department of Pharmacology & Therapeutics, The University of Melbourne[1], Melbourne, Victoria, Australia

Introduction: To be able to critically evaluate the work of others, and to objectively assess the quality of one's own work is an expectation of students who have completed undergraduate study. Peer assessment is a foundational skill for many types of careers. It is routinely used by scientists, clinicians, academics and non-academics alike. Peer assessment offers an opportunity for students to develop those skills, and in the process, encourages life-long learning, examination and reflection. Although many educators recognise the advantages of peer assessment, its implementation is often challenging, even to the extent of being thought impractical for undergraduate classes with large to very large enrolments, coupled with concerns regarding the reliability of the marking process.
Aims: To deliver an authentic learning experience through the use of peer assessment in large cohorts. Data will be collated to evaluate the reliability of results, and student perceptions of the peer assessment process.
Methods: A variety of different types of written assignments are applicable to the following method. Students submit de-identified assignments electronically through the university online subject management tool. Using a custom designed software program (note other commercially available programs are available), students receive via email their own assignment and five randomly assigned assignments from their peers, with a carefully designed marking guide and instructions. On completion of the process students were encouraged to provide feedback on the process via survey. We have also performed comparisons between peer marks and academic or expert markers, and between peer marks and self-assessment.
Results: We have implemented peer assessment over several years to thousands of undergraduate students, to a class size of up to 470. The assessment of work by peers, using the median of scores from five students, ensure reliability and robustness of marks. There is a strong correlation between peer marks and expert marking. To date, survey results suggest that students find the peer assessment process challenging but report positively on the learning process.
Discussion: This presentation will explore our experience of the merits of peer assessment. This form of assessment driven learning is a reliable and relevant pedagogical tool, applicable to small and large cohorts.

119 Development of interprofessional communication skills for interprofessional collaboration

Karen Luetsch, School of Pharmacy, The University of Queensland, Brisbane

Interprofessional collaboration in health care results in better outcomes for the people cared for as well as in increased satisfaction by health carers. Successful communication between health care professionals promotes collaboration. This presentation will draw on theory, research and experience in exploring the prerequisites, antecedents and environments promoting effective communication between health professionals and how to guide the development of communication skills of students. Most education in health care focuses on task orientated communication, using structured frameworks and processes to share information, avoid risk, increase safety and confirm responsibilities and actions. While this transmission of messages and information is employed successfully in critical situations, it has limitations when large interprofessional teams with fluctuating membership communicate over extended periods in the care of people with complex illnesses. Creating a common sense of purpose and shared meaning via communication and an understanding of each other's roles and strengths will enable health professionals and students to work together for the benefit of people they care for in an increasingly complex system. Strategies to achieve these in stages over a health professional's career will be introduced and discussed.

120 Student perspectives on peer assessment, feedback and team work

Jayden Kelly[1], Mohammadali Taher[1], School of Rural Health[1], Department of Medicine, Monash University, Melbourne, Victoria, Australia.

Students are one of the primary stakeholders in any educational system, and their performance and success are directly affected by the administrations' decisions. This is particularly true in regards to the types of teaching methods implemented and the modes of content delivery. For instance, despite the ample evidence in favour of interactive teaching, universities often continue to opt for didactic methods. Often the decision is made because interactive teaching methods require more time and resources; ultimately resulting in the sacrifice of course content quantity. This perpetuation of the classical teaching model may also be reduced to the old adage; it is often hard to break old habits.

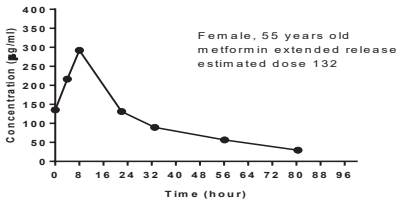
For the past three years, The School of Rural Health at Monash University has adopted the Flipped classroom teaching method for their MBBS post-graduate course. Flipped classroom is a reversal of traditional teaching methods, where students learn new material at home, through recorded lectures or reading textbooks, and spend class time applying their knowledge as they interact with their teachers and peers.

This talk will be a reflection on our experience of the flipped classroom model, as part of Monash MBBS course, and how it impacted our learning and interactions with our peers.

121 Quantification of metformin in human serum by hydrophilic interaction liquid chromatography - Mass spectrometry

Ahmed M. Abdalla[1, 2], Geoffrey K Isbister[3] and Michael S. Roberts[1, 4], [1]School of Pharmacy & Medical Sciences, University of SA, Basil Hetzel Institute for Translational Health Research, Adelaide, SA, [2]Pharmaceutical Chemistry Dept, Helwan University, Cairo, Egypt, [3]Clinical Toxicology Research Group, University of Newcastle, Newcastle, NSW, [4]Therapeutics Research Centre, Diamantina Institute, University of Qld, Translation Research Institute, Brisbane, Qld, Australia

Introduction: Metformin is widely used to treat diabetes mellitus type II and obesity.
Large metformin ingestion can cause severe and even fatal metabolic acidosis with hyperlactatemia. Hydrophilic interaction liquid chromatography (HILIC) is increasingly being used to quantify polar solutes, which traditionally have a low retention and poor separation on conventional reversed phase HPLC. Consequently, although most current metformin HPLC – tandem mass spectrometry (MSMS) methods involve a complex sample procedure.



Aims: Here, we used HILIC – ESI MSMS to quantify metformin in serum of patients who had overdosed on metformin.
Methods: The HILIC, coupled to a tandem mass spectrometer, was used to analyse serum metformin samples injected on to a Kinetex Polar C_{18} 2.6 µm HILIC (Phenomenex) 50 X 2.1 mm HILIC column after simple protein precipitation and centrifugation. Chromatographic separation was achieved using a gradient flow of (10mM Ammonium Acetate) and (10mM Ammonium Acetate in 95:5 Acetonitrile: Water). Pregabalin was used as the internal standard.
Results: The HILIC – MSMS method for serum metformin was a robust, reproducible and easy to use assay. It had a LOQ of 3.5 µg/mL and the following variabilities for the concentrations of 6.25, 20 and 40 µg/mL: intra-day 4.4, 5.6, and 4.5%; Inter-day: 3.2, 5.1 and 3.9%; and recovery: 98.4, 94.6 and 97.2%. MS-MS multiple reaction monitoring decreased matrix interference and enhanced the specificity of the assay for metformin. Figure 1 shows an example of one patient's metformin serum concentration versus time profile after an overdose and was accompanied by a severe metabolic acidosis. It is evident the peak metformin serum concentration of 292µg/mL at 8h post-ingestion is very high compared to a typical value of 1.78 µg/mL seen after 2g extended release metformin in normal patients.[1]
Discussion: HILIC chromatography is provided to be an effective method for analysing metformin in serum.
[1] Timmins et al. Clin. Pharmacokin. 44, 721–729, 2005

122 ORAI1 calcium channels in cell death during mammary gland involution

Felicity M Davis, Pharmacy Australia Centre of Excellence and Mater Research Institute, The University of Queensland1, Brisbane, QLD, Australia

Introduction: The nourishment of neonates by nursing is a defining characteristic of all mammals. Yet a mechanistic understanding of how mature luminal and myoepithelial cells in the breast perform their most primitive physiological functions (i.e. the production and expulsion of milk during lactation) has remained largely unexplored. We previously demonstrated that the store-operated Ca2+ channel subunit Orai1 is required for optimal Ca2+ transport into milk and for milk ejection (Davis et al., 2015 PNAS). Indeed, mammary glands from lactating Orai1-null mice exhibit pronounced milk stasis, owing to impaired Ca2+-dependent myoepithelial cell contractility in response to oxytocin.
Aims: As milk stasis is a trigger for post-lactational cell death (involution) in the mammary gland, our work is now seeking to investigate whether ORAI1 channels also play an essential role in decoding involution signals in the postpartum breast.
Methods: Mammary gland involution is marked by a dramatic switch in signal transducer and activator of transcription (STAT) signaling. Whilst STAT5 activation is required for the differentiation of luminal secretory cells during pregnancy and lactation, STAT3 activation drives cell death and remodeling during involution. STAT3 and STAT5 activation are examined using immunoblotting, immunofluorescence and immunohistochemistry on wildtype and transgenic mouse tissue as well as mouse mammary epithelial cell lines in response to lactogenic hormones and involution stimuli.
Results: Preliminary analyses demonstrate that luminal epithelial cells from Orai1-null mice remarkably express both phospho-STAT5 and phospho-STAT3, and are thus suspended in state resembling both lactation and involution.
Discussion: Ongoing studies in our laboratory using lineage-specific conditional knockout mice will provide important insights into the roles for ORAI1 calcium channels in the post-lactational mammary epithelial cell death cascade. An appreciation of the signaling pathways regulating cell death in the mammary epithelium under physiological conditions will provide valuable insights into cell death and cell death resistance in breast cancer, and how this enormous cell death cascade could be exploited therapeutically.

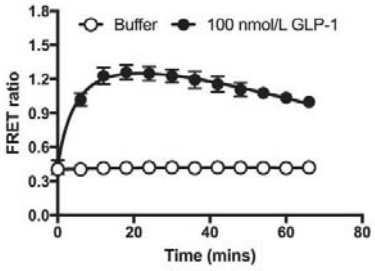
123 Pre-clinical pharmacokinetic development of the hypoxia-activated cytotoxin SN36506

Matthew Bull[1,2], Chris Guise[1,2], Maria Abbattista[1,2], Amir Ashoorzadeh[1,2], Jan Theys[3], Ludwig Dubois[3], Philippe Lambin[3], Jeff Smaill[1,2] and Adam Patterson[1,2], [1]Auckland Cancer Society Research Centre, University of Auckland, Auckland, New Zealand, [2]Maurice Wilkins Centre for Molecular Biodiscovery, School of Biological Sciences, University of Auckland, Auckland, New Zealand, [3]MAASTRO, GROW, MUMC, Maastricht, The Netherlands

Introduction: Cytotoxic prodrugs designed to target the hypoxic tumour microenvironment have the potential to selectively eliminate cancer cells whilst minimising normal tissue toxicities. Here we report the pre-clinical evaluation of the pharmacokinetics of SN36506, a novel second generation hypoxia-activated DNA crosslinking agent.
Aims: The primary aim of this research was to assess the pharmacokinetics and metabolism of SN36506, with a view to development towards clinical trial.
Methods: Plasma stability was assessed under physiological conditions and plasma protein binding was evaluated using microdialysis. Metabolic stability was determined in preparations of liver microsomes and under anoxic conditions in cancer cells. Metabolite profiles were obtained from microsomal incubations and in vivo plasma samples from dosed NIH-III mice. An LCMSMS method was developed and validated for the quantitation of SN36506. The pharmacokinetic profile of SN36506 was evaluated in tumour-free NIH-III mice using three routes of administration. Efficacy was evaluated in vivo in tumour growth delay models against triple-negative breast cancer xenografts.
Results: Under severe hypoxic conditions metabolism by human neoplastic cell lines in vitro produced the major cytotoxic amine metabolite (SN36506M). SN36506 exhibited low human plasma protein binding (11.90 ± 10.71%) and high human plasma stability (99.35 ± 3.08% at 37°C, 30 min). In microsomal incubations SN36506 was primarily metabolised via N-dealkylation of the mustard arm. SN36506 was 47% orally bioavailable and, at 1.17 mmol/kg ip, half-life was 0.54 hr and AUC was 261.4 hr.µmol/L. N-dealkylation products were also observed. Monotherapy SN36506 (1.17 mmol/kg ip) resulted in significant tumour growth delay in the xenograft cancer models.
Discussion: The pre-clinical pharmacokinetics of SN36506 represents an improvement in hypoxia-activated prodrug design in comparison to first generation phase II candidate prodrugs and further clinical development of SN36506 is being pursued.

124 A new high-throughput approach for investigating GPCR internalisation in real-time

Simon R Foster[1], Alexander S Hauser[1], David E Gloriam[1] & Hans Bräuner-Osborne[1], Department of Pharmacology and Drug Design, University of Copenhagen[1], Copenhagen, Denmark



Introduction: Endocytic trafficking represents an important mechanism for G protein-coupled receptor (GPCR) regulation, serving to internalise the receptors and attenuate G protein-dependent signalling. In addition, accumulating evidence suggests that GPCRs can signal independently of G proteins and from intracellular compartments. In this context, receptor internalisation has attracted renewed interest within the GPCR field.
Aims: To develop and optimise a real-time time-resolved fluorescence resonance energy transfer (TR-FRET) assay to investigate GPCR internalisation.
Methods: SNAP-tagged GPCRs were stably expressed in an inducible HEK293 cell line (T-REx™-293 Cell Line). Cell-surface receptors were irreversibly labelled with a terbium cryptate derivative (Cisbio Bioassays, Codolet, France) and stimulated with agonist in the presence of a cell-impermeable energy acceptor, and TR-FRET was recorded using an Envision 2104 Multilabel Reader (Perkin–Elmer, USA). The resulting donor:acceptor emission ratio was used to assess internalisation over time.
Results: Agonist stimulation evoked robust receptor internalisation, as shown for GLP-1 on SNAP-GLP1R expressing cells. The response was reproducible and concentration-dependent (EC_{50} 26 nmol/L). Conducted in 384-well format, the assay had a Z' value of 0.7, making it ideally suited for high throughput screening efforts.
Discussion: We have now applied this technique to study internalisation of numerous class A, B and C receptors, including the β_2-adrenoceptor, GLP1R and GPRC6A (Jacobsen SE et al, 2017; Roed SN et al, 2014) and a variety of orphan receptors. This assay is a sensitive, easily-quantified, unbiased and real-time readout of receptor movement, that can be used for investigating the kinetics of ligand–dependent and constitutive internalisation.

Jacobsen SE et al (2017) J Biol Chem 292:6910-6926.
Roed SN et al (2014) Mol Cell Endocrinol 382:938-49.

125 CSKSSDYQC peptide conjugated N-trimethyl chitosan enhance the oral bioavailability of gemcitabine by targeting goblet cells

Guanyu Chen[1], Darren Svirskisa, Weiyue Lub, Man Ying[2], Yuan Huang[3], Jingyuan Wen[1], [1]School of Pharmacy, FMHS, University of Auckland, New Zealand, [2]Department of Pharmaceutics, School of Pharmacy, Fudan University, China, [3]Key Laboratory of Drug Targeting, West China School of Pharmacy, Sichuan University, China

Introduction: Gemcitabine is a nucleoside analogue effective against a number of cancers. However, its highly hydrophilic nature and poor permeability over intestinal epithelium results in low oral bioavailability while the short half-life leads to frequent dosing requirements. This study reports the synthesis, *in-vitro*, *ex-vivo* and *in-vivo* evaluation of trimethyl chitosan (TMC) conjugated with CSKSSDYQC (CSK) peptide to enhance the oral bioavailability of gemcitabine due to the ability to target intestinal goblet cells and promote cellular uptake.
Aims: To enhance gemcitabine oral bioavailability via goblet cell targeting.
Methods: Gemcitabine loaded TMC-CSK nanoparticle (NP) was fabricated via an ionic gelation method. The TMC polymer was synthesized by using a new two-step methylation method. The physical and chemical properties of the delivery systems were determined including particles size, zeta potential, entrapment efficiency and in-*vitro* drug release study. In vitro cellular uptake mechanism was investigated using co-cultured Caco-2 and HT29-MTX-E12 cell models. Finally, the pharmacokinetic parameters were determined using a Sprague-Dawley (SD) rat model and the tumour growth rate associated with the drug solution and the drug loaded NPs were investigated using a BALB/c nude mouse model.
Results: Drug loaded TMC-CSK delivery system provides a particle size of 173.6 ± 6.8 nm, zeta potential of +18.5 ± 0.2 mV and entrapment efficiency of 66.4 ± 0.1%, with the ability to release drug in a sustained manner. The cellular uptake was time- and concentration- dependent associated with clathrin and caveolae mediated endocytosis.
In pharmacokinetic studies, drug loaded TMC-CSK NPs showed an improved oral bioavailability of 60.14% compared to gemcitabine solution of 9.86%. In pharmacodynamics study has shown the drug loaded TMC-CSK NPs reduced the tumour growth rate in a BALB/c nude mouse model, with a 5.1-fold reduction compare to the control group.

126 Nicotine-loaded chitosan nanoparticulate dry powder inhaler formulation for its activity

N. Islam[1], H. Wang[1], J. Holgate[2], S. Bartlett[2] G. George[3], [1]School of Clinical Sciences, Queensland University of Technology (QUT), Brisbane, QLD, [2]The QIMR Berghofer Medical Research Institute, Brisbane, QLD, [3]Science and Engineering Faculty, QUT

Introduction: Currently available dosage forms for the management of nicotine addiction are inefficient due to the substantial required dose or serious withdrawal symptoms. Inhalation is an efficient therapy method which delivers drugs directly into deep lungs for systemic effect in short period of time.
Aim: To develop nicotine nanoparticles as dry powder inhaler (DPI) formulation for behaviour test in mice.
Methods: Nicotine hydrogen tartrate (NHT)-loaded chitosan nanoparticles were prepared using a W/O emulsion method and characterized using SEM, TEM, Mastersizer. Using a twin stage impinger (TSI) the aerosolization properties were determined. In vivo locomotor test (n=8 each group) in the photocell activity chambers was applied to evaluate the efficiency of nicotine nanoparticles compared with NHT by injection, and saline injection was as control.
Results and Discussion: The prepared nicotine loaded chitosan nanoparticles were produced FPF of 30.6%, which is comparable to currently available DPI products. The drug rapidly released from the nanoparticles initially due to the rapid dissolution of surface adhered/entrapped drug, and gradually became slower because of the penetration of the PBS release medium into the nanoparticles and dissolution of the entrapped drug. The maximum cumulative release was found to be around 70% in 7 days. A dose-related response to nicotine was observed from locomotor activity test from injection, with a longest travelled distance seen at the dose of 0.5 mg/kg on NHT and nicotine nanoparticles, in comparison to saline control groups ($P<0.05$), indicating the greatest stimulation was produced at such dose. The higher dose caused hypoactive effects for mice confirmed by travelling a shorter total distance.
Conclusion: The prepared nicotine-loaded chitosan nanoparticles can achieve prolonged release of nicotine from nanoparticulate DPI formulations. The outcomes from mice locomotor activity test confirmed that the novel nicotine nanoparticles were active and comparable to injectable dosage form.

127 Monitoring NanoBRET ligand binding to endogenous adenosine A2B receptors

Elizabeth KM Johnstone[1,2], Kevin DG Pfleger[1,2,3], Carl W White[1,2,4], [1]Mol Endocrinol and Pharmacol, Harry Perkins Inst of Med Res, Nedlands, WA, [1]Centre for Med Res, Univ of Western Australia, Crawley, WA, [3]Dimerix Ltd, Nedlands, WA, [4]Cell Signaling Res Group, Univ of Nottingham Med School, Nottingham, UK

Introduction: Bioluminescence resonance energy transfer (BRET) is a versatile biophysical tool, enabling monitoring of many facets of G protein-coupled receptor (GPCR) function, including ligand binding and signalling, as well as trafficking and internalisation. However, the requirement for exogenous expression of a luciferase-tagged fusion protein has the potential to impact on the physiological relevance of the assays. Recently, we published the first study showing that through the use of CRISPR/Cas9-engineering, BRET could be used to monitor proximity to endogenous proteins, including GPCR-mediated β-arrestin recruitment, receptor internalisation and trafficking, as well as heteromerisation.
Aims: This study aimed to further investigate the potential of using BRET to monitor fluorescent ligand binding to endogenous GPCRs.
Methods: CRISPR/Cas9-mediated homology-directed repair was used to insert Nluc into the *ADORA2B* genomic locus in HEK293 cells, resulting in N-terminally tagged A_{2B} receptors. NanoBRET ligand binding assays (Stoddart et al, 2015) were then used to assess ligand binding.
Results: Functionality of the CRISPR/Cas9 engineered A_{2B} receptors was confirmed in cAMP assays. The engineered cells were then successfully used to assess binding of several different fluorescent or unlabelled ligands in kinetic, saturation and competition NanoBRET ligand binding assays. Comparisons with cells expressing exogenously expressing Nluc/A2B receptors were also made.
Discussion: Using CRISPR/Cas9-mediated genome engineering, we have shown that NanoBRET can be used to observe fluorescent ligand binding at GPCRs under endogenous promotion.

Stoddart et al. (2015) Nat Methods 12: 661-663.
White et al. (2017) Sci Reports 7: 3187.

128 Dual action calcium sensing receptor modulator, calhex231, unmasks novel mode-switching mechanism

K.J. Gregory[1], I Kufareva[2], E Khajehali[1], A.N. Keller[1], H. Mun[3], A. Panwar[1], A.P. Townley[1], R.S. Mason[3], B. Capuano[1], A.D. Conigrave[3], A. Christopoulos[1], K. Leach[1], [1]Drug Discov Biol and Dept Pharmacol, MIPS, Monash Univ, Parkville, VIC, Australia, [2]UCSD, La Jolla, CA, USA, [3]Uni Syd, Sydney, NSW, Australia

Introduction: Negative allosteric modulators (NAMs) of the human calcium sensing receptor (CaSR) have failed to show efficacy in human osteoporosis clinical trials but there is now significant interest in repurposing these drugs for hypocalcaemic disorders and inflammatory lung diseases. However, little is known about how CaSR NAMs inhibit the response to endogenous activators. An improved understanding of CaSR negative allosteric modulation may afford the opportunity to develop therapeutically superior CaSR-targeting drugs.
Aims: We aimed to elucidate the mechanistic and structural basis of allosteric modulation mediated by the previously reported CaSR NAM, calhex231, in comparison with the well-validated NAM, NPS-2143.
Methods: We used high-throughput signalling assays (intracellular Ca^{2+} (iCa^{2+}) mobilisation and IP1 accumulation) in recombinant cells stably expressing human CaSR (and mutants thereof) to rigorously quantify calhex231 pharmacology. To compare wild-type and mutant receptors we used one-way ANOVA with Dunnett's post-test ($P<0.05$). Interpretation of mutagenesis data was aided by docking to a CaSR homology model based on related metabotropic glutamate receptor x-ray structures. In addition, we assessed CaSR modulation of parathyroid hormone (PTH) release from primary human parathyroid cells.
Results: As expected, NPS-2143 behaved as a CaSR NAM, reducing the potency of, and maximal response to, extracellular Ca^{2+} (Ca^{2+}_o) in IP1 accumulation and iCa^{2+} mobilisation assays. Surprisingly, calhex231 potentiated Ca^{2+}_o potency in a concentration dependent manner between 0.1-1uM; however, at concentrations >3uM, calhex231 inhibited CaSR activity. These profiles were recapitulated when measuring PTH release from human parathyroid cells. Through site-directed mutagenesis in combination with computational modelling, we found that key residues within the common allosteric site significantly reduce calhex231 affinity and/or cooperativity.
Discussion: We find that calhex231 actually potentiates or inhibits the activity of multiple CaSR agonists depending on whether it occupies one or both protomers in a CaSR dimer. These findings reveal a novel mechanism of mode-switching at a Class C G protein-coupled receptor that has implications for drug discovery and potential clinical utility.

129 Cardiomyocyte ErbB4 receptors are essential for cardiac hypertrophy and growth of neonatal mice, and contribute to maintenance of cardiac function in adult hearts

Reichelt ME[1], Wang Z[2], Thorn C[3], Paravacini T[4], Thomas WG[1], [1]School of Biomedical Sciences, University of Queensland, St Lucia, QLD, [2]University of California, Davis, Davis CA, USA, [3]Department of Pharmacology, University of Oxford, Oxford, UK, [4]School of Medical Sciences, RMIT, Melbourne, VIC

Introduction: Activation of ErbB4 by neuregulin 1 (NRG1) promotes cardiomyocyte hypertrophy and proliferation in neonatal and adult mice, while application of NRG1 following myocardial infarction reduces scar size and improves function. Less is known about ErbB4 participation in physiological and pathophysiological cardiac hypertrophy.
Aim: Evaluate the role of cardiomyocyte ErbB4 in developmental, exercise-, and angiotensin-induced hypertrophy.
Methods: For adult studies, ErbB4 was deleted in αMHC-MerCreMer (cCre $Tg^{+/-}$)/ErbB4 floxed ($ErbB4^{ff}$) mice at ~2 months of age with 10 injections of Tamoxifen (20 mg/kg/day). Mice were aged for up to 8 months, exposed to Angiotensin II (Ang II, 1000ng/kg/min, 14 days) or exercised (twice daily swimming, 20 min/session increasing 10 min/day to 90 min followed by 7 days at 90 min/session). Neonates ($ErbB4^{ff}$ or $ErbB4^{ww}$) received temporal vein injections of AAV9-cTNT-iCre ($2.16x10^{11}$ viral particles) at p1-2 and were culled at p6-7.

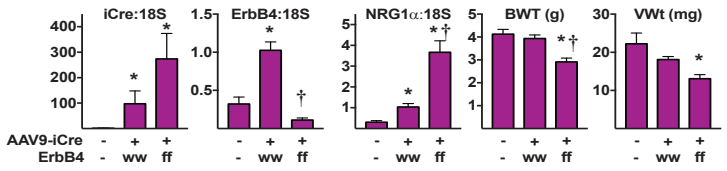


Figure: Cardiomyocyte ErbB4 deletion in neonatal mice. *, $p < 0.05$ vs non-viral control; †, $p<0.05$ vs $ErbB4^{ww}$ + AAV9-eGFP-iCre

Results: Three months after deletion of ErbB4 in adult hearts, contractile function was reduced *in vivo* (echocardiography, 16%) and *ex vivo* (isolated-perfused, 33%), however deletion failed to modify heart size, survival for 8 months or hypertrophy in response to Ang II or exercise. In neonates, the presence of iCre mRNA in hearts confirmed virus infection, and suppression of ErbB4 in $ErbB4^{f/f}$ mice was coincident with increased NRG1α, and reduced body and ventricular weights (Figure).
Discussion: ErbB4 is critical to cardiac hypertrophy and growth in neonatal mice, and maintains adult heart function.

130 Comparing the anti-fibrotic effects of emerging treatments: Serelaxin and the IRAP inhibitor, HFI-419 to a clinically-used ARB and ACE inhibitor in a high salt-induced mouse model of kidney disease.

Matthew Shen, Adithya Shastry, Yan Wang, Tracey A. Gaspari, Robert E. Widdop, Chrishan S. Samuel. Biomedicine Discovery Institute and Department of Pharmacology, Monash University, Clayton, VIC 3800, Australia.

Introduction. Fibrosis is a hallmark of chronic kidney diseases and its inability to resolve causes severe organ dysfunction and end-organ failure. The limited anti-fibrotic efficacy of current therapies suggests a need for alternative treatments.
Aims. To compare the anti-fibrotic effects of serelaxin (human recombinant relaxin; RLX) and HFI-419 to the AT1 receptor blocker, Candesartan cilexetil (CAND) or ACE inhibitor, Perindopril (PERIN) in a murine high salt (HS) diet-induced model of kidney disease.
Methods. 8-10 week male C57Bl/6J mice were subjected to 8-weeks of HS (5% NaCl) diet-induced renal injury. From weeks 5-8, sub-groups (n=4-8) were treated with either vehicle, RLX (0.5mg/kg/day), HFI-419 (0.72mg/kg/d), CAND (2mg/kg/day) or PERIN (4mg/kg/d). Each drug dose used had previously demonstrated anti-fibrotic efficacy in other experimental models. Mice maintained on a normal salt (NS) diet (0.5% NaCl) for 8-weeks were used as controls. Various measures of renal inflammation and fibrosis as well as plasma urea levels were evaluated.
Results. HS diet-fed mice were associated with significantly increased renal inflammation, TGF-β1 expression levels, myofibroblast differentiation, glomerulosclerosis, interstitial fibrosis, TIMP-1 levels and vascular rarefaction (determined by morphometry of Masson's trichrome- or immunohistochemically-stained sections and/or Western blotting), total kidney collagen concentration (hydroxyproline analysis) and plasma urea compared to that measured from NS diet-fed counterparts (all $P<0.01$ vs NS group). RLX or HFI-419 significantly reduced most measures of HS-induced renal fibrosis and plasma urea levels back to that measured in mice fed the NS diet (all $p<0.05$ vs HS group). RLX or HFI-419 demonstrated similar, if not greater, anti-fibrotic effects compared to that offered by PERIN, but which also reduced blood pressure, body weight and worsened plasma urea levels at the dose used ($p<0.01$ vs HS group). CAND, however, did not demonstrate any marked anti-fibrotic effects in the model/organ studied.
Discussion. RLX or HFI-419 offers improved anti-fibrotic efficacy and renoprotection compared to CAND and safer anti-fibrotic efficacy compared to PERIN in the setting of HS-induced kidney damage.

131 Role of TRPC3 in endothelium-dependent vasodilation of rat mesenteric arteries

Sarah E Wright and Timothy V Murphy. Dept of Physiol, Sch of Med Sci, UNSW Sydney, Sydney NSW, Australia.

Introduction. Endothelium-dependent dilation (EDD) of arteries is an important auto-regulatory function of the microvasculature. Previous studies suggested a role for transient receptor potential canonical-3 channels (TRPC3) in EDD (Senadheera et al., 2012) using pyrazole-3, a TRPC3 blocker with poor selectivity (Schleifer et al., 2012).
Aims. The present study further examined the role of TRPC3 in both agonist and flow-stimulated EDD of arteries utilizing a new, more selective TRPC3 blocker, pyrazole-10 (PYR10; Schleifer et al., 2012).
Methods. Cumulative stimulus-response curves to ACh (1 nM/L - 10 µM/L) or intra-luminal flow (0-20µL/min) were performed in isolated, pressurized (60 mmHg), phenylephrine-constricted rat mesenteric arteries. Data is presented as % maximum dilation from baseline.
Results. In control arteries, increasing flow caused dilation, with peak dilation observed at 14uL/min (17.2 ± 3.2%, n=6). The flow-mediated dilation (FMD) was not altered by inhibition of nitric oxide (NO) synthase and guanylate cyclase using a combination of L-NAME (100 µM) and ODQ (10 µM). In the presence of PYR10 (1 µM), some FMD persisted at low flow rates (<10 µl/min), but at flow ≥12µL/min significant flow-induced constriction of vessels was observed (max constriction -21.8 ± 10.5% $P\leq0.05$, n=4). ACh caused a concentration-dependent dilation of mesenteric arteries (pEC_{50} = 7.63 ± 0.09, max 95.1 ± 2.6%, n = 4). The ACh-induced dilation was inhibited by PYR10 (max 51.0 ± 1.5%, $P<0.05$, n = 4). The combination of L-NAME, ODQ and PYR10 further reduced ACh-induced dilation (max 10.0 ± 1.1%, $P<0.05$, n = 4). PYR10 did not alter phenylephrine-induced vasoconstriction of the arteries.
Discussion. These studies support a role for TRPC3 in mediating both agonist- and flow-induced EDD of rat mesenteric arteries. TRPC3 appears to be coupled to non-NO-dependent signaling pathways, presumably involving endothelium-derived hyperpolarization of vascular smooth muscle.

Schleifer H, *et al.* (2012). Br J Pharmacol 167**:** 1712-1722.
Senadheera S, , *et al.* (2012). Cardiovasc Res 95**:** 439-447.

132 Targeting IRAP: A Novel Treatment to Stabilize Existing Abdominal Aortic Aneurysms

Kaki Fan[1], Robert Widdop[1], Ekaterina Salimova[2], Siew Yeen Chai[3] & Tracey Gaspari[1]. Dept of Pharmacol, Monash University[1], Clayton, VIC, Australia; ARMI, Monash University[2], Clayton, VIC, Australia; Dept of Physiol, Monash University[3], Clayton, VIC, Australia.

Introduction. Abdominal aortic aneurysm (AAA) is a degenerative disease with no pharmacological treatment available to prevent progression or risk of rupture. Preliminary evidence from our laboratory indicated inhibition/deficiency of the enzyme, insulin regulated aminopeptidase (IRAP) prevented AAA formation in angiotensin (Ang) II-infused mice, indicating IRAP may be a novel target in treatment of AAA.
Aim. To determine if the IRAP inhibitor, HFI-419 can stabilize established AAA in Ang II-infused apolipoprotein E deficient (ApoE KO) mice.
Methods. 12 week old male ApoE KO mice were infused with Ang II (1000ng/kg/min) for 6 weeks to induce AAA. Once presence of established AAA was confirmed mice were randomized to receive either vehicle or HFI-419 (500ng/kg/min; s.c.) from weeks 2-6. Ultrasound imaging (to measure aortic diameter and area) and systolic blood pressure (SBP; tail cuff method) measurements were performed fortnightly to track AAA development and SBP changes
Results. Two-week infusion of Ang II induced aneurysm formation in >90% of all mice. Co-infusion of HFI-419 with Ang II significantly reduced aneurysm area and diameter in the absence of any effect on SBP. Immunohistochemistry analyses confirmed increased expression of IRAP in proximal aorta and AAA sections taken from Ang II infused mice whilst IRAP inhibition tended to reduce IRAP expression. HFI-419 treatment attenuated elastin degradation which was correlated with reduced matrix metalloproteinase (MMP)-9 and macrophage expression in AAA sections.
Discussion. Inhibition of IRAP significantly reduced progression of established AAA, although underlying protective mechanisms are still under investigation. This study highlights the potential of inhibiting IRAP as a novel therapy for treatment of AAA

133 Inhibition of the transient receptor potential melastatin 7 (TRPM7) channel-kinase improves cardiac function in an ex vivo model of ischaemia/reperfusion injury

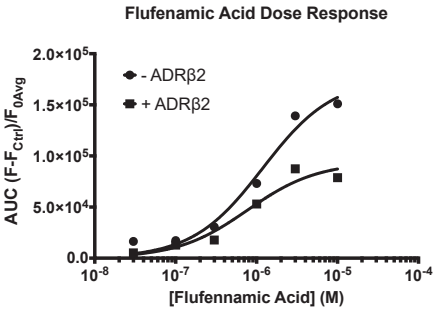
Tamara M Paravicini, Owen L Woodman, School of Health and Biomedical Sciences, RMIT University, Melbourne VIC, Australia

Introduction: TRPM7 is a Mg^{2+} and Ca^{2+}-permeable channel that is critical for cellular growth and development. Importantly, the TRPM7 channel also contains an active kinase domain, making it unique amongst ion channels in the ability to both transport ions and directly activate intracellular signalling cascades. TPRM7-mediated Ca^{2+} influx is increased in neuronal and renal ischaemia/reperfusion (I/R) injury, and inhibition of TRPM7 prevents cell death in these models of I/R injury. However, whether TRPM7 also contributes to myocardial I/R injury remains unknown.
Aims: To determine if TRPM7 inhibition can reduce myocardial I/R injury in an *ex vivo* model.
Methods: Hearts were isolated from adult male rats, perfused in the Langendorf mode at constant flow (10 mL/min), and subjected to 25 minutes of global no-flow ischaemia followed by 30 minutes of reperfusion. Hearts were treated with either vehicle (0.03% dimethyl sulfoxide) or the TRPM7 inhibitor NS8593 (3 µM) for 10 minutes prior to ischaemia and throughout reperfusion, or during reperfusion alone.
Results: In vehicle-treated hearts, the left ventricular developed pressure (LVDP) at the end of reperfusion was reduced by ~ 70% compared to the pre-ischaemic baseline. This was significantly improved by treatment with NS8593 (% pre-ischaemic baseline: NS8593 58.4±8.6% vs vehicle 28.3±3.3%, n=8-10, $P<0.05$). Similarly, TRPM7 inhibition improved both +dP/dt (% pre-ischaemic baseline: NS8593 48.1±7.7 vs vehicle 23.5±4.0, n=8-10, $P<0.05$) and –dP/dt (% pre-ischaemic baseline: NS8593 54.9±7.0 vs vehicle 30.6±5.1, n=8-10, $P<0.05$). NS8593 had no significant effect on heart rate during reperfusion. The beneficial effects of NS8593 on cardiac function were only evident if administered prior to ischaemia, as administration of NS8593 during reperfusion only did not significantly improve LVDP or +dP/dt compared to vehicle-treated hearts
Discussion: Pharmacological inhibition of TRPM7 with NS8593 improves ventricular function after ischaemia and reperfusion in isolated hearts if administered prior to ischaemia. This suggests that TRPM7 contributes to myocardial damage during I/R injury, and that the cardioprotection induced by NS8593 may involve activation of signalling pathways involved in cardiac preconditioning.

134 Functional regulation of bitter taste receptors (T2Rs) by ß2-adrenergic and M2 muscarinic acetylcholine receptor

Jilai Zhao[1], Conor J Bloxham[1], Simon R Foster[2], Brooke Purdue[1] & Walter G Thomas[1], [1]School of Biomed Sci, Univ of Queensland, Brisbane, QLD, Australia, [2]Dept of Drug Design and Pharmacol, Univ of Copenhagen, Copenhagen, Demark

Introduction: G protein-coupled receptors (GPCRs) are key mediators of cardiac physiology and targeted for therapeutics. The ectopic expression of bitter taste receptors (T2Rs) in heart was first reported by the Thomas Laboratory. Stimulation of T2R14 in human right atrial tissue with bitter ligands produces a dramatic cardiodepressant effect, but it is not known whether the actions of T2R14 are modulated by other GPCRs related to cardiac contractility, principally the adrenergic and muscarinic receptors.



Aims: To determine the effect of co-expressing and activating the β2-adrenergic receptor and the M2 muscarinic receptor on the activation of the T2R14 bitter receptor.

Methods: AD293 cells were transfected with T2R14, chimeric G protein $G\alpha_{16/gust44}$, and the Ca^{2+} sensor GCaMP5. Ligand stimulated intracellular Ca^{2+} was measured by fluorescence imaging via an automated fluorometric plate reader. Fluorescently tagged T2Rs were used in confocal imaging studies, focusing on the expression and localisation of T2Rs.

Results: The co-expression of the β2-adrenergic receptor significantly reduced T2R signalling in response to flufenamic acid (see figure). Conversely, an increase in T2R function was observed when co-expressed with the cardiac parasympathetic regulator, M2 muscarinic acetylcholine receptor. These changes did not involve alterations in the expression and cellular localisation of T2R14. Pre-treatment with adrenergic/muscarinic ligands did not affect subsequent activation of the T2R14.

Discussion: Co-expression of T2Rs with the adrenergic and muscarinic receptors alters their responsiveness and efficacy to bitter ligands, leading to consequent effects on cardiomyocyte contractility. Ongoing investigations are probing the mechanism involved.

135 Defining the progression of diabetic cardiomyopathy in a mouse model of type 1 diabetes

Miles J De Blasio[1,3], Nguyen Huynh[1], Leslie Dubrana[1], Darnel Prakoso[1,3], Chengxue Qin[1,4], Mitchel Tate[1], Minh Deo[1], Osezua Oseghale[1], Helen Kiriazis[2], Xiao-Jun Du[2,5], Rebecca H Ritchie[1,4,5], [1]Heart Failure Pharmacology; [2]Experimental Cardiology; Baker Heart and Diabetes Institute, Melbourne, VIC, [3] School of BioSciences; Department of Pharmacology and Therapeutics[4]; University of Melbourne, Parkville VIC, [5]Department of Medicine; Monash University, Clayton, VIC

Introduction: The incidence of diabetes is rapidly expanding and its association with increased risk of cardiovascular disease represents a major health issue worldwide. Hyperglycaemia is implicated as a central driver of responses seen in the diabetic heart such as hypertrophy, fibrosis and oxidative stress, together termed diabetic cardiomyopathy. The timing of onset of each response in the setting of diabetes has not been studied to date.

Aims: To determine the time-course of development of characteristics of diabetic cardiomyopathy in a mouse model of type 1 diabetes *in vivo*.

Methods: Diabetes was induced in 6-wk-old male FVB/N mice via streptozotocin (55mg/kg i.p. for 5 d; controls received citrate vehicle). After 2, 4, 8, 12 or 16-wks of untreated diabetes, left ventricular (LV) function via Doppler echocardiography was determined, prior to cull and subsequent measurement of markers of cardiomyocyte hypertrophy, LV collagen deposition, DNA fragmentation and markers of the hexosamine biosynthesis pathway (HBP).

Results: Blood glucose and HbA1c were elevated from 2-wks of diabetes. Relative to tibia length, LV and muscle weights were reduced from 8-wks, whereas liver and kidney weights were increased from 2 and 4-wks, respectively. LV diastolic function worsened with diabetes progression demonstrated by decreased E/A ratio from 4-wks of diabetes, and increased deceleration time, isovolumic relaxation time and A wave amplitude from 8-wks of diabetes. Cardiac hypertrophy (cardiomyocyte size) was evident from 8-wks, however gene expression of the hypertrophic marker β-myosin heavy chain and systemic inflammation (plasma TNFα) were increased earlier (from 2-wks of diabetes). Cardiac fibrosis (% collagen deposition, CTGF gene expression) and DNA fragmentation were increased from 4-wks of diabetes. Markers of the HBP machinery (gene and protein levels) were increased at 16-wks of diabetes.

Discussion: This is the first study to investigate the progression of markers contributing to development of diabetic cardiomyopathy. Hyperglycaemia and systemic complications precede cardiac remodelling and dysfunction.

136 Systemic and cardiac-selective targeting of histone deacetylase 4 (HDAC4) to limit diabetic cardiomyopathy

Andrew M. Willis[1,2], Mitchel Tate[1], Miles J. De Blasio[1], Darnel Prakoso[1], Minh Deo[1], Helen Kiriazis[1], Xiao-Jun Du[1], Paul Gregorevic[1], Hong-Wei Qian[1], Marianne Tare[3], Rebecca H. Ritchie[1,3], Baker Heart and Diabetes Institute[1], Melbourne, VIC, [2]Dept. of Physiology and Dept. of Medicine[3], Monash University, Clayton, VIC

Introduction: Diabetic cardiomyopathy is characterised by left ventricular (LV) diastolic dysfunction and structural changes, including cardiomyocyte hypertrophy and interstitial fibrosis. Epigenetic modifications, such as histone deacetylation, have been implicated in the molecular pathways that drive structural changes in this setting. HDAC4 is associated with the pathological cardiac remodelling similar to that observed in diabetic cardiomyopathy.
Aims: To determine whether inhibiting HDAC4, via a cardiac-selective approach using adeno-associated virus (AAV), or globally (by tasquinimod), ameliorates diabetic cardiomyopathy in a murine model of type-1 diabetes (T1D).
Methods: T1D was induced in 6 week old male FVB/N mice with streptozotocin (5 days, 55mg/kg/d or vehicle, i.p.). Echocardiography was performed at 6 (baseline), 14 (pre-treatment), and 22 (endpoint) weeks of age in anaesthetised mice (ketamine/xylazine/atropine, 60/6/0.6 mg/kg). The first approach utilised cardiac-selective rAAV6-dnHDAC4 ($2x10^{11}$ genomes or null vector). The second approach utilised tasquinimod (10mg/kg/d or vehicle administered via daily i.p.). Both approaches commenced after 8 weeks of diabetes with a follow-up period of 8 weeks.
Results: Blood glucose and HbA1c levels were increased with diabetes ($P<0.0001$). Diabetes reduced heart mass, however rAAV6-dnHDAC4 significantly increased LV mass compared to untreated diabetes ($P<0.05$). Diabetes-induced prolongation of isovolumetric relaxation time and increased LV connective tissue growth factor (CTGF) gene expression; both were attenuated by rAAV6-dnHDAC4 ($P=0.08$ and $P<0.05$, respectively) in T1D mice. Treatment with rAAV6-dnHDAC4 also blunted the diabetes-induced expression of hypertrophic genes including B-type natriuretic peptide (BNP) and β-myosin heavy chain (β-MHC, both $P<0.05$). Treatment with tasquinimod ameliorated diabetes-induced LV diastolic dysfunction with improved E/A and e'/a' in comparison to untreated diabetes (both $P<0.01$) and a reduction in deceleration time ($P<0.01$). Diabetes increased LV BNP gene expression ($P<0.05$) and superoxide levels ($P<0.001$) both of which were reduced by treatment with tasquinimod (both $P<0.05$).
Conclusions: Inhibition of HDAC4 attenuates characteristics of diabetic cardiomyopathy including cardiomyocyte hypertrophy, fibrosis, superoxide generation and LV diastolic dysfunction, in a model of T1D.

137 Developing a new unit in a new curriculum

Betty Exintaris, Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Melbourne, VIC, Australia

Introduction: As of 2017, the Faculty of Pharmacy and Pharmaceutical Sciences at Monash University introduced a new Bachelor of Pharmacy (Honours)/Master of Pharmacy degree. The new degree seeks to equip graduates with the necessary skills and knowledge to lead practice in the ever-changing world of healthcare and medicine.
Aims: To develop a new, foundational, double credit point unit (How the Body Works).
Methods: The way in which the unit was to be delivered differed significantly from previous iterations of the unit. Firstly, the unit was a double credit point unit. Secondly the unit was delivered using a very structured approach: the 'DEAR' model. Briefly, on a weekly basis, for every 4 hours of pre-learning **D**iscovery (the information was presented in Moodle books, including revision questions), there were 4 hours of integrated lectures (students **E**xplored the discovery material using questions / scenarios posed by staff) and 4 hours of workshops (where students **A**pplied the information from discovery and the integrated lectures. Finally students were asked to continuously **R**eflect on their learning. An important aspect of the new unit was the focus on skill development. In How the Body works we focussed on communication and teamwork.
Results: As a team, we developed and delivered a dynamic unit incorporating the new teaching approach. Staff reported that students were better communicators and team players by the end of the unit. Exam and unit results were noticeably higher (~20%) than the previous year.
Given the new teaching approach, it could be anticipated that students would initially struggle with the concept of having to be prepared before class so that the integrated lectures and workshops were meaningful. This was also true of students who had transferred from the old course or another course and were therefore used to the 'old' style of teaching. It was not surprising that the overall unit evaluation result was lower than other years (~3.5/5 vs ~4.5/5). Students provided meaningful feedback by identifying areas which could be improved.
Discussion: Utilising a different teaching approach, we developed a new unit as part of the new Pharmacy curriculum which focuses on skill development. Qualitative data suggests that the students were noticeably better communicators and team players by the end of the unit. Exam results also demonstrated that the students performed comparably better than last year. Feedback obtained from staff and students will be used to further develop the unit.

138 What are the predictors of persistent prescription opioid analgesic use for non-cancer pain in Australia?

Samanta Lalic[1, 2], Natasa Gisev[3], J Simon Bell[1], Maarit J Korhonen[1], Jenni Ilomäki[1]. Centre for Medicine Use and Safety, Monash University[1], VIC, Australia; Pharmacy Department, Austin Health[2], VIC, Australia; National Drug and Alcohol Research Centre, UNSW Australia[3], NSW, Australia

Introduction. Long-term opioid analgesic use for chronic non-cancer pain is associated with uncertain clinical benefits but clear harms.
Aims. To identify patterns of opioid analgesic use and determined predictors of persistent opioid use among people without cancer.
Methods. A population-based cohort study of Australians initiating prescription opioids from July 2013 to December 2015 was conducted using data from a random 10% sample of people who accessed medicines through Australia's Pharmaceutical Benefits Scheme. A 12-month look-back period was used to define opioid initiation, exclude people with cancer, and determine comorbidities. Persistent use over 12-months since initiation was identified through group-based trajectory modelling. Odds ratios (OR) and 95% confidence intervals (CIs) for predictors of opioid persistence were estimated using logistic regression.
Results. The cohort consisted of 126,903 people who had opioids dispensed in ≥2 months during the 12-month follow up. A total of 11,323 (8.9%) persistent opioid users were identified. Predictors of persistence included initiation with transdermal opioids (OR 3.2, 95% CI 3.0-3.4), or with oral morphine equivalents (OME) ≥ 750 mg (OR 2.8, 95% CI 2.6-3.1), having depression (OR 1.3, 95% CI 1.3-1.4), or psychotic illness (OR 1.9, 95% CI 1.7-2.0). Previous dispensing of paracetamol (OR 1.7, 95% CI 1.6-1.8), pregabalin (OR 1.6, 95% CI 1.5-1.8) and benzodiazepines (OR 1.3, 95% CI 1.2-1.4) predicted persistence. Compared to people aged 18-44 years, those ≥75 years were 2.4 (95% CI 2.2-2.6) times more likely to be persistent users.
Discussion. Mental health comorbidities, older age, initiation with transdermal opioids and higher OMEs strongly predicted persistent opioid use among people without cancer. This information may help prescribers target monitoring and early intervention efforts in order to prevent opioid-related harms.

139 Development of comorbidities in men with prostate cancer treated with androgen deprivation therapy: An Australian population-based cohort study

Huah Shin Ng[1], Bogda Koczwara[2], David Roder[3] & Agnes Vitry[1], [1]School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA, Australia, [2]Flinders Centre for Innovation in Cancer, Flinders University, Adelaide, SA, Australia, [3]Cancer Epidemiology and Population Health, Centre of Population Health Research, School of Health Sciences, University of South Australia[3], Adelaide, SA, Australia

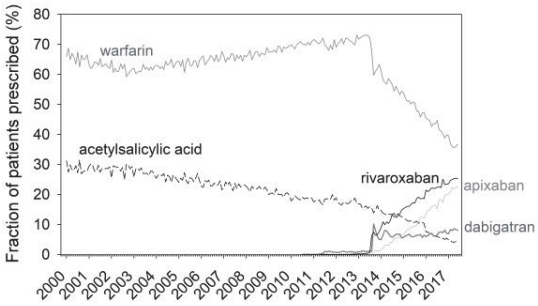
Introduction: Many studies examined the prevalence of comorbidities at the time of cancer diagnosis but there is little information on the pattern of comorbidities following cancer diagnosis.
Aims: This study aims to assess the development of comorbidities among Australian men with prostate cancer treated with androgen deprivation therapy.
Methods: Pharmaceutical Benefits Scheme 10% data between January 2003 and December 2014 was utilised for this retrospective cohort study. Men who had received their first androgen deprivation therapy between years 2004 and 2010 were selected as the prostate cancer cohort. Dispensing claims data were used to identify comorbidities and classified with the Rx-Risk-V model. Comparisons were made between the prostate cancer cohort and specific control groups (age- and sex-matched at 1:10 ratio without any dispensing of anti-neoplastic agents during the study period and without the individual comorbidity of interest evaluated at baseline) for the development of nine individual comorbidities over time using Cox regression models.
Results: The prostate cancer cohort had a significant higher risk of developing cardiovascular conditions (Hazard Ratio 1.37, 95% CI 1.26-1.48), depression (1.86, 1.73-2.01), diabetes (1.30, 1.15-1.47), gastric acid disorders (1.48, 1.39-1.57), hyperlipidaemia (1.18, 1.09-1.29), osteoporosis (1.65, 1.48-1.85) and pain/pain-inflammation (1.47, 1.39-1.55) compared to non-cancer control groups. The Hazard Ratios for cardiovascular conditions and depression were highest in the first year and declined over time. There were no significant differences between the two groups for reactive airway diseases and dementia.
Discussion: Men with prostate cancer treated with androgen deprivation therapy had a higher incidence of developing new comorbidities than men without cancer. Our results support the need for developing coordinated models to effectively address multiple chronic diseases experienced by prostate cancer survivors.

140 Antithrombotic prescribing for patients with a history of atrial fibrillation: An analysis using MedicineInsight data

Daniel Taylor[1], Ludmila Ovchinikova[1], NPS MedicineWise[1], Sydney, NSW, Australia

Introduction: Patients who receive an anticoagulant therapy for atrial fibrillation (AF) have typically been treated with warfarin. This has recently changed in Australia with the listing of three novel oral anticoagulants (NOACs) on the Pharmaceutical Benefits Scheme (PBS).

Aims: The aim of this study was to examine historical trends in antithrombotic prescribing and to examine the impact that the PBS-listing of NOACs has had on warfarin prescribing for patients with AF. The study also examines whether general practitioners (GPs) who participated in an academic detailing and discussion programme about anticoagulant use had different patterns of warfarin and NOAC prescribing behaviour following the PBS-listing.



Methods: Clinical data from MedicineInsight – a national database of longitudinal patient-level clinical information from general practices – was used to construct a monthly time series of the number of prescriptions and the number of AF patients prescribed each antithrombotic drug between 2000 and 2017. Autoregressive-moving-average models were used to estimate the trends and trend-changes that underlay each time series.

Results: In the AF-patient population, the total number of warfarin scripts and the total number of patients prescribed warfarin declined sharply following the PBS-listing of NOACs. Since the listing, the fraction of patients prescribed warfarin as part of an anticoagulant therapy declined from 72% to 36% and the fraction of patients prescribed a NOAC rose from 2% to 56%. General practitioners who participated in an academic detailing program prescribed warfarin and NOACs at a rate similar to those who did not, but they switched a larger fraction of patients onto NOACs in the first three months of the PBS-listing.

Discussion: The results of this study show that MedicineInsight data is a useful tool for evaluating the impact of drug policy changes and academic interventions on drug utilisation.

141 Questions from Australian public and health professionals on medication use in breastfeeding: Comparative call analysis of two national medicines call centres

Treasure M McGuire[1,2], Amelia Stephens[3], Wendy Brodribb[3], Laura Deckx[3], [1]Mater Pharmacy, Mater Health[1], Brisbane, QLD, Australia, [2]School of Pharmacy, UQ, Brisbane, QLD, Australia, [3]Discipline of General Practice, School of Medicine, UQ, Brisbane, QLD, Australia

Introduction: There is considerable uncertainty regarding medication use in breastfeeding. Resources provide differing data, making evidence-based information difficult for primary carers to deliver and consumers to access.

Aims: This study aimed to compare lactation-related questions from consumers and health professionals, to target education for safer medication use.

Methods: We conducted a retrospective, mixed method study of lactation-related calls extracted from two Australian medicines call centre databases National Prescribing Service (NPS) Medicines Line (ML) for the general public (2002-30 June 2010) and Therapeutic Advice and Information Service for health professionals (2000- 30 June 2010). Top ranked medicines and classes of interest were identified and classified by their Anatomical Therapeutic Chemical Classification. Call narratives were explored to compare key themes.

Results: ML and TAIS received 5,662 and 2,219 lactation calls, respectively. Women, calling for themselves or family constituted 95% of consumer calls; while health professionals were mainly general practitioners (46%), community pharmacists (35%) and nurses (12%). Top ranked class of interest was nervous system for both consumers (21.8%) and health professionals (27%); however second ranked was respiratory system (17.2%) for consumers versus systemic anti-infectives (20%) for professionals. The most common classes of concern to women were medicines mainly accessible over-the-counter, with the top ranked individual medicines paracetamol (6.9%), ibuprofen (4.8%) and codeine (4.2%).In contrast, professional questions focused on prescription medicines such as antidepressants (16.9%), with queries on sertraline (3.7%), levonorgestrel (2.7%) and domperidone (2.4%) of most common. Themes of queries were, however, similar for both cohorts, focusing mainly around medication safety, risk minimisation and milk supply.

Discussion: Compelling and common themes drive medicines help-seeking in breastfeeding, with a general over-estimation of risk. Understanding where consumers' and health professionals' concerns differ is key to developing targeted resources; so primary carers can address mothers' concerns and information gaps.

142 Prevalence of potentially inappropriate medication use in older inpatients with and without cognitive impairment: a systematic review

Mitchell R Redston[1], Sarah N Hilmer[2,3], Andrew J McLachlan[1,4], Alexander J Clough[1], Danijela Gnjidic[1,5]. Faculty of Pharmacy[1], University of Sydney, Sydney, NSW, Australia; Sydney Medical School[2], University of Sydney, Sydney, NSW, Australia; Departments of Aged Care and Clinical Pharmacology, Kolling Institute of Medical Research, Royal North Shore Hospital[3], Sydney, NSW, Australia; Centre for Education and Research on Ageing, Concord Repatriation General Hospital[4], Sydney, NSW, Australia; Charles Perkins Centre[5], University of Sydney, Sydney, NSW, Australia

Introduction. Older people with cognitive impairment are high users of acute care services in Australia and internationally. Potentially inappropriate medication (PIM) use may be associated with adverse outcomes, including hospital re-admission, functional disability and mortality.
Aims. This systematic review aims to quantify and compare the prevalence of PIMs in older inpatients with and without cognitive impairment.
Methods. A systematic search for observational studies was performed in Embase, Medline/PubMed, PsycINFO, International Pharmaceutical Abstracts, Scopus and Informit. Articles published in English during the period January 2007–June 2017 that reported the prevalence of PIMs in hospital inpatients ≥65 years were included. PIMs were defined as exposure to polypharmacy (multiple medication use) or using implicit or explicit tools, such as the Beers criteria and *Screening Tool of Older Person's Prescriptions* (STOPP). Two reviewers independently assessed the articles for eligibility and extracted the data.
Results. 47 articles were included. The prevalence of PIMs defined by polypharmacy exposure (n=15) ranged from 53.2% to 89.8% when cognitive impairment was reported, and 24.0% to 97.1% when unreported. In studies employing explicit and implicit tools (n=35), the prevalence of PIMs in where cognitive impairment was reported ranged from 20.6% to 80.5% using the Beers criteria, and 39.3% to 88.5% using STOPP. When cognitive status was unreported, the prevalence of PIMs ranged from 7.0% to 79.2% using the Beers criteria, and 20.0% to 63.4% using STOPP.
Discussion. Current published evidence suggests a substantial variation in the prevalence of PIMs in older inpatients with and without cognitive impairment. Future studies should investigate the impact of PIM use on patient-centred outcomes to inform enhanced acute care services and pharmacist interventions to reduce inappropriate prescribing.

143 Health professionals' and researchers' opinions on conducting clinical deprescribing trials

Alexander J Clough[1,2], Sarah N Hilmer[2], Lisa Kouladjian-O'Donnell[2], Sharon L Naismith[3], Danijela Gnjidic[1,2,3], [1]Fac of Pharmacy, Univ of Sydney, Camperdown, NSW, Australia, [2]Kolling Inst, Royal North Shore Hospital and Univ of Sydney, St Leonards, NSW, Australia, [3]Brain & Mind Research Inst, Univ of Sydney, Camperdown, NSW, Australia

Introduction: Clinical deprescribing trials can be conducted to produce favourable health outcomes in people taking potentially harmful medications. At present, there are no guidelines on conducting deprescribing studies.
Aims: To determine the perspectives, attitudes, interests, barriers, and enablers in relation to conducting clinical deprescribing trials among health professionals and researchers.
Methods: An anonymous survey was developed, reviewed and piloted by all investigators for content validity. Experts were contacted to inform the questionnaire content, which explored the purposes, enablers, and barriers of conducting deprescribing trials. The survey was distributed to members of national and international: deprescribing, pharmacological, and pharmacy organisations; and to researchers published in deprescribing.
Results: The survey was completed by 96 participants from June-August 2017. Participants indicated the main rationale for conducting deprescribing trials is to assess the efficacy of interventions to optimise clinical centred outcomes (79.2%). Common barriers to conducting deprescribing trials were forming relationships and maintaining communication with other health professionals involved in the deprescribing process. This barrier commonly affected the: effective completion of trials (32.0%); recruitment of potential patients (31.0%); and overall conduction of trials (17.1%). The most common reported enabler was the belief of health professionals treating trial patients that deprescribing was beneficial (24.4%). Classical randomised controlled trials were considered the most appropriate method for conducting deprescribing trials (93.2%) vs. crossover trials (45.2%). 60.0% of participants indicated a legal, regulatory, and good practice framework required developing, but only 38.9% stated that the CONSORT list needed to be updated to encompass deprescribing trials.
Discussion: Preliminary findings indicate recognition of the need for high quality randomised controlled deprescribing trials and the importance of engagement of treating clinicians in trials of these complex multidisciplinary interventions. Furthermore, the findings of this survey could inform a future clinical deprescribing trial framework, which participants indicated was required.

144 Population pharmacokinetics of carboplatin, etoposide and melphalan (CEM) in children with high-risk neuroblastoma

Janna K Duong[1], Gareth J Veal[2], Christa E Nath[1,3], Peter J Shaw[3,4], Julie Errington[2], Alan V Boddy[2], [1]Faculty of Pharmacy, The University of Sydney,Sydney, NSW, Australia, [2]Northern Institute for Cancer Research, Newcastle University, Newcastle upon Tyne, United Kingdom, [3]The Children's Hospital at Westmead, Westmead, Australia, [4]Discipline of Child and Adolescent health, Faculty of Medicine, The University of Sydney, Sydney, NSW, Australia

Introduction: Carboplatin, etoposide and melphalan (CEM) are cleared by the kidneys and renal function is expected to influence the pharmacokinetics of CEM. In children, however, estimating the renal function (glomerular filtration rate, GFR) may be problematic.
Aims: The aims of this study were to investigate factors that influence the pharmacokinetics of component CEM drugs in children and to determine whether pre-defined exposures for carboplatin were achieved using current dosing regimens.
Methods: Data were obtained from the European SIOP Neuroblastoma study (SIOPEN). The data were used to build a population pharmacokinetic model for CEM component drugs. Various covariates (weight, age, sex, BSA, BMI, GFR and study site) were investigated. The final model was used to simulate whether target carboplatin exposures (16.4 mg/mL·min) were achieved using the paediatric Newell formula, Calvert formula or weight-based dosing.
Results: A total of 51 patients with 1031 observations were used to build a population model. The median age of the patients was 3.5 years (1.7 – 8.3 years, range) and median GFR was 38 mL/min (23 – 75 mL/min). A two-compartment model provided the best fit for each of the three drugs. An allometric weight model was used for all pharmacokinetic parameters. None of the other covariates, including GFR, were significant after accounting for weight. For carboplatin, the Newell formula was successful in achieving the target area under the curve (AUC) for children with GFR of 30 mL/min (43%), 30 – 60 mL/min (43%) and >60 mL/min (32%), but a weight-based dose of 50 mg/kg was found to target the AUC more consistently than the Newell formula across a range of GFR values (46%, 45% and 47% respectively). Use of the Calvert formula would result in significant overdosing.
Discussion: Weight-based dosing is an adequate alternative to dosing carboplatin to achieve target AUC.

145 The novel fatty acid epoxide analogue CTU targets the mitochondrion and depletes cardiolipin to promote killing of MDA-MB-231 breast cancer cells

Hassan Choucair[1], Bala Umashankar[1], Kirsi Bourget[1], Yongjuan Chen[1], Tristan Rawling[2], Michael Murray[1], [1]Discipline of Pharmacology, University of Sydney, Sydney, NSW, Australia, [2]School of Mathematical and Physical Sciences, University of Technology Sydney, Sydney, NSW, Australia

Introduction: The atypical phospholipid cardiolipin plays an important regulatory role in apoptosis by modulating the release of cytochrome c from the mitochondrial membrane. We have prepared a metabolically stable fatty acid epoxide bioisostere (termed CTU) that targets the mitochondrion and activates endoplasmic reticulum stress in MDA-MB-231 breast cancer cells leading to decreased cell viability (Choucair et al, ASCEPT 2016).
Aims: This study was undertaken to evaluate the role of the mitochondrion in CTU-mediated cancer cell killing.
Methods: In MDA-MB-231 cells, cardiolipin/phosphatidylglycerol was estimated using a commercial kit. Cell viability was assessed by ATP formation, measurement of caspase-3/7 activity and annexin V/7AAD staining. Gene profiling was undertaken by real-time RT-PCR, and altered protein expression was assessed by Western immunoblotting.
Results: Addition of CTU to MDA-MB-231 cells significantly decreased the cellular content of cardiolipin and its precursor phosphatidylglycerol at 24 h. Mitochondrial cytochrome c release was increased in cells treated with CTU at 24 h but not at 6 h. However, the expression of pro-apoptotic mitochondrial membrane permeabilizing proteins of the Bcl-2 family, Bax and Bak, was decreased at 6 and 24 h. Neither the Ca^{2+} chelator BAPTA-AM nor the mitochondrial permeability transition pore inhibitor cyclosporin A altered the CTU-mediated decrease in ATP formation. Co-supplementation with the monounsaturated fatty acid oleic acid, which is essential for cardiolipin maintenance, prevented the CTU-mediated depletion of cardiolipin/phosphatidylglycerol, upregulation of endoplasmic reticulum stress genes, mitochondrial cytochrome c release, caspase-3/7 activation and annexin V/7AAD staining.
Discussion: The novel fatty acid bioisostere CTU has emerged as the first in a new class of agents with activity against cancer cells produced by targeting of the tumor cell mitochondrion and cardiolipin depletion. CTU-mediated apoptosis in MDA-MB-231 cells is independent of Bax and Bak and the mitochondrial permeability transition pore.

Choucair H et al (2016) ASCEPT 2016.

146 The potential of MK2 inhibitors in glioblastoma therapy

Lenka Munoz[1], [1]School of Medical Sciences, Faculty of Medicine, The University of Sydney, Sydney, NSW, Australia

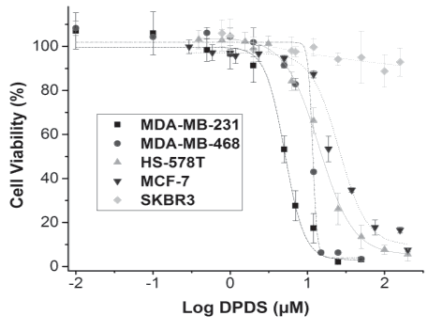
Introduction: MAPK-activated protein kinase 2 (MK2) is a checkpoint kinase regulating DNA damage response (DDR), a mechanism that is crucial for survival of cancer cells. Defects in the DNA damage response can be exploited therapeutically and kinases of the DDR machinery, including MK2, have been identified as promising avenues for targeted cancer therapeutics.
Aims: We aimed to determine whether MK2 inhibition attenuates glioblastoma cell survival.
Methods: Orthogonal MK2 inhibitors and genetic knock-down, including CRISPR deletion of MK2, were tested in an array of functional and mechanistic studies employing established and patient-derived glioblastoma stem cell lines.
Results: We determined that MK2 inhibition improves efficacy of chemotherapy in glioblastoma-relevant models through a novel mechanism targeting the p53 tumour suppressor protein. Intriguingly, we also discovered an unexpected non-kinase target for an allosteric MK2 inhibitor CMPD1. The intellectual property of CMPD1 has been licensed to an industry partner and preclinical development of CMPD1 for the treatment of glioblastoma is currently ongoing within our academia-industry collaboration.
Discussion: I will present published and novel data revealing MK2 signalling axis in glioblastoma cells, as well as the latest data on the preclinical development of CMPD1. I will discuss how in-depth pharmacological understanding of a molecular target is necessary in the early stages of the drug discovery and how mechanism of action can determine later success or failure of the emerging drug candidates.

Gurgis F et al (2015) Cell Death Discov 1: 15028
Phoa A et al (2016) Biochem Pharmacol 98:587-601
Munoz L (2017) Nature Rev Drug Discov 16:424 - 440

147 Induction of apoptosis in triple negative breast cancer cells by selenium derivatives

Jackmil P Jogy, Gregory I Giles, Department of Pharmacology and Toxicology, University of Otago, Dunedin, Otago, New Zealand

Introduction: Triple negative breast cancer (TNBC) is the most common cancer among New Zealand women and is highly difficult to treat, with approximately a 30 % mortality rate. Previous studies have indicated that organoselenium compounds exhibit cytotoxicity against some cancer cell lines, raising the possibility that selenium based drugs could be effective as therapeutics for breast cancer.
Aims: To investigate the effect of the organoselenium agents diphenyl selenide (DPS) and diphenyl diselenide (DPDS) on cell growth in the TNBC cell lines: MDA-MB-231, MDA-MB-468 and HS-578T; and as a comparison MCF-7 oestrogen positive (ER+) cells, and SKBR3 human epidermal growth factor receptor 2 positive (HER2+) cells.
Methods: Cell viability was assessed using MTT assay and validated by double labelling with the fluorescent probes Hoechst 33342 and propidium iodide. Morphological changes were observed using phase contrast microscopy. Expression of p53 and caspase-3 was assessed using western blotting and an Ac-DEVD-AMC fluorogenic substrate assay was used to measure caspase-3 activity. Apoptotic cells were detected using a YO PRO-1 assay.



Results: DPS showed no anti-cancer effect against any breast cancer cells; however, DPDS showed potent cytotoxicity with IC_{50}s in the range 7-18 µM against towards TNBC cells, and 27 µM against MCF-7s. Interestingly DPDS did not display cytotoxicity towards SKBR3, suggesting selective action towards TNBC cells. Molecular analysis indicated that DPDS induced cell death via apoptosis in TNBC cells correlating with increase in p53 and caspase-3 activation.
Discussion: Generally DPDS is cytotoxic against cell lines at concentrations greater than 30 µM. The present data indicate that DPDS displays considerably higher cytotoxicity towards TNBC compared to other cancer cell lines, suggesting that DPDS could find therapeutic applications as a treatment for TNBC.

148 The effect of curcumin on in vitro metabolism and predicted in vivo exposure of imatinib

Jeffry Adiwidjaja[1], Alan V Boddy[1] & Andrew J McLachlan[1,2], [1]Fac of Pharmacy, Univ of Sydney, Sydney, NSW, Australia, [2]Centre for Education and Research on Ageing, Concord Repatriation General Hosp, Sydney, NSW, Australia

Introduction: Imatinib is the first-line agent for the treatment of chronic myeloid leukaemia (CML) and is a substrate for CYP3A4 (Hochhaus et al, 2017). Curcumin has been investigated for anti-cancer activities, including for CML, and is a relatively potent CYP3A4 inhibitor (Adiwidjaja et al, 2017).
Aims: The aim of this study is to investigate the metabolism-based interaction between curcumin and imatinib.
Methods: Imatinib metabolism was investigated in pooled human liver microsomes (HLM) and recombinant CYP3A4 enzymes in the presence and absence of curcumin using LC-MS/MS assay for N-desmethyl metabolite. Azamulin, a specific CYP3A4 mechanism-based inhibitor, was used to study the effect of curcumin on imatinib N-demethylation by other (non-CYP3A4) pathways.

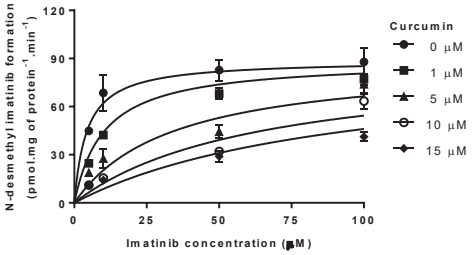


Figure 1

Results: A simple Michaelis-Menten model best fitted to N-desmethyl imatinib formation kinetic in HLM (K_m = 6.16 ± 0.63 µM; V_{max} = 94.27 ± 3.83 pmol.mg protein^{-1}.min^{-1}). Curcumin inhibited CYP3A4 and non-CYP3A4-mediated imatinib N-demethylation competitively (Figure 1) and noncompetitively with a K_i of 0.73 ± 0.12 and 1.88 ± 0.19 µM respectively. Using a static drug interaction model, a single 160 mg- and multiple (320 mg every 12 h)-oral dose of curcumin were predicted to increase imatinib exposure ($AUC_{0-\infty}$) by 16 and 21%, respectively.
Discussion: Based on the K_i value, the formation of N-desmethyl imatinib mediated by CYP3A4 was more susceptible to inhibition by curcumin than that through non-CYP3A4 (most likely by CYP2C8) pathway. Curcumin at a clinically-relevant concentration was predicted to increase imatinib systemic concentrations by up to 21%. This moderate interaction is worthy of further study in the clinic.
Adiwidjaja J et al (2017) Expert Opin Drug Metab Toxicol 13(9):953-72
Hochhaus A et al (2017) N Engl J Med 376(10):917-27

149 Triterpenoid micellar nanoparticles for the treatment of glioblastoma: Potential inhibition of the PI3K/Akt signalling

Rebecca H Roubin, Yat Sum William Wah, Peter Pirotta, Ramin Rohanizadeh, Jane R Hanrahan, Faculty of Pharmacy, The University of Sydney, Sydney, NSW

Introduction: Glioblastoma is the most aggressive type of malignant brain tumour and is associated with a high mortality rate. Current standard therapy for glioblastoma is inadequate due to tumour resistance and recurrence. Recent efforts in producing targeted therapies for glioblastoma have also faced challenges due to the blood brain barrier and the tumour heterogeneity of glioblastomas. As a result, there is a need for novel treatment strategies. Triterpenoid derivatives are well known to possess a wide range of anti-cancer effects. With its multifaceted action, selective toxicity, chemosensitising effect and ability to penetrate the blood brain barrier, triterpenoids are believed to have a potential role in the treatment of glioblastoma. However, the limited aqueous solubility and non-specific bio-distribution of triterpenoid derivatives have been obstacles to its clinical application. An effective method for delivering triterpenoid derivatives has yet to be developed that would further elucidate the precise mechanism of triterpenoid derivatives in treating glioblastoma.
Aims: To develop triterpenoid derivative micellar nanoparticles that would further elucidate the precise mechanism of triterpenoid derivatives in treating glioblastoma.
Methods: Triterpenoid derivatives were synthesised into nanoparticles using micelles. The particle size, encapsulation efficiency, in vitro release, stability, cytotoxicity, and cellular uptake of these triterpenoid nanoparticles were characterised in human glioblastoma (U87MG) cells.
Results: Micellar nanoparticles significantly improve triterpenoid derivatives solubility, stability, and bioavailability in vitro ($n = 3$, $P<0.05$). Micellar nanoparticles significantly improve the anti-glioblastoma dose dependent inhibition of the triterpenoids compared to the standard chemotherapeutic agent, temozolomide ($n = 3$, $P<0.05$).
Discussion: We hypothesise that triterpenoid derivatives may be inhibiting the PI3K/Akt signalling pathway, which plays a major role in mediating the responses of glioblastoma cells to triterpenoid derivatives, and the potential use of triterpenoid derivatives in treating glioblastoma.

150 Predictors of adverse drug reaction-related hospitalisation in Southwest Ethiopia: A prospective cross-sectional study

Mulugeta Tarekegn Angamo[1], Leanne Chalmers[1], Colin Michael Curtain[1], Daniel Yilma[2], Luke Bereznicki[1], School of Medicine, University of Tasmania[1], Hobart, Tasmania; Faculty of Medical Sciences, Jimma University[2], Jimma, Ethiopia.

Introduction: Adverse drug reactions (ADRs) are important causes of morbidity and mortality in the healthcare system; however, there are no studies reporting on the prevalence and risk factors associated with ADR-related hospitalisation in Ethiopia.
Aim: To identify predictors of ADR-related admission to the Jimma University Specialised Hospital, Southwest Ethiopia.
Methods: A prospective cross-sectional study was conducted from May 2015 to August 2016 among patients aged ≥18 years consecutively admitted to medical wards of Jimma University Specialised Hospital taking at least one medication prior to admission. ADR-related hospitalisations were determined through expert review of medical records, laboratory tests, patient interviews and physical observation. ADR causality was assessed by the Naranjo algorithm followed by consensus review with senior internist. ADR preventability was assessed using the Schumock and Thornton criteria. Only definite and probable ADRs that provoked hospitalisation were considered.
Results: Of 1,001 patients, 103 (10.3%) had ADR-related admissions. A total of 119 ADRs (1.2 ADRs per patient) were identified. Common ADRs responsible for hospitalisation were hepatotoxicity (35, 29.4%) and acute kidney injury (28, 23.5%). The drug classes most frequently implicated were antitubercular agents (43, 23.9%) followed by antivirals (21, 11.7%) and diuretics (21, 11.7%). Independent predictors of ADR-related hospitalisation were body mass index (BMI) <18.5 kg/m^2 (adjusted odd ratio [AOR]=1.69; 95%CI=1.10-2.62; P=0.047), pre-existing renal disease (AOR=2.84; 95%CI=1.38-5.85, P=0.004), pre-existing liver disease (AOR=2.61; 95%CI=1.38-4.96; P=0.003), number of comorbidities ≥4 (AOR=2.09; 95%CI=1.27-3.44; P=0.004), number of drugs ≥6 (AOR=2.02; 95%CI=1.26-3.25; P=0.004) and history of previous ADRs (AOR=24.27; 95%CI=11.29-52.17; P<0.001). Most ADRs (106, 89.1%) were preventable.
Discussion: Over half of the ADR-related admissions were due to hepatotoxicity and acute kidney injury. The majority of ADRs were preventable, highlighting the need for monitoring and review of patients with lower BMI, ADR history, renal and liver diseases, multiple comorbidities and medications. ADR predictors should be integrated into clinical pathways and pharmacovigilance systems.

151 Investigating the Impact of Universal Healthcare Coverage on the practice of Indonesian Community Pharmacy: A Qualitative Study

Andi Hermansyah[1,2], Erica Sainsbury[1], Ines Krass[1], [1]Faculty of Pharmacy, The University of Sydney, Sydney, NSW, Australia, [2]Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia

Introduction: The introduction of Universal Healthcare Coverage (JKN) to Indonesian health system in 2014 has changed the landscape of Community Pharmacy (CP) sector opening up opportunity for CPs to operate within the JKN scheme including receiving remuneration for supply of medicines. However, to date, there has been no research investigating the impact of such changes to the practice of pharmacy and pharmacists.
Aims: To explore key stakeholders' perception and experiences on the influence of JKN on CP practice.
Methods: In-depth, semi structured interviews were conducted to broad range of key stakeholders in CP and healthcare system from February to July 2016. The interviews were audio-recorded, transcribed verbatim and analysed for emerging themes. Ethics approval was obtained from the University of Sydney
Results: A total 29 key informants participated. Three levels of practice i.e micro (individual pharmacist), meso (organisational context of CP) and macro (external CP environment) were analysed interdependently. Stakeholders perceived that JKN has not improved scope of practice in CP which still predominantly focuses on dispensing. In addition, there has been little impact for pharmacists in terms of remuneration and role acknowledgement. Stakeholders also perceived no significant benefits for a CP joining JKN. However, they were aware that the limited opportunity under JKN was the result of a number of barriers including pharmacists' shortage, poor law enforcement and lack of pharmacists' clinical competence of which may not always relate to policy changes provided by JKN.
Discussion: While JKN has been designed to improve primary care system, it has not addressed key structural changes within CP sector. As a result, community pharmacy continues to be hampered by structural and fundamental issues even after the introduction of JKN.

MoH Indonesia (2004) National Social Security Law
Plummer V and Boyle M (2016) Financing Healthcare in Indonesia, *Asia Pac J of Health Man*, 11(2), pp.33-38

152 Home Medicines Reviews – Exploring accredited pharmacists' work processes

Marea Patounas[1], Esther Lau[1], Greg Kyle[1], Debbie Rigby[1], Lisa Nissen[1], Vincent Chan[2], [1]Faculty of Health, School of Clinical Sciences, QUT, Brisbane, QLD, Australia, [2]RMIT University[2], Melbourne, VIC, Australia

Introduction: In healthcare, work processes shape patient, professional and organisational outcomes. Little is known about the specific tasks and activities that form the work processes of accredited pharmacists (APs) performing Home Medicines Reviews (HMRs) in Australia.
Aims: To explore APs' work processes and the time taken to conduct the three stages of HMR: pre-interview (preparation phase); home interview (with the patient); and post-interview (collation of findings and recommendations into a HMR Report for the patient's General Practitioner).
Methods: Focus groups and semi-structured interviews were conducted with Australian APs. Participants were recruited via professional pharmacy networks and organisations. The sessions were transcribed verbatim and thematically analysed using Leximancer and NVivo 11 software.
Results: There were 10 APs in the focus groups and 15 APs who participated in the semi-structured interviews. Participants for the two focus groups were from southeast Queensland, and interview participants ranged from urban, regional and far north Queensland, to northern regional and western regional New South Wales. The configural work system processes for each stage of HMR were categorised as: person, task, technology, organisation, and internal and external environment factors. The APs focussed on establishing rapport and trust with the patient as a top priority. The majority of APs spent an estimated 4 hours performing a HMR from beginning to end, with the majority of pre-interview, home interview and post-interview stages taking 30-60 minutes, 45-60 minutes and 1.5-2 hours respectively. Most HMR reports were 2-4 pages in length, although this varied depending on whether the AP worked from a home office or if they were a practice pharmacist (integrated into a clinic/practice setting).
Discussion: A detailed account of APs' HMR tasks and work processes may be of practical value to medical home decision makers, funding bodies, professional organisations, educators and health professionals involved in medication reviews. Further investigation of APs' work processes and the time taken to conduct HMRs is warranted.

153 Adoption of the Ohio Emergency Department opioid prescribing guidelines

Jonathan Penm[1], Neil MacKinnon[2], Jill Boone[2], Erin Winstanley[2], Michael Lyons[3], Edmond Hooker[3], Steve Carlton-Ford[4], Rebecca Mashni[2], Chloe Connelly[2], Erica Tolle[2], [1]Faculty of Pharmacy, University of Sydney, NSW, [2]College of Pharmacy, College of Medicine[3], College of Arts and Sciences[4], University of Cincinnati, OH, USA

Introduction: Ohio has the fifth highest rate of prescription opioid-related overdose deaths in the United States. The Ohio Department of Health has disseminated multiple guidelines, including the Emergency Department (ED) opioid prescribing guidelines, to aid address this issue.
Aims: To evaluate the adoption of the Ohio ED opioid prescribing guidelines, their perceived impact and factors affecting its adoption.
Methods: The study design was a cross-sectional survey of ED medical directors, or appropriate person identified by the hospital, perception of the impact of the Ohio ED Opioid Prescribing Guidelines on their departments practice. All hospitals with an ED in Ohio were contacted in 2016. Distribution followed Dillman's Tailored Design Method, augmented with telephone recruitment. Hospital chief executive officers were contacted when necessary to encourage ED participation. At the end of the survey, respondents were asked to participate in a semi-structured interview to assess barriers related to the implementation of the guidelines.
Results: A 92% response rate was obtained (150/163 EDs). In total, 112 (75%) of the respondents stated that their ED has an opioid prescribing policy, is adopting one, or is implementing prescribing guidelines without a specific policy. Of these 112 EDs, 81 (72%) based their policy on the Ohio ED Opioid Prescribing Guidelines. The majority of respondents strongly agreed/agreed that the prescribing guidelines have increased the use of the prescription drug monitoring program (86%) and have reduced opioid prescribing (71%). Main themes identified from 20 interviewees included the need for (1) increasing organizational responsibility, (2) assistance with prescription monitoring program utilization, (3) reducing the effect of patient satisfaction scores on opioid prescribing, and (4) increasing patient involvement.
Discussion: This study showed that the Ohio ED opioid prescribing guidelines have been widely disseminated and that the majority of EDs in Ohio are using them to develop local policies. The majority of respondents believed that opioid prescribing guidelines reduced opioid prescribing. However, prescribing practices still varied greatly between EDs.

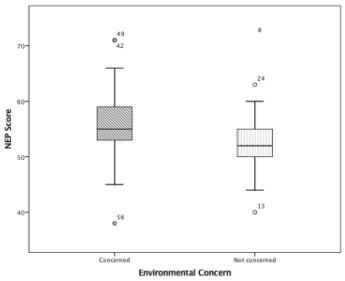
154 Pharmacy in the community: The potential of role extension

Caroline Morris[1], Janet McDonald[2], Phoebe Dunn[2], Ausaga Fa'asalele Tanuvasa[2], Jane McCormack[2], Kirsten Smiler[2], Lynne Russell[2], Jacqueline Cumming[2], Department Primary Health Care and General Practice, University of Otago[1], Wellington, NZ, Health Services Research Centre, Victoria University[2], Wellington, NZ

Introduction: Community pharmacists (CPs) are a very accessible, highly trained and skilled workforce not currently being used to their full potential. They are well positioned to contribute to improvements in health outcomes and a reduction in health disparities by expanding their roles in both the individual patient care and population health arenas. In a similar way to other countries internationally, changes are occurring in pharmacy models of care, services and funding in New Zealand (NZ) to optimise the use of pharmacists' skills.
Aims: To understand current developments in community pharmacy services in NZ including the extent to which the expansion of roles is successfully occurring and what the enablers or barriers to this progress might be.
Methods: Thirty key informant, semi-structured, audio-recorded interviews conducted face-to-face or by telephone have been undertaken to date with a diverse range of stakeholders from the policy, pharmacy, consumer, general practice and nursing sectors (including Maori and Pacific views). Participants' views on current pharmacy services and policy were explored, as were their perceptions of what expanded pharmacy services might look like over the next three to five years. Interviews were transcribed verbatim, coded and analysed using a thematic approach.
Results: Data identified a range of factors with the potential to impact on current and future pharmacy roles. These were: national drivers for change, national and local policy development, CP workforce development, relationships with other health professional groups, impact of role change on service stakeholders including consumers, pharmacists and the wider health system. Other factors identified as influencing implementation and success included funding models, infrastructure within the pharmacy premises and national and local leadership.
Discussion: These key informant interviews form the first part of a larger study exploring how changes in community pharmacy services in NZ are expected to influence health and health service outcomes, identify the context in which success is occurring (or being hindered) and the mechanisms by which change is being achieved. The findings will be used to focus the second phase of the study, a national questionnaire e-survey of CPs.

155 Just rubbish? Examining the concerns and attitudes of pharmacists to pharmaceuticals entering the environment

Judith A. Singleton[1,2], Esther T.L. Lau[1,2], Lisa M. Nissen[1,2], [1]School of Clinical Sciences, QUT, Brisbane, QLD, Australia, [2]Institute of Health and Biomedical Innovation, QUT, Brisbane, QLD, Australia



Introduction: Pharmaceuticals entering the environment have a cumulative negative effect on human health and wildlife (Daughton & Ruhoy, 2008).
Aims: To explore if an individual's level of environmental concern regarding the impact of pharmaceuticals entering the environment is a predictor of their environmental attitude.
Methods: A purposive sample of 41 pharmacists and 25 pharmacy technicians (n = 66) working in five hospitals in Brisbane, Australia, first completed the 15-item NEP scale questionnaire (to determine their environmental attitude) and then answered the question, 'How concerned are you personally about pharmaceuticals entering the environment?"
Results: A two-sample t-test was used to determine if there was a statistically significant association between participants' concern and environmental attitude. Equality of variances between the two groups 'Concerned' and 'Not Concerned' was checked using Levene's test, and equality was assumed to be the same ($F = 0.181$, $p = 0.672$). There was a statistically significant difference in mean NEP scores between concerned participants and participants who were not concerned ($t_{62} = 2.342$, $p = 0.022$). The mean NEP score was 3.631 points lower for participants who did not express concern regarding the impact of pharmaceuticals on the environment.
Discussion: This study demonstrated that participants who reported being concerned about the impact of pharmaceuticals on the environment had a higher NEP score (a more pro-environmental attitude). Since environmental attitude influences pro-environmental behaviour, providing environmental knowledge to raise concern may indirectly influence pro-environmental behaviours in hospital pharmacy departments and warrants further investigation.

Daughton, C. G., & Ruhoy, I. S. (2008). The Afterlife of Drugs and the Role of PharmEcovigilance. Drug Safety, 31(12), 1069-1082. doi:10.2165/0002018-200831120-00004

156 Adherence to lipid lowering medications for secondary prevention of stroke

Judith A Coombes[1,2], Debra Rowett[1], Jennifer Whitty[1], Darshan Shah[2], William N Cottrell[1], [1] School of Pharmacy, University of Queensland, Brisbane, QLD, Australia, [2]Medical Stroke Unit, Princess Alexandra Hospital2, Brisbane, QLD, Australia

Introduction: To maximise risk reduction of recurrent stroke, good adherence to medications for secondary prevention is desired.
Aims: To compare patient self-report of adherence to lipid lowering medications with adherence calculated using Australian pharmaceutical benefits scheme (PBS) claims data.
Methods: Participants with a diagnosis of stroke or transient ischemic attack (TIA), and Mental Status Quotient (MSQ) of 10/10 who provided consent were recruited into the study. Participant self-report of adherence using the Medication Adherence Questionnaire (MAQ)(Morisky, et al. 1986) with a best possible score of 4/4, was obtained by telephone follow-up at least 3 months after discharge from hospital. Pharmaceutical claims data was used to obtain prescription refill dates and calculate the Proportion of Days covered by their medications (PDC)(Hedegaard, et al. 2014). Comparison of the results of these two adherence measures were analysed using Mann-Whitney U Test.
Results: We obtained both PBS and patients self-report adherence data for 43 of 60 recruited participants. At a mean of 120 days, 33/43(77%) participants self-reported good adherence (MAQ=4/4). In those participants with self-reported good adherence, the median PDC for 120 days was significantly higher (p=0.047) at 96% (IQR 18%) compared 83% (IQR 18%) to those with adherence scores less than 4/4 on the MAQ.
Discussion: The analysis showed that there was a relationship between participant self-reported adherence and PBS medication refill data. The combination of both these results provides a clearer picture than each one taken in isolation.

157 Cost-effectiveness of pharmacist management of hypertension

Carlo A. Marra[1], Karissa Johnston[2], Valerie Santschi,[3] and Ross T. Tsuyuki[4], [1]School of Pharmacy, University of Otago, Dunedin, NZ, [2]Broadstreet Health Outcomes, Vancouver, BC, Canada, [3]La Source School of Nursing Sciences, University of Applied Sciences Western Switzerland, Lausanne, Switzerland, [4]University of Alberta, Edmonton AB, Canada

Background: Over half of all heart disease and stroke are attributable to hypertension, which is associated with approximately 10% of direct medical costs globally. Clinical trial evidence has demonstrated that the benefits of pharmacist intervention, including education, consultation and/or prescribing, can help to reduce blood pressure—a recent Canadian trial found an 18.3 mmHg reduction in systolic blood pressure associated with pharmacist education and prescribing. The objective of this study was to evaluate the economic impact of such an intervention.
Methods: A Markov cost-effectiveness model was developed to extrapolate potential differences in long-term cardiovascular and renal disease outcomes, using Framingham risk equations and other published risk equations. A range of values for systolic blood pressure reduction were considered (7.6-18.3 mmHg), to reflect the range of potential interventions and available evidence. The model incorporated health outcomes, costs and quality of life to estimate an overall incremental cost-effectiveness ratio (ICER). Costs considered included direct medical costs as well as the costs associated with implementing the pharmacist intervention strategy. Probabilistic analysis to account for the joint uncertainty and costs and outcomes was conducted as were several scenario analyses.
Results: For a systolic blood pressure reduction of 18.3 mmHg, the estimated impact is 0.21 fewer cardiovascular events per person and, discounted at 5% per year: 0.3 additional life years, 0.4 additional quality-adjusted life years and $6,364 cost-savings over a lifetime. Thus, the intervention is economically dominant, being both more effective and cost-saving relative to usual care.
Discussion: Comprehensive pharmacist care of hypertension, including patient education and prescribing, has the potential to offer both health benefits and cost savings to payers and as such, has important public health implications.

158 Troches or orally dissolving tablets for delivery of pilocarpine in treatment of xerostomia (dry mouth)?

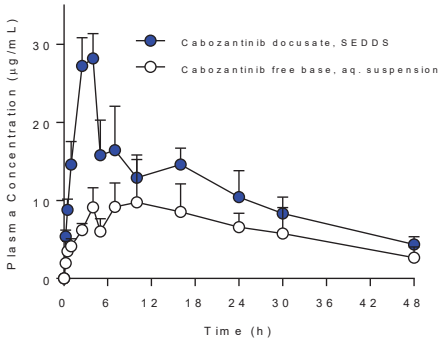
Rose M Estafanos[1], Esther T Lau[2], Geoffrey Mitchell[3], Hugh Senior[3], Kathryn J Steadman[1], [1]School of Pharmacy, University of Queensland, Brisbane, QLD, [2]School of Clinical Sciences, Queensland University of Technology, Brisbane, QLD, [3]School of Medicine, University of Queensland[3], Brisbane, QLD

Introduction: Troches and orally dissolving tablets (ODTs) are dosage forms that can be compounded in pharmacies for buccal drug delivery. As part of a larger clinical trial into pilocarpine for treatment of xerostomia, the acceptability of compounded pilocarpine troches and ODTs was tested by healthy volunteers and patients who suffer from dry mouth of different aetiologies.
Aims: 1- To assess the taste acceptability of troches containing 5 mg pilocarpine and flavoured with 5 different flavours (Lemon, Chocolate, Raspberry, Mint and Non-flavour) to mask the bitter taste of pilocarpine. 2- To rate preference for troches vs ODTs as a dosage form for future treatment of dry mouth in Australia.
Methods: Ethics approval was obtained from the UQ Human Research Ethics Committee. A total of 34 healthy volunteers and 14 people who suffer from dry mouth were recruited. The dry mouth resulted from various aetiologies: head and neck cancer (6), Sjogren's syndrome (3), medication-induced (2), and non-identified reason (2). Participants tasted 5 different flavoured medicated troches by sucking each for no more than 10 seconds (to minimise pilocarpine absorption) and rating the relative acceptability. Participants then sucked a non-medicated troche followed by a non-medicated ODT, both flavoured the same, and rated their preference of the given dosage forms.
Results: Healthy volunteers preferred lemon flavour (35%) followed by raspberry flavour (20%). For the xerostomic patients, raspberry was preferred (31%) followed by chocolate (23%) and lemon (23%). ODTs were preferred rather than troches by 71% of the healthy volunteers and all of the xerostomic patients (100%). ODTs were preferred because of their small size along with quick and easy dissolution in the mouth without the need of water.
Discussion: ODTs can be easily be prepared in a compounding pharmacy that is equipped with an oven and a specially-designed mould. The preferred dosage form – raspberry flavoured pilocarpine ODTs – will be tested for effectiveness in a clinical trial using a N-of-1 trial design.

159 Lipophilic Salts of Small Molecule Kinase Inhibitors for Increased Oral Bioavailability Using Lipid Formulations

Hywel D Williams[1], Leigh Ford[2], Kristian Tangso[3], Annabel Igonnin[4], Hassan Benameur[4], Colin W Pouton[3], Peter J Scammells[2], Christopher JH Porter[3], [1]Lonza R&D, [2]Medicinal Chemistry, [3]Drug Delivery Disposition Dynamics at Monash Institute of Pharmaceutical Sciences, Melbourne, VIC, Australia, [4]Lonza Pharma Sciences, Strasbourg, France

Introduction: The purpose of this study was to increase the oral exposure of high log P (>5) small molecule kinase inhibitors by (i) transformation into lipophilic salts and (ii) delivery in lipid formulations.
Methods: Docusate salts of cabozantinib and ceritinib were prepared in-house. The solubility of the docusate salts was evaluated in several lipidic excipients and model self-emulsifying lipid formulations (SEDDS). Cabozantinib docusate containing SEDDS and crystalline cabozantinib free base were orally dosed to fasted rats at 25 mg/kg, and absolute bioavailability determined based on an IV treatment arm (at 5 mg/kg). Solubilization by the SEDDS formulas in an in vitro gastric–small intestine model was also evaluated.



Discussion: Docusate salts were significantly more soluble in lipidic excipients, with 50–100 mg/g (free base equivalents) concentrations achieved in at least three excipients (see Figure insert). The high lipid solubility of the lipophilic salt forms allowed at least 100 mg/g loading in model SEDDS formulations—a 4–fold enhancement in loading over the free base forms. Cabozantinib docusate containing SEDDS resulted in higher drug solubilization *in vitro* at pH 2 and pH 6.5 when compared to crystalline free base. In fasted rats, cabozantinib free base oral bioavailability was 47.2±10.9%. Bioavailability increased ~2–fold to 83.4±3.3% when dosed as the lipophilic salts in the SEDDS (see Figure insert), confirming that a combined lipophilic salt–SEDDS approach was effective in increasing cabozantinib absorption. Overall, the data suggest that for kinase inhibitors demonstrating challenging physicochemical properties, conversion to lipophilic salts can unlock the well-known absorption enhancing benefits of lipid formulations.

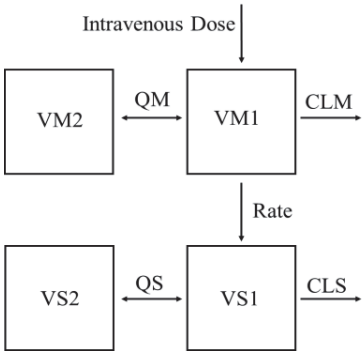
160 Triglyceride-mimetic prodrugs of testosterone significantly enhance lymphatic transport and oral bioavailability

Tim Quach[1,2,3], S. Fern Lim[1,2,3], Sifei Han[1,3], Luojuan Hu[1,3], Jamie S. Simpson[1,2], Natalie L. Trevaskis[1], Christopher J. H. Porter[1,3], Drug Deliv, Disp and Dynamics[1], Med Chem[2], The ARC Centre of Excellence for Conv Bio-Nano Science[3] MIPS, Monash Uni (Parkville), Melbourne, VIC

Introduction: After oral administration, drug metabolism on first-pass through the liver may be a significant barrier to clinical success. High first-pass metabolism limits oral bioavailability for marketed drugs such as testosterone (TST) and likely limits the progression of many experimental drug candidates. One means of circumventing this problem is to promote drug transport through the lymphatic system via association with endogenous lymph lipoproteins. The intestinal lymph drains from the intestine, via the thoracic duct, directly into the major veins in the neck, thus bypassing the liver. The current study describes a triglyceride (TG) mimetic prodrug strategy to increase lymphatic transport and bioavailability of TST. The design strategy was based on the realisation that following oral ingestion, dietary TG is very efficiently transported into the intestinal lymphatics via incorporation into lipoproteins.
Aims: To evaluate the effectiveness of different self-immolative (SI) groups in facilitating the release of parent drug from TG mimetic prodrugs of TST following transport via the lymphatics.
Methods: Prodrugs were prepared using standard methods, including those previously reported by our group (Hu et al, 2016). Lymphatic transport and bioavailability studies were conducted in mesenteric lymph duct or carotid artery cannulated rats, respectively. Rats received the TST prodrugs via intraduodenal infusion (lymph) or oral gavage (bioavailability).
Results. TG prodrugs of TST were transported into the lymphatics with varying efficiency (2.8-28.1% of the dose, vs <0.1% for TST), depending on the linker. Incorporation of SI groups facilitated TST release from the prodrugs, leading to marked enhancement in oral bioavailability (up to 90-fold) compared to the marketed product, TST undecanoate.
Discussion: TG mimetic prodrugs successfully increased the lymphatic transport and systemic exposure of TST following oral administration. Prodrugs with linkers that promoted stability in the GI tract maximally enhanced lymphatic transport while those containing a labile SI group gave the highest increases in systemic exposure.
Hu L et al (2016) Angew Chem Int Ed 55:13700-13705.

161 Characterising and predicting the in vivo kinetics of therapeutic mesenchymal stem cells and their secretome

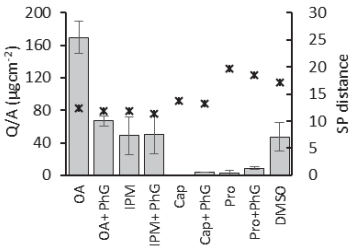
Haolu Wang[1], Xiaowen Liang[1], Anastasia Brooks[1,2], Michael S. Roberts[1], [1]Diamantina Institute, The University of Queensland, Brisbane, QLD, Australia, [2]School of Biomedical Sciences, The University of Queensland, Brisbane, QLD, Australia



Cell therapy has emerged as an evolutionary therapeutic force especially for diseases not curable by traditional therapeutics. However, the success of many cell therapies has been grossly impeded by the poorly-understood cell-tissue interactions and ill-defined cell pharmacokinetics in the body. Mesenchymal stem cells (MSCs) and the immunomodulatory cytokines produced by MSCs have considerable potential for the treatment of for many debilitating diseases including liver cirrhosis, diabetes, spinal cord injury and myocardial infarction. Here, we developed the first physiologically-based kinetic model of therapeutic MSCs, and two-compartment pharmacokinetic model of MSC secretome (Interleukin 6 and Interleukin 8). The utility of these models was examined across species and administration routes by extrapolation of this model to rats and humans, as well as to intra-hepatic arterial injection. The clinical application of this model was also tested with data obtained from stem cell-based therapies to patients with liver cirrhosis. Our model successfully characterised the *in vivo* kinetics of therapeutic MSCs and their secretome. This is the first study accurately characterises and predicts the *in vivo* kinetics of therapeutic mesenchymal stem cells and their secretome. It provides the optimised dosage, route of administration, and targeting strategies for MSC-based therapy to achieve the maximum effectiveness with the lowest risk. By adapting specific parameters, this model can be easily applied to other types of therapeutic cells for designing standardised treatment protocols.

162 Permeation of quercetin through the human epidermis

Azadeh Alinaghi[1], Ana Macedo[1] Pauline Dréan[2], Amy Holmes[1], Ahmed Abdalla[1], H. Srikanth Cheruvu[1], Michael S. Roberts[1, 3]
[1] Therapeutic Research Centre, School of Pharmacy and Medical Sciences, University of South Australia, Basil Hetzel Institute for Translational Health Research, Adelaide, SA; [2] University of Rennes 1, Rennes, France, [3]Therapeutics Research Centre, Diamantina Institute, University of Queensland, Translation Research Institute, Brisbane, QLD, Australia



Introduction: Quercetin is a naturally occurring antioxidant, which has the potential to treat actinic keratosis but also has a poorly defined human skin permeability.
Aim: In this work, we designed and tested a range of formulations that may facilitate the human skin permeation of quercetin.
Methods: Various topical microemulsions and liquid formulations were designed using a series of skin permeation enhancers that varied in their 3D relative differences between formulation, quercetin and stratum corneum solubility parameters. Human epidermal membranes were prepared from excised human skin and mounted in Franz diffusion cells to assess the epidermal permeation of quercetin (1 mg/ml) from the formulations over time at 32°C. The skin permeation enhancers included the fatty acids and esters (oleic acid, OA; isopropyl myristate, IPM; Capryol 90, Cap), phospholipids (Phospholipon 90G, PhG), hydrogen bond solvent (dimethyl sulfoxide, DMSO) and propanol (Prop).
Result: Fig. 1 shows that the permeation of quercetin through human epidermal membranes varied greatly with the topical formulation used and was not well described by solubility parameter differences. The most and least effective formulations were microemulsions containing oleic acid and Capryol 90, respectively.
Discussion: This work suggests that solubility parameters are limited in their ability to describe the permeation enhancement of quercetin through human epidermis by various formulations. A more likely explanation for the formulation induced human epidermal permeation enhancement are specific molecular interactions between the permeation enhancers and molecules associated with the stratum corneum barrier, such as the intercellular lipids.

163 Evaluation of optimised piperacillin plus tobramycin combination dosage regimens against *Pseudomonas aeruginosa* (Pa) for patients with altered pharmacokinetics *via* the hollow fibre infection model and mechanism-based modelling

Rajbharan Yadav[1], Kate E. Rogers[1,2], Phillip J. Bergen[2], Jürgen B. Bulitta[3], Carl M. J. Kirkpatrick[2], Steven C. Wallis[4], David L. Paterson[5], Roger L. Nation[1], Jeffrey Lipman[4], Jason A. Roberts[4] and Cornelia B. Landersdorfer[1,2]. Drug Deliv, Dispos and Dynamics[1], Centre for Medicine Use and Safety[2], Monash Univ, Parkville, VIC, Australia; Dept of Pharmaceutics, University of Florida[3], Orlando, FL, USA; Burns, Trauma Crit Care Res Centre[4], Cent for Clin Res[5], Univ of Queensland, Brisbane, Australia.

Introduction. Augmented renal clearance (ARC) in critically-ill patients can result in suboptimal drug exposures and potential treatment failure.
Aims. This study aimed to design and evaluate optimised combination dosage regimens of piperacillin (PIP) and tobramycin (TOB) against a Pa clinical isolate in the hollow fibre infection model (HFIM) for patients with ARC.
Methods. We studied clinically relevant PIP and TOB concentrations, alone and in combinations in *in vitro* static concentration time-kills (SCTK), against a Pa clinical isolate at two inocula ($10^{5.7}$ and $10^{7.5}$ cfu/mL) over 72h. We optimised PIP + TOB regimens *via* mechanism-based modelling (MBM) of SCTK data. The effect of optimised PIP (4g q4h, 0.5h infusion) plus TOB (5 mg/kg q24h, 7 mg/kg q24h and 10 mg/kg q48h as 0.5h infusions) regimens on bacterial killing and regrowth was evaluated in the HFIM for patients with ARC (creatinine clearance 250 mL/min) over 8 days.
Results. PIP monotherapy (4g every 4h) in the HFIM provided 2.4 $\log_{10}$ killing at 13h followed by rapid regrowth at 24h with resistance emergence. TOB monotherapies displayed rapid initial killing (≥5 $\log_{10}$ at 13h) followed by extensive regrowth. The PIP + TOB dosage regimens were synergistic and provided ≥5 $\log_{10}$ killing with resistance suppression over 8 days in the HFIM.
Discussion. Optimised PIP + TOB regimens provided significant bacterial killing and suppressed resistance emergence as predicted by MBM, and therefore translated well from SCTK to the dynamic HFIM. This highlights the utility of MBM to select optimised regimens that maximise bacterial killing and minimise resistance emergence against Pa, an especially important finding given that Pa can rapidly develop MDR. Thus, these regimens are highly promising for effective and early treatment, even in the near-worst case scenario of ARC.

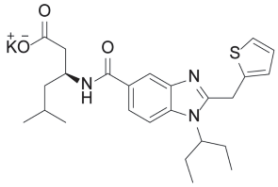
164 CMF-019, the first G protein biased small molecule apelin agonist, is a vasodilator and positive inotrope in vivo

Cai Read[1], Christopher Fitzpatrick[2], Peiran Yang[1], Rhoda E. Kuc[1], Duamene Nyimanu[1], Janet J. Maguire[1], Robert Glen[3], Richard Foster[2], Anthony P. Davenport[1], [1]EMIT, Univ of Cambridge, Cambridge, UK, [2]Chem Biol and Med Chem, Univ of Leeds, Leeds, UK, [3]Ctr for Mol Info, Univ of Cambridge, Cambridge, UK

Introduction: Pulmonary arterial hypertension (PAH) has poor prognosis and is associated with pulmonary vasoconstriction and right ventricular failure. Apelin, a vasodilator and inotrope, is a promising target but lacks bioavailability, is limited by half-life and internalises the receptor through β-arrestin signalling. CMF-019 ((S)-3-[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino-5-methyl-hexanoic acid), a biased small molecule apelin agonist, could overcome these issues (Read *et al.* 2016).

Aims: To further characterise CMF-019 as an apelin mimetic *in vivo* and as a potential therapeutic against PAH.

Methods: CMF-019 was synthesised (Tocris). Male Sprague-Dawley rats (271±3g, n=17) induced (3%) and maintained (1.5%) under anaesthesia with inhaled isoflurane carried by oxygen (1.5L/min) were catheterised in the left ventricle and femoral artery with pressure-volume catheters. CMF-019 (1mg/kg) was injected iv. Male Sprague-Dawley rats (209±2g, n=35) received a sc injection of monocrotaline (MCT, 60mg/kg) or saline and thereafter, daily ip injections of CMF-019 (10mg/kg) or saline. After 21 days, left and right ventricles were catheterised (as above) and the Fulton index recorded.



CMF-019 (Potassium Salt)

Results: Acutely, CMF-019 induced arterial dilatation (5.96±1.15mmHg, n=8) and cardiac contractility (458±51mmHg/s, n=8) without receptor desensitisation. Chronically, CMF-019 did not reduce the Fulton index or right ventricular pressure of MCT compared to saline treated animals.

Discussion: CMF-019, induced dilatation and inotropy *in vivo* and preliminary studies using human pulmonary arterial endothelial cells have suggested disease modifying potential. However, there was insufficient target engagement chronically to alleviate induced PAH. In conclusion, CMF-019 provides a starting point for the rational design of novel biased apelin analogues but more work is required to assess its PK properties for chronic administration.

Read C. *et al*. (2016). Biochem Pharmacol. 166:63-72

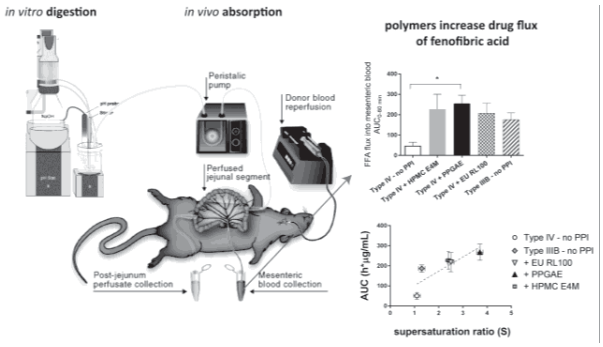
165 Polymer precipitation inhibitors can maintain drug supersaturation and increase in vivo absorption from lipid-based formulations

Estelle Suys[1,2], David K. Chalmers[3], Colin W. Pouton[1], Christopher J.H. Porter[1,2], [1]Drug Delivery, Disposition and Dynamics [2]ARC Centre of Excellence in Convergent Bio-Nano Science and Technology, [3]Medicinal Chemistry, Monash University, Melbourne, VIC, Australia

Introduction: Lipid-based formulations (LBFs) have emerged as a promising formulation strategy to overcome the issue of solubility-limited absorption, thereby improving the oral bioavailability of poorly water-soluble drugs (PWSDs). After oral dosing, supersaturation often arises with the potential for drug precipitation. To stabilize the metastable supersaturated state, polymer precipitation inhibitors (PPIs) may be added to LBFs to inhibit drug precipitation, potentially resulting in increased drug absorption.

Aims: The current project is exploring the solubility-supersaturation-absorption relationship when using PPIs in LBFs, by measuring drug flux in an *in vivo* experimental model.

Methods: A coupled *in vitro* digestion - isolated rat jejunum model, has been employed to evaluate in real time the impact of PPIs on drug flux. Fenofibrate and saquinavir were chosen as model PWSDs.



Results: Addition of selected PPIs prolonged supersaturation and led to increases in fenofibric acid absorption of up to ~ 4-fold. Reasonable correlation was evident between the degree of supersaturation and drug flux suggesting that increases in the intraluminal free drug fraction were driving increased absorption.

Discussion: This work demonstrates the utility of the coupled *in vitro* digestion-*in vivo* absorption model in developing a better understanding of drug absorption from polymer-containing LBFs. The data suggest that PPIs can support prolonged drug supersaturation and that this results in improved absorptive drug flux *in vivo*.

166 Pulsed magnetic stimulation for persistent post-prostatectomy stress urinary incontinence: A pilot study

Renly Lim[1], Men Long Liong[2], Kah Hay Yuen[1], [1]School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia, [2]Department of Urology, Island Hospital, Penang, Malaysia

Introduction: Stress urinary incontinence following radical prostatectomy is a significant side-effect which severely impairs quality of life. The first-line non-surgical treatment for post-prostatectomy stress urinary incontinence is the pelvic floor muscle training. However, treatment regimens are not standardised and success rates are modest. Pulsed magnetic stimulation is a non-surgical method which increases the pelvic floor muscle strength and endurance through automatic repetitive contractions.
Aims: To evaluate the efficacy of the pulsed magnetic stimulation in patients with persistent post-prostatectomy stress urinary incontinence.
Methods: Patients with persistent stress urinary incontinence (more than 12 months) after radical prostatectomy were recruited from the urology department, Island Hospital, Malaysia. The treatment regimen involved two sessions per week for eight weeks (16 sessions of 25 minutes each). The device uses a pulsed magnetic stimulation repetition cycle of 50 Hz in an 8 seconds on-4 seconds off pulsing manner. The primary outcome measure was the International Consultation on Incontinence Questionnaire for Urinary Incontinence-Short Form (ICIQ-UI SF) (range 0-21). The secondary outcome measures included the International Consultation on Incontinence Questionnaire-Lower Urinary Tract Symptoms Quality of Life (ICIQ-LUTSqol) (range 19-76) and the Patient Global Impression of Improvement (PGI-I). Evaluation was conducted pre- and post-treatment.
Results: A total of fifteen patients were enrolled (mean age 65, range 57-74). There was a significant reduction in the mean ICIQ-UI SF score from 13.5±0.9 to 9.1±0.8 ($p<0.001$). Similarly, there was a significant reduction in the ICIQ-LUTSqol score from 44.1±2.2 to 35.1±1.9, $p=0.002$. Nine of fifteen patients (60%) felt that their condition was “very much better” or “much better” as measured using the PGI-I. No side effects were observed.
Discussion: Among patients with persistent post-prostatectomy stress urinary incontinence, our preliminary results suggested that eight weeks of pulsed magnetic stimulation improved symptoms of incontinence significantly. A large randomized-controlled trial is required to confirm the findings of our pilot study.

167 Pharmacological effects of a jungle ginger on rat prostatic smooth muscle

Eunice NN Su[1,3], Jamie S Simpson[2], Philip Thompson[2], Sabatino Ventura[1], Drug Discovery Biology[1] and Medicinal Chemistry[2], Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC, Australia. Sarawak Biodiversity Centre, Kuching, SWK, Malaysia[3]

Introduction. Jungle ginger has been traditionally used by Sarawak natives to treat urological disorders. Since drugs that relax prostatic smooth muscle are used to manage urinary symptoms associated with urological disorders.
Aims. To assess the pharmacological effects of a jungle ginger on prostate contractility and to isolate its bioactive components.
Methods. This is original work reporting the biological effects of jungle ginger on isolated rat prostate contractility. Jungle ginger rhizome, roots, leaves and stem were harvested from Sarawak. Extracts of dried and ground plant materials were extracted using water at room temperature. Activity of these extracts was evaluated pharmacologically by assessing their effects on contractions of isolated rat prostate gland maintained in a modified Krebs solution at 37ºC and bubbled with carbogen gas. Nerve mediated contractions were evoked electrically (0.1-20 Hz, 0.5 ms pulse duration, 60 V) while direct muscle stimulation was achieved by application of the exogenously administered agonists. Pharmacological tools were used to identify mechanisms of action.
Discussion. Jungle ginger rhizome ($p=0.0004$, n=6), root ($p<0.0001$, n=6) and stem ($p=0.0057$, n=6) extract inhibited electrical field stimulation (EFS) induced contractions of rat prostatic smooth muscle, while leaf extract did not exhibit bioactivity ($p=0.0988$, n=6). Contractions mediated by exogenous administration of noradrenaline (1 nM-1 mM, n=6), acetylcholine (1 nM-1 mM, n=6) or ATP (0.3 uM-1 mM, n=6) were not inhibited by rhizome extract. Tyramine (10 nM-0.1 nM) induced contractions were also not effected by the rhizome extract (n=4). EFS-induced contractions were still attenuated by the rhizome extract in the presence of prazosin (300 nM, n=6), suramin (30 nM, n=6), yohimbine (1 µM, n=6), idazoxan (1 µM, n=6), propranolol (1 µM, n=6), atropine (1 µM, n=6), methysergide (1 µM, n=6), mepyramine (1 µM, n=6), hexamethonium (10 µM, n=6), desipramine (100 nM, n=6), 8-phenyltheophylline (10 µM, n=6), and AH6809 (10 µM, n=6). Jungle ginger rhizome, stem and root extracts inhibit contractility of rat prostatic smooth muscle by an indirect prejunctional mechanism that inhibits exocytotic release of neurotransmitter.

168 Post-hospital changes in medication regimen complexity and potentially inappropriate medication use in older adults with chronic kidney disease

W Tesfaye[1], RL Castelino[2], BC Wimmer[1], C McKercher[3], MD Jose[1,3], STR Zaidi[1], [1]University of Tasmania, Hobart, TAS, AU
[2]The University of Sydney, Sydney, NSW, AU, [3]Menzies Institute for Medical Research, Hobart, TAS, AU

Introduction: Significant medication change related to hospitalisation is an important contributor to patient morbidity in chronic kidney disease (CKD). Little is known about the impact of such changes on medication regimen complexity and potentially inappropriate medications (PIMs) use in older adults with CKD.
Aims: To evaluate the impact of hospitalisation on medication regimen complexity and PIMs use in older adults with CKD.
Methods: Medical records of patients aged ≥ 65 years with a documented stage 3 and 4 CKD admitted to the study hospital during Jan-Jun, 2015 were reviewed. Data on age, sex, Charlson's comorbidity index (CCI), serum creatinine, eGFR, length of hospital stay (LOS) and use of drug administration aids (DAA) were collected. The medication regimen complexity index (MRCI) and medication appropriateness index (MAI) were used to compute medication regimen complexity and PIMs, respectively. Differences in the study variables were analysed using Wilcoxon signed rank test whereas a generalised linear model was used to determine association between study variables.
Results: A total of 100 patients were included. Mean age of participants was 81.3 ± 7.9 years and most (75%) were men. The mean number of medications per patient was 10.3 ± 4.1 at admission and 10.4 ± 3.9 at discharge. There was a non-significant increase in MRCI from admission to discharge [27.7 ± 11.4 to 29.2 ± 11.8]. A significant decline in the use of PIMs was observed at the time of discharge from the hospital (MAI of 8.4 ± 6.3 vs. 6.4 ± 5.4; $p<0.01$). Patients who stayed longer were likely to have a significantly higher change in MRCI after adjusting for the effect of age, sex, CCI, renal functions at admission, and use of DAA ($\beta=0.31$, Std Err=0.05, $p<0.01$).
Discussion: Despite the added medication regimen complexity, hospitalisation resulted in a significant reduction in PIMs in older adults with CKD. Moreover, longer hospitalisations have led to higher medication regimen complexity at discharge. This could pose concerns regarding medication adherence after patient discharge from hospital. Future studies should explore the determinants of the observed reduction in PIMs use and the increase in medication regimen complexity with prolonged hospital admission to optimise medication use in older adults with CKD.

169 Effect of Rho-kinase inhibitors on contractility of porcine corpus cavernosum

Amelia J Jack, Dr. Donna Sellers, Prof. Russ Chess-Williams, Centre for Urology Research, Bond University, Gold Coast, QLD, Australia

Introduction: The main oral pharmacotherapy available for erectile dysfunction (ED) are not effective for 32% of men (Eardley et al, 2010). As smooth muscle relaxation is a desired outcome of treatment, the RhoA/Rho-kinase (ROCK) pathway is under investigation as a novel target in the control of muscle tone in the corpus cavernosum, as previous research has shown a role for ROCK in maintaining the contractility of the corpus cavernosum in rodents (Chitaley et al, 2001).
Aim: This study investigated the role of the ROCK signalling pathway in mediating smooth muscle tone in porcine corpus cavernosum.
Methods: Functional organ bath studies investigated the contractility of porcine corpus cavernosum in the absence and presence of the ROCK inhibitors Y-27632 (10μM) and GSK-269962 (100nM). Phenylephrine concentration-response curves determined maximum contraction and potency (pEC_{50}) values. Student's t-test identified differences between tissue responses ($p<0.05$ = significant difference).
Results: Mean maximum contractions induced by phenylephrine were significantly decreased by 75.2±3.6% ($p<0.01$, n=19) by Y-27632 and 36.6±5.2% ($p<0.01$, n=15) by GSK-269962 compared to control. The potency of phenylephrine was reduced in the presence of Y-27632 (5.84±0.12 vs. 4.50±0.27, ($p<0.01$), and in the presence of GSK-269962 (5.85±0.17 vs. 5.18±0.16, $p<0.01$).
Discussion: The ROCK signalling pathway is involved in mediating smooth muscle tone in porcine corpus cavernosum. Y-27632 produced a greater inhibitory effect on the contractions induced by phenylephrine than GSK-269962. Y-27632 also affected the potency of phenylephrine more than GSK-269962. This could be due to the non-selective action of Y-27632 on other kinases involved in smooth muscle tone. The ROCK signalling pathway may be a potential target molecule for development of alternative therapy, providing a new treatment option for ED.
Chitaley K et al (2001) Nat Med 7:119-122.
Eardley I et al (2010) J Sex Med 7:524-540.

170 The effects of aging on polarization in collagen sandwich-cultured hepatocytes

Sun Woo Sophie Kang[1,2], Dong Fu[3], David G. Le Couteur[1,2] and Victoria C. Cogger[1,2], [1]Aging and Alzheimers Institute, ANZAC Research Institute, Concord Clinical School/Sydney Medical School, Concord, NSW, Australia,[2]Charles Perkins Centre, University of Sydney, Sydney, NSW, Australia, [3]UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, NC, United States of America

Introduction: Hepatocytes have a unique polarized phenotype where apical domains of adjacent cells make up a tubular structure, known as bile canaliculus. This polarized morphology is important for hepatocyte function and viability. Loss of polarity can result in excessive accumulation of bile, toxins and metabolites that can lead to hepatocellular damage such as seen in drug-induced hepatotoxicity and liver diseases such as cholestasis, fibrosis and cirrhosis. Ageing is associated with increased susceptibility to impaired hepatic function, which can increase the risk of adverse drug reactions that are associated with hepatotoxicity and liver disease. However, the effect of ageing on hepatocyte polarization is unknown. Using collagen sandwich cultures of hepatocytes, we compared the reestablishment of hepatocyte polarization in isolated hepatocytes from young and old mice.
Methods: Hepatocytes were freshly isolated from young (3 months) and old (24 months) C57BL6 male mice and cultured in a collagen sandwich configuration. Polarization was assessed every 12 hours over 72 hours using lipid droplet staining and immunofluorescence of apical protein ATP-binding cassette sub-family B member 1 and tight junctional protein Zonula occludens-1. ATP levels were also quantified.
Results: Immunofluorescence revealed that hepatocytes from old mice polarized at a faster rate than young hepatocytes. Furthermore, there were significantly more and larger lipid droplets in the hepatocytes of old mice from the beginning of hepatocyte polarization. Lipid droplets remained large in old hepatocytes after 60 hours even after the formation of the bile canalicular network. In young mice, the reduction of lipid droplet numbers was evident after 24 hours. Polarization is an energy-dependent cellular process. ATP levels rapidly peaked within 24 hours in old hepatocytes whereas in young hepatocytes levels increased more slowly and peaked after 48 hours.
Discussion: Hepatocytes from old mice polarize and accumulate ATP more rapidly than young hepatocytes. These changes might contribute to age-related changes seen in hepatic function and susceptibility to drug-induced hepatotoxicity and liver diseases such as fatty liver.

171 Human 5-HT3AC receptors are subtly different to 5-HT3A receptors

Helen R. Irving[1,2], Isaiah Abad[1], Ray L. Fam[1], Dan-Thanh Nguyen[1], Cameron Nowell[1], Phuc Trinh[1], Jay Chakrabarti[1], David T. Manallack[3], Nor S. Yaakob[1,4], Betty Exintaris[1], [1]Drug Discovery Biology, Monash University, Melbourne, VIC, Australia, [2]La Trobe Institute for Molecular Science, La Trobe University, Bendigo, VIC, Australia, [3]Medicinal Chemistry, Monash University, Melbourne, VIC, Australia, [4]Drug & Herbal Research Centre, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

Introduction: Five different subunits of the human 5-HT_3 receptor exist and these are present in both central and peripheral systems. 5-HT_3 receptor antagonists are used to treat diarrhea predominant-irritable bowel syndrome (IBS-D), chemotherapy induced nausea and vomiting (CINV) and depression. Receptor subunit arrangement is poorly understood and may contribute to differences in efficacy observed with the 5-HT_3 receptor antagonists.
Aims: To characterise the effect of the C subunit on 5-HT_3 receptor cell surface expression and function.
Methods: HEK293T cells were transiently transfected with constructs of 5-HT_3 receptor subunits containing fluorescent protein inserts between the 3rd and 4th transmembrane spanning region. Heteromers containing the C and A subunits were compared with homomers containing only the A or C subunit using whole cell patch clamp recording and super resolution microscopy.
Results: The A subunit is necessary to obtain functional AC subunits at the cell surface. Approximately 15-40% 5-HT_3 receptors at the cell surface are AC heteromers and the remainder are receptor homomers. Overall surface distribution of C subunits is in the range of 20-60% and A subunits is 40-80%. The surface distribution and co-localization is reflected in internal receptor assembly. The 5-HT_3 receptor C subunits contributed subtle changes in the electrophysiological responses to 5-HT. However, ondansetron exhibited reduced efficacy on the AC heteromer relative to the A homomer.
Discussion: C subunits interact with A subunits to form functional receptors. Patch-clamp experiments indicate that the presence of C subunits alters the efficacy of the clinically used antagonist ondansetron. The C subunit is widespread and found co-localized with the A subunit. Predisposition to forming 5-HT_3 receptor heteromers could contribute to poor responses observed in up to 40% of patients treated for CINV and IBS-D.

172 Characterization of Na_v Channels in Colon-Innervating Dorsal Root Ganglion Neurons in Mice

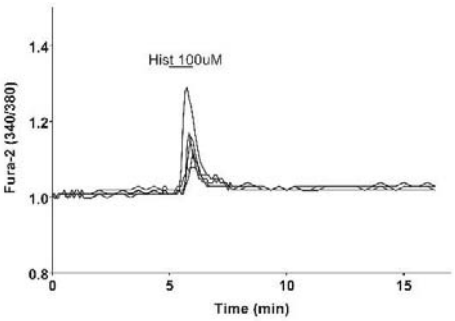
Andelain Erickson[1,3], Sonia Garcia-Caraballo[1,3], Joel Castro[1,3], Luke Grundy[1,3], Grigori Rychkov[1], Richard Lewis[2], Irina Vetter[2], Glenn King[2] and Stuart M. Brierley[1,3], Discipline of Medicine, SAHMRI, University of Adelaide[1], SA, AUSTRALIA, Institute for Molecular Bioscience, University of Queensland[2], St Lucia, QLD, AUSTRALIA, Visceral Pain Research Group, Human Physiology, Flinders University[3], Adelaide, SA, AUSTRALIA.

Chronic visceral pain is a poorly managed symptom of functional and inflammatory gastrointestinal disorders and there is a lack of analgesics that are efficacious without gastrointestinal side effects. Voltage-gated sodium (Na_v) channels regulate action potential generation and cell membrane excitability in sensory neurons, and they are implicated in several pain or loss-of-pain phenotypes in humans, which has inspired investigation into the therapeutic potential of Na_v channel modulation. In this study, we show that Na_v channels and their auxiliary β-subunits are abundantly expressed in dorsal root ganglia (DRG) neurons at thoracolumbar (TL) and lumbosacral (LS) levels from C57BL/6J mice, and heterogeneously expressed in colon-innervating DRG neurons. Using retrograde labeling and whole-cell patch clamp electrophysiology, we found that colonic TL and LS neurons exhibited comparable peak sodium current densities (TL: –894 pA/pF, n = 23; LS: –883 pA/pF, n = 14), however, colonic TL neurons were significantly less excitable compared to colonic LS neurons (rheobase: TL: 183 pA, n = 32; LS: 85 pA, n = 22. p = 0.0143). The Na_v channel blocker tetrodotoxin (TTX, 100 nM) significantly increased the minimum current required to fire an action potential in colonic TL and LS neurons, however, sodium current densities in colonic TL neurons were less affected by TTX compared to colonic LS neurons (TL: 50% reduction, n = 14; LS: 70% reduction, n = 8).

In conclusion, voltage-gated sodium channels and auxiliary β subunits are highly abundant in whole DRG and colonic DRG from T10–S1 spinal levels. However, TTX-S channels may have differing contributions to colonic DRG neurons innervating the thoracolumbar versus lumbosacral regions, which may underlie their differing functions.

173 Histamine receptor (Hrh) subtypes mediate bladder afferent sensitivity in mice

Ashlee Caldwell[1], Luke Grundy[1,2], Andelain Erickson[1], Grigori Rychkov[2], Stuart Brierley[1,2]. Dept of Medicine, Univ of Adelaide[1], Adelaide, SA; Dept of Hum Physiol, Flinders Univ[2], Bedford Park, SA.



Introduction: Pelvic pain conditions such as overactive bladder syndrome and interstitial cystitis are associated with enhanced bladder sensation, leading to the symptoms of frequency, urgency and pain. Histamine, released from activated mast cells, is a key mediator of neurogenic inflammation and pain in the bladder and other visceral organs. However, the exact role and distribution of histamine receptor subtypes (Hrh1-4) in bladder sensory structures is unknown.
Aims: To determine the expression and function of histamine receptors in bladder sensory structures.
Methods: RT-PCR was performed on primary urothelial cells and mucosal and detrusor layers of mouse bladders. Retrogradely labelled bladder DRG neurons from mice were isolated and dissociated for single-cell RT-PCR and calcium imaging. *Ex-vivo* bladder afferent recordings determined bladder mechanosensitivity.
Results: RT-PCR revealed mRNA expression of Hrh1-3 in dissociated urothelial cells, and 10-fold higher expression in bladder mucosal and detrusor tissue. Hrh4 mRNA expression was 1000-fold lower in both cells and tissues. Single cell PCR data identified Hrh1 mRNA expression in 29% of bladder afferent neurons whilst histamine (100µM) induced significant calcium transients in 18% of bladder DRG neurons. Histamine (300µM) perfused into the bladder lumen induced mechanical hypersensitivity to bladder distension versus saline ($p<0.01$, n=6) which was attenuated by Hrh1 antagonist pyrilamine (100uM) and completely abolished by combined Hrh1 and Hrh4 antagonists.
Discussion: Histamine receptors are present and functional in bladder sensory structures, and their activation is able to induce calcium transients in isolated bladder neurons and enhance bladder mechanosensitivity to distension. This work provides valuable insight into the action of histamine, and the role of histamine receptors in the bladder, unravelling potential mechanisms of pelvic pain pathology.

174 Morphine dosing affects development of antinociceptive tolerance and motor behaviour

Alok K Paul[1], Nuri Gueven[1], Nikolas Dietis[1,2]. Division of Pharmacy, School of Medicine, University of Tasmania[1], Hobart, TAS, Australia; Medical School, University of Cyprus[2], Nicosia, Cyprus.

Introduction. Clinical development of antinociceptive tolerance after repeated administration morphine limits its chronic use. Despite growing knowledge about the molecular mechanisms of morphine tolerance, we know little about the influence of dosage regimen in its development.
Aims. We hypothesized that morphine dose, as well as dose increments, contribute to tolerance development. In addition, morphine-induced behavioural changes also might follow similar pattern of antinociception and tolerance.
Methods. Four groups of male Sprague Dawley rats received different daily doses of intermittent subcutaneous morphine for 14 days. After the development of antinociceptive tolerance, different increments of morphine doses were administered until tolerance redeveloped (Group A: 2.5 (b.i.d) → 5 → 10 mg/kg/day, Group B: 5 (b.i.d.) → 10 mg/kg/day, Group C: 5 (b.i.d.) → 15 mg/kg/day and Group D: 10 (b.i.d.) → 20 mg/kg/day). Antinociceptive responses were measured daily by tail-flick and hot-plate assays pre-treatment and at various post-treatment time-points. Motor behavioural effects were also measured using automated open-field paradigm and visual observations.
Results. Animals treated with lower starting-doses of morphine developed antinociceptive tolerance faster than those started on higher doses. Higher starting-doses and higher dose-increments after tolerance development resulted in more sustained antinociception and delayed the re-development of tolerance. These results were replicated by both anti-nociceptive assays and are therefore not assay-specific. The kinetics of morphine-induced motor suppression and desensitization were similar to those of antinociception and antinociceptive-tolerance respectively.
Discussion. These results suggest that morphine dosing regimen in rats significantly influences the manifestation of antinociceptive tolerance and the total antinociception (Paul et al., 2017). Our results also indicate that repetitive morphine dosing leads to desensitization of motor suppression in all major motor-behavioural parameters and manifests desensitization in conjunction with antinociceptive tolerance. Therefore, our results highlight that an optimized morphine dosing strategies can delay antinociceptive tolerance and reduce behavioural adverse effects.
Paul AK et al (2017) Neuropharmacology 121:158-166

175 Increased osmotic pressure promotes glioblastoma invasiveness

Wenjun Pu, Samira Khabbazi, Nan Xie, Marie-Odile Parat, School of Pharmacy, the University of Queensland[1], Brisbane, QLD, Australia

Introduction: Both hydrostatic and osmotic pressures are altered in the tumour microenvironment. Glioblastoma (GBM) is a brain tumour with high invasiveness and poor prognosis. We hypothesized that higher osmotic pressure regulates glioblastoma (GBM) invasiveness. Better understanding the molecular and cellular mechanisms of how increased pressure promotes GBM invasiveness may help to develop innovative therapeutic approaches.
Aims: To evaluate the effect of osmotic pressure on GBM invasive potential.
Methods: The osmotic pressure of GBM cell culture medium was adjusted using sodium chloride or water. Cells were incubated in serum-free medium of various osmolality (from 260 to 440 mOsm) for 48 hours. Cell viability was tested using the MTT assay. The proteolytic profile and epithelial–mesenchymal transition (EMT) were investigated using zymography and real-time qPCR. The EMT markers assessed were snail-1, slug, twist, vimentin and N-cadherin. Invasion was investigated *in vitro* using Transwell™ inserts coated with basement membrane-like protein.
Results: In response to osmotic stress, GBM cell lines U87 and U251 upregulated the expression of urokinase-type plasminogen activator (uPA) and matrix metalloproteinases (MMPs) well as some of the EMT markers tested.
Discussion: GBM respond to osmotic pressure by increasing matrix degrading enzyme production, and adopting a gene expression phenotype reminiscent of EMT.

176 Discovering methyllycaconitine analogues specific for α4 β2 over α7 nAChR subtypes

Taima Qudah[1], Ryan Gallagher[2], Nathan Absalom[1], Thomas Balle[1], Malcolm McLeod[2], Mary Chebib[1], [1] Faculty of Pharmacy, The University of Sydney, NSW, [2]Research School of Chemistry, The Australian National University, ACT, Australia

Introduction: Nicotinic Acetylcholine Receptors (nAChRs) are pentameric ligand-gated ion channels where the α7 and α4β2 subtypes are the most predominant in the brain. The α4β2 nAChR is known to exist in two functional isoforms with different ACh-activation properties, namely the $(\alpha4)_2(\beta2)_3$ and $(\alpha4)_3(\beta2)_2$ receptor that differ by the presence of an additional agonist binding site at the α4-α4 interface on $(\alpha4)_3(\beta2)_2$ receptors. Methyllycaconitine (MLA) is a natural toxic potent antagonist that competes with ACh at the same binding site. MLA is 1000-fold more selective for α7 than at α4β2 despite high potency at both receptors. Identifying selective α4β2 nAChR antagonists have significant therapeutic potential and contribute to understanding the physiological roles of these subtypes *in vivo*.

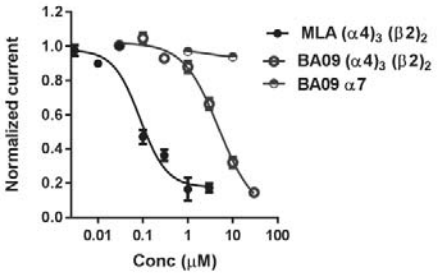


Figure 1. Inhibition of $(\alpha4)_3(\beta2)_2$ receptors by MLA and BA09, and α7 receptors by BA09.

Hypothesis: we hypothesize that the AE succinimide component of MLA has higher selectivity at the α4-α4 in $(\alpha4)_3(\beta2)_2$ over the α7-α7 interface.

Method: we synthesized MLA analogues and screened these by co-applying 10 μM of each compound with 1 mM ACh for $(\alpha4)_3(\beta2)_2$ and α7 and 100 μM ACh $(\alpha4)_2(\beta2)_3$ on human recombinant receptors expressed in *Xenopus* oocytes using the two-electrode voltage clamp techniques.

Result: we identified three analogues (BA09, BA11 and BA12) that inhibited the ACh induced current at $(\alpha4)_3(\beta2)_2$ by 80%, 82% and 70%, respectively with no effect at the α7 subtype (e.g BA09 in Figure 1). The same analogues only inhibited the ACh evoked current by 35%, 30% and 33% at $(\alpha4)_2(\beta2)_3$ respectively. Based on these results, we identified lead molecules that distinguish between α4β2 and α7 receptors.

177 Inhibition of α5β1 with the clinically validated small peptide ATN-161 is neuroprotective and functionally restorative in experimental stroke

Danielle N Edwards[1], Katie Salmeron[1], Justin F Fraser[1,2,3,4], Gregory J Bix[3], [1]Neuroscience, University of Kentucky, Lexington, KY, USA, [2]Neurosurgery, University of Kentucky, Lexington, KY, USA, [3]Neurology, University of Kentucky, Lexington, KY, USA, [4]Radiology, University of Kentucky[4], Lexington, KY, USA

Introduction: Stroke is the second leading cause of death and the leading cause of long-term disability worldwide. Blood-brain barrier (BBB) dysfunction exacerbates reperfusion-induced injury after recanalization in ischemic stroke. Endothelial cell integrin receptors, specifically the β_1 subtype, play a direct role in this BBB dysfunction through regulation of barrier-forming tight junction (TJ) proteins.

Aims: We hypothesize that inhibition of a specific β_1 integrin subtype, $\alpha_5\beta_1$, after experimental stroke will stabilize the BBB through the TJ protein claudin-5, and thereby reduce infarct volumes and improve functional recovery.

Methods: Transient middle cerebral artery occlusion was performed on 12-week-old mice for 1 hour. Intraperitoneal injection of saline vehicle or the small peptide $\alpha_5\beta_1$ inhibitor ATN-161 (1mg/kg), which has been successfully employed in cancer clinical trials as an anti-angiogenic therapy, was performed immediately after reperfusion, on post stroke day (PSD) 1, and PSD2 (n=12). Infarct volume was determined by TTC staining of brain sections on PSD3. In additional experiments, a 5-point Neuroscore determined functional behaviour after ATN-161 treatment through PSD14 (n=10). Physiological measurements, including pulse distention, heart rate and body temperature, were obtained before, during and after the initial dose of ATN-161. Immunohistochemical analysis of $\alpha_5\beta_1$, claudin-5, NeuN, GFAP, and IgG expression was performed on PSD3 and PSD14.

Results: Therapeutic inhibition of $\alpha_5\beta_1$ significantly reduced infarct volume and improved functional recovery. Additionally, immunohistochemistry stains demonstrated neuroprotection and reduction of BBB permeability after inhibition of $\alpha_5\beta_1$.

Discussion: Inhibition of $\alpha_5\beta_1$ with the repurposed small peptide inhibitor ATN-161 produced significant benefits after experimental stroke and could represent a novel stroke therapy worthy of further investigation.

178 Morphine regulates cellular migration and invasion by modifying the circulating proteolytic profile in mice

Nan Xie[1], Samira Khabbazi[1], Zeyad D. Nassar[1], Kye Gregory[2], Tharindu Vithanage[2], Bela Anand-Apte[3], Peter J. Cabot[1], David Sturgess[2], Paul N. Shaw[1], Marie-Odile Parat[1,] [1]School of Pharmacy, The University of Queensland, St Lucia, QLD, [2]Mater Research Institute (MRI-UQ), The University of Queensland, Brisbane, QLD, [3]Department of Ophthalmology, Cole Eye Institute, Cleveland Clinic Lerner College of Medicine, Case Western Reserve University[3], Cleveland, OH, USA

Introduction: Opioids have been suggested to modulate cell adhesion and migration in different cancer types, thereby influencing their metastatic potential. We have previously demonstrated that administration of morphine to tumour-bearing mice significantly decreased circulating matrix metalloprotease (MMP)-9 (Afsharimani et al, 2014). In this study, we report that morphine administration to tumour-free mice alters their circulating proteolytic profile.
Methods: Serum from morphine (1 or 10 mg/kg every 12 h for 3 days)- or control, saline-treated, mice was collected at different time points and tested *ex vivo* in endothelial, lymphatic endothelial and breast cancer cell migration and reconstituted basement membrane cell invasion assays. Circulating MMP and Tissue Inhibitor of Matrix Protease (TIMP) activities were assessed by zymography and reverse zymography. Quantitative RT-PCR was used to measure MMP-9 and TIMP expression in multiple organs collected at day 3 from these mice.
Results: Serum from mice treated with 10 mg/kg morphine for 3 days displayed reduced chemotactic potential for endothelial and breast cancer cells, and elicited lesser breast cancer cell invasion compared to serum from saline-treated mice. This was associated with decreased circulating MMP-9 and increased circulating TIMP-1 and -3/4. This was confirmed by variations of MMP-9 and TIMP expression in several organs after morphine administration. Pharmacological inhibition of MMP-9 nullified the difference of the ability of breast cancer cells to migrate or invade towards serum from saline-or morphine-treated mice, indicating that MMP-9 may play a key role in the effect of morphine on *ex vivo* cell migration and invasion.
Discussion: This novel mechanism signals that morphine administration may promote an environment less conducive to tumour growth, invasion and metastasis.

Afsharimani B et al (2014) Clin Exp Metastasis 31:149-58.

179 Stress induced analgesia is reduced in neuropathic pain states

Nicholas Atwal and Christopher W Vaughan, Pain Management Research Institute, Kolling Institute for Medical Research, University of Sydney, Sydney, NSW, Australia

Introduction: It is well known that acute stress can produce pain relief (stress-induced analgesia) and that this is mediated by a descending analgesic pathway (Butler and Finn, 2009). It is known that this analgesic pathway is altered in chronic neuropathic pain states, but the effect of this on stress-induced analgesia is unknown.
Aims: The objective of this study was to determine if stress-induced analgesia is altered in a neuropathic pain state.
Methods: Adult male C57BL/6 mice underwent chronic constriction injury (CCI) of the sciatic nerve, or matched sham surgery, and animals were assessed at 8 days post-surgery. Stress was induced using restraining devices for 30 mins. Analgesia was measured using the hot plate and Hargreaves test. The nature of the stress-induced analgesia produced was determined through acute subcutaneous drug injections of various antagonists which included naltrexone (15mg/kg), AM281 (3mg/kg), AM630 (3mg/kg) and RU-486 (50mg/kg).
Results: Sham operated mice which were subjected to restraint stress demonstrated longer hot plate and Hargreaves latencies than those which were not restrained ($P<0.05$). For the hot plate test, naltrexone and RU-486 reduced stress-induced analgesia compared to their respective vehicles ($P<0.05$). In the Hargreaves test, only the co-administration of naltrexone and AM281 diminished stress-induced analgesia ($P<0.05$). CCI operated mice displayed significantly lower stress-induced analgesia compared to their sham counterparts ($P<0.05$).
Discussion: Stress-induced analgesia produced in sham animals was largely opioid and cannabinoid receptor mediated. In neuropathic pain states however, stress-induced analgesia was diminished. These findings suggest the descending analgesic pathway is dysfunctional in neuropathic pain states.

Butler RK, Finn DP (2009). Stress-induced analgesia. Prog Neurobiol 88**:** 184-202.

180 Phytocannabinoid actions in an animal model of neuropathic pain

Jessica A Falon[1], Vanessa A Mitchell[1], Sherelle L Casey[1], Jonathon C Arnold[2], Iain S McGregor[3], Bryony L Winters[1], Christopher W Vaughan[1], [1]Pain Management Research Institute, Kolling Institute for Medical Research, [2,3]Lambert Initiative for Cannabinoid Therapeutics, [2]Discipline of Pharmacology, [3]School of Psychology, University of Sydney, Australia

Introduction: Emerging evidence has revealed the potential analgesic efficacy of phytocannabinoids from the plant *Cannabis sativa* in neuropathic pain states. Only its two most prominent constituents have been characterised in regards to pain – Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC displays high analgesic efficacy in animal neuropathic pain models, though alongside numerous side-effects. By contrast, CBD has lesser analgesic efficacy and lacks cannabinoid-like side-effects (Casey et al, 2017). In light of this, it is possible that one or more of the uncharacterised phytocannabinoids could be effective against neuropathic pain.
Aims: To investigate three previously uncharacterised CBD-based phytocannabinoids – cannabadiolic acid (CBDA), cannabidavarin (CBDV) and cannabidavarinic acid (CBDVA) – in a mouse model of neuropathic pain.
Methods: Sciatic nerve injury was induced in C57BL/6 mice using the chronic constriction injury (CCI) model and cannabinoids were administered 9 days post-CCI (0.01ml/g s.c. in saline with 10% dimethylsulfoxide, 5% Tween80) under anaesthesia (2% isoflurane in saturated oxygen). Mechanical paw withdrawal threshold and number of pain-like responses to acetone applied to the affected hind paw were used to measure mechanical and cold allodynia. Side effects were also monitored: motor incoordination (rotarod), sedation (dark open field) and catalepsy (bar test).
Results: Of the phytocannabinoids tested, CBDV produced the greatest decrease in mechanical and cold allodynia (25 % reduction). CBDV, CBDA and CBDVA produced no significant side-effects. In combination with THC, CBDVA produced a greater reduction in allodynia than THC alone, while producing no significant change in any of the THC side-effects.
Discussion: This data indicates that while only minimally effective alone, CBDVA may act synergistically with THC in an animal model of neuropathic pain, and therefore may be a potential candidate for treatment of the condition.

Casey SL, Atwal N, Vaughan CW (2017) Cannabis constituent synergy in a mouse neuropathic pain model. Pain (in press); PMID: 28885457.

181 Nesfatin-1 suppresses feeding and induces emesis in Suncus murinus (House Musk Shrew)

Sze Wa Chan[1], Zengbing Lu[1,2], Takafumi Sakai[3], Ichiro Sakata[3], Ge Lin[2], John A Rudd[2,4], [1]School of Health Sciences, Caritas Institute of Higher Education, [2]School of Biomedical Sciences and [4]Brain and Mind Institute, The Chinese University of Hong Kong, Hong Kong SAR, China, [3]Graduate School of Science and Engineering, Saitama University, Saitama, Japan

Introduction: Nesfatin-1 is an 82-amino acid anorectic peptide derived from nucleobindin2 (NUCB2). NUCB2/nesfatin-1 is expressed in peripheral tissues and also in brain areas involved in the regulation of feeding, emotion and emesis. However, the potential involvement of nesfatin-1 in emesis control is essentially unknown.
Aims: The present studies examine the effect of a central administration of nesfatin-1 on feeding, emesis and locomotor activity in *Suncus murinus*.
Methods: Animals were anaesthetised with sodium pentobarbitone (40 mg/kg, i.p.) and then stereotaxically implanted with a guide cannula into the lateral ventricle and allowed a 7-days recovery before experimentation. Animals were fasted 12 h prior to administration of drugs. Nesfatin-1 (1-50 pmol, i.c.v.) or saline (5 µl, i.c.v.) was administered to conscious fasted animals. Emesis and spontaneous behaviour were measured for 6 h, while food and water consumption was measured hourly for 6 h and at 24 h post-administration.
Results: Compared to saline-treated animals, nesfatin-1 (5 pmol, i.c.v.) suppressed the amount of food eaten at 4-, 5- and 6-h by 30.9%, 32.9%, and 29.4%, respectively ($P<0.01$; cumulative measurements), but it failed to affect the latency to eat ($P>0.05$). Nesfatin-1 at 1 pmol, i.c.v. suppressed cumulative water intake assessed at 5-h ($P<0.05$); higher doses (5-50 pmol) had no effect. No statistically significant differences in the 24-h cumulative food and water intake between treatment groups were found. Additionally, nesfatin-1 at 5 pmol i.c.v. induced emesis in 5 out of 6 animals with 7.5 ± 4.4 retches + vomits following a median latency of 39.7 min ($P<0.05$). Nesfatin-1 had no effect on the locomotor activity.
Discussion: To the best of our knowledge, nesfatin-1 is the most potent peptide to induce emesis and inhibit feeding in *S. murinus*. The studies were fully supported by a grant from the Research Grants Council of the Hong Kong SAR, China (Project no. UGC/FDS11/M02/16).

200 Innovations in clinical pharmacology education

Clare Guilding[1,2], [1]Faculty of Medical Sciences, Newcastle University, Newcastle Upon Tyne, UK, [2]Newcastle University Medicine Malaysia, Johor, Malaysia

Education in clinical pharmacology and therapeutics (CPT) is fundamental for the successful practice of medicine, with prescribing an essential skill for most doctors. Yet medical graduates feel underprepared for prescribing in the work place. This is substantiated by high medication error rates in the National Health Service, which combined with the recent introduction of the Prescribing Safety Assessment for UK medical students has sharpened focus on the undergraduate teaching of CPT and prescribing[1].

We undertook a wholesale review of the CPT curriculum within the MBBS degree programme at Newcastle University, and working with the British Pharmacological Society's core curriculum[1] designed a 'Clinical Pharmacology, Therapeutics and Prescribing' (CPTP) strand which now run throughout our 5 year programme. This strand introduces prescribing competencies into the early years of the course, and includes more experiential learning to provide students with an experience which more closely mirrors the clinical workplace. A range of educational tools have been employed including team based learning, case based learning, interprofessional education and high-fidelity simulation using the sophisticated virtual patient SimMan.

SimMan simulations of medical emergencies (e.g. acute asthma attack, sepsis) have been delivered both in the lecture theatre, and as a team based learning exercise in an interprofessional education conference for pharmacy and medical students. At a series of key clinical points throughout each scenario the students are asked to vote on the most appropriate course of action (e.g. which drug should be administered). The option with the most votes is applied to SimMan and the students then observe the physiological effects this has in real time.

Evaluations of the CPTP strand, simulations and interprofessional education activities have been extremely positive. Students reported that the simulation sessions contextualised the importance of basic pharmacology principles for clinical practice while the interprofessional education sessions allowed them to develop their prescribing, problem-solving, team-working and critical evaluation skills.

1. Ross and Maxwell, 2012. Br J Clin Pharmacol. 74(4): 644–661.

201 Increasing polypharmacy in aged care facilities: trends, problems and solutions

Natali Jokanovic, Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Melbourne, VIC, Australia

Polypharmacy is highly prevalent and increasing in residential aged care facilities with up to 74% of resident taking nine or more medications. The burden and harms associated with polypharmacy are well-known and have resulted in calls for a national strategy to reduce unnecessary or harm medication use. Medications contributing to polypharmacy have recently been highlighted in an Australian cross-sectional study of 27 facilities. These included beta-blockers, antithrombotics, statins, antidepressants and proton-pump inhibitors. Wide variability in the prescribing of these medications was also found across the facilities. A number of challenges and potential solutions have been identified to managing polypharmacy. Interventions currently underway to manage polypharmacy in residential aged care have included initiatives to improve the de-prescribing of unnecessary or inappropriate medications and improving existing medication advisory committees within aged care facilities.

202 How is Canada addressing the increasing burden of polypharmacy?

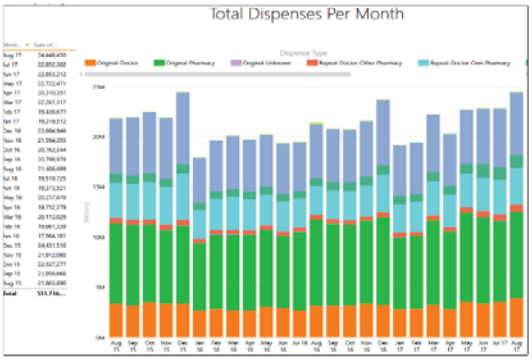
Justin Turner[1] and Cara Tannenbaum[2,3], [1]Faculté de pharmacie, Université d Montréal, Québec, Canada, [2]Faculté de pharmacie, [3]Faculté de Medicine Université d Montréal, Québec, Canada

Introduction: Neither sedative-hypnotics or chronic use of proton pump inhibitors (PPIs) are recommend in older adults, yet they are commonly prescribed across Canada. Prescribers' skills and capacity for successfully navigating conversations about deprescribing these medications remains unknown.
Aim: To identify conversation stumbling blocks that impede successful deprescribing conversations between prescribers and older adults about discontinuing sedative-hypnotics or PPIs.
Methods: Family physicians (n=12) and a nurse practitioner (n=1) from Family Medicine Teaching Units across greater Montréal, and patients aged ≥65 years who were prescribed sedative-hypnotics (n=7) or PPIs (n=15) were enrolled. Encounters involving conversations re-evaluating the use of sedative-hypnotics or PPIs were audiotaped. A qualitative thematic analysis was conducted. Emergent themes were coded, and areas for improvement identified.
Results: Areas for prescriber improvement include: difficulty clarifying the indication for PPIs; ambivalence towards and difficulty determining the balance of benefit and risk for both drug classes; greater concern about the harms from withdrawal than the harms of continued prescribing, especially for PPIs; fear and reluctance to deprescribe due to the risks of symptom return; lack of reference to tapering schedules; inadequate discussion of alternative drug and non-drug therapies including melatonin or cognitive behavioural therapy for insomnia; deferral to patient preference to continue sedative-hypnotics; discomfort with assertive deprescribing and lack of affirmation of the necessity for deprescribing
Discussion: Education, tools and coaching are required to increase prescribers' skills and confidence for successfully implementing a patient-centred deprescribing plan for sedative-hypnotics and chronic use of PPIs.

203 Integrating prescribing and dispensing data across primary care, hospitals and aged care: The MedView Project

David Freemantle, General Manger eHealth, Fred IT Group, Abbotsford, Victoria

Introduction. The Convergence of Health care and data has long been an identified opportunity to improve health outcomes, drive system efficiency and reduce the costs to the state and federal funders.



For the last 9 years, Fred IT Group has been operating the eRx Script Exchange prescription exchange service across Australia and the benefits of the data generated are starting to come to life. Whether it be data for Real Time Prescription Monitoring (RTPM) to help address prescription drug overdoses, providing better care in an Emergency Department due to improved quality and completeness of medications information, better managing a patient's transition between different parts of the health sector, or multiple other use cases, effective collection and use of medications data improves outcomes and saves lives.

Aged Care is an area requiring fundamental change in the way patient data is managed and maintained, particularly as patients transition from the community setting into aged care and between their facility and hospital. The sharing of comprehensive medications information is vital in enabling these improvements.

RTPM is another area of significant focus for Advocacy Groups, IT Companies, State and Federal Governments and Coroner's Courts across the nation. With three Australians dying every day from prescription drug misuse[1], the problem is widespread, growing and widely acknowledged.

Fred IT Group's MedView service consolidates data from multiple sources (including eRx Script Exchange) and presents that data to health practitioners and patients at the various points of care. Such initiatives have the potential to save lives, reduce load on the health system and improve clinical outcomes for patients.

[1] Penington Institute: Australia's Annual Overdose Report 2016

204 Application of a structured approach to simplify medication regimens in residential aged care

Janet K Sluggett[1,2], [1]Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Parkville, VIC, Australia, [2]National Health and Medical Research Council (NHMRC) Cognitive Decline Partnership Centre, Hornsby Ku-ring-gai Hospital, Hornsby, NSW, Australia

The high prevalence of polypharmacy, together with a multiplicity of medication administration times, formulations and special dosing instructions, means that complex medication regimens are common in residential aged care facilities (RACFs). Strategies to reduce unnecessary medication complexity in RACFs are likely to be valued by residents and aged care providers because complex regimens can be burdensome for residents and may present opportunity costs in terms of nursing time. In some cases, it may be possible to reduce unnecessary medication complexity by administering different medications at the same time of day and/or prescribing slow release or combination formulations. Researchers from the Centre for Medicine Use and Safety at Monash University are working closely with Helping Hand Aged Care and other members of the NHMRC Cognitive Decline Partnership Centre to undertake the 'SImplification of Medications Prescribed to Long tErm care Residents' (SIMPLER) study. SIMPLER is a non-blinded, matched-pair, cluster randomised controlled trial of a single multidisciplinary intervention to simplify medication regimens in RACFs. Trained study nurses have recruited more than 240 permanent residents from eight South Australian RACFs to participate in the SIMPLER study. An experienced pharmacist is using a validated, five-item implicit tool to identify opportunities to reduce the number of medication administration times for residents in the intervention arm, and discuss recommendations with relevant stakeholders. Participants will be followed for up to 36 months after study entry. The primary outcome of the SIMPLER study is the total number of medication administration times per day at four months post study entry. Secondary outcomes include the total number of medication administration times at 8 and 12 months after study entry, time spent administering medications, medication incidents, resident satisfaction and quality of life, hospitalisations, falls and mortality. Early results indicate that opportunities for medication regimen simplification may be present for up to two thirds of residents who have received the intervention. SIMPLER will quantify the impact of medication regimen simplification on a range of outcomes that are important for residents and aged care providers.

205 Adipokines, cardiovascular function and brain inflammation

Emilio Badoer, School of Health and Biomedical Sciences, RMIT University, Melbourne Victoria Australia

Introduction: Leptin and Resistin are adipokines produced in adipose tissue. Resistin acts centrally to increase renal sympathetic nerve activity (RSNA). This is similar to leptin, suggesting activation of some common brain pathways. High-fat feeding can reduce the number of activated neurons and effects on dietary intake observed following the central administration of leptin. In contrast, the sympatho-excitatory effects of leptin are retained. The effects on resistin were unknown.
Aims: We investigated whether the sympatho-excitatory actions of resistin and the pathways activated were influenced by a high fat diet. Further, since resistin and leptin combined can induce a greater sympatho-excitatory response than each alone in rats fed a normal chow diet, we investigated whether a high fat diet (22%) could influence this centrally mediated interaction.
Methods: MAP, HR and RSNA were recorded before and for 3 hours after intracerebroventricular saline (control) leptin (7 µg), resistin (7 µg) and leptin and resistin combined. The distribution of neurons in the brain that were activated by centrally administered resistin, or leptin alone, and, in combination, in rats fed a high fat (HFD) compared to a normal chow diet (ND) were compared. Immunohistochemistry for the protein, Fos, was used as a marker of activated neurons.
Results: With HFD, Leptin alone and resistin alone significantly increased RSNA (71±16%, 62±4% respectively). When leptin and resistin were combined there was a significantly greater increase in RSNA (195±41%) compared to either hormone alone. MAP and HR responses were not significantly different between hormones. When the responses in high fat fed rats were compared to normal chow fed rats, there were no significant differences in the maximum RSNA responses. The number of activated neurons in the paraventricular and arcuate nuclei were significantly increased following resistin or leptin, either alone or combined in rats fed a normal diet but this was not the case with HFD.
Discussion: The findings indicate that sympatho-excitatory effects of resistin on RSNA are not altered by high fat feeding. Our results suggest that diets rich in fat do not induce resistance to the increase in RSNA induced by resistin alone or in combination with leptin. This could have implications in understanding the mediators of the abnormally elevated RSNA observed in conditions of overweight / obesity.

206 Mineralocorticoid and estrogen receptors: Novel therapeutic targets in cardiovascular disease and stroke?

Quynh Nhu Dinh[1,2], Antony Vinh[1,2], Brad R.S. Broughton[2], Sophocles Chrissobolis[3], Grant R. Drummond[1,2] and Christopher G. Sobey[1,2], [1]Department of Physiology, Anatomy and Microbiology, La Trobe University, Bundoora, VIC, Australia, [2]Department of Pharmacology, Monash University, Clayton, VIC, Australia, [3]Department of Pharmaceutical and Biomedical Sciences, Raabe College of Pharmacy, Ohio Northern University, Ohio, USA

Introduction: Some effects of aldosterone may be modulated by the G protein-coupled estrogen receptor 1 (GPER) via an interaction with the mineralocorticoid receptor. The GPER agonist, G-1, can exert T cell-mediated anti-inflammatory actions, acutely lower blood pressure (BP), and reduce post-stroke infarct injury.
Aims and Methods: Here we tested the effects of G-1 (0.03 mg/kg/d) and G-15 (GPER antagonist; 0.3 mg/kg/d) on BP over 14 d in two models of hypertension: 1) aldosterone/salt (0.72 mg/kg/d + 0.9 % NaCl for drinking) and 2) angiotensin II (0.7 mg/kg/d); and assessed sex differences and also the role of lymphocytes in those effects.
Results: In male C57Bl6 mice, the aldosterone/salt-induced increase in BP (~25 mmHg) was attenuated by ~50 % with co-administration of G-1. G-15 did not alter aldosterone/salt-induced hypertension in male C57Bl6 but prevented the anti-hypertensive effect of G-1. Moreover, whereas aldosterone/salt alone had no effect on BP in female C57Bl6 mice for >7 d, co-administration of G-15 with aldosterone/salt resulted in a prompt increase of ~20 mmHg by d 7. There was virtually no effect of aldosterone/salt on BP in either male or female RAG1-deficient mice. Neither G-1 nor G-15 had any effect on angiotensin II-induced hypertension in male C57Bl6 mice. T cells, B cells, macrophages and neutrophils in spleen and kidneys were found to have high expression of GPER.
Discussion: Thus, aldosterone/salt-induced hypertension appears to be strictly lymphocyte-dependent and is markedly suppressed in females due to GPER activity. Activation of GPER on T and/or B cells by endogenous estrogen or by administration of G-1 selectively reduces hypertension caused by aldosterone/salt.

207 The paradox of Z-drugs in motor recovery after stroke

Mary Chebib[1], Petra van Nieuwenhuijzen,[1] Vanesse Chan[1], Philip Ahring[1], Andrew N. Clarkson[1,2], [1]Faculty of Pharmacy, The University of Sydney, Sydney, NSW, Australia, [2]Department of Anatomy, Brain Health Research Centre and Brain Research New Zealand, University of Otago, Dunedin, New Zealand

Zolpidem (Stilnox) is an intriguing molecule. Paradoxically, this “sleeping pill” is reported to reverse speech, cognitive and motor deficits in some Parkinson’s disease, progressive supranuclear palsy, severe brain injury and stroke patients. Generally, zolpidem mediates its hypnotic effects via cell surface proteins, called γ-aminobutyric acid type A receptors (GABAARs) and specifically the ubiquitous synaptic α1βγ2 subtype. Here zolpidem binds to the benzodiazepine (α1-γ2) site and acts similarly to benzodiazepines such as diazepam. However, the “awakening” effects of zolpidem in patients are not observed with benzodiazepines (e.g. diazepam and alprazolam) and are thus, unrelated to actions mediated from the classical benzodiazepine site. In this presentation, I will present the effects of zolpidem and other agents in mice stroked using a photothrombotic approach with drug intervention starting at various time points before assessing motor function, and discuss targets that could contribute to these effects in an attempt to identify the mechanism for this unusual effect.

208 Targeting oxidant-dependent pathways to treat cognitive dysfunction in chronic obstructive pulmonary disease

Ross Vlahos, School of Health & Biomedical Sciences, RMIT University, Bundoora, VIC, Australia

Chronic obstructive pulmonary disease (COPD) is a major incurable global health burden, affects 210 million people worldwide and is currently the 3rd largest cause of death in the world[1]. COPD costs the Australian community over $8.8 billion per year and causes substantial morbidity and mortality[2]. Importantly, much of the disease burden and health care utilisation in COPD is associated with the management of its comorbidities and viral and bacterial-induced acute exacerbations of COPD (AECOPD)[1]. Because comorbidities have a major impact on the severity and prognosis of COPD, the recent American Thoracic Society/European Respiratory Society Research Statement on COPD launched an urgent call for studies to elucidate the pathobiological mechanisms linking COPD to its comorbidities[3]. Recent clinical studies have shown that cognitive dysfunction is present in up to 60% of COPD patients, with impairment in memory, attention and executive function[4]. In addition, comorbid cognitive dysfunction impacts on important outcomes such as quality of life, hospitalisation and survival[4]. The high prevalence of cognitive dysfunction in COPD may also help explain the insufficient adherence to therapeutic plans and strategies, thus exacerbating and increasing the social costs in COPD subjects. The mechanisms underlying brain pathology and cognitive impairment in COPD are largely unknown. We propose that the increased oxidative stress and inflammation observed in COPD lungs 'spill over' into the systemic circulation causing damage to other organs (e.g. brain) manifesting in comorbidities of COPD such as cognitive dysfunction. Thus, an understanding of the mechanisms underlying neuroinflammation and cognitive dysfunction will reveal new targets, including oxidative stress, to treat cognitive dysfunction in COPD.

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209 Decoding spinal cord circuits to find novel targets for chronic pain

Wendy L Imlach, Monash Biomedicine Discovery Institute and Department of Physiology, Monash University, Melbourne, VIC, Australia

Introduction: The development of neuropathic pain involves persistent changes in signalling within nociceptive pathways. Reduced inhibitory signalling in the spinal cord following nerve-injury has been used to explain sensory signs of neuropathic pain but specific circuits that lose inhibitory input have not been identified. Understanding the molecular, cellular, and physiological basis of changes in circuit activity in disease is central to identifying novel drug targets and the development of more effective therapeutics.
Aims: In this talk I will discuss our recent identification and characterization of a nociceptive circuit that becomes more excitable in a rat model of chronic pain and our approaches to pharmacologically target the activity of affected neurons.
Methods: Studies of spinal cord signalling and circuit activity were performed using patch-clamp electrophysiology, optogenetic activation, calcium imaging and immunohistochemistry.
Results: We found that a specific population of spinal cord interneurons, radial neurons, lose glycinergic inhibitory input in a rat partial sciatic nerve ligation (PNL) model of neuropathic pain. These neurons also undergo a change in postsynaptic receptors, which may contribute to their change in activity. This study characterizes these interneurons and their inputs and outputs within the nociceptive circuit.
Discussion: This study has important implications as it identifies a glycinergic synaptic connection in a specific population of dorsal horn neurons where loss of inhibitory signalling may contribute to signs of neuropathic pain. This raises the challenge of identifying selective targets within this sub-circuitry to optimize therapeutics for minimal side effects.

210 Nav1.7 as a target for pain treatment: Therapeutic challenges and opportunities

Sulayman D. Dib-Hajj, PhD. Dept Neurology, Yale School of Medicine, West Haven, CT, USA, Center for Restoration of Nervous System Function, Veterans administration Medical Center, West Haven, CT, USA

Background: A monogenic link of *SCN9A*, the gene that encodes sodium channel $Na_v1.7$, and pain disorders in humans has provided compelling evidence that this channel is a major contributor to the pathophysiology of pain. Dominant and fully penetrant gain-of-function mutations in Nav1.7 have been found in two severe pain syndromes, inherited erythromelalgia (IEM) and paroxysmal extreme pain disorder (PEPD), while recessive loss-of-function mutations have been found in patients with congenital insensitivity to pain (CIP). CIP patients do not manifest cardiac, moto or cognitive deficits. Variants in Nav1.7 in patients with the more common painful disorder small fiber neuropathy have been identified and have shown in functional assays that they confer gain-of-function attributes on the channel, but are less penetrant and generally manifest symptoms at middle age. Electrophysiological characterization of mutations in Nav1.7 has now elucidated the molecular basis for altered excitability of DRG neurons that express these mutant channels, establishing a mechanistic link to human pain conditions. These findings validate the Nav1.7 peripheral sodium channels as a target for development of new pain therapeutics.
Discussion: A new class of sulfonamide-based isoform-selective blockers of Nav1.7 has been developed and a prototype was tested in a clinical trial on a small number of patients with IEM. Other molecules of the same class are under development. Another new sodium channel blocker with a reported Nav1.7 selectivity was tested in a cohort with trigeminal neuralgia. Both trials reported promising secondary endpoints. Approaches including atomic structural modeling and pharmacological testing in vitro have also proven useful to predict the response of neurons expressing specific Nav1.7 mutant channels to existing drugs, and the successful implementation of this strategy in a personalized clinical application was recently reported.

211 GPCRs and ion channels: The cause of and solution to chronic visceral pain?

Stuart M. Brierley[1,2], [1]Human Physiology, Centre for Neuroscience, Flinders University, Adelaide, SA, [2]South Australian Health and Medical Research Institute (SAHMRI), Adelaide, SA

There is increasing pre-clinical and clinical evidence that infection and inflammation are key risk factors for the development of some subtypes of Irritable Bowel Syndrome (IBS) [1]. Extrinsic sensory afferents are at the start of the pain-processing pathway and are therefore key targets for treating chronic visceral pain (CVP) associated with IBS.

This seminar will highlight the fundamental properties of extrinsic sensory afferent nerves innervating the gut and highlight how inflammation can trigger long-term neuroplasticity [1]. In particular, it will focus on the latest evidence for how specialized cells within the gut wall allow the gut to 'talk' to the brain [2]. It will also highlight the key ion channels [3] which ultimately underlie aberrant neuronal function and gastrointestinal symptoms. Finally, this talk with highlight recent evidence that has identified several novel receptors that hold promise for future selected pharmacotherapy for inhibiting colonic afferents in the treatment of CVP in IBS.

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212 Mechanosensors and pain

Kate Poole, EMBL Australia Node for Single Molecule Science, School of Medical Sciences, UNSW Sydney, NSW, Australia

Introduction: The skin is innervated by specialised mechanoreceptors that allow the perception of gentle touch. The initial transduction event that mediates this sense of touch is the conversion of mechanical movements into an electrical signal via activation of mechanosensitive ion channels. The sensitivity of these ion channels can be regulated by the membrane scaffolding protein STOML3. In some pathophysiological pain states, fine mechanical stimuli are falsely perceived as noxious. However, touch-evoked pain responses (that indicate such mechanical hypersensitivity) are inhibited in *Stoml3*$^{-/-}$ mice.
Aims: The aim of this study was to determine whether we could identify STOML3-targetting compounds that reverse mechanical hypersensitivity.
Methods: Elastomeric pillar arrays were used to characterise the role of STOML3 in tuning mechanosensitivity and a small-molecule screen was performed to identify compounds that disrupted STOML3 oligomerisation.
Results: We have identified compounds that disrupt STOML3 oligomerisation. The application of these compounds to cells changes STOML3-defined domains and inhibits sensitisation of mechanically gated ion channels by STOML3. These compounds were also found to reversibly attenuate touch perception and block mechanical hypersensitivity in some neuropathic pain states.
Discussion: Applying compounds to the skin that locally modulate mechanotransduction may represent a novel treatment for the mechanical hypersensitivity that occurs post nerve injury.

Poole K et al (2014) Nat Communs 5:3520
Wetzel C et al (2017) Nat Neurosci 20:209-218

213 CESTEM-1 clinical trials: using dynamin inhibitors to reverse resistance to monoclonal antibody therapy

Jermaine Coward[1,6], Katharine Cuff[2], Godwins Echejoh[3], Hui Yi Chew[3], Shannon Joseph[3], Blerida Belushi[3], Brigid King[3], Sally Yukiko[3], Priscilla De Olivia[3], Annabelle Genko[3], Alexander Grainger[3], Satomi Okano[3], Ian H. Frazer[3], James Wells[3], Matthew Foote[4], Jennifer Martin[5], Ben Panizza[2, 6] and Euan Walpole[1,2], Fiona Simpson[3,6], [1]Cancer Services, Department of Oncology, Princess Alexandra Hospital, Woolloongabba, Australia, [2]Faculty of Medicine, University of Queensland, Australia, [3]University of Queensland Diamantina Institute, Faculty of Medicine, University of Queensland at The Translational Research Institute, Woolloongabba, Queensland, Australia, [4]Department of Radiation Oncology, Princess Alexandra Hospital, Woolloongabba, Australia, [5]School of Medicine and Public Health, University of Newcastle, Newcastle, New South Wales, Australia, [6] Queensland Head and Neck Cancer Centre and The Department of Otolaryngology, Princess Alexandra Hospital, Queensland, Australia

The monoclonal antibody (mAb) cetuximab is an important component of cancer therapy for the treatment of squamous cell carcinoma (SCC). Cetuximab targets the epidermal growth factor receptor (EGFR) but patient responses are unpredictable and the biological determinants of antibody therapy sensitivity remain unknown. We hypothesised that the trafficking status of the EGFR may impact the efficacy of the monoclonal antibody treatments directed at this receptor. Analysis of pre-treatment patient SCC tumours showed EGFR trafficking defects which correlated to positive patient outcome after anti-EGFR mAb therapy. By modulating EGFR trafficking in vitro using dynamin inhibitors which blocked the EGFR on the plasma membrane we were able to enhance anti-EGFR mAb (cetuximab)-induced SCC tumour cell death by antibody dependent cellular cytotoxicity (ADCC) in both cetuximab-sensitive and insensitive SCC cells. In contrast, blocking endocytosis with clathrin inhibitors did not promote ADCC. While both classes of endocytosis inhibitor increased cell surface levels of EGFR, only the dynamin inhibitors induced their cell surface clustering, which may directly influence immune cell activation. Therefore induction of EGFR clustering may promote improved ADCC response in patients, suggesting a new model for targeted combination therapy of cetuximab with dynamin inhibitors. Significantly, we showed in vitro and in mouse models that the commonly used anti-nausea drug, prochlorperazine, inhibited dynamin, and in combination with cetuximab increased ADCC and cleared tumour burden, respectively. This data supported a phase 1 proof of mechanism trial where we showed in patient tumour biopsies that after prochlorperazine infusion, EGF ligand uptake was blocked at the cell plasma membrane. Together this data has informed the CESTEM study - Open-label Phase I study investigating the safety and efficacy of Cetuximab and prochlorperazine (STEMetil) combination therapy in patients with metastatic Head and Neck Squamous Cell Carcinoma, Triple Negative Breast Cancer and Adenoid Cystic Carcinoma. This work is a translation of our laboratory findings to the clinic and is being performed in collaboration with PA Hospital. This trial has the potential to change clinical practice for numerous mAbs used for cancer treatment and improve patient outcomes.

214 i-bodies against the chemokine receptor CXCR4 with novel pharmacology

Michael Foley[1,2], Kate Griffiths[1,2] William Darby [1,2] Chris hosking[1,2] Xilun Wang[1], [1]Adalta Limited, 15/2 Park Drive Bundoora, VIC Australia, [2]Department of Biochemistry and Genetics, La Trobe Institute for Molecular Science, La Trobe University, Bundoora, Melbourne, VIC Australia

i-bodies are small, stable, human scaffolds engineered from information gained from the shark single domain antibodies. The presence of a long CDR3 enables better access to complex proteins such as GPCRs and ion channels. We have screened this phage displayed i-body library on GPCRs and ion channels expressed in different formats. We have obtained a panel of high affinity single domain antibodies specific for the chemokine receptor CXCR4. CXCR4 is known to be upregulated in a number of cancers and recently has been implicated as a central player and a therapeutic target in fibrosis. Although all i-bodies bind with high affinity each of the i-bodies have different functional profiles with respect to modulation of cAMP, calcium efflux, inhibition of β-arrestin signaling and subsequently have different *in vitro* and *in vivo* activities. When the lead i-body Ad-114 was injected intraperitoneally they were found to completely block SDF-1-induced leukocyte recruitment in an air pouch model of inflammation in mice. Importantly, unlike most other CXCR4 antagonists, they did not mobilize stem cells from the bone marrow. Thus these i-bodies would be ideal for long-term anti-fibrosis therapy. Indeed we have shown that the i-bodies are able to block the recruitment of fibrocytes into the lungs of mice with bleomycin induced pulmonary fibrosis and that the anti CXCR4 i-bodies have anti-inflammatory and anti-fibrotic effects in several different animal models. Moreover we suggest that the i-body technology provides a unique resource for obtaining a toolbox of human antibody single domains to currently intractable membrane proteins.

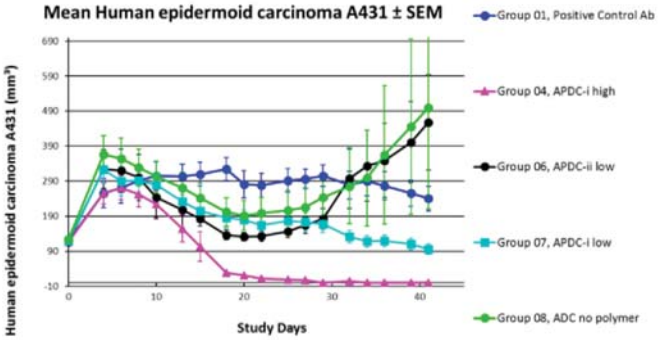
215 Antibody-polymer-drug conjugates for biomedical applications

Charlotte C Williams, Fei Huang, Xiaojuan Hao, Judith Scoble, Luisa Pontes-Braz, Tim Adams, Andrew Riches, Wioleta Kowalczyk, Ezio Rizzardo, Graeme Moad, John Chiefari, Manufacturing, CSIRO[1], Melbourne, VIC, Australia

Introduction: We have developed a platform drug-delivery technology based on the versatility of the Reversible Addition-Fragmentation chain Transfer (RAFT) process to help deliver polymer-based materials for biomedical applications.

Aims: The approach is based on developing RAFT technology to address key clinical and technical challenges for the use of polymeric materials in therapeutic delivery systems.

Methods: We report therapeutic antibody-polymer-drug conjugates, where the polymer acts as a carrier for both a small molecule cytotoxic drug as well as a therapeutic protein, such as an antibody. In order to understand the influence of polymer structure, composition and size on biological performance, we report the results of two, first in class, ADME studies. These studies assess the pharmacokinetics of a range of homo-polymer and co-polymer antibody-fragment conjugates, in animal models.



Results: All of the antibody fragment-polymer conjugates investigated had increased elimination phase half-lives over the PEG control, and although differences were observed within the circulating half-life between the conjugates (arising from the different polymer compositions), the excretion volume is fairly consistent.

Discussion: This result confirms that this range of RAFT polymers are a suitable platform for delivery of proteins and targeted delivery of small molecule drugs. We have conjugated an ADME optimised, complex, high molecular weight, terpolymer containing a number of cytotoxic drugs, attached via cleavable linkers, to antibody fragments and the results of a drug-loaded polymer-antibody fragment conjugate (Figure) in vivo efficacy study will be reported.

216 Downsizing disulfide-rich bioactive peptides

Richard J Clark[1], School of Biomedical Sciences, The University of Queensland, Brisbane, QLD, Australia

Disulfide-rich peptides typically exhibit high potency and selectivity for their molecular targets and therefore represent promising drug leads. The disulfide bonds within these peptides help to define the three-dimensional shape of the peptide, which is often crucial for function, and also provide stability against denaturation and proteases. However, the presence of multiple disulfide bonds in a peptide can often make the synthesis challenging as multiple disulfide regioisomers can be formed. In this talk I will present our work on elucidating the structure/function activity of disulfide-rich peptides, the challenges we have faced in correctly folding these peptides and how these studies have allowed us to minimize some peptides to key bioactive epitopes that are much simpler and efficient to produce but still retain the full activity of the parent peptide.

217 Gene delivery targeting cardiac O-GlcNAc modification limits diabetic cardiomyopathy

Darnel Prakoso[1,2], Helen Kiriazis[1], Mitchel Tate[1], Hongwei Qian[1], Minh Deo[1], Laura J Parry[2], Paul Gregorevic[1], Xiao-Jun Du[1], John C Chatham[4], Miles J De Blasio[1,2], Rebecca H Ritchie[1,3], [1]Baker Heart and Diabetes Institute, Melbourne, VIC, AU, [2]School of BioSciences and [3]Dept of Pharmacology and Therapeutics, University of Melbourne, Melbourne, VIC, AU, [4]Dept of Pathology, University of Alabama at Birmingham, Birmingham, AL, USA

Introduction: O-GlcNAc post-translational modification has been implicated in the development and progression of diabetic cardiomyopathy. Two enzymes regulate this modification; O-GlcNAc transferase (OGT) facilitates addition of the O-GlcNAc sugar moiety to ser/thr residues, and O-GlcNAcase (OGA) which facilitates its removal.
Aims: To study the impact of cardiac-targeted OGA and OGT adeno-associated viral (AAV) gene delivery in the setting of diabetic cardiomyopathy *in vivo*.
Methods: Diabetes was induced in 6wk-old male mice using streptozotocin (55mg/kg/day i.p./day, 5 days). After 8wks of diabetes, LV diastolic dysfunction was confirmed by echocardiography. A single i.v. injection of rAAV6-OGA, rAAV6-OGT or null ($2x10^{11}$ vg) was administered, and mice were followed for a further 8wks.
Results: As shown in the table, OGA gene delivery attenuated diabetes-induced LV diastolic and systolic dysfunction, and limits increases in hypertrophic and pro-fibrotic gene expression. In contrast, OGT gene delivery in nondiabetic mice tended to replicate characteristics of diabetic cardiomyopathy.
Conclusion: Targeting LV O-GlcNAc modification may be a potential therapeutic target in the setting of diabetic cardiomyopathy.

Results: (mean±SEM)	**Sham**			**Diabetes**		
	Null	**OGT**	**OGA**	**Null**	**OGT**	**OGA**
Body Weight (g)	34.8±0.9	35.4±1.0	33.6±0.7	31.2±0.7	31.1±0.7	30.1±0.6
Blood Glucose (mM)	10.1±0.5	9.6±0.4	9.7±0.5	32.0±0.7*	30.8±1.2*	29.4±1.0*
HbA1c (%)	3.2±0.1	3.7±0.2	3.5±0.2	9.6±0.6*	9.0±0.5*	8.7±0.5*
E/A Ratio	2.5±0.2	2.0±0.1	2.5±0.2	1.6±0.1*	1.6±0.1*	2.1±0.2†
IVRT (ms)	14.6±0.9	17.4±1.0	16.0±0.8	21.3±1.2*	19.6±0.7*	16.1±0.6†
FS (%)	39±0.7	33±0.7*	39±1.0	35±0.4*	36±0.7	41.0±1.6†#
LV β-MHC (fold)	1.0±0.1	1.8±0.5	0.9±0.1	3.2±0.6*	3.6±0.6*	2.4±0.3
LV CTGF (fold)	1.0±0.1	1.5±0.2	0.9±0.1	2.3±0.3*	2.0±0.3*	1.5±0.1†

*P<0.05 vs sham-null; †P<0.05 vs diabetic-null; #P<0.05 vs diabetic-OGT; HbA1c: glycated haemoglobin; IVRT: isovolumic relaxation time; FS: fractional shortening; CTGF: connective tissue growth factor; β-MHC: β-myosin heavy chain. n=10-15/group.

218 The Safety of Metformin in Haemodiafiltration

Felicity C Smith[1,2], Timothy J Furlong[3], Jerry R Greenfield[4], Sophie L Stocker[1,5], Jane E Carland[1,5], Garry G Graham[1,2], Kenneth M Williams[1,2], Richard O Day[1,5]. Dept of Clin Pharmacol, St. Vincent's Hospital[1], Sydney, NSW; School of Med Sci, Univ of NSW[2], Kensington, NSW; Dept of Nephrol, St. Vincent's Hospital[3], Sydney, NSW; Dept Endocrin, St. Vincent's Hospital[4], Sydney, NSW; St. Vincent's Clinical School, Univ of NSW[5], Kensington, NSW.

Introduction. The cardioprotective effects of the anti-hyperglycaemic agent metformin may be of great benefit to patients with type 2 diabetes mellitus (T2DM) and end-stage kidney disease (ESKD) who require haemodiafiltration (HDF). Metformin is extensively cleared from plasma during HDF (Smith et al, 2016). This indicates that metformin may be safely given to these patients if administration matches extraction during HDF, thereby preventing metformin accumulation and lactic acidosis. Further studies are required to confirm this.
Aims. To monitor the safety of metformin in patients with T2DM and ESKD undergoing HDF.
Methods. Patients received metformin (IR, 250 mg) after each HDF session (thrice weekly; 750 mg/week) for 6 months. Regular blood samples were collected prior to the start of HDF to monitor safety parameters (plasma lactate <5 mmol/L, plasma metformin <5 mg/L). Metformin concentrations were quantified by HPLC.
Results. Plasma lactate concentrations remained below 5 mmol/L in all patients (n=7) for the duration of treatment. Plasma metformin concentrations remained below 5 mg/L, except for 2 occasions in Patient 3 (max=5.3 mg/L). Unfortunately, Patients 1 and 6 passed away from cardiac events in the fourth month of the study. The study was subsequently ceased by local governance. No safety data from these patients was suggestive of lactic acidosis.
Discussion. Cardiovascular disease is the leading cause of death in HDF patients. Additionally, there is no evidence to date that associates metformin with an increased risk of cardiovascular events. Prior to study cessation, all data collected supported the safety of metformin in HDF. This information, particularly given the safety data collected from Patients 1 and 6, suggests it is unlikely that metformin contributed to these deaths. Regardless, further studies are required to investigate any potentially deleterious interactions between metformin and the rapid shifts in biochemistry and body fluid that take place during HDF.
Smith F et al (2016) Am J Kidney Dis 68:990-992

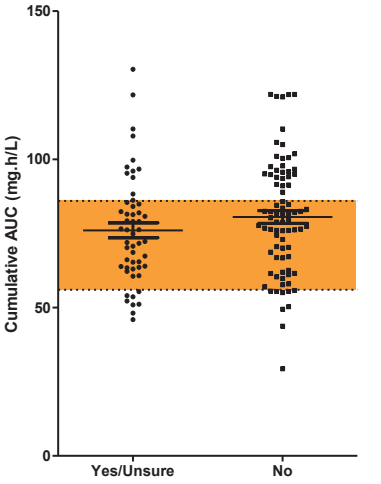
219 Neuronal calcium sensor-1 (NCS-1) in the regulation of calcium homeostasis and cell death in MDA-MB-231 basal breast cancer cells

Alice HL Bong[1], John J. Bassett[1], Sarah J Roberts-Thomson[1], Michael J. G. Milevskiy[2], Gregory R. Monteith[1,3]. School of Pharmacy, The University of Queensland[1], Brisbane, QLD, Australia; The Walter and Eliza Hall Institute of Medical Research[2], Melbourne, VIC, Australia; Mater Research, The University of Queensland[3], Brisbane, QLD, Australia.

Background: Altered calcium (Ca^{2+}) signalling in cancer cells may promote cancer hallmarks such as resistance to apoptosis. Proteins regulating these signals represent attractive therapeutic targets. Neuronal calcium sensor-1 (NCS-1) is associated with tumour aggression and poor prognosis in breast cancer patients. However, the characterisation of NCS-1 in breast cancer molecular subtypes, the effects of NCS-1 silencing on intracellular Ca^{2+} homeostasis in breast cancer cells and on the cytotoxic effect of the anti-cancer drug doxorubicin, remain unexplored.
Aim: To assess the expression of NCS-1 in public breast cancer datasets and assess the consequences of silencing NCS-1 on intracellular Ca^{2+} signaling and sensitivity to doxorubicin in the MDA-MB-231 basal breast cancer cell line.
Methods: The expression of NCS-1 in patient breast tumours was stratified by PAM50 molecular subtype and assessed using breast cancer public datasets. MDA-MB-231 cells stably expressing the GCaMP6m Ca^{2+} sensor were transfected with non-targeting control or NCS-1 siRNA. The effects of NCS-1 silencing on cytosolic Ca^{2+} in response to Ca^{2+}-mobilising agonists (ATP, trypsin and cyclopiazonic acid (CPA)) and on constitutive Ca^{2+} influx were measured using a Fluorescent Imaging Plate Reader (FLIPR). The sensitivity to doxorubicin (24 h) following gene silencing of NCS-1 was determined by propidium iodide staining.
Results: NCS-1 was expressed higher in basal molecular subtype breast cancers. Silencing NCS-1 did not alter cytosolic Ca^{2+} changes induced by ATP, trypsin or CPA treatment. However, NCS-1 silencing suppressed constitutive Ca^{2+} influx. NCS-1 silencing also promoted MDA-MB-231 cell death in combination with doxorubicin (1 µM) treatment.
Discussion: These results implicate NCS-1 in basal breast cancer, a subtype with poor prognosis. Indirect modulators of endoplasmic reticulum Ca^{2+} levels such as NCS-1 may alter constitutive Ca^{2+} influx pathways and influence processes important in cancer such as sensitivity to anti-cancer agents.
Monteith GR et al (2017) Nat Rev Cancer. 17:367-380.
Moore LM et al (2017) Mol Cancer Res. 15(7); 942–952

220 The Relationship Between Busulphan AUC and the Incidence of Sinusoidal Obstruction Syndrome in Haematopoietic Stem Cell Transplants

Parth J Upadhyay[1], Janna Duong[1], Christa Nath[2], Peter Shaw[2] and Alan V Boddy[1], [1]University of Sydney, NSW, Australia, [2] The Children's Hospital at Westmead, NSW, Australia



Introduction: High dose busulphan (Bu) is an essential component of myeloablative regimens prior to Haematopoietic Stem Cell Transplantation (HSCT), but is subject to significant inter- and intra-individual pharmacokinetic variability, which is a challenge for accurate dosing within the therapeutic window. Furthermore, sinusoidal obstruction syndrome (SOS) remains a major toxicity of Bu overexposure despite the addition of prophylaxis to the chemotherapy regimen.
Aim: To investigate the relationship between Bu exposure (cumulative area under the curve, AUC) and the incidence of SOS in paediatric patients.
Methods: Data from 131 individuals receiving Bu prior to HSCT (2006-2017) from the Children's Hospital at Westmead was used. Population pharmacokinetic analysis of Bu was performed (one-compartment model, NONMEM®) and associations with SOS were evaluated using the unpaired *t*-test (P <0.05).
Results: The data included patients, aged from 44 days to 23 years old, receiving Bu for 34 different immune, haematological and oncology conditions (30 different protocols prior to transplantation). There was a large variability in Bu clearance (0.78-13.06 L/h, range) and cumulative AUC (29.41-130.39 mg·h/L), with no significant differences between patients with or without SOS (P = 0.13). The incidence of SOS was 27% and median onset time was 12 days (5 to 31 days) post-transplant.
Discussion: There was no distinction in the cumulative AUC for patients with or without SOS but there was a large proportion of patients who were out of the targeted cumulative AUC of 56-86 mg·L/h (Figure). Based on these findings, variation in Bu AUC alone does not explain the incidence of SOS.

221 An investigation of the vascular effects of Sailuotong, a standardised Chinese herbal formula, for vascular dementia

Seungyeon Yeon[1], Dennis Chang[1], Hosen Kiat[1,2,3], Alan Bensoussan[1] and Sai Wang Seto[1], [1]NICM, School of Science and Health, Western Sydney University[1], Campbelltown, NSW, Australia. [2]Faculty of Medicine, University of New South Wales, NSW, Australia. [3]Faculty of Medicine and Health Sciences, Macquarie University, NSW, Australia

Introduction. Sailuotong (SLT) is standardised three-herb formulation consisting of *Panax ginseng C A Mey*, *Ginkgo biloba L* and *Crocus sativus L* for the management of vascular dementia (VaD). Although SLT has been shown to increase cerebral blow flow in animal and clinical studies, the direct effects of SLT on vascular reactivity have not investigated.
Aims. To examine the vasodilatatory effects of SLT and its underlying mechanisms of action in rat isolated tail artery.
Methods. Male, 250-300g Wistar Kyoto (WKY) rat-tail artery was isolated for isometric tension measurement.
Results. Cumulative administration of SLT (0.1 – 5000 µg/mL) caused a concentration-dependent relaxation in phenylephrine-preconstricted tail artery. Pre-incubation of endothelium nitric oxide synthase inhibitor (N-nitro-L-arginine methyl ester, L-NAME; 20 µM) did not inhibit the SLT-induced vasodilatation. In contraction experiments, SLT (10, 100 and 1000 µg/mL) significantly attenuated phenylephrine (0.001 to 10 µM)- and KCl (10 – 80 mM)-induced contraction. In Ca^{2+}-free solution, SLT (5000 µg/mL) markedly suppressed Ca^{2+}-induced (0.001 – 3 mM) vasoconstriction in both phenylephrine (10 µM) and KCl (80 mM) stimulated tail arteries.
Discussion. Putting these together, our results suggested that SLT induces relaxation of rat isolated tail arterial rings through an endothelium-independent pathway, involving blockade of extracellular Ca^{2+} influx.

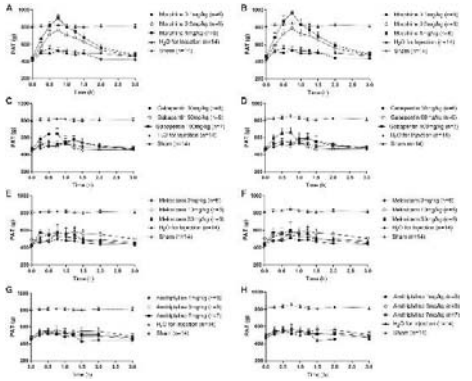
222 The Medication Regimen Simplification Guide for Residential Aged CarE (MRS GRACE): a novel tool to optimise medication regimens for residents of aged care facilities.

Esa YH Chen[1,2], Janet K Sluggett[1,2], Jenni Ilomäki[1], Sarah N Hilmer[2,3], Megan Corlis[2,4], J Simon Bell[1,2], MRS GRACE development group. Ctr for Med Use and Saf, Monash Univ[1], Parkville, VIC, Australia; NHMRC Cog Dec Partn Ctr, Hornsby Ku-ring-gai Hosp[2], Hornsby, NSW, Australia; Kolling Instit, Univ of Sydney[3], St Leonards, NSW, Australia; Helping Hand Aged Care[4], North Adelaide, SA, Australia.

Introduction. Residents of aged care facilities use increasingly complex medication regimens. Reducing unnecessary medication regimen complexity (e.g. by consolidating number of administration times or using alternative formulations) may benefit staff administering medications and residents taking medications.
Aims. To develop and validate an implicit tool to facilitate medication regimen simplification in aged care facilities.
Methods. A purposively-selected multidisciplinary expert panel used modified nominal group technique to identify and prioritise factors important in determining whether a medication regimen can be simplified. The five prioritised factors were formulated as questions, pilot-tested using non-identifiable medication charts and refined by panel members. The final tool was validated by two clinical pharmacists who independently applied the tool to medication charts for a random sample of 50 residents to identify opportunities for medication regimen simplification. Inter-rater agreement was calculated using Cohen's kappa.
Results. The Medication Regimen Simplification Guide for Residential Aged Care (MRS GRACE) was developed as an implicit tool and accompanying explanatory statement. The tool comprises five questions related to resident and facility related factors, drug interactions, and formulation. Using MRS GRACE, two pharmacists independently simplified medication regimens for 29/50 and 30/50 residents (Cohen's kappa=0.38, 95%CI 0.12-0.64), respectively. Simplification was possible for all residents with five or more administration times. Changing an administration time comprised 75% of the two pharmacists' recommendations.
Discussion. By applying MRS GRACE, two clinical pharmacists independently simplified two-thirds of residents' medication regimens with fair agreement. MRS GRACE is a promising new tool to guide medication regimen simplification in aged care facilities.

223 Behavioural, pharmacologic and histologic characterisation of a rat model of mechanical low back pain

Thomas S W Park[1], Andy Kuo[1], Maree T Smith[1,2]. CIPDD, The Univ of Queensland[1], Brisbane, QLD, Australia; School of Pharmacy, The Univ of Queensland[2], Brisbane, QLD, Australia.



Introduction. Low back pain (LBP) is a common health problem affecting humans globally. Hence, I have used behavioural, histological and pharmacological methods to characterise an optimised rat model of mechanical LBP established at the CIPDD.[1]
Aims. To use behavioural, histological and pharmacological methods to characterise our new rat model of mechanical LBP.
Methods. Ten small punctures (0.5 mm o.d.; 2 mm deep) were induced in the L4/L5 and L5/L6 intervertebral discs (IVDs). Sham rats had the same surgery but there was no IVD puncture. Pressure algometry thresholds (PATs) at L4/5 and L1 were assessed. Additionally, paw withdrawal thresholds (PWTs) were measured in the bilateral hindpaws using calibrated von Frey filaments. PATs and PWTs were measured at weekly intervals until study completion. Dosing solutions of morphine (0.1, 0.3, and 1.0 mg/kg; sc), gabapentin (30, 60, and 100 mg/kg; ip), amitriptyline (1, 3, and 7 mg/kg; ip), meloxicam (3, 10, and 30 mg/kg; ip) and vehicle (2 mL/kg; ip) were administered to rats by the first person and testing was undertaken in a 'blinded' manner by the second person. Both LBP and sham rats were also characterised using histologic methods.
Results. Mechanical hyperalgesia developed progressively at L4/L5 and L1 in LBP-rats but not sham-rats. Importantly, PWTs remained unaltered for the study period. Histological analysis of the IVDs from LBP-rats showed an apparent loss of sharp boundaries between the nucleus pulposus and annulus fibrosus. In LBP-rats, single bolus doses of morphine produced dose-dependent relief of primary and secondary mechanical hyperalgesia in the lumbar axial deep tissues at L4/L5 and L1, respectively, whereas gabapentin, amitriptyline, meloxicam and vehicle were inactive.
Discussion. We have characterised a new rat model of chronic mechanical LBP using behavioural, pharmacologic and histologic methods.

[1]Muralidharan A, Park TSW et al (2017) Front Pharmacol 8:493

224 Understanding the physiological role of endogenous allosteric modulators in the muscarinic acetylcholine receptors

Ee Von Moo, Patrick M Sexton, Arthur Christopoulos and Celine Valant. Drug Discovery Biology, Monash Institute of Pharmaceutical Science, Monash University, Parkville, VIC, Australia.

Introduction. Allosteric binding sites on G protein-coupled receptor (GPCR) can be targeted by synthetic or natural (endogenous) molecules (van der Westhuizen et al., 2015). However, the (patho)physiological role(s) of many endogenous allosteric modulators remain poorly understood. One interesting example is major basic protein (MBP), a highly basic peptide that acts as a negative allosteric modulator (NAM) of acetylcholine (ACh) at airway M_2 muscarinic acetylcholine receptors (mAChR; Jacoby et al., 1993). We hypothesized that, in addition to MBP, other endogenous basic peptides, including the antimicrobial, LL-37, involved in chemotaxis, maturation of immune cells and apoptosis (Kahlenberg et al., 2013) could also interact allosterically with the M_2 mAChRs and have major physiological impacts.
Aims. To characterise the pharmacological properties and the putative (patho)physiological roles of LL-37 at mAChRs.
Methods. Using IMR-32, a native cell line endogenously expressing human M_2 mAChRs and mouse tissues predominantly expressing mouse M_2 mAChRs, we performed [^{3}H]NMS radioligand binding and [^{35}S]GTPγS turnover as a functional measure of receptor activation, to assess the allosteric effect of LL-37.
Results. LL-37 mediated a concentration-dependent partial inhibition of the antagonist [^{3}H]NMS binding in IMR-32 cells and mouse cardiac tissues (pK_B=4.7±0.3 and 5.6±0.5, respectively), a hallmark of allostery. Additionally, LL-37 also negatively modulated ACh-mediated G protein activation in mouse hypothalamus preparations.
Discussion. Our results suggest that LL-37 is a NAM of antagonist binding and agonist function at the M_2 mAChR. The M_2 mAChRs are highly expressed on both neuronal and non-neuronal cells, including immune cells and epithelial cells, and are known to be involved in their survival outcome. In the context of inflammation and cancer, when LL-37 is highly expressed, the antagonism of M_2 mAChR activity by the peptide could therefore have unappreciated (patho)physiological consequences.

van der Westhuizen ET al. (2015) J Pharm Exp Ther 353(2):246-60.
Jacoby et al. (1993) J Clin Invest 91:1314-1318.
Kahlenberg et al. (2013) J immunol 191(10):4893-901.

225 Microdosed cocktail of apixaban, edoxaban and rivaroxaban can predict drug interaction with therapeutic doses

Gerd Mikus, Marlene Schaumäker, Kathrin Foerster, Marie-Louise Lehmann, Walter Emil Haefeli, Dept Clinical Pharmacology and Pharmacoepidemiology, University Hospital, Heidelberg, Germany

Introduction: The direct oral anticoagulants (DOAK) apixaban, edoxaban, and rivaroxaban are factor Xa inhibitors and plasma concentrations predict the pharmacological effect.
Aims: In order to facilitate more knowledge for the decision which one to use in individual patients with their comedication, we explored the use of a microdosed cocktail of the 3 DOAKs. The effect of ketoconazole on the pharmacokinetics of normal doses has already been studied.
Methods: This randomised study was approved by the competent authority and the ethics committee. Eighteen participants took the DOAK cocktail alone or in combination with ketoconazole (400mg qd, starting 1 day before the DOAK administration). Solutions of the DOAKs were prepared by the hospital pharmacy. Final drinking solution of apixaban (25µg), edoxaban (50µg), and rivaroxaban (25µg) were prepared just before intake. A 2 day pharmacokinetic profile was obtained. Plasma concentrations of microdosed apixaban, edoxaban, and rivaroxaban were quantified using an according to FDA & EMA guidelines validated ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) assay with a LLOQ of 2.5 pg/ml.
Results: Simultaneous administration of the DOAK cocktail shows similar pharmacokinetic data compared to published data using a normal therapeutic dose. Ketoconazole significantly increased AUC of all 3 DOAKs with an AUCR of 1.90 (apixaban), 2.35 (edoxaban), and 2.27 (rivaroxaban).
Discussion: Literature data of ketoconazole and normal doses of apixaban, edoxaban, and rivaroxaban showed an increase by 1.99, 1.87, and 2.58 (steady-state), respectively. Hence, the microdosed cocktail approach is able to predict the drug interaction with ketoconazole precisely. To study drug interaction with a drug class only one study has to be carried out and no pharmacological effects occur due to the microdosing approach.

Mueck W et al (2013) Br J Clin Pharmacol 76:455-66
Frost CE et al (2015) Br J Clin Pharmacol 79:838-46
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226 The influence of ABCG2 genotype on allopurinol dose predictions

Daniel FB Wright[1], Amanda Phipps-Green[2], Tony R Merriman[2], Murray L Barclay[3], Nicola Dalbeth[4], Lisa K Stamp[3], [1]School of Pharmacy, [2]Department of Biochemistry, University of Otago, Dunedin, New Zealand, [3]Department of Medicine, University of Otago, Christchurch, New Zealand, [4]Department of Medicine, University of Auckland, Auckland, New Zealand

Introduction: A genetic variant in the urate transporter ABCG2 (p.Lys141) has been associated with poor allopurinol response in gout patients. Tools designed to predict allopurinol dose requirements do not account for ABCG2 genetics.
Aims: To evaluate the influence of ABCG2 genotype (*rs2231142*) on the performance of two dosing tools for allopurinol therapy (Wright 2016, Graham 2013 - termed the 'Otago' and 'Sydney' models).
Methods: Allopurinol maintenance dose predictions were compared to the observed dose required to achieve a serum urate of < 0.36mmol/L in an external cohort of n=413 patients (Stamp et al 2017) using mean prediction error (MPE). MPE for the poor-response genotypes (GT/TT) for ABCG2 (*rs2231142* G>T) was compared to the GG genotype using a Students t-test. The variability in prediction error (PE) explained by ABCG2, other transporter genotypes, patient factors, and concomitant drugs was quantified using multi-linear regression.
Results: Allopurinol doses were over-predicted by both the Otago and Sydney dosing tools (MPE 150mg/day and 140 mg/day, respectively). ABCG2 genotype significantly influenced dose predictions from the Otago (MPE 201 mg/day [GG] and 88 mg/day [GT/TT], p<0.0001) and Sydney models (MPE 207 mg/day [GG] and 65 mg/day [GT/TT], p=0.0103). When examined in isolation, the TT genotype (n=15) lead to unbiased dose predictions (MPE 15 mg/day, 95% CI -99-129 and 25mg/day 95% CI -181-231). ABCG2 genotype and diuretic use explained 55% of the variability in PE (adjusted R^2=0.55, p=0.0002). The GT/TT genotype effect reduced PE by 90mg/day (p=0.032).
Discussion: *ABCG2 rs2231142* appears to have a significant influence on allopurinol dose predictions. Any future updates to the dosing tools will need to incorporate the influence of *ABCG2* genotype on allopurinol dose requirements.

Wright DFB et al (2016) Br J Clin Pharmacol 81(2):277-89
Graham et al (2013) Br J Clin Pharmacol 76(6):932-8
Stamp LK et al (2017) Ann Rheum Dis; 76:1522–1528

227 Late onset rise of 6-MMP metabolites in inflammatory bowel disease patients on azathioprine or mercaptopurine

Murray L Barclay[1,2], Erik Munnig-Schmidt[3], Mei Zhang[1], Chris J Mulder[3], [1]Dept of Medicine, Univ of Otago Christchurch, Christchurch, [2]Depts of Gastroenterol and Clin Pharmacol, Christchurch Hospital, Christchurch, New Zealand, [3]Dept of Gastroenterol, VU Medical Centre, Amsterdam, The Netherlands

Introduction: The thiopurines azathioprine and mercaptopurine remain pivotal in maintenance treatment in inflammatory bowel disease, however up to 15-20% of patients preferentially produce the hepatotoxic metabolite 6-methylmercaptopurine (6MMP) at the expensive of the main therapeutic metabolites 6-thioguanine nucleotides (6TGN). This metabolic shunting usually occurs within 3 months of therapy, but we noted patients developing shunting many months or years after starting treatment.
Aims: To determine how often this late shunting occurs and whether this could be explained by patient factors, or concomitant medications.
Methods: The New Zealand national database of thiopurine metabolite results from 2002 to 2016 (19085 6TGN/6MMP pairs from 7130 patients) was interrogated to identify patients developing preferential 6MMP production, as defined by 6MMP/6TGN ratio >20, after more than four months of treatment. Dosing history, concomitant therapy and comorbidity data were assessed.
Results: Fifteen percent of all patients in the database developed preferential 6-MMP production and of these, we found 29 patients with late onset of preferential 6MMP production with sufficient medical data available to validate this. This equates to an estimate of 90 patients if all data had been available, representing 1.7% of IBD patients on thiopurines, or 10% of all those with preferential 6-MMP production. Time from starting therapy to shunting was 5 months to 10.4 years (median 21 months). Eleven patients had abnormal liver function when shunting was recognised, all with 6MMP >5900 pmol/8x10^8 RBCs. No common factors were found to explain the late occurrence of shunting.
Discussion: A group of IBD patients develop preferential 6MMP production many months or years after commencing therapy. This is important to recognise when considering frequency of metabolite monitoring and when considering failure of therapy, or abnormal liver function.

228 Minimising the Functional Burden of Medications in Older Inpatients: Implementation of the Drug Burden Index

Rayan Nahas[1,2], Danijela Gnjidic[1], Terry Finnegan[1], Emily Reeve[1], Jenny Crane[2], Lisa Kouladjian O'Donnell,[1] Sarah N Hilmer[1]
[1]Kolling Institute, Royal North Shore Hospital, Sydney, NSW, Australia, [2]Pharmacy Department, Royal North Shore Hospital, Sydney, NSW, Australia

Introduction: The Drug Burden Index (DBI) is a score that measures exposure to anticholinergic and sedative medications.
Aims: This study investigated the impact of a pharmacist-led intervention on changes in DBI score at discharge and clinical outcomes in older inpatients.
Methods: Patients over 70 years admitted to a tertiary referral hospital under medical services, and taking at least one DBI medication were recruited, and randomised to intervention or control arms. In the intervention group, on admission the pharmacist calculated DBI score using the DBI Calculator© and discussed the report and their recommendations with the treating team. The control group received usual care. Primary outcome was proportion of patients in whom DBI was decreased, unchanged or increased at discharge (chi-squared analysis, SPSS®). This study was approved by the institutional ethics committee and registered by the online registry of clinical trials.
Results: Intervention (n=122) and control groups (n=131) both had a median age of 85 years, with similar prevalence of females (59.8% intervention and 55.7% control) and frailty (68.9% intervention and 61.1% control) which was not statistically significant (P>0.05). More patients were from aged care facilities in the intervention group (18.7% vs 9.9%; P>0.05). Mean ± SD baseline DBI score was 1.08±0.67 in the intervention and 0.98±0.65 in the control group. DBI score was decreased during admission for 67.8% of participants in the intervention and 29.2% in the control group (P<0.001). Fewer new adverse drug events were reported in intervention (20.2%) compared to control group (34.4%; P<0.01). There was no significant difference between groups in length of stay, falls, pressure areas or mortality during hospitalisation. The mean ± SD time the pharmacist spent per participant to conduct the intervention was 6.09±3.03 minutes.
Discussion: An intervention targeting older inpatients' DBI scores significantly decreased DBI exposure on discharge with no significant adverse effects. Future analyses will investigate prescribing and clinical outcomes six months after discharge.

229 A stimulation study to assess the possible contribution of measurement error in quetiapine depression trials

Jia Ning Careen Tan[1], Holly Foot[1], Christine Staatz[1], Karl Winckel[1,2], Adam La Caze[1], [1]School of Pharmacy, University of Queensland, Brisbane, QLD, [2]Princess Alexandra Hospital, Brisbane, QLD

Introduction: There is concern that the inclusion of somatic items in depression rating scales may lead to measurement error in the assessment of depression; e.g. the scale may be influenced by a side effect of treatment such as sedation rather than an improvement in affect (Komossa et al, 2010). Quetiapine causes sedation and has randomised trial data claiming significant benefit against major depressive disorder (Bortnick et al,2011).

Table 1: Percent of successful trials in each drug group

Comparators	Percent of successful trials (%)
Quetiapine vs Placebo	98.55
Drug A vs Placebo	27.53
Drug B vs Placebo	85.06

Aim: To assess the possible contribution of measurement error to the assessment of quetiapine as the treatment of depression.
Methods: We used data from quetiapine depression trial (Bortnick et al,2011) to undertake a simulation study that attempts to isolate the effects of quetiapine on sleep. We simulated 10,000 trials comparing quetiapine, Drug A and Drug B with placebo. Drug A was a fictional drug that has placebo effect combined with the sedative effects of quetiapine and Drug B was a fictional drug that has all effects of quetiapine except the sedative effects. Each trial compared the response rate for the drug against with placebo using Fisher's Exact Test. Simulations were conducted under the assumption that drug and placebo effects are evenly distributed throughout the sample.
Results: The presence or absence of quetiapine's sedative effects (Drug A, Drug B) influences the likelihood of trial success (Table 1). Relaxing the assumption that drug and placebo effects are evenly distributed has a disproportionate effect on placebo response rate and reduces the likelihood of successful trials (especially for Drug A).
Discussion: The beneficial effects of quetiapine on depression may not be explained by its sedative side effects alone. The contribution of measurement error in assessment of antidepressant efficacy needs further attention.

Bortnick B et al (2011) J of Affective Disorders 128:83-94
Komossa K et al (2010) Cochrane Database Syst Rev 12:CD008121

230 A Multicentre Open-Label Pharmacokinetic-Pharmacodynamic Study of Febuxostat in Patients with Chronic Gout

Bishoy Kamel[1,2], Garry G Graham[1,2], Kenneth M Williams[1,2], Sophie L Stocker[2,3], Jane E Carland[2,3], Kevin D Pile[4], Louis E McGuigan[5], Ian J Portek[6], Neil W McGill[7], Richard O Day[1,2,3], [1]School of Med Sc, Univ of New South Wales, [2]Dept of Clin Pharmacol and Toxicol, St Vincent's Hosp, [3]St Vincent's Clin School, Univ of New South Wales, [4]Dept of Med, Western Sydney Univ, [5]Dept of Rheum, Narrabri Hosp, [6]Dept of Rheum, St George Hosp, [7]Dept of Med, Univ of Sydney

Introduction: There are conflicting data concerning the effect of renal function on the pharmacokinetics and response to febuxostat (Fbx).
Aims: To explore relationships between the concentrations of serum urate (SU) and plasma Fbx in patients with chronic gout and examine the influence of renal function on the plasma concentrations of Fbx and the efficacy of Fbx.
Methods: Baseline demographics including SU and serum creatinine concentrations were collected. Plasma Fbx concentrations and SU were measured at four times during long term treatment with Fbx over the dosage interval (24 h). Data is presented as mean ± S.D.
Results: Chronic gout patients (20 males, 6 females) were recruited. The duration of Fbx treatment (40-120 mg/day) was 6 weeks to 66 months. Baseline SU and eGFR were 0.59 ± 0.09 mmol/L and 61 ± 24 mL/min, respectively. Fbx 40 (n=8), 80 (n=17) and 120 (n=5) mg/day achieved similar reductions of SU; 0.34 ± 0.09, 0.36 ± 0.11 and 0.31 ± 0.07 mmol/L, respectively. Target SU ≤ 0.36 and ≤ 0.30 mmol/L were achieved by 90% (24/26) and 77% (20/26) of patients, respectively, with Fbx doses of up to 120 mg/day. At Fbx 80 mg daily, the reduction in SU was 0.37 ± 0.09 and 0.34 ± 0.13 mmol/L in patients with eGFR < 60 (n=9) and ≥ 60 (n=8) mL/min, respectively. At Fbx dosage of 80 mg daily, trough concentrations of Fbx were significantly higher in patients with eGFR < 60 mL/min (0.17 ± 0.11) than those with eGFR ≥ 60 mL/min (0.03 ± 0.01) (P= 0.009). Renal function had no significant effect on peak Fbx concentrations. There was a 50-fold fluctuation in plasma Fbx over 24 h while SU did not fluctuate significantly over this time.
Discussion: Higher trough Fbx concentrations in patients with eGFR < 60 mL/ min may be due to the retention of Fbx-glucuronide and the subsequent regeneration of the parent drug. Renal function does not influence the hypouricaemic response to Fbx. We suggest that the small fluctuation in SU over 24 h is due to the long half-life of urate (20 to 30 h). A larger sample size is required to confirm present results.

231 The safety and pharmacokinetics of metformin in heart failure

Gina Chowdhury[1], Felicity C Smith[1], Peter S Macdonald[2], Jane E Carland[1], Sophie L Stocker[1], Shaun S Kumar[3], Jerry R Greenfield[4], Kenneth M Williams[1], Garry G Graham[1], Richard O Day[1], [1]Dept of Clin Pharmacol, St. Vincent's Hosp, School of Med Sci, Univ of NSW, Sydney, NSW, Australia, [2]Heart Transplant Unit, St Vincent's Hosp, Sydney, NSW, Australia, [3]Div Clin Pharmacol, Dept Ped, Univ of Utah, UT, USA, [4]Dept Endocrin, St Vincent's Hosp, Sydney, NSW, [5]St Vincent's Clinical School, Univ of NSW, Kensington, NSW

Introduction: Metformin, a type II diabetes (T2DM) drug, is contraindicated in heart failure (HF) in Australia due to a perceived increased risk of lactic acidosis. The safety of metformin in HF, described in epidemiological studies, has facilitated approval of its use in HF patients in the US, UK, Canada and New Zealand. Detailed prospective data on the safety and PK of metformin is required to confidently remove this contraindication in Australia.
Aim: To explore the safety and PK of metformin in HF patients and compare with healthy subjects (Timmins et al, 2005) and T2DM patients without HF (T2DM Control) (Duong et al, 2013)
Methods: This cross-sectional study consisted of two cohorts of HF subjects; those with T2DM receiving metformin (n=10), and those without T2DM and metformin naïve (n=26). Biochemical parameters (including lactate, anion gap and bicarbonate) and plasma metformin concentrations were determined. Metformin PK parameters were determined using NONMEM.
Results: In HF patients with T2DM, plasma lactate, anion gap and bicarbonate concentrations did not correlate with plasma metformin concentrations. The apparent CL of metformin (37 ± 17 L/h) was similar to the T2DM patients (49 ± 26 L/h), but significantly lower than healthy subjects (75 ± 14 L/h; $p < 0.05$). The peripheral V was significantly lower in HF patients compared to healthy subjects ($p=0.04$). Lactate concentrations of HF patients without T2DM (1.5 ± 0.7 mmol/L) were significantly lower than in T2DM patients with or without HF (1.9 ± 0.9 mmol/L; $p < 0.05$).
Discussion: The PK of metformin in T2DM HF patients are similar to those in T2DM patients without HF. Additionally, hyperlactatemia was not associated with HF patients both with and without T2DM. These results provide the support for a larger interventional study with metformin in HF patients.
Duong JK et al (2013) Clin Pharmacokinet 52:373-384
Timmins P et al (2005) Clin Pharmacokinet 44: 721-729

232 Vignettes from hospital-level electronic prescribing data

Paul KL Chin[1,2], QianYi Chuah, Matt P Doogue[1,2], [1]Department of Clinical Pharmacology, Canterbury District Health Board, Christchurch, NZ, [2]Department of Medicine, University of Otago, Christchurch, NZ

Introduction: Canterbury District Health Board (CDHB) have rolled out the electronic prescribing and administration (ePA) software, MedChart™, to 1354 hospital beds as of December 2016. Data from these medication charts can be used to monitor user behaviour, and to inform design and evaluate MedChart clinical decision support (CDS) tools.
Aims: To describe a sample of CDHB MedChart analyses that are used clinically.
Methods: Data for 1/1/2017-30/6/2017 were extracted and parsed from the CDHB MedChart database with data cleaning and analytics using R and Tableau. The data requirements were specified by the CDHB CDS Working Group and analysed by the medicines utilisation review (MUR) team.
Results: There was a median (range) of 74,418 (70,868 to 84,174) prescriptions per month.

1) Medical student prescribing: A median (range) of 5 (2-14) prescriptions per month were 'signed' by medical students. Students should not be 'signing' prescriptions; feedback was provided to each student.
2) MedChart prescribing method: in 22 patients admitted for upper gastrointestinal bleeding, the use of protocol prescriptions were associated with more administrations of intravenous omeprazole than 'long-hand' prescriptions (median 12 vs 8 administrations, p = 0.0125). Local guidelines stipulate 12 administrations. The use of preformatted protocol prescriptions facilitates implementation of guidelines.
3) Overdose prevention: Of 518 spironolactone prescriptions, 415 (80%) involved doses up to 25 mg, with the remainder between 37.5 and 200 mg. This informed the setting for the spironolactone high-dose alert.
4) Drug-drug interaction warnings: Alerts fired 34 times against the combined prescribing of enoxaparin and dabigatran, with 25 (74%) associated with changes to the antithrombotic prescriptions. This combination has been associated with major bleeding events.
5) Adverse drug reactions (ADRs) recording: Of 29,714 ADRs, 5,719 (19%) were against drug classes, and 4,875 (16%) were against brand names. ADRs should be recorded against generic names to facilitate recognition by MedChart and users.

Discussion: Integrated MUR and CDS teams can effectively utilise ePA data to improve the use of ePA.

233 Identifying clinical pharmacist patient prioritisation criteria

Nazanin Falconer[1], Michael Barras[1,2], Neil Cottrell[1], [1]School of Pharmacy, The University of Queensland, Brisbane, QLD, Australia, [2]Department of Pharmacy, Princess Alexandra hospital, Brisbane, QLD, Australia

Introduction: An estimated 7% of hospitalised patients experience serious medication harm and 0.3% die due to an adverse drug event (ADE). In increasingly busy hospitals, with high patient throughput and scarce resources, identifying patients at high-risk of ADEs is crucial to enable early and targeted clinical pharmacist intervention.
Aims: To determine key criteria used by clinical pharmacists to identify and prioritise high-risk patients.
Methods: Clinical pharmacists at the Princess Alexandra Hospital were invited to participate in focus groups designed to elicit their perspectives and approaches when prioritising patients for clinical pharmacy services. Seeding questions and clinical vignettes were used to identify their key criteria.
Results: Twenty clinical pharmacists took part in four, one-hour, audio recorded focus groups. Pharmacists used a combination of criteria to determine patient priority. These included: reason for admission (e.g. acute kidney injury and atrial fibrillation), complex co-morbid conditions (e.g. patients with cardiovascular disease, diabetes and mental health history) and older age. High risk medications (e.g. anticoagulants, insulin, antibiotics, immunosuppressants and Parkinson's medications), and laboratory test results (non-therapeutic INR, potassium and sodium levels, and rising creatinine levels) were also identified as key criteria. Organisational demands, such as time of discharge and supply of medications were other factors that influenced patient priority. Pharmacists frequently commented on prioritisation being challenging and time consuming.
Discussion: Clinical pharmacists identified patient prioritisation as a complex multifactorial process that is important in the quality versus quantity battle. The identification of key criteria will help inform the development of a predictive risk score to facilitate an efficient and systematic approach to patient prioritisation that enables the best use of clinical pharmacist resources and optimises patient outcomes.

Lazarou J et al (1998) JAMA 279 15:1200-1205

234 Evaluation of a quantitative approach for analysis of semi-structured pharmacy consumer interviews

Ardalan Mirzaei[1], Claudia Rittsteuer[2] Stephen R Carter[1], Carl R Schneider[1], [1]Faculty of Pharmacy, The University of Sydney, Sydney, NSW, Australia, [2]Karolinska Institutet, Stockholm, Sweden

Introduction: Thematic analysis of interview data can be laborious and time consuming. Contemporary software and computers have the processing speed and capacity to identify relationships amongst text transcripts. Yet, it is uncertain if they have the same capacity as humans to derive deeper meaning. One such mathematical approach to determine the deeper meaning of text is to see how words cluster and whether clustering can inform thematic analysis. Further, the sentiment of text can also be calculated.
Aims: To determine the information quantitative analysis can extract from qualitative transcription data from community pharmacy consumers' perceptions of service quality.
Methods: The transcripts from 26 semi-structured interviews were subject to cluster analysis and sentiment analysis. The combined interviews, were processed using the statistical software program "R". Using multiple packages, and website resources, the data was first cleaned for; repetition of unhelpful words (such as "speaker 1"), punctuation, numeric characters, and English stop words. A term document matrix was then created before subjecting the data to cluster analysis and sentiment analysis. Previous thematic analysis performed on the transcripts was used to ascertain the validity of the results.
Results: The 4 different packages utilised for cluster analysis suggested between 2 to 20 clusters of words existing, as opposed to 27 themes identified by traditional thematic analysis. Sentiment analysis suggested that the conversations were predominately favourably disposed.
Discussion: Quantitatively analysing text can provide quick insight and helpful graphics. However, the human skill of qualitative interpretation provided greater definition in development of themes as determined via cluster analysis. However, associations between clusters can indicate relationships between themes which may be a useful contribution to future psychometric testing. Furthermore, the sentiment analysis of text highlights a quantitative approach to calculate emotion in conversation. However, sentiment analysis does not take into account paraverbal information such as tone.

235 Response of Community pharmacy staff to a request for an antibiotic product without a valid prescription: A simulated client study in Sri Lanka

Shukry Zawahir[1], Sarath Lekamwasam[2] and Parisa Aslani[1], [1]Faculty of Pharmacy, the University of Sydney, Sydney, NSW, Australia, [2]Population Health Research Centre, Faculty of Medicine, the University of Ruhuna, Galle, Sri Lanka

Introduction: Dispensing antibiotics without a prescription was forbidden by Sri Lankan law in 1989 in order to prevent misuse of antibiotics. The effect of this policy change has not been evaluated yet.
Objectives: To evaluate the response of community pharmacy staff to an antibiotic product request without a prescription and to explore possible factors influencing such practice.
Methods: A cross-sectional study was conducted from Jan-June 2017. A total of 232 (response rate, 92%) community pharmacies from all 9 provinces in Sri Lanka consented to participate, and were visited by trained simulated clients (SCs) who requested one specific antibiotic (erythromycin tabs, or amoxicillin syrup, or metronidazole tabs by name; or ciprofloxacin tabs by showing an empty strip). Data on the interaction (availability of pharmacists, antibiotic dispensed and recommendations provided) were recorded immediately after each visit using a data collection sheet.
Results: Of the 232 pharmacies visited, 108 (47%) had a qualified pharmacist present during the visit. Pharmacy staff asked for a prescription for the requested antibiotic in 106/232 (46%) of the SC visits. Only 16/232 (7%) pharmacies correctly referred the SC to a doctor, but 5 of them still dispensed the antibiotic. Overall, 144/232 (62%) pharmacies dispensed antibiotics without a prescription, and 88/232 did not. Of the 88, 7 (8%) were out of stock at that time. The highest dispensed antibiotic was ciprofloxacin 41/54 (76%) followed by metronidazole 38/57 (67%), erythromycin 33/59 (56%) and amoxicillin 32/62 (52%). The availability of a pharmacist reduced the risk of dispensing antibiotics without a prescription (Adj. OR=0.49, 95% CI: 0.28-0.86; *P*=0.013); whilst requesting an antibiotic by showing an empty strip (ciprofloxacin) vs requesting by name increased the risk of prescribing an antibiotic without a prescription (OR=2.44, 95% CI: 1.11-5.58; *P*=0.027).
Conclusion: In Sri Lanka, a large proportion of community pharmacies dispensed antibiotics without a prescription despite the law prohibiting such practice. Making a professionally qualified pharmacist available at all times, strong enforcement of existing laws, and implementation of guidelines on antibiotic dispensing may change the antibiotic dispensing practice among community pharmacies in Sri Lanka.

236 What Is Polypharmacy Exactly (WIPE)

Nashwa Masnoon[1,2], Sepehr Shakib[3,4], Lisa Kalisch-Ellett[1], Gillian Caughey[1,3,4], [1]School of Pharmacy and Medical Sciences, Univ of South Australia, Adelaide, SA, [2]Dept of Pharmacy, Royal Adelaide Hosp, Adelaide, SA, [3]Dept of Clinical Pharmacol, Royal Adelaide Hosp, Adelaide, SA, [4]Dept of Clinical Pharmacol, Univ of Adelaide, Adelaide, SA

Introduction: There are various definitions of polypharmacy and it is unclear how different clinicians define and assess polypharmacy in practice, which can provide important insight into medication review and rationalisation.
Aims: To develop a website which allows evaluation of different clinicians' assessment of polypharmacy and identification of medication related factors which are considered during medication review and rationalisation.
Methods: A website called What Is Polypharmacy Exactly (WIPE) was developed which presents de-identified patient cases from clinical practice at wipe.logicsquad.net/signup. For each case, the website presents the patient's age and setting, list of comorbidities and medications and asks users to i. rate the degree of polypharmacy ii. rate the potential for harm from medications iii. rate the potential to deprescribe medications and iv. nominate medication classes for deprescribing. WIPE provides users with feedback by expert clinicians after case completion as well as the ability to post comments and engage in clinical discussion regarding each case with other users on the website.
Results: There have been 212 responses on WIPE from 61 users comprising of hospital and community pharmacists, consultant physicians, resident medical officers and medical students. Initial data analysis shows that medication classes such as benzodiazepines, opioids, sedating antihistamines and antipsychotics obtained higher ratings regarding the degree of polypharmacy and the potential for harm compared to statins, inhaled medications and paracetamol. Clinicians were more likely to nominate the medication classes which were associated with higher degree of polypharmacy and potential to cause harm for deprescribing.
Discussion: Clinician ratings reflect important aspects of medication review and rationalisation where medications which are identified as having the potential to cause harm are assessed for the possibility of deprescribing in order to optimise patient outcomes. WIPE can be used as an educational tool and allows a novel platform for users at the national and international level to work together to collectively define polypharmacy, in order to develop clear prescribing guidelines and improve patient outcomes.

237 Psychotropic medicines use in Residents And Culture: Influencing Clinical Excellence (PRACTICE) tool: A development and content validation study

Mouna Sawan[1], Yun-Hee Jeon[2], Timothy F Chen[1], [1]Faculty of Pharmacy, University of Sydney, Camperdown, NSW, [2]Faculty of Nursing, University of Sydney, Camperdown, NSW

Introduction: Organizational culture has been identified to be a key factor that contributes to the high-level prescribing and significant variation in the use of psychotropic medicines across aged care homes. There are gaps in existing tools used to link organizational culture to the use of psychotropic medicines.
Aims: The aim of this research was to develop and content validate a tool that measures organizational culture concerning the use of psychotropic medicines in aged care homes, named the Psychotropic medicines use in Residents And Culture Influencing Clinical Excellence (PRACTICE) tool.
Methods: The tool was developed based on a comprehensive systematic review, qualitative research and generated by the research team. Content validity was assessed using the CVI (Content Validity Index). The content relevance and importance of the PRACTICE tool items were rated by an expert panel with relevant knowledge and experience. Any modified or re-worded items were presented to the panel members in a subsequent round for re-rating.
Results: The PRACTICE tool had 68 items that assessed all aspects of culture. Sixty-two items out of 68 (91%) met predefined cut-off values (≥0.78) for the item level CVI. The remaining six items (9%) did not fully meet the cut-off values, but based on the systematic review and qualitative research it deemed important to be included in the tool.
Discussion: The PRACTICE tool is a step forward in validating an instrument that will help inform managers and policy makers to identify target areas for improvement to create a culture of appropriate psychotropic prescribing in aged care homes.

238 "Good prescribing is a bit like good driving; everybody thinks they're a good driver." An exploratory study on the barriers and facilitators to using quality prescribing indicators (QPIs) in general practice

Li Shean Toh, Angus Thompson, Anuj Shah, Justin Cousins, Shane Jackson, Nick Cooling, Gregory Peterson, School of Medicine, University of Tasmania[1], Hobart, TAS, Australia

Introduction: Medication-related problems (MRPs) are an important source of patient morbidity in Australia. Quality prescribing indicators (QPIs) have been developed to prevent and reduce MRPs. In Australia, a set of QPIs for general practice was published in 2006 by NPS MedicineWise, but these have not been updated or widely used.
Aims: To explore the perceived barriers and facilitators to using QPIs in general practice.
Methods: Focus group discussions (FGDs) were conducted with general practitioners (GPs) using a semi-structure topic guide (n=4, each group had 2-6 GPs and one had a GP-based pharmacist). Participants were purposively sampled based on their experience and practice location. Interviews were transcribed verbatim and thematically analysed. Arising themes were then categorised according to an adapted Reason's model from the protocol for the investigation and analysis of clinical incidents.
Results: Six main categories of barriers to using QPIs were identified: governmental, organisational and management, work environment, task, individual and patient. GPs perceived that there is currently no government funding targeted at quality prescribing activities, leading to prioritization of other activities. The fragmented healthcare system contributed to a lack of standardisation in medical records systems resulting in inconsistent data extraction and sharing. GPs cited time and staffing constraints in the work environment. Having a GP-based pharmacist was seen as a facilitator to using QPIs. The task and technology barrier highlighted that QPIs were seen to be targeting areas that were not useful or out of context to practice, were difficult to interpret or outdated. GPs cited alert fatigue with their prescribing software and concerns that conspicuous alerts created unnecessary anxiety for patients. At an individual level, GPs had a lack of awareness and were reluctant to engage with the QPIs. Time pressure to see patients, increasing patient complexity and medication adherence were also barriers. Nonetheless, GPs perceived QPIs to be potentially useful, similarly to NPS MedicineWise audit reports, and the GPs had a willingness to improve practice.
Discussion: The implementation of QPIs in general practice faced barriers at various levels. A multi-level intervention approach is required for their implementation to be successful.

239 Contextualised medication information is critical to treatment uptake and adherence among people living with HIV

Amary Mey[1], Shai Dukie[1], Gary Rogers[2], Maree O'Sullivan[3], David Plummer[4], [1]School of Pharmacy & Pharmacology, Griffith University, Gold Coast, QLD, Australia, [2]School of Medicine, Griffith University, Gold Coast, QLD, Australia, [3]Sexual Health Service[3], Gold Coast, [4]College of Public Health, Medical & Veterinary Sciences, James Cook University, Townsville, QLD, Australia

Introduction: Despite the well-established life-preserving benefits of anti-retroviral therapy (ART), some people living with HIV choose to decline, delay or diverge from prescribed regimens[(1)]. Understanding how treatment decisions are made may facilitate the development of strategies to overcome barriers to treatment uptake and adherence.
Aim: To explore beliefs of people living with HIV about treatment.
Methods: In-depth interviews were conducted with adults living in or around the Gold Coast region of Australia between March 2016 and July 2017. Interviews were audio recorded, transcribed verbatim and analysed using grounded theory framework. Ethical approval HREC / 15 / QGC / 256.
Results: Forty adults who had been living with HIV for between one month and 39 years were interviewed. The majority identified information as a key unmet need. Fears about side effects, association of medication taking with loss of previous uninfected identity, and negative views towards pharmaceuticals, were reasons for rejecting or delaying treatment with treatment fatigue, planning for pregnancy and going on holiday as reasons for deliberate non-adherence. Fear of death, wanting to protect others, ongoing support and receipt of contextualised medication information were strong motivators for treatment uptake and adherence.
Discussion: Contextualised information and ongoing support are crucial to treatment decisions for this vulnerable population group. These findings suggest a potential for pharmacists to be involved in caring for people living with HIV beyond the current confines of their practice locations.

1. Mey A, Plummer D, Dukie S, Rogers GD, O'Sullivan M, Domberelli A. Motivations and Barriers to Treatment Uptake and Adherence Among People Living with HIV in Australia: A Mixed-Methods Systematic Review. AIDS and behavior. 2017;21(2):352-85.

240 A study on usual Residential Medication Management Review (RMMR) practice

Leila Shafiee Hanjani[1], Christopher R Freeman[2], Nancye M Peel[1], Liam J. Caffery[3], Len C. Gray[1], [1]CRGM, UQ, Brisbane, QLD; PACE, UQ[2], Brisbane, QLD; COH, PAH[3], Brisbane, QLD

Introduction: RMMR is available to residents of Residential Aged Care Facilities (RACFs) and aims to identify, resolve and prevent medication-related problems. Ideally, RMMRs should be conducted and reported to RACFs in a timely fashion.
Aims: To describe current practice model for RMMRs and areas for potential enhancement of the model.
Methods: A questionnaire on usual practice of conducting RMMRs, seeking information on distance pharmacists travelled to and from the facility, time taken to complete the review including travel, locating and reviewing required information and reporting, contact with residents and staff, number of reviews conducted in the visit and issues or barriers encountered, was developed and piloted. Five experienced RMMR accredited pharmacists were asked to complete the questionnaire in their 5 consecutive visits to 5 different RACFs.
Results: Pharmacists completed the questionnaire in 24 visits to 24 RACFs. They conducted an average of 10 RMMRs per visit and the median distance they travelled to do these was 61 kilometres (km) with a range of 10 to 1774 km. Median time spent for each review, including time for travel, locating and reviewing required information and report writing, was 63 min. Nurses were consulted frequently (83% of visits) and patients were only consulted in 17% of the visits. In 33% of the visits they encountered an issue or barrier affecting their capacity to conduct RMMRs such as nurses not being available or computer and login issues. On most occasions (17/24), the reports were made available to the facility 48 hours or more after the visit.
Discussion: Although the median distance pharmacists travelled to conduct RMMRs was less than the results of the Government report on evaluation of RMMR service in 2010, the range in distance travelled was immense. Travel time and distance can both act as barriers to performing timely and efficient medication reviews. Conducting timely reviews can be further affected by late availability of the reports to the facilities which occurred on majority of visits in our study. Alternative ways to conduct RMMRs, such as telehealth-enabled medication reviews, may provide a mechanism to overcome these issues which is of particular importance to regional, rural and remote settings where access to these services is generally poor.

241 IRAK3 modulates NFκB through its guanylate cyclase activity

Lubna A. Freihat, David T. Manallack, Janet I. Wheeler, Helen R. Irving. Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences - Monash University, 381 Royal Parade, Parkville, VIC 3052, Australia.

Introduction. Interleukin-1 receptor associated kinase 3 (IRAK3) acts as a negative regulator of inflammation. The role of IRAK3 is critical to maintaining homeostasis in the innate immune response and in preventing the development of autoimmune diseases. It is involved in various inflammation-associated disorders such as lung injury, metabolic syndrome and tumour growth. Prior studies identified IRAK3 as a potential novel guanylate cyclase (GC) catalyzing cyclic guanosine monophosphate (cGMP) synthesis. IRAK3 is predicted to be a mammalian representative of a new class of GCs containing a GC centre encapsulated within the kinase domain. (Freihat et al., 2014).
Aims. To investigate if IRAK3 is capable of generating cGMP and if modifying the GC centre modulates the downstream signaling pathways.
Methods. GC activity was assessed using the GE Amersham cGMP enzyme immunoassay kit. HEK BLUE hTLR4 cells containing a SEAP reporter system were transfected with either IRAK3 or IRAK3 mutant constructs, effects on NFκB activity in the presence of lipopolysaccharide (LPS) and cGMP were investigated.
Results. Recombinant IRAK3 protein produced significant amounts of cGMP in vitro, whilst the IRAK3 GC mutant did not. Overexpression of IRAK3 in HEK BLUE hTLR4 cells significantly reduced LPS induced, NFκB activation. Whereas IRAK3 GC mutants with reduced cGMP-generating capacity failed to inhibit LPS induced NFκB activity. The presence of cell-permeable cGMP restored IRAK3 function and significantly reduced NFκB activity in IRAK3 mutants with reduced cGMP-generating capacity.
Discussion. Low levels of cGMP are important for IRAK3 action and these findings are providing insight into the hidden functions of IRAK3 and may assist in explaining its selectivity and functionality in the inflammatory signalling cascade. Understanding how this novel GC function impacts the anti-inflammatory effect of IRAK3 is likely to be important when targeting this protein in different disease states.

Freihat, L., Muleya, V., Manallack, D.T., Wheeler, J.I., and Irving, H.R. (2014). Biochemical Society Transactions *42*, 1773-1779.

242 Intranasal delivery of the TLR7 agonist, imiquimod, protects against influenza A virus-induced morbidity in mice

Jonathan R. Erlich[1], Eunice E. To[1,2], Raymond Luong[1,2], Felicia Liong[1], Keshia Hendricks[2], Steven Bozinovski[1], John J. O'Leary[3], Doug A. Brooks[4], Ross Vlahos[1], Stavros Selemidis[1,2]. [1]School of Health and Biomedical Sciences, RMIT University Bundoora, VIC, Australia; [2]Dept of Pharmacology, Monash University, Clayton, VIC, Australia. [3]School of Medicine, Trinity Translational Medicine Institute, Trinity College Dublin, Ireland. [4]School of Pharmacy and Medical Sciences, Sansom Institute for Health Research, University of South Australia, Adelaide, Australia.

Introduction. Influenza is a significant global burden with 5 million cases per year, 10% of which are fatal and thus, there is an urgent need for new therapeutics (WHO factsheet, 2017). Toll like receptor 7 (TLR7) is a pattern recognition receptor, which drives a powerful anti-viral signalling pathway that helps clear virus infections.
Aim. To determine the effect of the TLR7 agonist imiquimod on lung inflammation, oxidative stress and antibody production caused by influenza A virus (IAV) infection in mice.
Methods. Saline or imiquimod (50μg/mouse) was delivered intranasally to anaesthetised (inhaled isoflurane; 3%) male C57BL/6J mice one day prior to infection with a low (10^3PFU/mouse), moderate (10^4PFU/mouse) or high dose (10^5PFU/mouse) of the mouse adapted Hong Kong X31 (x-31) virus strain and everyday thereafter until mice were culled day 3 (d3) or 7 (d7) post-infection for analysis. Bronchoalveolar lavage (BAL) was performed to assess airways inflammation, and oxidative burst by L-012 enhanced chemiluminescence. In addition, BAL fluid and serum was used to determine antibody titres. The lungs were harvested and used to assess inflammation (H&E staining) and pro-inflammatory cytokine gene expression by qPCR. Bodyweights were recorded daily during the experimental process.
Results. Imiquimod significantly suppressed body weight loss caused by IAV infection with a maximum reduction of ~60% starting from day 4 (10^3 PFU/mouse, n=7-13, $p<0.001$). At d3 post infection, imiquimod treatment caused a significant reduction (~50-60%) in airway and peri-bronchial inflammation and BALF neutrophil populations (10^5 PFU/mouse, n=8-15, $p<0.01$) but had no effect on macrophage and lymphocyte populations, and the oxidative burst. TNF-α and IL-6 mRNA expression was supressed by ~60% ($p<0.01$ and $p<0.05$, respectively). Day 7 showed a modest but significant increase in IgE, IgM, IgG1, and IgG2a ($p<0.05$) in BALF following imiquimod treatment.
Discussion. Our findings highlight an exciting potential of imiquimod as a therapeutic option for the treatment of influenza disease.

243 A novel endosomal NOX2 oxidase inhibitor protects against high pathogenicity influenza A virus-induced disease

Eunice E. To[1,2], Raymond Luong[1], Felicia Liong[1], Jiayin Diao[3], Steven Bozinovski[1], Christopher J.H. Porter[3], Tim Quach[3], John O'Leary[4], Doug A. Brooks[5], Ross Vlahos[1], Stavros Selemidis[1,2], [1]School of Health and Biomedical Sciences, RMIT University, Bundoora, VIC, Australia, [2]Dept of Pharmacology, Monash University, Clayton, VIC, Australia, [3]Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC, Australia, [4]School of Medicine, Trinity Translational Medicine Institute, Trinity College Dublin, Ireland, [5]School of Pharmacy and Medical Sciences, Sansom Institute for Health Research, University of South Australia[5], Adelaide, Australia

Introduction: We have shown that influenza A viruses, *irrespective* of strain, cause a burst of reactive oxygen species (ROS) production via NOX2 oxidase that occurs in endosomes (To et al, 2017). We also showed that an endosome targeted NOX2 oxidase inhibitor called cholestenol conjugated gp91ds-TAT (Cgp91) was significantly more effective at inhibiting NOX2 oxidase than an unconjugated version of the same drug. Strikingly targeted inhibition of endosomal ROS production with Cgp91 abrogated disease caused by a seasonal strain of influenza A virus (IAV) in mice.
Aim: Determine the effect of Cgp91 treatment on the lung pathology induced by a highly pathogenic strain of IAV.
Methods: Male C57Bl/6J mice were treated daily *via* intranasal administration with Cgp91 (0.2mg/kg) or DMSO (2%; control) over a 4-day period. Mice were infected with the PR8 (H1N1; 500 PFUs) strain of IAV or PBS control, one-day post initial drug treatment and analysed at day 3 (d3) post infection. Bronchoalveolar lavage (BAL) fluid collected from mice was used to assess airway inflammation. Histopathological analysis of lung was assessed using H&E stain and scored for alveolitis, inflammatory cell infiltrate and peribronchiolar inflammation. Superoxide generation in the BAL was measured using L-012 enhanced chemiluminescence and changes in cytokine and viral mRNA expression in the lung were quantified using real-time QPCR.
Results: Cgp91 treatment significantly ($P<0.05$) reduced airway inflammation, neutrophil influx, and pulmonary inflammation as measured by the degree of alveolitis, inflammatory cell infiltrate and peribronchiolar inflammation. Additionally, Cgp91 attenuated ROS generation and influenza viral mRNA expression in PR8-infected mice.
Discussion: The spatial inhibition of NOX2 in endosomal compartments with Cgp91 could be used as a potential treatment strategy for highly pathogenic influenza A virus infections.
To *et al*. Nature Communications, **8**, Article number: 69(2017).

244 Localisation of polymyxin in human alveolar epithelial cells

Maizbha U Ahmed[1, 2], Mohammad AK Azad[2], Alex Fulcher[3], Tony Zhou[4], Fanfan Zhou[5], Kim Chan[5], Tony Velkov[1], Jian Li[2]
[1]Monash Institute of Pharmaceutical sciences, Monash University, Parkville, VIC, Australia, [2]Department of Microbiology, Monash University, Clayton, VIC, Australia, [3]Monash Micro Imaging, Monash University, Clayton, VIC, Australia, [4]Department of Industrial and Physical Pharmacy, College of Pharmacy, Purdue University, West Lafayette, IN, USA; Faculty of Pharmacy, The University of Sydney[5], Camperdown, NSW, Australia

Introduction: Inhaled polymyxin therapy is currently empirical and often the large doses administered could lead to potential pulmonary adverse effects. We demonstrated the involvement of both the death receptor and mitochondrial apoptotic pathways in polymyxin-induced pulmonary toxicity. Presently, there remains a dearth of information on the detail mechanisms of polymyxin induced lung toxicity and the intracellular localisation of polymyxins in lung epithelial cells.
Aims: This study aimed to investigate the intracellular localisation of polymyxin B (PMB) in A549 lung epithelial cells.
Methods: A549 cells were subject to PMB treatments (0.1, 0.5, and 1.0 mM for 1, 4 and 24 h), and various organelles along with ubiquitin and PMB were visualised by immunostaining. Cells were imaged using confocal microscopy.
Results: PMB co-localised with early endosomes across all time points. Significant co-localisation of PMB with mitochondria was observed that led to the alteration of mitochondrial morphology from filamentous to fragmented (n=3, $p < 0.001$). PMB also co-localised with lysosomes and ubiquitin. Significant increases in the autophagic protein LC3A were observed at higher concentrations (0.5 mM and 1.0 mM) of PMB.
Discussion: The subcellular imaging of A549 cells reveals that PMB significantly co-localised with mitochondria and caused severe mitochondrial damage which may account for the polymyxin-induced activation of mitochondrial apoptosis pathway we previously observed in A549 cells. The formation of autophagosomes and lysosomes is likely a cellular response to the drug-induced stress and plays a defensive role by disassembling dysfunctional organelles and proteins. Our study provides fundamental knowledge for understanding the mechanisms of polymyxin-induced lung toxicity, which would be vital for optimising their use in the clinic.

Ahmed MU *et al* (2017) Antimicrob Agents Chemother 61(6): e02690-16

245 Pharmacological characterisation of small molecule C5aR1 inhibitors in primary human macrophages

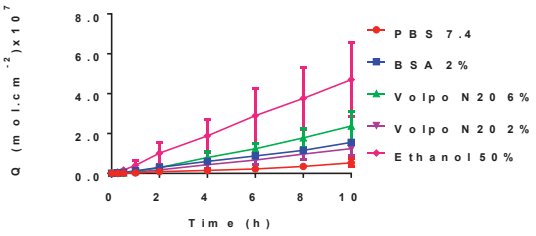
Xaria X. Li, Daniel E. Croker, Richard J. Clark Trent M. Woodruff, School of Biomedical Sciences, The University of Queensland, Brisbane, QLD, Australia

Introduction: The complement system is an essential component of innate immunity. The complement factor C5a is a core effector protein that exerts potent proinflammatory and immunomodulatory functions through its major receptor C5aR1. Over-activation of the C5a-C5aR1 axis has been implicated in a plethora of acute and chronic diseases, propelling the development of therapeutic inhibitors of C5aR1. Despite a number of these inhibitors being developed, to date, no systematic pharmacological characterisation of these compounds has been reported in human immune cells.
Aims: To compare the antagonistic potency and duration of inhibition of selected C5aR1 inhibitors against C5a-mediated cytokine release and phospho-ERK1/2 signalling respectively in primary human macrophages *in vitro*.
Methods: The peptidic (PMX53, PMX205, JPE1375) and non-peptide (W54011, NDT9513727) C5aR1 inhibitors were profiled in human monocyte-derived macrophages (HMDMs). IL-6 and IL-10 release in the co-presence of LPS was quantified using ELISA. Time-lapse pERK1/2 activity was examined using a AlphaLISA-based kit.
Results: The peptidic compounds were significantly more potent than the non-peptide small molecules in inhibiting the immunomodulatory effect of C5a. The rank order of potency was JPE1375 > PMX53 > PMX205 > NDT9513727 > W54011 for both IL-6 and IL-10 assays. In the wash-off study for pERK1/2 activity, PMX53 and JPE1375 possessed significantly longer duration of antagonistic activity ($t_{1/2}$ > 24 h) compared to the remaining inhibitors ($t_{1/2}$ ~ 5 h).
Discussion: The peptidic C5aR1 inhibitors are more effective at inhibiting C5aR1-mediated immunomodulatory effects in primary human immune cells, possibly due to their prolonged duration of receptor antagonism. The peptidic inhibitors may thus represent more ideal clinical drug candidates due to their potent and prolonged antagonistic activities.

246 Getting under the skin – Why receptor fluid choice is crucial in in vitro skin permeation tests

Ana Macedo[1,2], Azadeh Aliganhi[1,2], Amy Holmes[1,2], Michael Roberts[1,2,3]. Therapeutics Research Centre[1], School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA, Australia; Therapeutics Research Centre[2], The Basil Hetzel Institute for Translational Health Research, Adelaide, SA, Australia; Therapeutics Research Centre[3], School of Medicine, The University of Queensland, Brisbane, QLD, Australia

Introduction. *In vitro* human skin permeation tests (IVPT) are used as an alternative to *in vivo* studies in assessing skin penetration of drugs, pesticides, and cosmetics. The Organisation for Economic Co-operation and Development (OECD) guidelines advise that a physiologically relevant receptor solution should be selected (e.g. phosphate buffer saline, PBS pH 7.4) for permeation studies. However, this has not been validated for key solutes.



Aims. To examine the effect of receptor composition on the IVPT using a homologous series of aliphatic alcohols.

Methods Experimental solubility and human epidermal IVPT data were generated for a series of ^{14}C alcohols (ethanol, propanol, pentanol, heptanol, octanol, and decanol) using OECD recommended receptor solutions in side-by-side diffusion cells at 25°C±1°C. Transient and stead-state epidermal fluxes, as well as permeability coefficients, were estimated without and with adjustment for possible non-sink receptor conditions.

Results. Higher permeability coefficients were observed with the longer carbon chain alcohols and these permeability coefficients depended on the solubility of the alcohol in the receptor phase. The permeation fluxes of alcohols in this study were dependent on the receptor phase composition for the more lipophilic solutes, as depicted for decanol in the figure.

Discussion. The selection of the IVPT receptor phase is crucial for poorly water soluble solutes.

247 Can an educational intervention lead to a sustained reduction in gastric lavage for poisoning admissions?

J Raubenheimer[1]; A Dawson[1]; L Senarathna[2], S Jayamanne[3], P L Ariyanadana[4], I Gawarramana[5] and N Buckley[1], [1]University of Sydney, NSW, Australia, [2]Rajarata University, Sri Lanka, [3]University of Kelaniya, Sri Lanka, [4]University of Ruhuna, Sri Lanka, [5]University of Peradeniya, Sri Lanka

Introduction: A clustered RCT of educational interventions on treatment of patients with acute poisoning in rural Asian hospitals collected data on all acute poisonings for the period October 2010 to December 2014 in four provinces of Sri Lanka, providing 20 759 cases in total.

Aims: One of the major aims of the study was to effect a reduction in forced emesis and/or gastric lavage for poisoning admissions in primary hospitals, together with an increase in the use of activated charcoal, where applicable.

Methods: Primary hospitals from four Sri Lankan regions were randomised (1:1:1) between three study arms. The first obtained a set of poisoning treatment guidelines only (considered the placebo arm). The second (intervention 1) received a half-day interactive teaching session using a lecture/workshop format delivered by an expert (consultant physician) in the primary hospital to medical and other hospital staff. The third (intervention 2) received a "train-the-trainer" intervention where a full day educational session was provided to available primary care doctors and nursing staff from a number of health institutions in a central location, where they were equipped, and provided with materials, for repeating the training at their institutions. The interventions were rolled out between February and December 2011. All poisoning admissions were recorded for a period of two years, with a complete history of treatment and outcomes.

Results: For the expert presentation group, an immediate increase in the use of activated charcoal was seen, which was sustained throughout the study period. Gastric lavage did not decrease immediately, but did subside in the long term. The train-the-trainer arm showed very little change over the study period, while the guideline grouped showed increases in both the use of activated charcoal and gastric lavage.

Discussion: It appears that the intervention was moderately successful when the training was done by an expert on site, although the full impact took time to develop. Even the train-the-trainer intervention seemed to be able to prevent a worsening of the situation, while the guidelines appeared to have no effect.

248 Optimising medicines for optimal patient outcomes? Perhaps we need more comparative ineffectiveness research!

Nicholas A Buckley, Sydney Medical School, The University of Sydney, NSW, Australia

Many terms around drug regulation and policy have an Orwellian turn of phrase. The FDA Office of Drug Safety is tasked with monitoring drug toxicity. Pharmacovigilance largely refers to a passive process of waiting for someone else to notify adverse drug effects. Comparative effectiveness research seems to largely be applied to identify treatments that are less effective or more harmful, generally or in specific populations or settings.

My research over the years has identified many drugs that are more toxic, more misused, less appropriate, cause more adverse reactions, more drug interactions, and/or reduced adherence; sadly, it has yet to identify any single drugs that stand out from the pack due to superior characteristics. This may be a reflection of where all new truths about marketed drugs are most likely to be found. Alternatively, it might just reflect the typical focus of an academic research career in pharmaco-epidemiology, clinical pharmacology & toxicology.

My early research focussed on using clinical databases on poisoned patients and coronial data to identify drugs with higher toxicity relative to other agents used for the same indications. For example, dothiepin, desipramine, thioridazine, short acting barbiturates, chloral hydrate, pheniramine, propranolol, temazepam gel caps, venlafaxine were all singled out as being more toxic in overdose and/or having more fatal poisonings per prescription than alternative substitute treatments. This led to various changes in regulations, scheduling, product information and treatment guidelines, but typically these were decades or more after the drugs first came to market.

More recently, it is apparent that linked routinely collected health data, the National Coronial database and Poisons Centre identified cohorts have the potential to identify such problems much more efficiently and rapidly, and determine if regulatory interventions are effective. Modified release paracetamol, DMAA, alprazolam, codeine, oxycodone, Targin, fentanyl, quetiapine, pregabalin, are examples of drugs where emerging issues are being identified and a much more rapid targeted response with susbequent evaluation is possible. ASCEPT members are enthusiastic about sowing the seeds to work the field of therapeutics. But somebody also needs to weed the garden.

300 Colloids, carriers and collaborations: A pathway to enhanced drug delivery

Christopher J.H. Porter[1,2], [1]Monash Institute of Pharmaceutical Sciences and [2]ARC Centre of Excellence in Convergent Bio-Nano Science and Technology, Monash University, Parkville, Vic, Australia

In an era of increasingly complex drug targets, drug delivery science remains an essential component of the drug development continuum. Great strides have occurred in drug discovery through an understanding of complex biology and disease progression pathways, however next generation medicines present greater and greater challenges for effective delivery.

Over the last several years my lab has been exploring ways in which 'problem' drugs may be better delivered – be they anticancer therapies with low activity and high toxicity, poorly soluble drugs with limited oral bioavailability or immunomodulators where traditional delivery modalities fail to promote access to lymphocyte resident targets. A common theme across the approaches we have taken has been to better understand endogenous transport pathways and to harness (rather than fight) these mechanisms for drug delivery. In this presentation I will describe our efforts to utilise lipid-based formulations to promote drug solubilisation in the gastrointestinal tract, and to develop novel models to better understand drug absorption from intestinal colloidal species. I will outline the most recent results from a long term collaboration to enhance tumour specific drug delivery using dendrimer-based nanomedicines, and finally I will highlight a program of work to harness an alternate transport pathway, the lymphatic system, to enhance bioavailability and promote drug delivery to immune tissues and lymph nodes. Across all of these programs, a highlight has been the opportunity to collaborate with a wide range of world-class scientists, both locally and internationally, in industry and academia; these relationships have underpinned the work we have been able to do and the research areas we have been able to progress.

301 The use of oral anticoagulants in people in dementia

Jenni Ilomäki[1,2]. Centre for Medicine Use and Safety, Monash Univ[1], Parkville, VIC, Department of Epidemiology and Preventive Medicine, Monash Univ[2], Melbourne, VIC

Introduction. People with dementia may be less likely to be prescribed guideline recommended medicines for prevention of ischaemic stroke (IS) and other chronic conditions. It is unclear whether this disparity reflects 1) legitimate consideration of the lack of evidence and efficacy in people with dementia and concern about susceptibility to adverse drug events (ADEs), 2) recognition of peoples' changing goals of care, or 3) the unjustified exclusion of people with dementia from receipt of guideline recommended health care.
Aims. To describe pharmacoepidemiological research on medication use in people with dementia focusing on oral anticoagulant use.
Methods. An increasing range of data are available to investigate medication use in Australia and internationally. These data include electronic medical records from hospitals, prescribing data from primary care centres and pharmacy dispensing data. The 10% random sample of the Australian Pharmaceutical Benefits Scheme (PBS) provides opportunities to investigate the prevalence and uptake of oral anticoagulants in people with dementia from March 2005.
Results. Meta-analysis suggests the prevalence of oral anticoagulant use is lower in people with dementia than in people without dementia in all practice settings. In Australia, the overall prevalence of warfarin use in people with dementia increased from 3.6% in 2009 to 4.7% in 2016 while direct oral anticoagulant (DOAC) use increased from 0.04% to 7.0% over the same time period. International literature shows that people with dementia are more likely to experience ADEs related to oral anticoagulant use. INR control has been shown to be poorer in people with than without dementia.
Discussion. The prevalence of anticoagulant use in people with dementia has increased sharply in Australia since the introduction of DOACs. This may indicate more people with dementia receive appropriate treatment. However, there is a need for further research in the benefits and risks of DOAC use in people with dementia.

302 Strategies for the precision use of targeted anti-cancer medicines

Andrew Rowland[1], Madelé van Dyk[1], Michael J Sorich[1], [1]Department of Clinical Pharmacology, College of Medicine and Public Health, Flinders University, Adelaide, SA, Australia

Introduction: The clinical implementation of a precision dosing strategy depends on three core elements: (1) the predictive performance and capacity to improve outcomes, (2) the ability to generate high quality evidence of clinical validity, and (3) the practicality of application. In Medical Oncology a major barrier to clinical translation of 'classical' precision dosing strategies such as therapeutic drug monitoring (TDM) is the preclusive cost and logistical complexity required to develop high quality prospective of validity.
Aims: To develop novel complementary strategies that facilitate the routine clinical translation of precision dosing for targeted anti-cancer medicines.
Methods: This program of research utilises a continuum of techniques spanning from physiological based-pharmacokinetic modelling (PBPK) and *in vitro* reaction phenotyping through to healthy volunteer and patient based clinical trials.
Results: Verified PBPK models identified an optimal set of covariates that define variability in exposure for a number of targeted anti-cancer medicines. By way of example, 94 % of the variability in steady-state dabrafenib exposure was defined by a model incorporating patient weight, and CYP3A4, CYP2C8 and P-gp protein abundances. In terms of defining protein abundances, an R^2 of 0.904 was attained for the correlation of circulating CYP3A4 protein expression in exosomes isolated from human plasma and midazolam apparent oral clearance (CL/F) in a cohort of 18 to 35 year old healthy Caucasian males of CYP3A4 *1/*1 (wild type) and CYP3A5 *3/*3 (non-functional) genotype pre- and post- rifampicin dosing (300mg QD for 7 days). Furthermore, the change in exosomal CYP3A4 expression defined 92% of the variability in the extent of CYP3A4 induction following treatment with rifampicin.
Discussion: Through the use of novel strategies to identify and quantify biomarkers defining drug exposure exposure, this program is demonstrating the capacity to derive clinically actionable insights from routinely collected samples from pivotal late phase RCTs regarding the pathways defining drug exposure in diagnostically amenable samples.

303 Big data: Driving innovation for geriatric pharmacoepidemiology and pharmacovigilance research

Dr Prasad Nishtala, University of Otago, New Zealand

A rapid increase in the quantity, diversity and accessibility of big electronic patient data has provided unprecedented opportunities for the assessment of drug safety in older people. Randomized controlled trials (RCTs) are considered the ''gold standard'' for producing evidence relating to the comparative risks and benefits of pharmaceuticals; however, RCTs have their own limitations. Importantly, they lack external validity and they often exclude older people with multiple comorbidities, and findings may not be generalisable to high-risk populations. Well-designed pharmacoepidemiological studies have been shown to correlate well with RCTs in terms of estimates of risk and effect size. My research will highlight some of the recent advancements in both pharmacoepidemiology and pharmacovigilance to understand medication safety in older people. In summary, my research addresses an important gap in international drug safety research, combining the power of a large population-based sample with innovative pharmacoepidemiology designs that can be used to identify frequent medication combinations associated with adverse drug events.

304 Developing the next generation of analgesics

Jennifer R Deuis, Inst for Molecular Bioscience, Univ of Queensland, St Lucia, QLD, Australia

Voltage-gated sodium (Na_V) channels are integral membrane proteins that allow influx of sodium ions, essential for action potential generation and propagation in electrically excitable cells. Nine voltage-gated sodium channel subtypes have been described to date ($Na_V1.1$-$Na_V1.9$), several of which are implicated as causative contributors to pain. Of particular interest is $Na_V1.7$, as loss-of-function mutations cause congenital insensitivity to pain, a rare condition resulting in individuals who are otherwise normal except for the inability to sense pain. This has led to intensive efforts by the pharmaceutical industry to develop Nav1.7-selective inhibitors as novel analgesics. $Na_V1.7$ selectivity is key, as activity at other Na_V subtypes, including $Na_V1.4$, which is expressed in skeletal muscle, $Na_V1.5$, which is expressed in cardiac muscle, and $Na_V1.6$, which is expressed on motor neurons, is likely to cause dose-limiting adverse effects. We recently identified μ-theraphotoxin-Pn3a, a novel peptide isolated from venom of the tarantula *Pamphobeteus nigricolor* that potently inhibits $Na_V1.7$ (IC_{50} 0.9 nM) with at least 40–1000-fold selectivity over all other Na_V subtypes, making it one of the most selective $Na_V1.7$ inhibitors reported to date. Despite on-target activity, Pn3a alone displays no analgesic activity in multiple rodent models of acute inflammatory pain, including formalin-, carrageenan- or FCA-induced pain. However, when administered with a subtherapeutic dose of the opioid oxycodone, Pn3a exhibits profound analgesic activity. Thus, the combination of an opioid and a $Na_V1.7$ selective inhibitor such as Pn3a is a promising new approach for the treatment of pain.

305 BBB permeability of molecularly-targeted anti-tumor agents: Necessary for effective treatment of brain tumors

Prof William Elmquist, University of Minnesota, USA

This talk will focus on the issues surrounding effective drug delivery to the invasive cells in brain tumors, both primary and metastatic. Many of the newer, molecularly-targeted anti-cancer agents have impressive inhibitory action against various signaling pathways that drive tumor growth. However, they have been ineffective in treating brain tumors. The mechanisms responsible for this failure must be explored before progress can be made, and inadequate drug delivery across an intact BBB may be one critical factor for invasive primary tumors, as well as the early micro-metastases from peripheral tumor sites. The molecularly-targeted signal transduction inhibitors are often substrates for active efflux transporters at the BBB, and this delivery-limiting mechanism must be overcome before these inhibitors can be adequately tested in clinical trials.

306 Clearance of beta-amyloid is facilitated by apolipoprotein E (apoE) and circulating high-density lipoproteins (HDL) in bioengineered human vessels

Jerome Robert, Emily B. Button, Brian Yuen, Megan Gilmour, Kevin Kang, Arvin Bahrabadi, Sophie Stukas, Wenchen Zhao, Iva Kulic, Cheryl L. Wellington, Department of Pathology and Laboratory Medicine, Djavad Mowafaghian Centre for Brain Health University of British Columbia, Vancouver. British Columbia, Canada, V6T 1Z3

Introduction: Amyloid plaques, consisting of deposited beta-amyloid (Aβ, are a neuropathological hallmark of Alzheimer's Disease (AD). Cerebral vessels play a major role in AD, as Aβ is cleared from the brain by pathways involving the cerebrovasculature. Most AD patients have cerebrovascular amyloid, known as cerebral amyloid angiopathy, and cardiovascular risk factors increase dementia risk.
Aims: To develop the first functional three-dimensional model of cerebral amyloid angiopathy in bioengineered human vessels.
Methods: Three-dimensional scaffold-directed blood vessels consisting of primary human endothelial cells and smooth muscle cells, with or without primary human astrocytes, were generated under flow conditions. Vessels were treated with Aβ at the "brain" side with or without HDL at the "blood" side, followed by analysis of Aβ transport into the circulating medium and accumulation of Aβ in the engineered vessel wall.
Results: Brain apoE and circulating HDL synergize to facilitate Aβ transport across bioengineered human cerebral vessels. These lipoproteins facilitate Aβ42 transport more efficiently than Aβ40, consistent with Aβ40 being the primary species that accumulates in CAA. Moreover, apoE4 is less effective than apoE2 in promoting Aβ transport, also consistent with the well-established role of apoE4 in Aβ deposition in AD.
Discussion: As circulating HDL synergizes with brain-derived apoE to maintain Aβ solubility and transport from brain to blood, therapeutic strategies to optimize HDL function may be of interest for AD as a complementary therapeutic approach amenable to systemic administration.

307 HIV infection and Alzheimer's disease: The integral role of the blood-brain barrier

Michal Toborek and Ibolya E Andras, Department of Biochemistry and Molecular Biology, University of Miami School of Medicine, Miami, FL 33136, USA

Introduction: Increased amyloid deposition is characteristic of HIV-1-infected brains, resembling pathology of Alzheimer's disease (AD). It has been hypothesized that brain vascular dysfunction and HIV-1 infection contribute to this phenomenon, with a critical role suggested for the blood-brain barrier.
Aims: To evaluate the impact of HIV infection on amyloid metabolism at the blood brain barrier.
Results and Discussion: We demonstrated that HIV-1 can elevate amyloid beta levels in human brain endothelial cells and enhance its transendothelial transfer. Mechanistically, we identified the involvement of the receptor for advanced glycation end products (RAGE), lipid rafts, and the dynamin-dependent EEA1 and TGF-beta/Smad signaling pathways in this process. Potentiation of neurotoxic impact of HIV by amyloid beta was reported by us and others in mouse models characterized by amyloid accumulation in the brain. Advanced amyloid plaques are typically surrounded by a microvessel network with substantial capillary leakage, indicating a compromised BBB.
Extracellular vesicles (ECV) are formed by budding from the endosomal membranes, followed by the endosome membrane fusion. ECV were recently postulated to have a significant involvement in various neurodegenerative diseases, including amyloid pathology. Indeed, elevated levels of proteins pathogenic in AD in blood-derived ECV were found to predict the development of AD up to 10 years before clinical onset. Our studies indicate that HIV enhances the number and size of ECV produced by brain endothelial cells and increases their amyloid content. Endothelial-derived ECV can also transfer amyloid cargo into other CNS cells, including neural progenitor cells and astrocytes. Infusion of brain endothelial ECV carrying fluorescent amyloid beta into the internal carotid artery of mice resulted in association of amyloid with brain microvessels and brain parenchyma. These results suggest that ECV carrying amyloid can be successfully transferred across the BBB into the brain. We conclude that HIV-1 facilitates the shedding of brain endothelial ECV carrying amyloid beta; a process that may increase amyloid exposure of cells of neurovascular unit, and contribute to amyloid deposition in HIV-infected brain.
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308 The cerebral vascular basement membrane: A target for Alzheimer's disease and stroke

Gregory Bix[1], Departments of Neurology, Neurosurgery and Neuroscience, University of Kentucky[1], Lexington, KY, USA

Introduction: Alzheimer's disease and ischemic stroke both represent debilitating neurologic conditions in great need of new therapies.
Aims: We investigated the pathophysiology and therapeutic potential of domain V (DV), a proteolytic protein fragment of the cerebral vascular basement membrane proteoglycan, perlecan, in mouse models of ischemic stroke and Alzheimer's disease.
Methods: Endogenous brain DV expression was evaluated immunohistologically in a mouse model of ischemic stroke (transient middle cerebral artery occlusion). DV was then administered 24 hours after stroke induction to assess its therapeutic potential (infarct size, functional assessment, etc.). The ability of DV to block amyloid-beta (a major effector of Alzheimer's disease) angio- and neurotoxicity, as well as affect its brain clearance was assessed in vitro. Next, DV was administered every 5 days for 6 months to a pdAPP mouse model of Alzheimer's disease to determine whether it could lessen brain amyloid-beta burden.
Results: Brain DV levels were rapidly and persistently elevated after experimental stroke. Post-stroke administered DV reduced ischemic brain infarct volume, and improved functional outcomes. DV blocked amyloid-beta angio- and neurotoxicity and enhanced its clearance into brain microvessels in vitro. DV had non-significant effects on total brain amyloid burden in pdAPP mice after 6 months.
Discussion: The cerebral vascular basement membrane protein fragment perlecan DV may play an important pathophysiologic and therapeutic role in Alzheimer's disease and stroke.

309 Complementary medicines, health professional responsibilities and trust

Prof Eleanor Milligan, Griffith University, Brisbane, QLD, Australia

In 2017, the Pharmaceutical Society of Australia (PSA) released a revised Code of Ethics. The new Code provides clear guidance regarding the supply and promotion of complementary medicine stating, '*a pharmacist will only purchase, supply or promote any medicine, complementary medicine, herbal remedy or other healthcare product where there is credible evidence of efficacy and the benefit of use outweighs the risk*'. The Pharmacy Board of Australia's Code of Conduct further clarifies that good care involves "*providing treatment options based on the best available information and not influenced by financial gain or incentives*" and "*practising in accordance with the current and accepted evidence base of the health profession, including clinical outcomes"*.

While it may seem self-evident that any health professional should only promote medications which have evidence of effectiveness, many pharmacies continue to supply medications or products that do not meet this professional standard.

In the complex environment that shapes modern pharmacy practice, this presentation will explore the ethical tensions between patient choice, professional self-interest and trustworthiness, the commercial drivers of practice and the profession's need to maintain public trust.

310 "What are the potential harms of complementary medicines?"

Geraldine M Moses, School of Pharmacy, University of Queensland, Brisbane, QLD, Australia

Consumers spend millions of dollars on complementary medicines (CMs) every year. These purchasing decisions are often made on limited and unbalanced information from advertising and promotional material emphasizing the benefit of CMs without much, if any, mention of risk. Unlike registered medicines, CMs do not have to produce a consumer information leaflet to support consumers in their health decision making. Without information about potential benefits AND risks, consumers cannot make informed decisions about their CMs.

So what are the potential risk of CMs? Like any medicine, CMs have potential for adverse effects and drug interactions although finding and retrieving this information may require training. CMs tend not to be subsidized by third parties so their cost, and consultation fees can represent financial harm. Delay in more effective therapy is a potential harm especially for consumers with cancer, when wasting valuable time using ineffective CMs. Health fraud and false hope are well-known and soul-destroying potential harms experienced when vulnerable consumers are preyed upon by unscrupulous purveyors of CMs. Finally, medication burden should be considered a potential harm, as CMs may simply add to the number of medicines being taken, creating the usual risks of polypharmacy including medication error, adverse effects and drug interactions. All these potential risks will be discussed in this presentation using a case-based approach.

311 Selling complementary medicines and the new Code of Ethics for pharmacists

Adam La Caze, School of Pharmacy, The University of Queensland.

Many complementary medicines lack compelling evidence of efficacy. The sale of these products in community pharmacy cause a number of ethical challenges. The current *Code of Ethics for Pharmacists* provides the following directive as part of Integrity Principle 1 (h):

> A pharmacist will only purchase, supply or promote any medicine, complementary medicine, herbal remedy or other healthcare product where there is credible evidence of efficacy and the benefit of use outweighs the risk.

This talk will examine arguments for and against this directive. I will argue that pharmacists have more responsibilities when recommending complementary medicines as opposed to selling complementary medicines. Good reasons can be given for pharmacists selling complementary medicines in community pharmacy even when these medicines lack evidence of efficacy. These reasons are only compelling, however, if pharmacists meet a number professional responsibilities. These responsibilities include pharmacists ensuring they are available to provide advice to consumers regarding complementary medicines and that the *recommendations* they provide are evidence-based.

312 Regulating complementary medicines and pharmacy practice

H Laetitia Hattingh, School of Pharmacy and Pharmacology, Griffith University, Gold Coast, QLD, Australia

Pharmacy practice is regulated at national as well as jurisdictional levels through a hierarchy of legislative instruments. At a national level pharmacists' conduct need to comply with the Pharmacy Board requirements specified in the Board's Code of Conduct and practice guidelines. Additionally, the Board has endorsed standards and guidelines developed by professional organisations and could refer to these as a frame of reference in disciplinary procedures. Specifically in terms of pharmacists' obligations when supplying complementary medicines, several of these documents address practice requirements and the standard of care to be provided by pharmacists and staff members and hence should be complied with.

Complementary medicines are regulated by the Therapeutic Goods Administration (TGA) and most are evaluated as 'low risk' and as such are only listed and not registered on the Australian Register of Therapeutic Goods. The TGA does not individually evaluate listed medicines before they can be available for use in Australia. However the sponsors of listed medicines need to comply with marketing and advertising criteria and may not claim testament of serious diseases.

The regulatory framework with regard to complementary medicines is grey in some areas and open to interpretation. As community pharmacies are a major supplier of these products which are very popular amongst the Australian population it is important for pharmacists to use professional judgement in order to minimise the risk to consumers. Pharmacists have a professional obligation towards consumers when supplying complementary medicines and each pharmacist needs to independently use his/her professional judgement. This presentation will cover the various regulatory aspects that should be considered by pharmacists.

313 How to reliably measure customers' perceptions of service quality in community pharmacy

Stephen R Carter[1], Ardalan Mirzaei[1], Bethany Grew[1], Jennifer Chen[1] & Carl R Schneider[1], Faculty Pharmacy, Uni of Syd, Sydney, NSW, Australia[1]

Introduction: Recent changes within community pharmacy have seen a shift towards some pharmacies providing "value-added" services. However, providing high levels of service is resource intensive revenues from dispensing are declining. Many pharmacies have responded by reducing service levels and employing a price-focussed marking strategy (PMFS). Of significance therefore, is how consumers perceive service quality and whether changing service levels changes loyalty. However, at present there are no validated and reliable instruments to measure consumers' perceptions of service quality in community pharmacy.
Aim: The aim was to build a theory-grounded model of service quality and to create a valid and reliable survey instrument to measure consumers' perceptions of service quality.
Methods: There were 5 steps involved: 1) Item generation using a literature review and semi-structured interviews; 2) Content and face validity testing; 3) Administration to customers of PMFS pharmacies. Exploratory factor analysis (EFA) elucidated the dimensions of service quality and allowed for item reduction. 4) Administration to customers of high service pharmacies. Confirmatory factor analysis (CFA) was used to validate the model; 5) CFA was performed on the combined datasets to test that the instrument was valid for both PMFS and high service pharmacies
Results: Initially, 119 service quality items were generated. Content validity testing with 3 pharmacy academics and face validity testing with 9 consumers resulted in 61 items selected. EFA was performed on the data obtained from 4 PFMS pharmacies (n = 687) which revealed 6 dimensions of service quality. CFA performed on the data from 3 high service pharmacies (n=319), confirmed the convergent validity of a 20-item model. Internal consistency was high (all Cronbach α's exceed 0.85). Criterion validity was demonstrated as each dimension was highly correlated with loyalty intentions (α ranged 0.61 - 0.71). Tests of measurement invariance revealed weak invariance between settings.
Discussion: A 20-item survey measuring consumers' perceptions of service quality in community pharmacy has been developed and rigorously tested over a period of three years. Statistical analyses demonstrate that the measure is reliable and valid regardless of the level of service provided by the pharmacy.

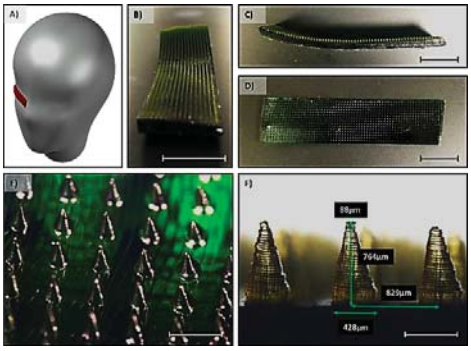
314 The safety of transdermal fentanyl initiation in Australian clinical practice

Natasa Gisev[1], Sallie Pearson[2], Briony Larance[1], Sarah Larney[1], Bianca Blanch[3], Louisa Degenhardt[1], [1]National Drug and Alcohol Research Centre, UNSW Sydney, Sydney, NSW, Australia, [2]Centre for Big Data Research in Health, UNSW Sydney, Sydney, NSW, Australia, [3]The Centenary Institute, Sydney, NSW, Australia

Introduction: Safety concerns regarding transdermal (TD) fentanyl initiation have been raised in Australia and internationally due to increasing reports of unintentional fatal overdose resulting from inappropriate prescribing. Although guidelines caution against initiation of TD fentanyl among people who are opioid naïve, there is concern that some patients are not receiving adequate prior opioid exposure in clinical practice.
Aims: To determine the proportion of people in Australia that are opioid naïve at the time of transdermal (TD) fentanyl initiation; examine the strengths initiated; and determine the characteristics associated with being opioid naïve.
Methods: This was a retrospective population-based cohort study representing a 10% sample of Pharmaceutical Benefits Scheme concessional beneficiaries initiating TD fentanyl between 29 September 2009-31 December 2013. Individuals were deemed to be opioid naïve if they had no opioid dispensings in the previous 90-days. Socio-demographic characteristics, likely comorbidities and previous analgesic use were compared among those opioid naïve/opioid exposed. Logistic regression was used to calculate adjusted odds ratios (aORs) and 95% confidence intervals (CIs) to determine characteristics associated with being opioid naïve.
Results: A total of 13,166 people initiated TD fentanyl; 60.4% were females and 76.2% were aged ≥65 years. Three in ten (30.4%) were opioid naïve and 63.2% initiated the 12 mcg/hr patch. Being opioid naïve was associated with being female (aOR 1.35, 95% CI 1.25-1.46), being older (aOR 1.58, 95% CI 1.33-1.87 for those 65-84 years and aOR 1.84 (95% CI 1.53-2.20) for those ≥85 years) and having dementia (aOR 1.39; 95% 1.06-1.82). Those with a cancer history were less likely to be opioid naïve (aOR 0.57; 95% CI 0.48-0.66).
Discussion: Three in ten Australians initiating TD fentanyl are opioid naïve. Our findings suggest that specific patient sub-populations already at increased risk of opioid adverse effects are not receiving prior opioid treatment before initiation, highlighting the need for greater adherence to current treatment guidelines.

315 Personalized microneedle eye patches by 3D printing to treat Peri-orbital wrinkles with a small peptide

Seng H Lim[1], Wen J Tiew[1], Lifeng Kang[2]. Department of Pharmacy, National University of Singapore[1], Singapore, Republic of Singapore; Faculty of Pharmacy, University of Sydney[2], Sydney, NSW, Australia.



Introduction: Microneedle (MN) assisted transdermal drug delivery was extensively researched for flat MN patches. However, flat MN patches may be inadequate for efficient drug delivery through the human skin surface, which is undulating in nature. In this study, 3DP was used to fabricate a curved personalized MN patch for anti-wrinkle therapy. Acetyl hexapeptide-3 (AHP-3) was used as the anti-wrinkle drug.
Methods: Curved patches with various microneedle geometries were designed and fabricated, via photopolymerisation-based 3D-printing, with various curvatures. These patches were assessed for their respective mechanical strength, skin penetration efficiency and drug delivery efficiency.
Results: In general, a longer, sharper and more widely spaced microneedle achieved a better skin penetration efficiency. Furthermore, for each microneedle geometry, patches of intermediate curvatures consistently achieve the best skin penetration efficiency compared to the gentle or sharp curvatures. In all, the optimized geometry was determined to be that of microneedle length 800µm; tip diameter 100µm; interspacing 800µm; and base diameter 400µm. Confocal imaging of the skin sample after in vitro skin permeation using a fluorescence dye, demonstrated enhanced transdermal delivery compared to a commercial flexible microneedle eye patch.
Discussion: Microneedle geometry for curved microneedle patches is critical for efficient skin penetration. Using an optimized geometry and actual patient scans, we also demonstrated the use of 3D scanning and 3D printing technology to fabricate a personalized microneedle eye patch for transdermal drug delivery for peri-orbital wrinkles.

Lim SH, Ng JY, Kang L (2017). Biofabrication. 9(1):015010.

316 The provision of enhanced and extended services in Western Australian community pharmacies

P. Czarniak[1], L. Hattingh[1, 2], B. McKay[1], T.F. Sim[1], B. Sunderland[1], School of Pharmacy, Faculty of Health Sciences, Curtin University[1], Bentley, WA; School of Pharmacy and Pharmacology, Griffith University[2], Gold Coast Campus, QLD

Introduction: Data on the provision of, and remuneration for, enhanced (not routinely provided) and extended (require additional credentialing) services in Australian community pharmacies are limited.
Aims: This study aimed to quantify the prevalence of enhanced and extended services provided by Western Australian (WA) community pharmacies, and identify barriers and facilitators to the provision of these services.
Methods: A questionnaire was sent to 421 (66.7%) randomly selected pharmacies in WA (303 metropolitan, 118 rural).
Results: Of 417 questionnaires, 205 (49.2%) useable questionnaires were returned. The most frequent enhanced service was blood pressure (BP) testing (195; 95.1%) with weekly BP tests ranging from < 6 to > 40 (mean = 8.6) for which 171 (87.7%) pharmacies received no remuneration. Enhanced services funded under the Sixth Community Pharmacy Agreement included the supply of dose administration aids (193; 94.1%), clinical interventions (190; 92.7%), MedsChecks (151; 73.7%) and Diabetes MedsChecks (125; 61.0%). Extended services offered included credentialed compounding (25; 12.2%), diabetes education (5; 2.4%), home medicines reviews (105; 51.2%), residential medication management reviews (13; 6.3%), and pharmacist- (94; 45.9%) and nurse-administered influenza vaccinations (39; 19.0%). The main reasons for offering these services in pharmacies included improved relationships with patients, enhancing the role of pharmacists, for pharmacists' professional satisfaction and to provide health promotion opportunities. Almost all pharmacists (199, 97.1%) agreed that good relationships as well as easy access to a general practitioner (GP) (196, 95.6%) facilitated inter-professional collaboration. Main barriers included time constraints of pharmacists (188, 91.7%), inadequate remuneration (178, 86.8%) and a lack of adequate return on investment (161, 78.5%).
Discussion: The health system increasingly relies on community pharmacists to provide services. Although the Sixth Community Pharmacy Agreement has increased the scope for further professional services to be provided, remuneration is limited. In WA alone, approximately 249,626 BP tests are carried out annually for no remuneration. Without improved remuneration options, many community pharmacy services will not be sustainable.

317 Reversal of age related pseudocapillarization utilizing VEGF-related, NO-dependent drug treatments on in vitro liver sinusoidal endothelial cells

Nicholas Hunt[1, 2], Glen Lockwood[1, 2], Hong Mao[3], Alessandro Warren[1], Peter McCourt[2, 3], David Le Couteur[1, 2], Victoria Cogger[1, 2], [1]Biogerontology, ANZAC Research Institute, [2]Charles Perkins Centre, University of Sydney, NSW, Australia, [3]Medical Biology, University of Tromsø, Troms, Norway

Introduction: The liver is a key driver in lipid metabolism and the actions of insulin with its function imperative to reducing the risk of metabolic disorders. The transcellular pores, known as fenestrations, within the liver sinusoidal endothelial cells are critical to these functions. With increasing age there is a loss of fenestrations referred to as pseudocapillarization. This impairs transfer of lipids and insulin and contributing to the postprandial hypertriglyceridemia and insulin resistance. The biological regulation of fenestrations is promoted via a VEGF–related, nitric oxide (NO)-dependent pathway to promote either actin or lipid membrane remodeling.
Aim: This exploratory study investigated the actions of VEGF-related NO-dependent modifying drugs to promote re-fenestration in old (18-24 months, n=3), compared to young mice (3-4 months, n=3).
Methods: Isolated mice LSECs were incubated for 30 mins with 5 drugs active on separate parts of the VEGF-related NO signaling pathway (Drugs A-E). Cells were fixed and prepared for visualization under scanning electron microscopy (SEM), or direct stochastic optical reconstruction microscopy to examine changes in actin organization. SEM images were captured at 10,000x to examine fenestration porosity, diameter and frequency across the cell surface.
Results: In both young and old LSECs, increased porosity ($P<0.05$) and frequency ($P<0.05$) were observed for Drugs A, B, D and E; increased diameter ($P<0.05$) was shown in old mice treated with Drug C. Age-related reductions in fenestrations were observed between controls groups, while treatment with Drugs A and B promoted refenestration of old LSECs similar to young control mice.
Discussion: This preliminary study has shown that promotion of the VEGF-related NO pathway via Drugs A and B promotes re-fenestration in old mice similar to young control mice. These findings demonstrate that the regulation of fenestrations may be performed by NO-dependent pathways and may be regulated *in vivo* by changes in this pathway. Both these drugs demonstrate potential therapeutic use to treat age related pseudocapillarization.

318 Cell-specific and biased signalling of a peptide mimetic and small molecule at the relaxin receptor RXFP1

Martina Kocan[1], Mohammed Akhter Hossain[1], Chrishan S. Samuel[2], Roger J. Summers[3], Ross A.D. Bathgate[1,4], [1]The Florey Institute of Neuroscience and Mental Health, Parkville, VIC, Australia, [2]Dept of Pharmacology, Monash University, Clayton, VIC, Australia, [3]Monash Inst of Pharmaceutical Sciences, Monash University, Parkville, VIC, Australia, [4]Department of Biochemistry and Molecular Biology, University of Melbourne, Parkville, VIC, Australia

Introduction: Relaxin mediates anti-fibrotic, anti-inflammatory, post-injury healing and vasodilatory effects via its cognate receptor, RXFP1. A peptide mimetic, B7-33, and small molecule, ML290, were recently developed and demonstrated to be cell-specific and biased agonists at RXFP1, respectively (Kocan et al., 2017. Sci Rep 7:2968; Hossain et al., 2016. Chemical Science 7:3805-3819).
Aims: To use these agonists to better understand signalling at the RXFP1 receptor with particular emphasis on the anti-fibrotic effects of relaxin.
Methods: We compared B7-33, ML290 and H2 relaxin-mediated signalling in HEK cells overexpressing RXFP1 (HEK-RXFP1) and cell lines endogenously expressing RXFP1 including primary fibroblasts. We used Surefire, Alphascreen or HTRF assays to investigate short-term MAPK, cAMP and cGMP signalling and applied novel bioluminescence resonance energy transfer (BRET)-based biosensors to investigate spatiotemporal aspects of the p-ERK1/2 and cAMP responses. We also examined longer-term actions on markers of fibrosis (matrix metalloproteinase (MMP)-2 expression and TGF-β1-induced smad2 and smad3 phosphorylation) in human cardiac myofibroblasts.
Results: B7-33 was a weak agonist in HEK-RXFP1 cells and some native cells but exhibited equipotent activity to H2 relaxin in other native cells including myofibroblasts. B7-33 stimulated p-ERK1/2 within 10 min in rat renal myofibroblasts whereas 48-72 hour treatment increased MMP-2 expression to an extent comparable to H2 relaxin in human cardiac and rat renal myofibroblasts. In contrast, ML290 was a biased agonist that lacked activity at the p-ERK1/2 pathway in all cell lines tested. Although ML290 did not activate p-ERK1/2 in human cardiac myofibroblasts, it exhibited similar anti-fibrotic effects to H2 relaxin and promoted MMP-2 expression and inhibited TGF-β1-induced smad2 and smad3 phosphorylation; the latter related to its ability to potently activate cGMP.
Discussion: The discovery of ML290 and B7-33 has provided valuable tools to dissect downstream actions of RXFP1, especially the association of cGMP and p-ERK1/2 signalling with the long-term anti-fibrotic effects of relaxin.

319 Investigation of the insulin mimetic effect of *Teucrium polium* in vitro

Adnan Mannan[1], Erik Helmerhorst[2], Marco Falasca[2], Rima Caccetta[1], [1]School of Pharmacy, [2]School of Biomedical Sciences, Curtin Health Innovation Research Institute, Faculty of Health Sciences, Curtin University, Perth, WA, Australia

Introduction: *Teucrium polium* is a herb that grows in the Mediterranean region. It is widely used by the locals to treat diabetes mellitus. The glucose lowering effect of the extract of this herb *in vivo* has been reported previously from our laboratory.
Aim: To investigate whether the constituents of the *Teucrium polium* extract lower blood glucose levels by acting in a similar way to insulin.
Methods: The extract was assessed on different insulin sensitive cells in culture. Glucose and glycogen were measured using flow cytometry, fluorometric and colourimetric assays. Proteomics screening of phosphorylated kinases was conducted off shore by Kinexus Bioinformatics Corporation (Canada) as well as Western blots conducted in our laboratory. GLUT4 (insulin-regulated glucose transporter) expression was measured using immunofluorescence microscopy and Western blots.
Results: The extract increased glucose uptake in a concentration dependent manner with an apparent efficacy similar to a maximal dose of insulin in 3T3-L1 adipocytes (1.5-fold, $p<0.05$), differentiated C2C12 muscle cells (1.4-fold, $p<0.01$) and differentiated L6 muscle cells (1.6-fold, $p<0.01$). The ability of the extract to promote glucose uptake in differentiated L6 muscle cells coincided with a 3 to 4-fold increase in the expression of GLUT4 ($p<0.01$). The glycogen content of the differentiated L6 muscle cells increased (1.6-fold, $p< 0.01$) in the presence of either insulin or extract. Phosphorylation of some of the key signaling molecules of the PI3K pathway such as PDK-1, Akt, GSK3ab and p70S6K were significantly ($p<0.05$) increased, examined in L6 muscle cells, by the extract within 30min. The effect of the extract in promoting glucose uptake and glycogen synthesis in insulin sensitive cells correlated with an increased phosphorylation of several key phosphokinases that are involved in insulin-mediated signaling pathways.
Discussion: These findings are consistent with component(s) within the *Teucrium polium* extract promoting both the PI3K/Akt and the Grb2-SOS-Ras-MAPK pathways that are involved in insulin action.

320 Measuring ligand-binding in endosomes: a signalling platform for pain transmission

Nicholas Veldhuis[1,2], Joshua Conner[3], Quynh Mai[1,2], Holly Yeatman[1], Chris Lumb[1], Bim Graham[3], Meritxell Canals[1,2], and Nigel Bunnett[1,2,5], [1]Drug Discovery Biology, [2]ARC Centre of Excellence for Bio-Nano Science and Technology and [3]Medicinal Chemistry, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC, Australia
[4]Department of Surgery, Columbia University, New York City, NY, USA

Introduction: G protein-coupled receptors can signal from the cell surface and from endosomal membrane compartments to initiate distinct spatiotemporal signalling processes and physiological outcomes. We have recently shown that blocking endosomal-mediated Neurokinin 1 Receptor (NK_1R) signalling leads to inhibition of central pain transmission when compared to drugs that non-selectively bind throughout the cell (Jensen, 2017). We therefore propose that targeting receptors in endosomes may be therapeutically advantageous. However, quantitative measures for specifically assessing endosomal drug targeting are currently limited and require further development.
Aims: To characterise endosomal ligand-receptor interactions of antagonists designed to be delivered to endosomes.
Methods: Acceptor photobleaching FRET studies were performed, using SNAP-labelled NK_1R and synthesised fluorescent probes incorporating spantide (NK_1R antagonist), cholestanol (lipid raft anchor for endosomal delivery) and fluorescent dye Cy5. Two bioluminescent energy transfer (BRET)-based assays were developed to measure 1) NK_1R coupling to Arrestin-YFP, and 2) endosomal ligand binding using NanoLuc-NK_1R and fluorescent Substance P.
Results: Acceptor photobleaching FRET studies and BRET-based assays indicate that lipid-anchored antagonists can inhibit arrestin binding. For receptors that can 'escape' this inhibition and still undergo internalisation, lipid-anchored antagonists can achieve ligand binding in endosomes, providing a secondary, additional inhibitory mechanism.
Discussion: These studies provide new and valuable approaches for pre-clinical assessment of ligand-receptor interactions in a therapeutically relevant intracellular location. Lipidated antagonists have the potential to inhibit endosomal NK_1R signalling by blocking: 1) NK_1R internalisation; and 2) endosomal ligand binding.

Jensen D, et al. (2017) Neurokinin 1 receptor signalling in endosomes mediates sustained nociception and is a viable therapeutic target for prolonged pain relief, Sci. Transl. Med., 9(392): eaal3447.

321 Mutations in the NPxxY motif stabilise different conformational states of the α1B- and β2-adrenoceptors

Lotten Ragnarsson[1], Åsa Andersson[1], Walter G Thomas[2] and Richard J Lewis[1], Institute for Molecular Bioscience[1] and School of Biomedical Sciences[2], The University of Queensland, Brisbane, QLD, Australia

Introduction: G protein-coupled receptors (GPCRs) link diverse extracellular stimuli to a set of intracellular responses that regulate numerous physiological processes in health and disease. Recent crystallographic and biophysical advances in GPCR structure-function have helped clarify our understanding of these dynamic receptors, but the molecular mechanisms associated with activation and signalling for individual GPCRs may be more complex than previously appreciated.
Aims: Here we investigated the proposed water-mediated hydrogen bonded activation switch between the conserved NPxxY motif on transmembrane helix (TMH) 7 and a conserved tyrosine in TMH5, which contributes to α_{1B}-adrenoceptor (α_{1B}-AR) and β_2-AR activation, with the aim to pharmacologically characterise these major drug targets.
Methods: We stabilised inactive state conformations of α_{1B}- and β_2-ARs by mutating the conserved NPxxY motif and the interacting residue $Y^{5/58}$ in TMH5 to destabilise their active state conformations. These inactive state mutants were pharmacologically characterised using α_{1B}-AR orthosteric (prazosin) and allosteric (ρ-TIA) inhibitors, and the β_2-AR inhibitor propranolol and partial agonist CGP-1217743, using radioligand binding assays. In addition, we determined alterations in norepinephrine (NE) and isoproterenol signalling through α_{1B}-ARs and β_2-ARs to inositol 1-phosphate (IP_1), cAMP and β-arrestin.
Results: Inactive state α_{1B}- and β_2-AR mutants showed decreased potency for agonist-induced IP_1 and cAMP signalling. Surprisingly, inactive state β_2-ARs exhibited decreased agonist affinity, whereas mutations producing inactive state α_{1B}-ARs had enhanced agonist affinity. Conversely, antagonist affinity was unchanged at both α_{1B}-AR and β_2-AR inactive state conformations. Furthermore, β-arrestin recruitment was dramatically reduced or abolished at both α_{1B}-AR and β_2-AR inactive state conformations, whereas measurable agonist potency was little altered. Removing the influence of agonist affinity on agonist potency gave a measure of signalling efficiency, which was dramatically decreased for these α_{1B}-AR mutants but practically unchanged for β_2-AR inactive state conformations.
Discussion: These findings suggest multiple receptor-specific inactive state GPCR conformations with differing pharmacology, which may facilitate rational drug design with distinct pharmacological effects.

322 Drug delivery to the intestinal lymphatics enhances the immunosuppressant effects of mycophenolic acid in mice

Ruby Kochappan[1,2], Sifei Han[1,2], Luojuan Hu[1,2], Timothy Quach[2,3], Danielle Senyschyn[1,2], Enyuan Cao[1], Given Lee[1,2], Fern Lim[2,3], J.S. Simpson[2], Justine Mintern[4], Natalie L Trevaskis[1], Christopher J.H. Porter[1,2]. [1] Drug Deliv Dispos and Dyn, [2]ARC CoE in Bio Nano Sci and Tech, [3]Med Chem, Monash Inst of Pharm Sci, Melbourne, VIC, Australia, [4]Biochem and Mol Bio, Bio21 Instit, Univ of Melbourne, Melbourne, VIC, Australia.

Introduction: The lymphatic vessels that drain the intestine, the gut associated lymphoid tissue (GALT) and the mesenteric lymph nodes (MLN) are central to gut immune surveillance. The intestinal lymphatics also serve to transport dietary lipids (triglycerides, TGs) from the gut to the systemic circulation (Trevaskis et al 2015).
Aim: To evaluate the pharmacodynamic benefit of targeting an immunomodulatory agent (mycophenolic acid, MPA) to gut lymphatic immune cells by mimicking the endogenous transport pathway of TGs into the lymph. This was achieved via the design of a TG mimetic prodrug of MPA (MPA-2-TG) (2) to target lymphocytes in intestinal lymph.
Methods: The intestinal lymph transport of MPA and MPA-2-TG, was assessed after intraduodenal infusion, by cannulating the mesenteric lymph duct of anaesthetised mice (100 mg/kg ketamine and 10 mg/kg xylazine, ip). Immunosuppression was studied by adoptive transfer of dye labelled CD8+ T cells, purified from lymph nodes (LN) from OT 1 mice, into syngeneic mice fed 50 mg ovalbumin (OVA). Mice were then administered MPA or MPA-2-TG (50 mg/kg) twice daily for 3 days. At the end of the treatment, T cell proliferation in mesenteric and peripheral LNs was evaluated using flow cytometry.
Results: The lymphatic uptake of MPA-2-TG (17.3 % dose) was higher than MPA (0.14 %). MPA-2-TG treatment significantly reduced the proliferation of CD8+ T cells in the MLN, with most dye labelled cells (~80%) being found in generation 4 or lower after OVA stimulation. In contrast, MPA had no significant effect on cell replication.
Discussion: Targeting lymphocytes in intestinal lymph, via the use of a lipid-mimetic prodrug significantly enhanced the immunosuppressive effects of MPA. This approach may have the potential to enhance the pharmacodynamic benefit of other drugs, such as cytotoxic or immunomodulators that act within the mesenteric lymphatics and MLN.

1. Han S et al (2014) J Control Release 177:1-10.
2. Trevaskis NL et al (2015) Nat Rev Drug Discov 14:781-803.

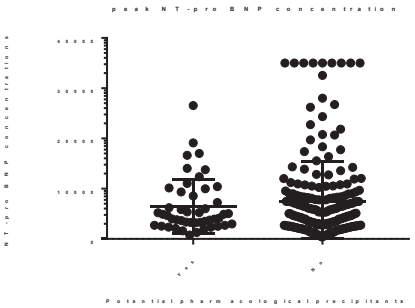
323 A randomised controlled trial of patient information leaflets as a medication counselling tool

Richard McNeill[1], Paul Chin[1,2], Elle Coberger[1] Matthew Doogue[1,2], [1]Dept of Clin Pharmacol, Christchurch Hosp, Christchurch, New Zealand, [2]Dept of Medicine, Univ of Otago, Christchurch, New Zealand

Introduction: Counselling patients on medication use has been shown to improve adherence, safety and patient satisfaction. We have developed standardised patient information leaflets (PILs) as medication counselling aids. No studies to date have directly compared different types of written medicines information as counselling aids.
Aims: To compare the utility of PILs with a drug monograph as a counselling aid for patients starting a new medication.
Methods: A single blinded randomised controlled trial comparing PILs with the New Zealand Formulary monograph (NZF) was undertaken. Medication counselling was assessed using a 5th year medical student examination station. Students were block randomised to receive a PIL or NZF drug monograph. Actors were recruited as simulated patients and counselled on starting methotrexate (n=48) or prednisone (n=48). Eight domains of information transfer were assessed by the simulated patients using a Likert scale, 1 (poor) – 4 (good). The primary outcome was overall satisfaction, the remaining domains and a composite score were secondary outcomes. Aid usage was assessed using four secondary outcomes: if the aid was used, how it was used, how long for, and if the aid was given to the patient.
Results: There were no differences in information transfer outcomes between the study arms, except for contingency planning which favoured the PIL (PIL 3.4 vs NZF 3.0, P=0.02). Outcomes for aid usage favoured the PIL which was used for longer (P<0.01), more frequently (91% vs 77%, P=0.09), more frequently as a counselling tool (74% vs 40%, P=0.09) and given to the patient more often (58% vs 42%, P=0.15).
Discussion: In a medical school clinical examination station of medication counselling, the PIL was as effective as the NZF monograph for patient-assessed information transfer, and superior for specific information regarding managing ADRs. The PIL had higher usage than the NZF monograph, which may reflect greater student satisfaction with the PIL. The strengths of the study included a randomised, blinded methodology with low resource requirements. Future work should involve further evaluation of written medicines information in a clinical context.

324 "Therapy induced" Takotsubo Cardiomyopathy: Does it matter?

Gao Jing Ong[1,2], Thanh Ha Nguyen[1,2], John D Horowitz[1,2], [1]Cardiology Unit, Queen Elizabeth Hospital, Woodville, SA, Australia, [2]University of Adelaide, Basil Hetzel Institute, Woodville, SA, Australia



Introduction: Takotsubo Cardiomyopathy (TTC) is an acute inflammatory condition mimicking myocardial infarction but occurring mainly in ageing women. The inflammation in TTC represents the results of aberrant β2-adrenoceptor signalling and as such may be precipitated by both endogenous (eg associated with emotional stress) or exogenous catecholamines (CA) surges. TTC has been reported with administration of exogenous CA or agents that potentiate CA effect. B-type natriuretic peptide (BNP) release is markedly increased in TTC, and peak NT-proBNP levels represent an index of attack severity.
Aims: We utilised the QEH TTC Registry (between August 2009 and August 2017) to compare patients with and without exogenous CA associated TTC, with emphasis on size of the initial attack.
Methods: Patients in whom TTC occurred secondary to life threatening extracardiac disorders (n=4) were excluded, and the remainder categorised according to whether there was presence (CA+) or absence (CA-) of CA enhancing drug administration. Apart from NT-proBNP, demographics and other parameters of attack severity (acute left ventricular ejection fraction [LVEF] or development of hypotension) were compared.
Results: Demographics of CA+ patients (n=47) and CA- patients (n=211) did not differ significantly. Tricyclic antidepressants (n=18), mainly in low dose, represent the most common CA source. As would be expected, CA+ patients had marginally higher concentrations of CA metabolite, normetanephrine (p=0.07). However, neither peak NT-proBNP (p=0.98), nor acute LVEF (p=0.61), nor proportion of hypotension (p=0.33) varied between the 2 groups.
Discussion: Overall, CA+ patients account for approximately 18% of "primary" TTC cases. However, a similar demographic spectrum and severity of acute attacks applies, irrespective of pharmacological precipitants.

325 A physiological based pharmacokinetic model to guide dosing of ivacaftor in the presence of pharmacoenhancers

Angela Rowland, Arduino Mangoni, Tilenka Thynne, Andrew Rowland, Department of Clinical Pharmacology, College of Medicine and Public Health, Flinders University, Adelaide, SA, Australia

Background: Ivacaftor is a breakthrough treatment for cystic fibrosis patients that harbour a mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) gene, but is among the highest cost medicines in Australia. It is almost exclusively cleared by CYP3A4-mediated metabolism and exposure is known to be altered by co-administration with strong CYP3A4 inhibitors. CYP3A4 inhibitors have previously been used as "pharmacoenhancers" and when used with Ivacaftor, can reduce the required dose while still achieving comparable plasma concentrations.
Aim: This study developed a full physiologically based pharmacokinetic (PBPK) model for ivacaftor to define dosing in the presence of pharmacoenhancers.
Methods: Simulations were performed using the Simcyp Simulator® (version 15.1). Ivacaftor absorption was simulated using the ADAM sub-model, and distribution and elimination using a full-PBPK model. Reported pharmacokinetic data was used to construct the ivacaftor profile, then verified against reported age and gender matched trial data using a ratio of simulated to observed area under the plasma concentration time curve (AUC). Secondary analysis compared maximum plasma concentration (C_{max}) and AUC at steady state dosing (150 mg BD). The validated model was used to simulate Ivacaftor dosing in the presence of pharmacoenhancers and define potential dosing regimens.
Results: Simulated and observed mean (± SD) ivacaftor AUCs following a single dose were 10,014 (±2925) ng/mL/hr and 10,600 (±5260) ng/mL/hr, respectively, while simulated and observed mean (±SD) C_{max} were 801 (±163) ng/mL and 768 (±233) ng/mL, respectively. With twice daily dosing, simulated and observed dose accumulation ratios were 2.0 to 3.1 and 2.2 to 2.9, respectively, while the geometric mean comparing simulated to observed parameters were contained within the range 0.9 to 1.1. Statistical comparison (unpaired *t*-test) demonstrated no difference between simulated and observed parameters defining ivacaftor exposure in single or steady-state dosing.
Conclusions: Here we report a full-PBPK model defining ivacaftor exposure. This model facilitates the capacity to evaluate the effect of covariates influencing ivacaftor exposure including co-administration of pharmacokinetic enhancers such as ritonavir, and may be applied to interrogate the capacity to exploit the use of such compounds to maintain ivacaftor exposure with a reduced dose intensity either through less frequent dosing or lower doses.

326 Evaluation of the role and impact of brain computed tomography scans in the assessment of clinically diagnosed overdose cases and an attempt to formulate a procedural framework

Emma MY Tay[1], Paul Preisz[2], Richard O Day[1,3], [1]Dept of Clinical Pharmacology and Toxicology, St Vincent's Hospital, Sydney, NSW, Australia, [2]Dept of Emergency Medicine, St Vincent's Hospital, Sydney, NSW Australia, [3]St Vincent's Clinical School, UNSW Medicine[3], Sydney, NSW, Australia

Introduction: Patients presenting to hospital with a clinical diagnosis of drug overdose commonly receive a brain computed tomography (CT) scan as part of their admission assessment. Whilst a useful investigation, every CT scan comes with risks including radiation exposure to patient, financial and time costs to the healthcare system.
Aims: We aim to evaluate the prevalence, role and impact of brain CT scans in the management of patients with clinical diagnosis of drugs and medicines overdose. We then attempt to formulate a procedural framework for future guidance with reference to brain imaging.
Methods: A retrospective study in a single site was conducted at St Vincent's Hospital, Sydney on all electronic records of patients who presented to the Emergency Department and diagnosed with drug overdose from the 1st of May 2014 to the 1st May 2016. Outcome measurements were the proportion of patients with a clinical diagnosis of overdose receiving a CT brain within the same hospitalisation episode, and the proportion of patients where CT brain results altered the management within the same hospitalisation episode.
Results: A total of 3807 hospital presentation episodes were included, involving 3012 patients. One in ten presentations (11.4%) with a clinical diagnosis of overdose received a CT brain, that is, 437 CT brains were conducted on 410 (13.6%) patients. 182 (41.6%) had a history of head injury. 20 patients received more than one CT brain over the two-year study period. There were 20 abnormal CT scans, but only 10 (2.4%) patients had a change in management due to the abnormal results.
Discussion: Our findings showed a high proportion of patients received CT brain imaging, with only a small proportion of patients with abnormal results requiring a change in management during admission. These findings emphasized the importance of a guidance or procedural framework to aid in the management of patients with overdoses, and to minimise the impact of non-indicated radiation risks to patients and operational costs to the health system.

327 Real-time review of electronic prescribing of restricted antimicrobials - A pilot of a new antimicrobial stewardship initiative for Christchurch Hospital

Niall Hamilton[1], QianYi Chuah[1], Paul Chin[1,4], Sharon Gardiner[1,2,3], [1]Department of Clinical Pharmacology, [2]Department of Infectious Diseases, [3]Department of Pharmacy Christchurch Hospital, Canterbury, New Zealand, [4]Department of Medicine, University of Otago, Christchurch, NZ

Introduction: Antimicrobial stewardship (AMS) reduces inappropriate antimicrobial use and improves clinical outcomes. Currently, AMS at Christchurch Hospital (CH), New Zealand, includes guidelines overseen by an AMS committee and an active infectious disease consulting service with a specialist antimicrobial pharmacist. The Pharmaceutical Management Agency (PHARMAC) has defined a list of broad-spectrum, toxic and/or high-cost antimicrobials that are restricted to specific specialties or indications. Recent introduction of an electronic prescribing and administration system (MedChart®) at CH presents a potential avenue for assessing adherence to these restrictions via a real-time AMS 'ward round'.
Aims: 1. To determine the proportion of interventions likely to be addressed via AMS ward rounds, using MedChart® data to identify inpatients on any restricted antimicrobial. 2. To determine time requirements for these ward rounds.
Methods: Medchart® data extracts were conducted three times weekly to identify all new prescriptions for restricted antimicrobials. Electronic clinical records were reviewed to exclude patients who met approval criteria. Physical review of hardcopy notes was then undertaken to identify AMS recommendations.
Results: Over the first two weeks, 193 unique prescriptions of restricted antimicrobials were identified. Of these, 25/193 (13%) lacked an indication and required review by the AMS team. From the reviewed clinical notes, 9/25 prescriptions (36%) met CH guidelines. AMS recommendations for the remaining 16/25 (64%) prescriptions were: deescalate to narrower spectrum antimicrobial (6/25, 24%), cease antimicrobial (3/25, 12%), change route of administration (2/25, 8%) or refer for review by the Infectious Diseases service (5/25, 20%). The ward round (conducted by a doctor and pharmacist) took a median of 40 minutes per day (range 10 - 48 minutes).
Discussion: An AMS ward round, using MedChart® prescribing data appears feasible, and provides prescribers with immediate feedback on adherence to current antimicrobial guidelines.

328 Thyroid immune-related adverse events following PD-1 inhibitors for cancer: Characteristics and associations

Frida Djukiadmodjo[1], David Liew[1,2], Jessica Leung[2], Bonnia Liu[2], Jonathan Cebon[3], Russell Buchanan[2], Albert Frauman[1], [1]Dept of Clinical Pharmacology and Therapeutics, Austin Health, Heidelberg, VIC, [2]Dept of Rheumatology, Austin Health, Heidelberg, VIC, [3]Olivia Newton-John Cancer and Wellness Centre, Austin Health, Heidelberg, VIC

Introduction: Immune checkpoint therapy has proven efficacious in the treatment of multiple cancers, but may cause immune-related adverse events (irAEs) that often mimic known autoimmune conditions. Thyroid irAEs have been described to be the most commonly reported endocrine adverse effect following treatment with programmed cell death protein 1 (PD-1) inhibitors (1). Characterising associations and clinical features of these irAEs might enable us to optimise patient care and may generate hypothesis about spontaneous disease pathophysiology (2).
Aims: To describe the frequency and characteristics of thyroid irAEs in a cohort of patients receiving PD-1 inhibitors. Factors associated with the development of thyroid irAEs were sought, including demographic and treatment factors.
Methods: All patients who were initiated on nivolumab or pembrolizumab in 2015 and 2016 at our centre were identified through hospital pharmacy dispensing records. A retrospective chart review interpreting existing documentation was performed to identify irAEs as well as patient, disease, and oncological treatment characteristics. Baseline and post-treatment thyroid stimulating hormone (TSH) levels, thyroid autoantibodies and imaging were recorded where available. The management and impact of thyroid irAEs were characterised.
Results: Of the 204 patients, thyroid irAEs were diagnosed in 25 (12.3%) patients, making it the most frequent non-cutaneous irAE in our cohort. Thyroid irAEs were more common in patients with an oncological response to therapy (RR 2.18; 95% CI 1.03 to 4.64). Sex, age greater than 70 years, cancer type, cancer stage, combination therapy with ipilimumab and baseline TSH were not found to be associated with an increased risk of developing thyroid irAEs.
Discussion: Thyroid irAEs are common in patients treated with PD-1 inhibitors, and are associated with an oncological response to therapy but not with baseline demographic or biochemical features. A prospective systematic investigation would be useful to further investigate mechanisms for the development of these adverse events.

1. Byun DJ et al (2017) Nat Rev Endocrinol. 13: 195-207
2. Delivanis DA et al (2017) J Clin Endocrinol Metab. 102: 2770-2780

329 No significant effect of *CYP3A*, *ABCB1*, *POR* and *NR1I2* polymorphisms on acute rejection and nephrotoxicity in the first 3 months post kidney transplantation in patients receiving tacrolimus

Rong Hu[1], Daniel T Barratt[1], Janet K Coller[1], Benedetta C Sallustio[1,2], Andrew A Somogyi[1]. Disc of Pharmacology, Univ of Adelaide[1], Adelaide, SA; Dept of Pharmacology, Queen Elizabeth Hospl[2], Adelaide, SA.

Introduction. Tacrolimus is a first line immunosuppressant used after kidney transplantation but with extensive inter-individual variability in PK and PD. Low or high tacrolimus concentrations are associated with acute rejection and nephrotoxicity, respectively. SNPs in its major metabolising enzyme (*CYP3A4/5*), P-glycoprotein efflux transporter (*ABCB1*), their expression regulator Pregnane X Receptor (*NR1I2*), and cytochrome P450 reductase (*POR*), have been studied for their effects on tacrolimus PK (Hesselink et al, 2014; Kurzawski et al, 2017). However, there are few studies on their effects on PD, especially in the first 3 months post-transplantation when acute rejection occurs more frequently.
Aims. To investigate the impact of *CYP3A4/5*, *ABCB1*, *NR1I2* and *POR* SNPs on acute rejection and nephrotoxicity in kidney transplant patients receiving tacrolimus in the first 3 months post-transplant.
Methods. A total of 165 kidney transplant recipients and 129 donors were included in this study. Biopsy- or clinical observation-confirmed acute rejection, delayed graft function (DGF) and eGFR data were collected from case notes. Acute rejection and DGF were analysed as binomial outcomes (Y/N) while eGFR (unit: ml/min/1.73m^2) as continuous variables. Genotyping was performed for: *CYP3A5*3*; *CYP3A4*22*; *ABCB1* 61A>G, 1199G>A, 1236C>T, 2677G>T, 3435C>T; *POR*28*; and *NR1I2* 8055 C>T, -25385C>T, 63396C>T. Recipient and donor genotype and predicted *ABCB1* haplotype (PHASE) differences in recipients with acute rejection and DGF in 3 months post-transplant, and 1- and 3-month log-transformed eGFR, were tested by χ^2 or Fisher's exact tests, and linear mixed effects models, respectively.
Results. No recipient or donor genotypes/haplotypes had a significant effect on occurrence of acute rejection (P>0.2), DGF (P>0.1), or eGFR (P>0.02) after adjusting for multiple testing (False discovery rate (α=0.05), P=0.002).
Discussion. Tacrolimus metabolism- and transport-related genetic factors do not significantly affect acute rejection or nephrotoxicity in the first 3 months post kidney transplantation.

[1] Hesselink D.A. et al. (2014) Clin Pharmacokinet, 53(2): 123-39.
[2] Kurzawski M. et al. (2017) Pharmacogenet Genomics. 2017;27(10):372-7.

330 HLA-B status leading to potential severe adverse drug reactions in Aboriginal Australians

Andrew A Somogyi[1], Daniel T Barratt[1], Discipline of Pharmacol, Univ of Adelaide[1], Adelaide, SA

Introduction: Life-threatening adverse drug reactions have been linked to specific HLA genotype status with ethnicity as a defining factor (Somogyi & Phillips, 2017). Some prescribing guidelines recommend pre-emptive genotyping of *HLA-B*15:02* for carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis. Little is known about the HLA-B medicines-related status of Aboriginal Australians.
Aims: To determine the HLA-B status of Aboriginal Australians (AA) and non-Aboriginal Australians (NA) for *HLA-B*57:01* (abacavir), *B*58:01* (allopurinol), *B*15:02* (carbamazepine), *B*13:01* (phenytoin- Han Chinese) and *B*56:02* (phenytoin - Aboriginal Australians (Harding et al, 2012)).
Methods: Following ethics committees' approvals and informed consent, participants provided a saliva sample for DNA isolation which was tested for HLA status using Sanger sequencing. In addition, data were also obtained from the Aboriginal communities in Cape York Peninsula (n=103), Groote Eylandt (n=75), Kimberly (n=45) and Yuendemu (n=191) (Takeshita et al, 2015), hereafter referred to as Other Sites.
Results: Thirty-two self-identified Aboriginal Australians and 36 non-Aboriginal participants' samples and data were obtained. For *HLA-B*57:01* the incidence was 1.6% and 1.4% (AA vs NA) and was 0.7-1.5% in the Other Sites; for *HLA-B*58:01* it was 0% vs 2.8% and 0-0.7% (Other Sites), *B*15:02* (1.6% vs 0%; 0-0.7%- Other Sites); *B*13:01* (4.7% vs 0%; 12-27% Other Sites) and for *B*56:02* its was 3.1% vs 0% and 1.3-19% Other Sites.
Discussion: The study shows that Aboriginal Australians would be less vulnerable to allopurinol hypersensitivity (*B*58:01*), similar to Caucasians for abacavir hypersensitivity (*B*57:01*), and to the predominantly Han Chinese phenytoin hypersensitivity (*B*13:01*), and highly vulnerable to phenytoin hypersensitivity due to *B*56:02* which is almost non-existent in Caucasian and Asian populations.

Somogyi AA and Phillips E (2017). Aust Prescr 40:101-4
Harding DJ et al (2012) Med J Aust 197:411-4
Takeshita LY et al (2015) Nucl Acid Res 28: D784-8

331 Potential simple and multifactorial drug and gene interactions of tricyclic antidepressants in older Australians

Mohitosh Biswas[1], Thilani H. Dias[1], Nilofar Daneshi[1], Elizabeth Holliday[2], Stephen Hancock[2], John Attia[2], Rodney Scott[1], David Newby[2], Karen P. Kerr[1], Elizabeth A. Milward[1], [1]School of Biomed Sci and Pharmacy, The University of Newcastle, Newcastle, NSW, Australia, [2]School of Med and Pub Health, The University of Newcastle, Newcastle, NSW, Australia

Introduction. Safety and efficacy of tricyclic antidepressants (TCAs) may be reduced when co-prescribed with interacting drugs or due to genetic variants or both (Hicks 2013).
Aims. To determine the prevalence of potential simple and multifactorial drug and gene interactions (DGI) of TCAs in older Australians where polypharmacy is common.
Methods. Co-prescribed interacting drugs were identified from self-reported medication data of 2,642 participants aged over 55 in the Hunter cohort community study (McEvoy 2010). Predicted drug and gene interactions were identified for gene variants determined from genotyping data obtained using Affymetrix Kaiser Axiom arrays and imputed data from the 1000 Genomes and HapMap Phase II European reference panels.

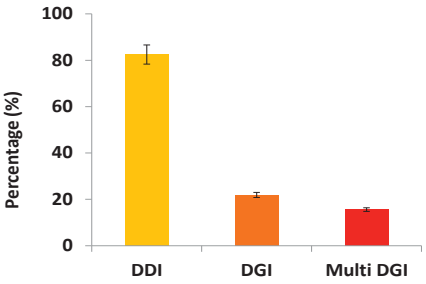


Figure: Potential simple and multifactorial DGI of TCAs in older Australians

Results. Of 57 participants on TCAs, 47 (83%; 95% CI 73%-92%) were co-prescribed at least one potential interacting drug, with on average 2.5 possible interactions per participant. About 22% of participants (95% CI 8%-36%) had clinically actionable genotypes and 16% (95% CI -1%-32%) were at risk of multifactorial DGI predicted to increase the likelihood of adverse effects.
Discussion. Considerable proportions of older people in the community using TCAs may be at increased risk of adverse reactions involving drug-gene interactions that may justify dose reduction. The findings emphasize the potential value of considering the pharmacogenomics of TCAs in conjunction with drug interaction analyses.
Hicks JK et al (2013) Clin Pharmacol Ther 93:402–408
McEvoy M et al (2010) Int J Epidemiol 39:1452-1463

332 Signalling modification by Single Nucleotide Polymorphisms in the third intracellular loop of the mu-opioid receptor

Marina Santiago & Mark Connor. Dept of Biomedical Sciences, Macquarie Univ, Sydney, NSW, Australia

Introduction: The third intracellular loop (ICL3) is a highly conserved region of opioid receptors and it is involved with G protein coupling. Three rare human mu-opioid receptor (MOPr) SNPs have been previously reported (R260H, R265H and S268P) to affect receptor signalling (Knapman et al 2015). This could be a result of impaired G protein coupling and phosphorylation site deletion (S268P). Changes in signalling, phosphorylation and internalisation of these receptor variants may explain some of the variability in clinical responses to opioids and understanding them may contribute to understanding the role of ICL3 in MOPr signalling and regulation.
Aims: In this *in vitro* study, we explored the effects of these MOPr ICL3 SNPs on signalling and regulatory pathways induced by morphine and the endogenous opioid analogue DAMGO in the pituitary cell line AtT-20.
Methods: AtT20-FLPIn cells were stably transfected with human WT, R260H, R265H, S268P and S268A MOP. Receptor levels were determined using [^{3}H]-DAMGO binding assays. MOP-induced K channel activation and signal desensitisation was measured with a membrane potential-sensitive dye in a Flexstation 3. Agonist-induced MOP phosphorylation at Ser377 and loss of cell surface MOPr were determined by Western blot and ELISA, respectively.
Results: DAMGO binding was within 30% of WT in each variant. At S268P, DAMGO potency was significantly reduced when compared to both WT and S268A (pEC50 WT 8.4±0.1; S268P 7.8±0.1; S268A 8.4±0.1 (n=6, $P<0.05$)). Phosphorylation of Ser377 was only affected at R260H mutation, where phosphorylation in response to DAMGO (1µM) was decreased by over 50%. 30 minutes exposure to DAMGO (10 µM) also produced less loss of surface R260H receptor (14±8%) compared to WT MOP (36±8%).
Discussion: The importance of the ICL3 MOPr for G protein signalling was confirmed by this study. Changes in the N-terminal region of the ICL3 had a greater effect on G protein coupling, while only R260H affected receptor regulation. By using S268A we determined that phosphorylation at S268 site is not crucial for pathways studied. All SNPs have the potential to affect opioid response in patients but the effect in heterozygous genotype need further investigation.
Knapman A et al (2015) Br J Pharmacol 172:349-363

333 *ABCB1* pharmacogenetics in Papua New Guinea HIV/AIDS patients and association with efavirenz CNS/Psychiatric adverse effects

Helena Van Schalkwyk[1], Joseph Tucci[2], Paul Pumuye[3], Daniel Barratt[1], Andrew A Somogyi[1] Disc Pharmacol, Univ Adelaide[1], Adelaide, SA; Dept of Pharmacy & Applied Science, La Trobe Univ[2], Bendigo, Vic; School of Medicine and Health Sciences, Univ Papua New Guinea[3], Boroko, Papua New Guinea.

Introduction. Papua New Guinea (PNG) has the highest prevalence of HIV/AIDS in the Pacific with efavirenz as the main treatment. *ABCB1* encodes the P-glycoprotein efflux transporter which is important for drug disposition, and *ABCB1* genotype has been linked to efavirenz CNS/Psychiatric adverse effects (Dickinson et al., 2016). However, nothing is known about key *ABCB1* SNPs in the PNG population. We hypothesised that *ABCB1* genetics would be associated with efavirenz CNS/Psychiatric adverse effects in PNG HIV/AIDS patients.
Aims. To determine the frequency of *ABCB1* 61A>G, 1199G>A, 1236C>T, 2677G>T and 3435C>T SNPs and haplotypes in PNG HIV/AIDS patients receiving efavirenz and examine genotype/haplotype differences in the incidence of CNS/Psychiatric adverse effects.
Methods. Demographic and clinical data, including CNS/Psychiatric adverse effects, and saliva were collected from 51 PNG HIV/AIDS patients. Salivary DNA was genotyped for *ABCB1* SNPs and allele frequencies compared to other populations (Caucasian, East Asian, African) (Auton et al., 2015). *ABCB1* haplotypes were inferred by PHASE. Incidence of CNS/Psychiatric adverse effects was compared between *ABCB1* genotypes and haplotypes by Fisher's exact tests.
Results. PNG HIV/AIDS patients have a high frequency of 1236T (82%), 2677T (62%) and 3435T (66%) alleles compared to other populations (14-63%, 0-13% and 15-52%, respectively). No variant alleles were observed for 61A>G and 1199G>A. There were no significant genotype/haplotype differences in CNS/Psychiatric adverse effects ($p>0.15$).
Discussion. PNG HIV/AIDS patients exhibit very high frequencies of key *ABCB1* SNPs which may have important implications for P-glycoprotein substrate drugs in this population. However, no significant association with efavirenz adverse effects was detected in this small study, and larger studies incorporating efavirenz PK are required.
Dickinson et al. (2016) Clin Pharmacokinet 55:861-873.
Auton et al. (2015) Nature 526:68-74.

334 Interleukin genetics and not COMT or OPRM1 may affect risk of persistent pain following total knee arthroplasty

Daniel Barratt[1], Hellen Victory[1,2], Lona Christrup[2], David Rice[3,4], Michal Kluger[3], Peter McNair[4], Gwyn Lewis[4], Andrew Somogyi[1], [1]Disc Pharmacol, Univ Adelaide, Adelaide, SA, [2]Dept Drug Design & Pharmacol, Univ Copenhagen, Copenhagen, Denmark, [3]Dept Anaesthesiology & Perioperative Medicine, Waitemata District Health Board, Auckland, New Zealand, [4]Health & Rehabilitation Research Inst, Auckland Univ Technology, Auckland, New Zealand

Introduction: Total knee arthroplasty (TKA) is a common procedure intended to alleviate pain, but up to 30% of patients experience persistent postsurgical pain (PPP) that lasts months to years after surgery. Identifying factors such as patient genetics that predict PPP can assist in its prevention and treatment. SNPs in catecholamine, opioid, and immune signalling pathway genes have been linked to PPP in other surgical settings (Hoojwijk et al, 2016). We hypothesised that SNPs in these pathways would also be associated with PPP following TKA.
Aims: To investigate *COMT*, *OPRM1* and immune genotype differences in the likelihood of PPP following TKA.
Methods: Patients were 264 Caucasians scheduled for primary TKA and followed 6 months post-surgery. PPP was classified as a numerical rating scale pain score ≥3 6 months after surgery. DNA from blood was genotyped for 17 SNPs (minor allele frequency >5%) in *COMT*, *OPRM1*, *IL1B*, *IL2*, *IL6*, *IL6R*, *IL10*, *CASP1*, *CRP*, *TLR2*, *TLR4*, *MYD88*, *TGFB1* and *TNFA*. Genotype differences in PPP were analysed by forward selection (ANOVA $P<0.05$) logistic regression controlling for patient age and acute post-surgical pain (Western Ontario and McMaster Universities Osteoarthritis Index score [0-100] with movement 24 hours after surgery).
Results: Seventy-eight patients (30%) had PPP. The likelihood of PPP was lower for variant genotypes of *IL6* -6331T>C (rs10499563) (adjusted odds ratio [95% CI] versus T/T: T/C = 1.2 [0.65 to 2.4]; C/C = 0.13 [0.01 to 0.73]; P = 0.03) and *IL2* -330T>G (rs2069762) (T/G = 0.55 [0.28 to 1.0]; G/G = 0.22 [0.03 to 0.87]; P = 0.04). *COMT* (rs4680, rs4818) and *OPRM1* (rs1799971) genotypes were not significantly associated with PPP ($P > 0.2$).
Discussion: Genetic variability in interleukin signalling, and not *COMT* or *OPRM1*, may affect predisposition to PPP following TKA, although these associations were not statistically significant after correction for multiple testing. Additional genetic factors associated with PPP in other surgical settings are still to be investigated in this TKA cohort.
Hoojwijk D et al (2016) Br J of Anaesth 117:708–19

335 Best Possible Medication History Gamification – Development and pilot study

Paulina Stehlik[1], Vien T. Truong [2, 3], Rebekah J. Moles[2], Carl R. Schneider[2], [1]CREBP, Bond Uni, Gold Coast, QLD, Australia, [2]Faculty of Pharmacy, Uni of Sydney, Sydney, NSW, Australia, [3]Dept of Pharmacy, Campbelltown Hosp, Sydney, NSW, Australia

Introduction: This study describes the development and pilot of an electronic adaptation of the Medication Mysteries Infinite Case tool (eMedRec). eMedRec provides an opportunity for students to simulate the history taking and documentation process, provide guided peer feedback and receive instant grading of history documentation accuracy.
Aims: To evaluate the game's impact on students' self-perceived confidence and competence, and to evaluate game usability.
Methods: Game and survey data were used to measure outcomes. Changes in self-rated confidence and competence scores of second-year Master of Pharmacy students in semester 1 (usual teaching: one medication history taking lecture, weekly problem based learning (PBL) tutorials, and four weeks of clinical placement) was compared to semester 2 (intervention: use of the eMedRec game and PBLs in weekly tutorials). System Usability Scale (SUS) was used to measure game usability.
Results: Changes in self-perceived confidence were equivalent during semester 1 control and semester 2 intervention (0.45 v 0.13; difference in mean change = -0.32, 95% CI = -0.72 to 0.08). There was a significant increase in self-perceived competence following eMedRec exposure in semester 2 (-0.06 v 1.16; difference in mean change = 1.23, 95% CI = 0.66 to 1.81). eMedRec SUS score was 48.5/100.
Discussion: eMedRec scored moderately on the SUS, despite significant server issues throughout the study period. We observed similar increase in self-perceived competence and greater increase in student self-perceived competence after intervention compared to usual teaching. Further evaluation of the game is warranted.

Sando KR, Elliott J, Stanton ML, Doty R. (2013) Am J Pharm Ed. 77(5):105.

336 Engaging students in learning outcomes and career relevance through a multi-dimensional, interactive map – *MyCourseMap*

Lisa BG Tee[1], Ieva Stupans[2], Jose Manuel Serrano Santos[3], [1]School of Pharmacy, Curtin University, Perth, WA, [2]School of Health and Biomedical Sciences, RMIT University, Bundoora, VIC, [3]School of Clinical Sciences, Queensland University of Technology, Brisbane, QLD, Australia

Introduction: Undergraduate students rarely see a program-wide view of their studies, and yet their programs are developed with just such a holistic view. Often the curriculum intent including program learning outcomes and graduate attributes are not "visible" to students. Degree structures are often difficult to comprehend and opaque to commencing students due to the complexity of the course information. The tool—*MyCourseMap*—utilises digital-touch technology and is designed for use on all mobile devices. *MyCourseMap* presents curriculum in a more student-centred and visible form and is used in this study.
Aims: To gather and evaluate the perception of students and staff regarding their awareness of the importance of graduate attributes and program learning outcomes. To also gather the perception of academics who have trailed the *MyCourseMap* tool regarding the benefits and barrier in using the tool.
Methods: The *MyCourseMap* tool was trialled in a few institutions across Australia. The perspectives of staff and students on visibility and awareness of curricula, graduate attributes and program learning outcomes for the Bachelor of Pharmacy were investigated. Specifically, participants attended a workshop presentation, followed by focus group discussion. Participants were also requested to complete an online survey following the focus group discussion.
Results and discussion: Preliminary result from online survey regarding the visibility of graduate attributes indicates an increased the percentage of respondents from 38% to 93% when the curriculum was presented using the MyCourseMap. Similarly there was an increased in the perception regarding visibility of program learning outcomes, an increased from 50% to 90%. Academics who have trialled the MyCourseMap valued the ease of set up and maintenance of the information, the cross-discipline applicability and the potential of the tool for other purposes such as visualisation and mapping of professional domains and competencies in a course. MyCourseMap allowed for ready identification of potential assessment issues and provided impetus for minor curriculum redevelopment.

337 "Visual thinking strategies" in early pharmacy undergraduate education can support the development of professional communication and cultural competencies

Trudi Aspden[1], Lynne Petersen[1], School of Pharmacy, University of Auckland[1], Auckland, New Zealand

Introduction: Visual Thinking Strategy (VTS) described by Yenawine P (2013) uses art to develop transferable skills. In 2016 we introduced VTS sessions in year 2 of our revised BPharm programme to assist students to apply learning from the Hauora Māori (Māori Health) and Clinical and Professional Skills domains to other areas of the BPharm curriculum.
Aims: To describe the implementation and refinement of VTS learning activities, and early assessment of the impact of VTS on developing professional competencies such as critical thinking, cultural competence and communication skills.
Methods: A series of deliberately themed images were used in 10 VTS workshops and linked across various activities, including a poverty simulation, a cross-cultural simulation, reflections on learning and an inter-professional Māori Health Intensive module. These all linked to the patient-centred communication frameworks developed by the part II teaching team that are used by students within practice lab sessions and are incorporated into assessments.
Results: Tutor and student feedback indicates that students' oral communication skills have improved: specifically their ability to listen actively, to link their ideas to those of others, and to respectfully offer alternative viewpoints. Modifications to the VTS sessions have been made based on student and tutor feedback; these include reducing VTS class sizes to <15 participants and offering students a choice of images to discuss in each session.
Discussion: We adapted Visual Thinking Strategy (VTS) methodology for use with adult learners and pharmacy contexts in New Zealand, and deliberately linked this to other activities relating to culture, communication and personal development in the curriculum and to the Pharmacy Council of New Zealand's Competence Standards for the Pharmacy Profession. VTS appears to have been a valuable addition to the curriculum, offering opportunities for students to integrate learning and transfer skills and knowledge across the curriculum. A comprehensive evaluation plan is being implemented in order to understand critical features of the VTS method and implications for teaching such as the extent to which students transfer VTS 'thinking and practices' to other domains of their learning.

Yenawine P (2013) Visual Thinking Strategies: Using art to deepen learning across school disciplines. Cambridge, Massachusetts: Harvard Education Press.

338 Experiences developing a pharmacology online careers portal: Evaluating impact on student career awareness

Barbara K Kemp-Harper, Emma Harris, Elizabeth A Davis, Dept Pharmacology, Monash University, Clayton, VIC, Australia

Introduction: Students undertaking courses without a defined vocational outcome (e.g. B.Sc, B.Biomed.Sci) are not always aware of potential career pathways, which can affect their motivation and engagement. In addition, they have little knowledge of the specific resources available to help prepare them for future employment.
Aim: The current study aimed to heighten the career awareness of pharmacology students, via the development, implementation and evaluation of an online careers portal with a focus on the pharmaceutical industry.
Methods: A Monash Pharmacology Alumni LinkedIn group was established, with graduates invited to join the group and participate in an on-line survey and/or video interview, focused on the nature of their job, their career journey and relevant skills required. A website was established, using the information they provided. Undergraduate students (n=58) enrolled in a third year pharmacology unit (semester 2, 2017), were invited to complete surveys pre- and post-implementation of the website. The surveys assessed students' knowledge and understanding of jobs within the pharmaceutical industry and resources available to help them prepare for future careers.
Results: To date, 62 Monash graduates have joined our LinkedIn group and 22 have completed the online survey. The survey information formed the basis of the careers website, providing an overview of jobs within the pharmaceutical industry and highlighting profiles of alumni. Eleven of the alumni completed video interviews, which were incorporated into the website. Prior to access to the online resource, students identified research (85%) and sales representatives (70%) as roles within the pharmaceutical industry of which they were aware. The majority of students (64%) indicated that they would use Google and/or speak to academic staff (40%) to obtain further information about career prospects. Student survey data post implementation of the website is pending. Feedback on the website from alumni participants has been positive. An unexpected outcome of the project has been the development of an alumni network, some of whom are now engaged in teaching activities within our department.
Discussion: Access to our online careers portal has the potential to increase awareness of career pathways available to pharmacology students. The alumni network will facilitate opportunities for student engagement with industry.

339 Exploring the use of a novel computer-based interactive pharmacy simulation program in university and professional pharmacy practice education

Kenneth Lee[1], Bryan Etherington[1], Lauren Tait[2], Mackenzie Williams[1], Joyce Cooper[3], Rohan Rasiah[4], Benjamin Geelan[1], Tristan Ling[1], Ivan Bindoff[1], [1]Pharmacy, University of Tasmania, Hobart, TAS, Australia, [2]Pharmacy Department, Townsville Hospital, Townsville, QLD, Australia, [3]School of Biomedical Sciences and Pharmacy, University of Newcastle, Newcastle, NSW, Australia, [4]Western Australian Centre for Rural Health, University of Western Australia, WA, Australia

Introduction: Experiential learning with repeated practice allows learners to consolidate knowledge and skills in a contextualised environment. A high fidelity, computer-based simulated environment has the potential to facilitate safe experiential learning and provide unlimited practice opportunities.
Aims: We aimed to 1) compare the use of various simulation modalities against a novel computer-based pharmacy simulation program ('Pharmacy Simulator'), 2) explore pharmacists and pharmacy students' perceptions and experiences with using the aforementioned program as an experiential learning tool, and 3) assess the need for the aforementioned program in pharmacy practice education.
Methods: We used a series of nested mixed-method studies to address the aforementioned aims: study 1 (Aim 1) was a randomised cross-over of simulation modalities, study 2 (Aim 2) used a pre-post intervention design with pharmacists and pharmacy students. Study 3 (Aim 3) gathered qualitative feedback from key stakeholders including pharmacists, pharmacy organisations, pharmacy students, and universities.
Results: Overall, participants were typically in favour of the use of 'Pharmacy Simulator' as a learning tool, perceived the program to have positive effects on confidence to practice, and agreed there is a place for 'Pharmacy Simulator' as an additional resource for experiential learning within universities and professional training organisations.
Discussion: Results suggest a positive uptake of 'Pharmacy Simulator' when used as a supplementary learning tool, as while it has comparable efficacy, it offers different benefits that extend typical experiential learning approaches.

340 The journey of a prescription: An interprofessional education simulation of the patient and prescription flow through prescriber and dispenser

James A Green[1], Jim Ross[1], Rhiannon Braund[1], Martyn Williamson[1], Tony Egan[1], [1]School of Pharmacy, University of Otago, Dunedin, New Zealand, [2]Department of General Practice and Rural Health, University of Otago, Dunedin, New Zealand

Introduction: Interprofessional education has been an increasing area of emphasis in health professional training, but exercises at the immersion level, where students are embedded in their professional roles are more challenging to design than exercises involving exposure to or engagement with other professions.
Aims: To investigate the feasibility of running a series of simulated pharmacies alongside an existing simulated medical clinic, as an interprofessional education exercise.
Methods: We ran a pilot project with 8 pharmacy students operating 4 simulated pharmacies, alongside a simulated medical practice with 18 medical students operating in pairs, with 23 actors serving as patients. Following 2 hours of simulation, students participated in a focus group/debrief in mixed profession groups.
Results: Overall, the session ran smoothly, despite the considerable complexity in setting up temporary pharmacies with computer software and stock, and managing the flow of patients and prescriptions between the medical and pharmacy settings. Analysis of the focus group/debrief transcripts showed that students found the experience beneficial and more authentic than their usual simulation experiences, and that they learned a lot about each other's' roles. We also had visitors from other health professional programmes, and are exploring how they could be integrated in the future.
Discussion: This successful pilot provides a model for further interprofessional education development. Through the simulation exercise and debrief discussion, both groups of students were able to learn about each other's roles in obtaining good outcomes for their shared patients.

400 Trends in anticoagulant use among people with dementia in Australia

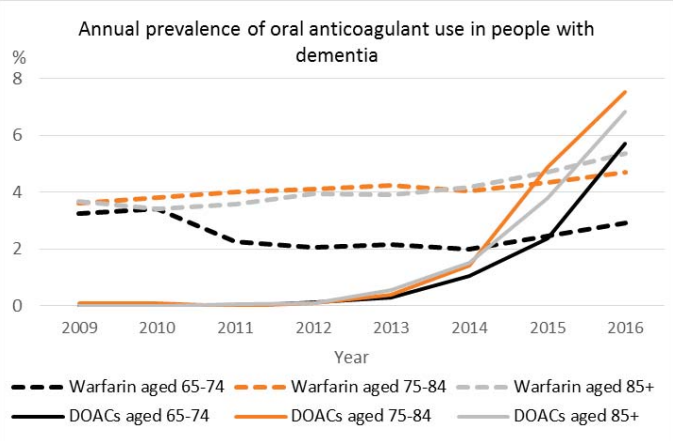
Jenni Ilomäki[1], Amy Page[1], Maarit Jaana Korhonen[1], Laura Fanning[1], Atte Meretoja[2], Kevin P Mc Namara[3], Janet K Sluggett[1], J Simon Bell[1]. Centre for Medicine Use and Safety, Monash Univ[1], Parkville, VIC, Helsinki Univ Hosp, Head and Neck Center[2], Helsinki, [3]School of Medicine, Deakin Univ[3], Warrnambool, VIC

Introduction. People with dementia are less likely to use anticoagulants for the prevention of thromboembolic events due to perceived increased bleeding risk. It is unclear to what extent the introduction of the direct oral anticoagulants (DOACs) has impacted the overall prevalence of anticoagulant use.

Aims. To investigate the trends in anticoagulant use in people with dementia in Australia between 2009 and 2016.

Methods. We analysed a random 10% sample of Australian Pharmaceutical Benefits Scheme individual-level dispensing data. People with dementia were identified as recipients of acetylcholinesterase inhibitors or memantine and categorised according to age 65-74 years, 75-84 years and ≥85 years.

Results. The annual number of people with dementia increased from 5,709 in 2009 to 8,937 in 2016. The overall prevalence of warfarin use increased from 3.6% to 4.7% and DOAC use from 0.04% to 7.0%. The pattern of anticoagulant use was similar in sensitivity analyses excluding under co-payment medications or restricting the cohort to concession card holders. Age-specific trends in annual prevalence are presented in the Figure.



Discussion. The overall prevalence of anticoagulant use in people with dementia has increased sharply since the introduction of DOACs. This may mean more people with dementia receive appropriate treatment. However, there is a need for further research in the benefits and risks of anticoagulant use in people with dementia.

401 Mapping medication burden, prescribing and dispensing patterns within community dwelling elderly clients of community pharmacies

Lauren J Corre[1], Elizabeth Hotham[1], Vijayaprakash Suppiah[1] School of Pharmacy and Medical Sciences, University of South Australia[1], Adelaide, SA, Australia.

Introduction. The coexistence of multiple illnesses in the elderly is common, and may lead to the use of multiple medicines. In turn, this can be associated with a patient visiting multiple prescribers, non-adherence and a plethora of negative consequences. Currently, there is a lack of knowledge surrounding the needs of older Australians residing independently within the community.

Aims. To quantify and describe: 1) Current patterns of medication load and presence of polypharmacy and, in particular, prevalence and variety of analgesics and any reported adverse events. 2) Prescribing and dispensing patterns for medications. 3) Each client's care team, how healthcare services are coordinated and his/her understanding of their regular medications.

Methods. Participants were recruited from three metropolitan community pharmacies in Adelaide, South Australia between June and August 2017. The study involved two stages – interviewing community dwelling older Australians and reviewing dispensing histories of those 65 years and over. Data analysis was conducted using descriptive statistics.

Results. Forty-five face-to-face interviews were conducted. Participants were taking 7.45 medicines on average with 76% using five or more regular medicines. Two hundred and twenty-three dispensing histories were collected. The average number of medicines taken by each participant was 8.27 with 86% of participants taking five or more regular medicines.

Discussion. A significant proportion of older Australians living in community dwellings were exposed to polypharmacy. Themes including lack of collaboration between healthcare professionals, the need for increased communication between prescribers and a requirement for increased education about medicines for patients were highlighted. ¶

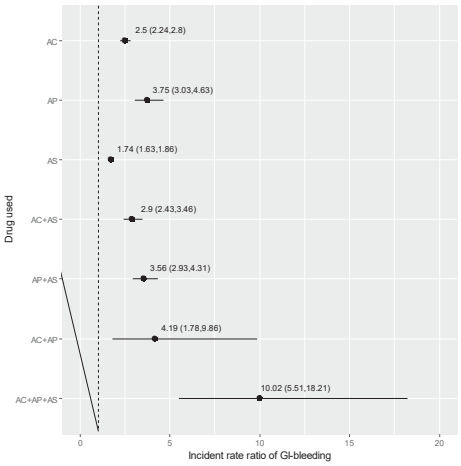
402 Use of medicines with sedative or anticholinergic properties and medicine-induced deterioration in older people: an intermediary pathway to frailty

Renly Lim[1], Lisa M. Kalisch Ellett[1], Imaina S. Widagdo[1], Nicole L. Pratt[1], Elizabeth E. Roughead[1]. Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute for Health Research, University of South Australia, Adelaide, SA, Australia.

Introduction. Medicines with sedative or anticholinergic properties have been associated with frailty but the intermediary pathways by which they contribute to frailty are less commonly studied.
Aims. To study the association between use of medicines with sedative or anticholinergic properties and i) medicine-induced deterioration (physical function, cognition or appetite), and ii) frailty.
Methods. The study population consisted of persons aged ≥65 years (n=2087) enrolled in the Australian Longitudinal Study of Ageing (ALSA). Physical function was measured using hand grip strength, walking speed, chair stands, activities of daily living (ADL) and instrumental activities of daily living (IADL). Cognitive function was measured using the Mini Mental State Examination (MMSE), while appetite was measured using the Center for Epidemiologic Studies Depression (CES-D) question 2, "I did not feel like eating; my appetite was poor". Frailty was measured using the frailty index.
Results. Almost half of the population were using medicines with sedative or anticholinergic properties (n=954, 45.7%). After adjusting for confounders, use of medicines with sedative or anticholinergic properties was associated with slower walking speed (p<0.001), poorer performance on chair stands (p=0.017) and poorer IADL score (p<0.001). There was no significant association between medicine use and cognitive function. Use of medicines with anticholinergic properties was associated with poorer appetite (p<0.001). Participants who used medicines with sedative or anticholinergic properties were significantly more likely to be frail compared with non-users (p<0.001).
Discussion. We described the pathways by which use of medicines with sedative or anticholinergic properties contribute to frailty, either directly or via an intermediary pathway. Preventing medicine-induced deterioration is important to reduce risk of frailty and subsequent adverse events such as falls and fractures.

403 'Real-world' haemorrhagic rates for antithrombotics using a self-controlled case series design

Prasad S Nishtala, PhD[1] and Te-yuan Chyou, PhD[1], School of Pharmacy, University of Otago, Dunedin, Otago, New Zealand,



Introduction: Population level evidence for the safety of using antithrombotics in older people within the multi-morbidity is limited.
Aims: The overarching aim of this study was to examine the major gastrointestinal (GI) bleeding risks associated with antiplatelets, anticoagulants either as monotherapy, dual antiplatelet therapy (DAPT) or triple therapy (TT) under the context of confounding due to multi-morbidity.
Methods: Self-controlled case-series (SCCS) design and conditional Poisson regression (CPR) were used in this investigation. We identified 3378 individuals aged 65 and above, who had been diagnosed for the first time with GI-bleeding event, between 01/01/2005 and 31/12/2014. SCCS design controls for time-invariant confounding variables was used to estimate the increased risk of GI-bleeding due to DAPT, TT or the monotherapies, as incident rate ratios (IRR). Multivariable conditional Poisson regression was used to estimate the adjusted IRR.
Results: Amongst the 3378 individuals in the cohort, 78% (n = 2624) had their first-time GI-bleeding with antithrombotic exposures. Antiplatelet monotherapy (adjusted IRR = 3.75, 95% CI = [3.03, 4.63]) and DAPT (adjusted IRR = 4.19, 95% CI = [1.78, 9.86]) were associated with a higher GI-bleeding risk compared to anticoagulant and aspirin monotherapies. The risk of GI-bleeding was highest with TT use compared with anticoagulant and antiplatelet dual therapy use and the monotherapies (adjusted IRR = 10.02, 95% CI = [5.51, 18.21]).
Conclusions: The GI bleeding risk was higher in individuals using TT compared to anticoagulant and antiplatelet dual therapy as well as the monotherapies. The findings inform real world risk assessment posed by antithrombotics in older people.¶

404 Health professionals' and researchers' opinions on conducting clinical deprescribing trials

Alexander J Clough[1,2], Sarah N Hilmer[2], Lisa Kouladjian-O'Donnell[2], Sharon L Naismith[3], Danijela Gnjidic[1,2,3]. Fac of Pharmacy, Univ of Sydney[1], Camperdown, NSW, Australia; Kolling Inst, Royal North Shore Hospital and Univ of Sydney[2], St Leonards, NSW, Australia; Brain & Mind Research Inst, Univ of Sydney[3], Camperdown, NSW, Australia

Introduction. Clinical deprescribing trials can be conducted to produce favourable health outcomes in people taking potentially harmful medications. At present, there are no guidelines on conducting deprescribing studies.
Aims. To determine the perspectives, attitudes, interests, barriers, and enablers in relation to conducting clinical deprescribing trials among health professionals and researchers.
Methods. An anonymous survey was developed, reviewed and piloted by all investigators for content validity. Experts were contacted to inform the questionnaire content, which explored the purposes, enablers, and barriers of conducting deprescribing trials. The survey was distributed to members of national and international: deprescribing, pharmacological, and pharmacy organisations; and to researchers published in deprescribing.
Results. The survey was completed by 96 participants from June-August 2017. Participants indicated the main rationale for conducting deprescribing trials is to assess the efficacy of interventions to optimise clinical centred outcomes (79.2%). Common barriers to conducting deprescribing trials were forming relationships and maintaining communication with other health professionals involved in the deprescribing process. This barrier commonly affected the: effective completion of trials (32.0%); recruitment of potential patients (31.0%); and overall conduction of trials (17.1%). The most common reported enabler was the belief of health professionals treating trial patients that deprescribing was beneficial (24.4%). Classical randomised controlled trials were considered the most appropriate method for conducting deprescribing trials (93.2%) vs. crossover trials (45.2%). 60.0% of participants indicated a legal, regulatory, and good practice framework required developing, but only 38.9% stated that the CONSORT list needed to be updated to encompass deprescribing trials.
Discussion. Preliminary findings indicate recognition of the need for high quality randomised controlled deprescribing trials and the importance of engagement of treating clinicians in trials of these complex multidisciplinary interventions. Furthermore, the findings of this survey could inform a future clinical deprescribing trial framework, which participants indicated was required.¶

405 Prevalence of potentially inappropriate medication use in older inpatients with and without cognitive impairment: a systematic review

Mitchell R Redston[1], Sarah N Hilmer[2,3], Andrew J McLachlan[1,4], Alexander J Clough[1], Danijela Gnjidic[1,5]. Faculty of Pharmacy[1], University of Sydney, Sydney, NSW, Australia; Sydney Medical School[2], University of Sydney, Sydney, NSW, Australia; Departments of Aged Care and Clinical Pharmacology, Kolling Institute of Medical Research, Royal North Shore Hospital[3], Sydney, NSW, Australia; Centre for Education and Research on Ageing, Concord Repatriation General Hospital[4], Sydney, NSW, Australia; Charles Perkins Centre[5], University of Sydney, Sydney, NSW, Australia

Introduction. Older people with cognitive impairment are high users of acute care services in Australia and internationally. Potentially inappropriate medication (PIM) use may be associated with adverse outcomes, including hospital re-admission, functional disability and mortality.
Aims. This systematic review aims to quantify and compare the prevalence of PIMs in older inpatients with and without cognitive impairment.
Methods. A systematic search for observational studies was performed in Embase, Medline/PubMed, PsycINFO, International Pharmaceutical Abstracts, Scopus and Informit. Articles published in English during the period January 2007–June 2017 that reported the prevalence of PIMs in hospital inpatients ≥65 years were included. PIMs were defined as exposure to polypharmacy (multiple medication use) or using implicit or explicit tools, such as the Beers criteria and *Screening Tool of Older Person's Prescriptions* (STOPP). Two reviewers independently assessed the articles for eligibility and extracted the data.
Results. 47 articles were included. The prevalence of PIMs defined by polypharmacy exposure (n=15) ranged from 53.2% to 89.8% when cognitive impairment was reported, and 24.0% to 97.1% when unreported. In studies employing explicit and implicit tools (n=35), the prevalence of PIMs in where cognitive impairment was reported ranged from 20.6% to 80.5% using the Beers criteria, and 39.3% to 88.5% using STOPP. When cognitive status was unreported, the prevalence of PIMs ranged from 7.0% to 79.2% using the Beers criteria, and 20.0% to 63.4% using STOPP.
Discussion. Current published evidence suggests a substantial variation in the prevalence of PIMs in older inpatients with and without cognitive impairment. Future studies should investigate the impact of PIM use on patient-centred outcomes to inform enhanced acute care services and pharmacist interventions to reduce inappropriate prescribing.

406 Exercise and Weight Loss Supplements: Understanding the Risks

Bell RA[1], Prior F[2], Bell J[1], Hinwood M[1], O'Hara K[2], Goon L[1], Newby D[1]. Discipline of Clinical Pharmacology, University of Newcastle,[1] NSW, Australia; Hunter Drug Information Service (HDIS),[2] NSW, Australia.

Introduction. Oral exercise and weight loss supplements (e.g. pre-work out, post-workout, fatburners, protein supplements) are increasingly used in Australia despite uncertain benefits and mounting evidence of harm. There is limited Australian data on the demographics of users, types of supplements used, characteristics of use and adverse outcomes.
Aims. To describe exercise and weight loss supplement use and outcomes among a sample of regular users.
Methods. Adults with a recent history of supplement use in the last five years were recruited via social media using targeted snowballing and invited to complete a 51-item questionnaire about the type, frequency, duration and outcomes of supplement use.
Results. Of 423 respondents (58% female, mean age 28 years), 375 had used supplements in the past year with 234 (63%) using one or more daily. Adverse reactions were reported by 28% (96/347) including: neurological, cardiac, abdominal and skin reactions. Around 50% (150/316) were not aware of any risks associated with supplement use. Of the 120 who were prescription medicine users, only 27% discussed possible interactions with their doctor or pharmacist (33/120). Common risk behaviours included: using more than recommended dose (37% 117/316); using a supplement with unfamiliar ingredients (72%, 229/316); and continuing to use a supplement after an adverse reaction (30%, 28/95). Most users looked for information about supplement use on the internet 77% (239/310), and only 15% (48/310) consulted their doctor or pharmacist.
Discussion. Exercise and weight loss supplement use involves substantial health risks, but many users will not discuss supplement use or seek reliable evidence based advice qualified health service providers, and may continue supplement use while experiencing adverse reactions.

407 SGLT2 inhibitors and diabetic ketoacidosis - review of PI's and comparison with Endocrinology position statement

Genevieve M Gabb[1,2], Sonya J Conrad[3], Emily J Meyer[2,4,5.] General Medicine, Royal Adelaide Hospital, Adelaide, SA, Australia[1]; Discipline of Medicine, University of Adelaide, Adelaide, SA, Australia[2]; Women's Information Service, Adelaide, SA, Australia[3]; Endocrine and Metabolic Unit, Royal Adelaide Hospital, Adelaide, SA, Australia[4]; Department of Endocrinology and Diabetes, The Queen Elizabeth Hospital, Adelaide, SA, Australia[5]

Introduction. Sodium glucose-cotransporter 2 (SGLT2) inhibitors are a new drug class for type 2 diabetes mellitus. They are available as single ingredient products, or as a combination product together with metformin. Case reports of diabetic ketoacidosis (DKA) in association with their use have emerged in clinical practice. In mid-2016 the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) issued a position statement on SGLT-2 inhibitors and DKA.
Aims. To review and compare Australian Product Information for SGLT-2 inhibitors (single and combination) regarding information on DKA, and also compare with information in the AACE/ACE position statement.
Methods. Text analysis for key information regarding DKA including frequency, risk factors, clinical presentation, diagnostic issues, management, risk mitigation strategies and specific advice in relation to surgery.
Results. All PI's had revision dates after the AACE/ACE position statement. All PI's listed DKA, in the precautions and adverse events sections. All identified usual presenting DKA symptoms, but that blood sugar levels may be lower than expected. Risk factors and precipitants were identified, although there was variation in relation to identification of surgery as a precipitant. There was variation in relation to information on disease severity, from no information, to identification that the outcome may be fatal. No PI's included information on diagnostic difficulties or specific recommendations listed in the position statement. Management information varied, regarding urgency, need for hospitalisation and specific treatments. Specific advice in relation to management around surgery was generally lacking for single products, although recommendations to withhold before and after surgery were present for combination products due to presence of metformin.
Discussion. There is variation between Product Information statements of SGLT2 inhibitors regarding DKA, and useful clinical information from the AACE/ACE position statement is not fully represented. Risk mitigation could be improved with further modification of Product Information.¶

408 Health literacy and uptake of osteoporosis medications in a population-based sample of Australian women

Sarah M Hosking[1], Sharon L Brennan-Olsen[2], Alison Beauchamp[3], Rachelle Buchbinder[4], Lana J Williams[1], Julie A Pasco[1]. Deakin University[1], Geelong, VIC, Australia; Australian Institute of Musculoskeletal Science, The University of Melbourne and Western Health[2], St Albans, VIC, Australia; Public Health Innovation, Deakin University[3], Burwood, VIC, Australia; Department of Epidemiology and Preventive Medicine, Monash University[7], Melbourne, VIC, Australia;

Introduction. Lower health literacy has been associated with poorer medication uptake and adherence in some chronic conditions, however, associations between health literacy and uptake of osteoporosis medications are currently unknown.
Aims. To investigate associations between health literacy and anti-fracture medication uptake in osteoporotic women.
Methods. Data were collected for women participating in the 15yr follow-up of the Geelong Osteoporosis Study (GOS), a population-based cohort in south-eastern Australia. Health literacy was ascertained using the Health Literacy Questionnaire (HLQ), a multi-dimensional tool that generates scores across nine scales. Bone mineral density (BMD) was measured by dual x-ray absorptiometry (DXA) (Lunar DPX-L) and osteoporosis was defined as a BMD T-score ≤2.5 at the hip and/or spine, or BMD in the osteopenic range (T-score -1 to -2.5) combined with any adult (aged ≥20yr) fracture. Self-reported current medications were classified using MIMS codes, with medications in category 6G 'Agent affecting calcium and bone metabolism' indicating osteoporosis treatment. Analysis of Variance (ANOVA) and Cohen's d effect sizes (ES [95%CI]) (categorised; Small >0.2-0.5, Moderate >0.5-0.8, Large >0.8) were calculated for differences in mean HLQ scale scores between participants with osteoporosis who did vs. did not self-report medication use.
Results. In our women, 134 (21.6%) had osteoporosis and 14 (10.5%) of those women were taking medication. Small and moderate ES observed indicated that women taking medication had lower HLQ scores in three scales; 'Navigating the healthcare system', 'Ability to find good health information' and 'Understanding health information' (ES 0.36 [0.25, 0.79], 0.41 [0.29, 0.87] and 0.64 [0.54, 1.03], respectively). No significant differences for any scales were observed using ANOVA; however, a trend was observed for the scale 'Understanding health information (p=0.09).
Discussion. These results suggest that women who may be less confident in their own ability to find and understand health information may be more likely to follow recommendations from their healthcare provider, and therefore take up prescribed medications more readily¶

409 SGLT-2 inhibitors and diabetic ketoacidosis - review of CMI and comparison with Endocrinology position statement

Fahmida Ilyas[1], Sonya J Conrad[3], Emily J Meyer[2,4] Genevieve M Gabb[1,2] 1. Dept of Medicine, Royal Adelaide Hosp, SA, Australia; 2. Discp of Medicine, Univ of Adelaide, SA, Australia; 3. Women's Information Service, SA, Australia; 4. Endocrine and Metabolic Unit, Royal Adelaide Hosp, SA, Australia;

Introduction. Sodium glucose-cotransporter 2 (SGLT-2) inhibitors are a new drug class for type 2 diabetes mellitus, available as single ingredient, or combination product with metformin. Reports of diabetic ketoacidosis (DKA) with their use have emerged in clinical practice. In mid-2016 the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) issued a position statement on SGLT-2 inhibitors and DKA.
Aims. To review the AACE/ACE position statement on SGLT-2 inhibitor associated DKA and compare with Consumer Medicines Information (CMI) for SGLT-2 inhibitors regarding information on DKA.
Method. Text analysis for key information regarding DKA including frequency, risk factors, clinical presentation and severity, risk mitigation strategies, management and specific advice in relation to surgery.
Results. The AACE/ACE position statement did not include any reference to patient education/consumer information regarding risk of diabetic ketoacidosis with SGLT-2 inhibitors. All CMI's had revision dates after the AACE/ACE position statement. All CMI's advised DKA was a contraindication for SGLT-2 inhibitors. All CMI's listed DKA, in the precautions and adverse events sections and reported incidence as rare. There was minimal or no documentation about risk factors that might precipitate DKA. All identified usual presenting DKA symptoms and disease severity as either serious or severe. Management information varied, regarding urgency and need for hospitalisation. Only one CMI suggested cessation of SGLT-2 inhibitor if symptoms of DKA occur. Advice in relation to management around surgery was generally lacking.
Discussion. There is an absence of consideration for patient education regarding SGLT-2 inhibitor associated DKA in the AACE/ACE position statement. The CMI statements of SGLT-2 inhibitors do not include information regarding risk factors and management of SGLT-2 inhibitor associated DKA that is present in the AACE/ACE position statement. CMI advice in relation to use of SGLT-2 inhibitors in the surgical setting is extremely limited. Risk mitigation could be improved with modification of CMI's. Patient education regarding risk of DKA with SGLT-2 inhibitors may have significant resource implications given use in the type 2 diabetes population where DKA is not generally expected.¶

410 Evaluation of bortezomib use in Queensland public hospitals for the treatment of multiple myeloma

Crystal Loke[1], Ian McPherson[2], Peter Mollee[2], Mimi Yue[2], Euan Walpole[2], Howard Mutsando[3], Phillip Wong[3], Helen Weston[4], Ross Tomlinson[4], Samantha Hollingworth[1]. School of Pharmacy, the Univ of Queensland[1], Brisbane, QLD, Australia; Dept of Cancer Services, Princess Alexandra Hosp[2], Brisbane, QLD, Australia; Cancer Care Services, Sunshine Coast Univ Hosp[3], Birtinya, QLD, Australia; Regional Cancer Care, Toowoomba Hosp, Darling Downs Hosp and Health Services[4], Toowoomba, QLD, Australia.

Introduction. Bortezomib (Velcade®) has been demonstrated to improve survival in patients with symptomatic multiple myeloma (MM). One phase III trial (VISTA) supported the PBS subsidy of bortezomib use as a first line treatment in non-transplant eligible MM patients. Bortezomib is expensive (approximately $6,000 per cycle) so we need to ascertain the health outcomes and costs in 'real world' patients.
Aims. We aim to examine the overall survival (OS) of patients using bortezomib and compare the results with trial data.
Methods. We retrospectively audited bortezomib use in non-transplant eligible MM patients in three Queensland public hospitals (October 2012 - December 2016). We retrieved data on patient characteristics, chemotherapy treatments, and survival outcomes from the oncology information system (CHARM®). We obtained pathology and clinical information from the pathology system (Auslab®) and medical chart audits at each site.
Results. We audited 75 patients who were treated with either CVD (bortezomib, cyclophosphamide, dexamethasone) or VMP (bortezomib, melphalan, prednisolone) regimens. The median age of the patients was 75 years, which was higher than that in the VISTA trial (71 years, n=344). The median cumulative dose of bortezomib was 19.14mg/msq, which was lower than the dose of VMP in the VISTA trial (38.5 mg/msq). The median OS was 40.7 months (VISTA trial 56.4 months) and median progression free survival (PFS) was 17.7 months (VISTA 21.75 months).
Discussion. MM patients in Queensland public hospitals were exposed to lower bortezomib doses, and achieved lower survival outcomes compared to key trial. This could be attributed to treatment and patient characteristics.

Abbreviation: meter squared – msq

411 What do women want to know about menopausal symptoms management: An Australian medicines call centre analysis

Rifani B Natari[1], Treasure M McGuire[1,2], Alexandra M Clavarino[1], Kaeleen D Dingle[3], Samantha A Hollingworth[1]. School of Pharmacy, University of Queensland[1], Brisbane, QLD, Australia; Mater Pharmacy, Mater Health[2], Brisbane QLD, Australia; School of Public Health & Social Work, Queensland University of Technology[3], Brisbane, QLD, Australia

Introduction. Management of menopausal symptoms has been shrouded in controversy over the last 15 years, with the evidence on safety and efficacy of hormonal treatments swinging back and forth. Despite much information on hormone therapy (HT) and complementary medicines (CM) for menopausal symptoms; women remain confused and uncertain.
Aims. To explore women's questions to an Australian medicines call centre regarding HT and CM.
Methods. We conducted a mixed method retrospective study on routinely collected data from an Australian national medicines call centre National Prescribing Service (NPS) *Medicines Line*. We quantitatively analysed data (September 2002 – 30 June 2010) for the demographic characteristics of callers, patients, motivations to help-seek, and enquiry types. We thematically analysed the callers' questions and derived key themes.
Results. We extracted 970 menopausal therapies (MTx) related calls (0.8% of calls). Most calls were made by women (97%) to seek information for themselves (95.3%). The top three enquiry types related to side-effects (23.1%), risks vs. benefits (16.4%), and interaction (14.9%). Most calls were prompted by inadequate information (38.5%), looking for second opinion (24.3%), and worrying symptoms (20.1%). There were no major changes in enquiry types and motivations to help-seek over time. Key question themes were: clarifying whether MTx caused/exacerbated symptoms; seeking advice for symptom management; and seeking reassurance to use or withdraw treatment. Concerns about the impact of MTx (especially HT) on underlying conditions focused on breast cancer, gynaecological, and cardiovascular conditions. In contrast, CM-related calls focused on efficacy and interactions.
Discussion. Women differ in their menopausal experiences and which medicines might be needed. Despite change in evidence to favour HT for up to five years for symptom management in perimenopause, women's concerns were fairly stable over time. These study elucidates women's information needs to enable the development of more directed and relevant information.

412 Patterns of oral anticoagulant use in people with and without dementia: A systematic review

Taliesin E Ryan-Atwood[1], Laura Fanning[1,2], J Simon Bell[1], Maarit J Korhonen[3], Atte Meretoja[4], Kevin P McNamara[5], Jenni Ilomäki[1] Centre for Medicine Use and Safety, Monash University[1], Melbourne, VIC, Australia; Eastern Health Clinical School, Monash University[2], Melbourne, VIC, Australia; Institute of Biomedicine, Turku University[3], Turku, Finland; Department of Neurology, Helsinki University Central Hospital[4], Helsinki, Finland; Deakin Rural Health, Deakin University[5], Melbourne, VIC, Australia.

Introduction. People with dementia are equally likely to experience stroke than those without, however people with dementia are less likely to receive warfarin. Direct oral anticoagulants (DOACs) may be an alternative to warfarin for people with dementia, however the safety profile has not been rigorously established.
Aims. To compare the prevalence of oral anticoagulant use, in people with and without dementia across all healthcare settings and indications for oral anticoagulation.
Methods. A search of the literature was undertaken using MEDLINE, EMBASE and CINAHL from 2000 until July 2017. Studies were included if they reported original research demonstrating cross-sectional assessment of oral anticoagulant use for people with and without dementia. Two independent reviewers extracted data from included studies. Prevalence estimates for oral anticoagulant use among people with and without dementia were calculated from data of included papers. A meta-analysis was performed using unadjusted odds ratio (OR) and 95% confidence interval (CI). Data were pooled using a random effects model and heterogeneity was explored using I_2 statistics.
Results. 3625 articles were retrieved Full texts of 56 articles were reviewed, 21 were included in the final review. No studies reported prevalence for DOAC use. Stroke prevention in atrial fibrillation was the main indication reported. The prevalence of warfarin use ranged from 8% to 64% in people with dementia and from 7% to 76% in people without dementia (OR (95% CI), 0.50 (0.40-0.63) compared with those without dementia).
Discussion. Results indicate people with dementia receive oral anticoagulation less frequently than people without, despite equal or increased risk of stroke for people with dementia. No studies reported prevalence of DOAC use in people with dementia. Findings indicate underutilisation of oral anticoagulation in people with dementia. Further work is required to understand the reasons for under-use and the impact of the introduction of DOACs on oral anticoagulant prevalence in people with dementia. ¶

413 Consumer information gaps and concerns regarding opioid analgesics and anxiolytic/hypnotic/sedative medicines

Kudrat Sidhu[1], Treasure M McGuire[1, 2], Mieke L van Driel[3], Samantha A Hollingworth[1]. School of Pharmacy, University of Queensland (UQ)[1], Brisbane, QLD, Australia; Mater Pharmacy, Mater Health Services[2], Brisbane, QLD, Australia; Discipline of General Practice, UQ[3], Herston, QLD, Australia

Introduction. Opioid analgesics (OA) are often prescribed to manage chronic pain; while anxiolytic, hypnotic and sedative (AHS) medicines are prescribed for insomnia and anxiety. These central nervous system depressants can produce physical and psychological dependence, resulting in tolerance, dose escalation, and misuse. These risks are of concern to patients, primary health care providers, and the wider public and media.
Aims. To identify consumer information gaps and concerns regarding use of OA and AHS medicines to enhance the utility of information made available to consumers.
Methods. We conducted a retrospective, mixed-method study of consumers' OA and AHS-related calls to the National Prescribing Service (NPS) *Medicines Line* (Sep 2002-30 Jun 2010). We analysed call characteristics and conducted a thematic analysis of question narratives for most common enquiry types when compared with rest of calls (ROC).
Results. Of 125,951 calls, 6,853 (5.4%) involved OA and 7,789 (6.8%) AHS. The mean age of OA callers and patients were 49.7 and 48.2 years, respectively. The mean age of AHS callers and patients was slightly older (50.8 and 49.7 years). While female callers predominated for both medicine classes, there were proportionately more male callers for AHS and OA medicines than other medicines. The two main motivations to help seek for both medicine classes were inadequate information (OA 44.1%; AHS 41.2%) and seeking a second opinion (OA 24%; AHS 24.2%). Side effects and interactions were the most common enquiry types but questions involving withdrawal or abuse were over three times more frequent for OA and AHS calls versus ROC (OA 12.6% versus ROC 2.7% and AHS 9.1 versus ROC 2.9%). The question themes were similar for both medicine classes: seeking additional information (e.g. risk of harm associated with misuse); therapeutic strategies (e.g. how to safely withdraw); seeking reassurance (e.g. drug will not cause addiction) and dose clarification.
Discussion. Consumers have many concerns about abuse and withdrawal of OA and AHS medicines, which may be under-recognised by healthcare providers. Developing user friendly, targeted information to address these concerns would contribute to safer and more effective use of medicines. ¶

414 The Medication Regimen Simplification Guide for Residential Aged CarE (MRS GRACE): a novel tool to optimise medication regimens for residents of aged care facilities.

Esa YH Chen[1,2], Janet K Sluggett[1,2], Jenni Ilomäki[1], Sarah N Hilmer[2,3], Megan Corlis[2,4], J Simon Bell[1,2], MRS GRACE development group. Ctr for Med Use and Saf, Monash Univ[1], Parkville, VIC, Australia; NHMRC Cog Dec Partn Ctr, Hornsby Ku-ring-gai Hosp[2], Hornsby, NSW, Australia; Kolling Instit, Univ of Sydney[3], St Leonards, NSW, Australia; Helping Hand Aged Care[4], North Adelaide, SA, Australia.

Introduction. Residents of aged care facilities use increasingly complex medication regimens. Reducing unnecessary medication regimen complexity (e.g. by consolidating number of administration times or using alternative formulations) may benefit staff administering medications and residents taking medications.
Aims. To develop and validate an implicit tool to facilitate medication regimen simplification in aged care facilities.
Methods. A purposively-selected multidisciplinary expert panel used modified nominal group technique to identify and prioritise factors important in determining whether a medication regimen can be simplified. The five prioritised factors were formulated as questions, pilot-tested using non-identifiable medication charts and refined by panel members. The final tool was validated by two clinical pharmacists who independently applied the tool to medication charts for a random sample of 50 residents to identify opportunities for medication regimen simplification. Inter-rater agreement was calculated using Cohen's kappa.
Results. The Medication Regimen Simplification Guide for Residential Aged Care (MRS GRACE) was developed as an implicit tool and accompanying explanatory statement. The tool comprises five questions related to resident and facility related factors, drug interactions, and formulation. Using MRS GRACE, two pharmacists independently simplified medication regimens for 29/50 and 30/50 residents (Cohen's kappa=0.38, 95%CI 0.12-0.64), respectively. Simplification was possible for all residents with five or more administration times. Changing an administration time comprised 75% of the two pharmacists' recommendations.
Discussion. By applying MRS GRACE, two clinical pharmacists independently simplified two-thirds of residents' medication regimens with fair agreement. MRS GRACE is a promising new tool to guide medication regimen simplification in aged care facilities.¶

415 What are the predictors of persistent prescription opioid analgesic use for non-cancer pain in Australia?

Samanta Lalic[1, 2], Natasa Gisev[3], J Simon Bell[1], Maarit J Korhonen[1], Jenni Ilomäki[1]. Centre for Medicine Use and Safety, Monash University[1], VIC, Australia; Pharmacy Department, Austin Health[2], VIC, Australia; National Drug and Alcohol Research Centre, UNSW Australia[3], NSW, Australia

Introduction. Long-term opioid analgesic use for chronic non-cancer pain is associated with uncertain clinical benefits but clear harms.
Aims. To identify patterns of opioid analgesic use and determined predictors of persistent opioid use among people without cancer.
Methods. A population-based cohort study of Australians initiating prescription opioids from July 2013 to December 2015 was conducted using data from a random 10% sample of people who accessed medicines through Australia's Pharmaceutical Benefits Scheme. A 12-month look-back period was used to define opioid initiation, exclude people with cancer, and determine comorbidities. Persistent use over 12-months since initiation was identified through group-based trajectory modelling. Odds ratios (OR) and 95% confidence intervals (CIs) for predictors of opioid persistence were estimated using logistic regression.
Results. The cohort consisted of 126,903 people who had opioids dispensed in ≥2 months during the 12-month follow up. A total of 11,323 (8.9%) persistent opioid users were identified. Predictors of persistence included initiation with transdermal opioids (OR 3.2, 95% CI 3.0-3.4), or with oral morphine equivalents (OME) ≥ 750 mg (OR 2.8, 95% CI 2.6-3.1), having depression (OR 1.3, 95% CI 1.3-1.4), or psychotic illness (OR 1.9, 95% CI 1.7-2.0). Previous dispensing of paracetamol (OR 1.7, 95% CI 1.6-1.8), pregabalin (OR 1.6, 95% CI 1.5-1.8) and benzodiazepines (OR 1.3, 95% CI 1.2-1.4) predicted persistence. Compared to people aged 18-44 years, those ≥75 years were 2.4 (95% CI 2.2-2.6) times more likely to be persistent users.
Discussion. Mental health comorbidities, older age, initiation with transdermal opioids and higher OMEs strongly predicted persistent opioid use among people without cancer. This information may help prescribers target monitoring and early intervention efforts in order to prevent opioid-related harms.

416 Anovulatory infertility in Australia: A retrospective analysis of medicine use and health outcomes

Mohammed Altaf[1], Hayden Homer[2] & Samantha A. Hollingworth[3]. Oocyte Biology Research Laboratory, Centre for Clinical Research, The University of Queensland[1,2], Brisbane, Queensland, Australia; School of Pharmacy, The University of Queensland[3], Brisbane, Queensland, Australia.

Introduction. Anovulation is when the ovaries do not release an oocytes during the menstrual cycle. It is a relatively common cause of infertility, accounting for about 25% of all cases. There are four different medicines which are subsidised under PBS for use in Anovulatory Infertility. The first line drug for inducing ovulation is Clomiphene citrate (CC), and the second line drugs are Follitropin alfa, Follitropin beta and Human chorionic gonadotrophin (HCG). CC is available as tablet, whereas all other medicines are available in the form of Injections and are taken via sc route.
Aims. To analyze the subsidized use, cost and reported adverse events of drugs used to induce ovulation in Anovulatory Infertility patients in Australia, following their inclusion on the Pharmaceutical Benefits Scheme (PBS).
Methods. Pharmacoepidemiological and Cost analysis of dispensed prescriptions from Medicare Australia. Adverse event data were obtained from the Therapeutic Goods Administration. Medicine use was measured by the defined daily dose (DDD) per 1000 population per day for each calendar year. Adverse events were counted by organ class system.
Results. There was significant increase in the use of second line drugs compared to first line therapy. The average percentage increase in the utilisation of three available strengths of Follitropin alfa (300 IU, 450 IU and 900 IU) and Follitropin beta (300 IU, 600 IU and 900 IU) was 728% (2004 to 2016, 0.0005 to 0.0051 DDD/1000 population/day) and 189% (2002 to 2016, 0.0008 to 0.0025 DDD/1000 population/day) respectively. Between 1992 and 2016, dispensing of HCG (1500 IU) in Australia increased 477% from 0.008 to 0.047 DDD/1000 population/day. Whereas First line drug (Clomiphene citrate) showed drastic decline (90%) in the usage from 1992 to 2016 (0.06 to 0.006 DDD/1000 population/day). The major reported adverse events were reproductive system and breast disorders, skin and subcutaneous tissue disorders, nervous disorders, eye disorders, and gastrointestinal disorders.
Discussion. The rising trend of gonadotrophins and significant decrease in the use of Clomiphene citrate over the years is a matter of concern and is pointing towards clinically inappropriate prescribing of ovulation induction agents for treating anovulatory infertility.

417 New drug formulation for combating antibiotic resistance

Hien Duong, Faculty of Pharmacy, The University of Sydney, Sydney, NSW.

Introduction. Bacterial biofilms are associated with 80–90% of infections. Bacteria in biofilms show significant resistance to antimicrobials and host immune defenses, compared with planktonic bacterial cells. Consequently, biofilm infections present many challenges including chronic inflammation, faulty wound healing, antimicrobial resistance, and the spread of infections.
Aims. To develop a novel 3-in-1 nanostructure-based formulation technology capable of storing nitric oxide (NO), which can provoke dispersal of biofilms into an antibiotic susceptible planktonic form, together with the aminoglycoside gentamicin and reactive oxygen species, capable of killing the bacteria.
Methods. In this study, we combined in one formulation a NO donor, reactive oxygen species and gentamicin. In this approach, the NO donor was directly obtained by reaction of gentamicin with NO gas to yield gentamicin-NONOate complex. By engineering the nanoparticles, a simultaneous and sustainable release of gentamicin, light induced reactive oxygen species and NO was obtained. All released agents acted synergistically on biofilms.
Results. The gentamicin-NONOate nanoparticles were found to effectively disperse biofilms of the model organism P. aeruginosa. At the NO concentrations of 10 µM, the viability of both biofilm and planktonic cells decreased by more than 90%. In contrast, gentamicin, reactive oxygen species and NO donor alone showed a lower efficiency against biofilm and planktonic cells.
Discussion. Combined and simultaneous delivery of NO, ROS and gentamicin is highly innovative concept that would allow eradicating the biofilm and also potentially overcome multidrug resistance. Encapsulated within nanostructures the three therapeutic agents are likely to have enhanced pharmacodynamic properties for systemic or local treatments. Furthermore, these compounds might be useful when applied as surface coating for the inhibition and prevention of biofilm formation on clinical surfaces or implants. The formulation is also very attractive for topical treatment with low risk of systemic side effects compared to parenteral or oral drug administration.

418 Angiotensin II receptor type 1 transactivation of EGFR via TRIO-dependent mechanisms.

Elizabeth KM Johnstone[1,2], Rekhati S Abhayawardana[1,2],Heng B See[1,2], Walter G Thomas[3], Kevin DG Pfleger[1,2,4]. Mol Endocrinol and Pharmacol, Harry Perkins Inst of Med Res[1], Nedlands, WA; Centre for Med Res, Univ of Western Australia[2], Crawley, WA; School of Biomed Sci[3], Univ of Queensland, St. Lucia, QLD; Dimerix Ltd[4], Nedlands, WA.

Introduction. The transactivation of receptor tyrosine kinases by G protein-coupled receptors is now a well-established paradigm. Of particular interest is the transactivation of epidermal growth factor receptor (EGFR) by the angiotensin II type 1 (AT_1) receptor, which has been shown to be crucial for AT_1 receptor-mediated growth effects, and involved cardiovascular pathologies. Although this transactivation has been described for many years, the mechanisms underpinning it are yet to be fully elucidated. Recently, a potential intermediate of this process was identified when it was discovered that the multidomain-containing kinase called TRIO was involved in the AngII/AT_1 receptor-mediated transactivation of EGFR (George et al, 2013).
Aims. To investigate the mechanism by which TRIO acts as an intermediate in AngII/AT_1 receptor-mediated EGFR transactivation.
Methods. To investigate this process, a variety of bioluminescence resonance energy transfer (BRET) protein-protein proximity assays were used.
Results. Upon AngII-induced activation of the AT_1 receptor, TRIO is trafficked around the cell through several cellular compartments. It also interacts with a variety of signalling and regulatory proteins. Many of these effects were specific to AngII-induced activation of the AT_1 receptor as they were not observed upon EGF-induced activation of the EGFR.
Discussion. Our data have demonstrated several AngII/AT_1 receptor-mediated effects on TRIO that appear to be involved in regulation of EGFR transactivation.

George et al (2013) J Cell Sci 126: 5377–5390. ¶

419 Smad2 linker region: a central integrating point for GPCR mediated transactivation of tyrosine and serine/ threonine kinase receptors.

Danielle Kamato[1], Narin Osman[1,2] and Peter J Little[1,2]. School of Pharmacy, University of Queensland[1], Brisbane, QLD Australia; School of Health and Biomedical Sciences, RMIT University[2], Melbourne, VIC, Australia

Introduction. G protein coupled receptors (GPCRs) can transactivate protein tyrosine kinase receptors (PTKR) and serine/threonine kinase receptors (S/TKR). GPCR transactivation of PTKR is approximately equally important as the transactivation of S/TKR with 209 and 177 genes regulated respectively, via either signalling pathway [1]. The two transactivation dependent signalling pathways share in over 65% of differentially expressed genes. The biochemical mechanisms between the two transactivation pathways are distinct [2].
Aims. To assess transcription factor Smad2 as a common integrating point for thrombin transactivation of PTKR and S/TKR with the downstream target as the expression of genes involved in the initiation and elongation of GAG chains on lipid-binding proteoglycans.
Methods. GAG synthesizing gene expression was measured and quantified by real time-PCR. Smad2 linker region phosphorylation was detected and quantified by western blotting.
Results. Thrombin phosphorylation of the serine residues in Smad2L are regulated by serine/threonine kinases. The differential action of these kinases regulate thrombin mediated expression of two genes that drive elongation of the GAG chain. Phosphorylation of the threonine residue in Smad2L is associated with the initiation of GAG chain synthesis.
Discussion. These findings highlight a specific signalling paradigm for GPCR mediated transactivation dependent pathways in the context of GAG initiation and elongation. Thus Smad2L integrates GPCR mediated transactivation of PTKR and S/TKR which can be therapeutically targeted to treat other pathophysiological conditions.

1.Kamato, D., et al., RNA sequencing to determine the contribution of kinase receptor transactivation to G protein coupled receptor signalling in vascular smooth muscle cells. PLoS One, 2017. **12**(7): p. e0180842.
2.Kamato, D., et al., The expansion of GPCR transactivation-dependent signalling to include serine/threonine kinase receptors represents a new cell signalling frontier. Cell Mol Life Sci, 2015. **72**(4): p. 799-808.¶

420 Reversal of age related pseudocapillarization using direct actin & lipid raft disruptor drugs on *in vitro* liver sinusoidal endothelial cells

Glen Lockwood[1, 2], Nicholas Hunt[1, 2], Hong Mao[3], Alessandra Warren[1], Peter McCourt[2, 3], David Le Couteur[1, 2], Victoria Cogger[1, 2]. [1] Biogerontology, ANZAC Research Institute, NSW, Australia; [2] Nutritional Ecology, Charles Perkins Centre, University of Sydney, NSW, Australia. [3] Medical Biology, University of Tromsø, Troms, Norway

Introduction: The liver is a key driver in lipid metabolism & insulin handling, functions imperative to the prevention of metabolic disorders. An age-related change that occurs in the liver is loss of transcellular pores, called fenestrations, within liver sinusoidal endothelial cells (LSEC), in a process called pseudocapillarization. Fenestrations act as ultra-filters allowing an exchange of lipoproteins & insulin; this is impaired by fenestration loss in old age contributing to postprandial hypertriglyceridemia & insulin resistance. Regulation of fenestrations is promoted via changes in LSEC plasma membranes. Lipid rafts are bound to the actin cytoskeleton forming a complementary structure across LSEC membranes. Both actin & lipid rafts can be modified by chemical agents.
Aim: This study aimed to investigate the actions of Cytochalasin D (CytoD), an actin disrupting agent, 7-ketocholesterol (7-KC), a lipid raft reducing agent, & a potential drug of interest (Drug A) to promoting re-fenestration in old (18m, n=3) & young mice (4m, n=3).
Methods: Mice LSECs were treated for 30 min with a single agent and prepared for scanning electron microscopy. Images of LSEC fenestrations were analyzed to determine their diameter & frequency, & calculate cell porosity.
Results: Both young & old LSEC showed an increase in porosity & fenestration frequency following treatment with CytoD (0.5µg/mL), 7-KC (4.5µM, 9µM) & Drug A. Fenestration diameter was also increased after 7-KC treatment. Age-related reductions in fenestrations were observed between young & old controls.
Discussion: This study has shown that actin & lipid raft modifying drugs can increase fenestrations. Both Drug A & CytoD showed re-fenestration while maintaining cellular architecture in young & old mice. These did not induce plasma membrane modifications, which were seen after 7-KC treatment. The novel finding that the porosity & number fenestrations are increased by Drug A, which potentially modulates lipid rafts & the actin cytoskeleton, further research is underway to understand this mechanism.

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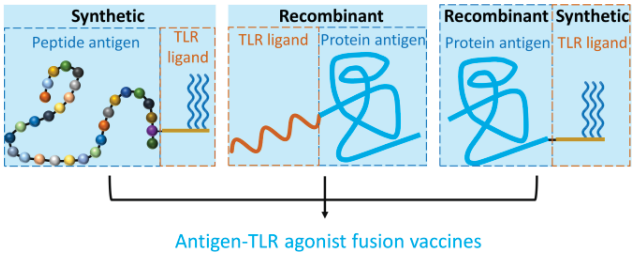
421 The rational design of self-adjuvanting subunit vaccines by site-specific conjugation of protein antigens with Toll like receptor ligands

Zhenghui Xu[1], Peter Michael Moyle[1]. School of Pharmacy, The University of Queensland[1], Brisbane, QLD, Australia.



Introduction. Simultaneous delivery of antigens and TLR agonists to antigen presenting cells ensures the colocalization of both molecules to the same endosome or phagosome, within the same APC, thereby enhancing the antigen presentation and processing efficiency. A number of strategies have been developed to fulfill the goal of codelivery, with enzyme-mediated ligation receiving significant attention due to their ability to simply and site-specifically modify proteins; and maintain the native 3-dimentional structure of protein antigens that is most critical in order to elicit protective immune responses. A number of enzymes have been successfully used for ligation reactions with proteins, with *Staphylococcus aureus* sortase A (SrtAsa) the most thoroughly characterised and commonly used.
Aims. To develop a platform technology to enable the efficient and simple site-specific conjugation of TLR agonists onto folded recombinant antigens using a semisynthetic-ligation approach under native conditions.
Methods. Expression and purification of polytope antigens and SrtAsa proteins. Synthesis of a lipid adjuvant peptide (TLR2/6 agonist). Immunization and challenge studies to investigate the vaccine efficacy against invasive disease.
Results. Reaction conditions were screened, optimized and confirmed for maximizing the ligation yield. Lipid adjuvant peptides were successfully conjugated onto polytope antigens with a high yield. Conjugate vaccines confer protection against lethal challenge in mice.
Discussion. The amount of SrtAsa required for conjugation reactions is significantly decreased due to introduction of a SrtAsa mutant. This platform technology provides high yield of protein antigen-lipid adjuvant conjugate vaccines that have the capacity to generate more efficient, potent, and protective immune responses when compared to their formulation with alum.

422 The novel fatty acid epoxide analogue CTU targets the mitochondrion and depletes cardiolipin to promote killing of MDA-MB-231 breast cancer cells

Hassan Choucair[1], Bala Umashankar[1], Kirsi Bourget[1], Yongjuan Chen[1], Tristan Rawling[2], Michael Murray[1]. Discipline of Pharmacology, University of Sydney[1], Sydney, NSW, Australia; School of Mathematical and Physical Sciences, University of Technology Sydney[2], Sydney, NSW, Australia.

Introduction. The atypical phospholipid cardiolipin plays an important regulatory role in apoptosis by modulating the release of cytochrome c from the mitochondrial membrane. We have prepared a metabolically stable fatty acid epoxide bioisostere (termed CTU) that targets the mitochondrion and activates endoplasmic reticulum stress in MDA-MB-231 breast cancer cells leading to decreased cell viability (Choucair et al, ASCEPT 2016).
Aims. This study was undertaken to evaluate the role of the mitochondrion in CTU-mediated cancer cell killing.
Methods. In MDA-MB-231 cells, cardiolipin/phosphatidylglycerol was estimated using a commercial kit. Cell viability was assessed by ATP formation, measurement of caspase-3/7 activity and annexin V/7AAD staining. Gene profiling was undertaken by real-time RT-PCR, and altered protein expression was assessed by Western immunoblotting.
Results. Addition of CTU to MDA-MB-231 cells significantly decreased the cellular content of cardiolipin and its precursor phosphatidylglycerol at 24 h. Mitochondrial cytochrome c release was increased in cells treated with CTU at 24 h but not at 6 h. However, the expression of pro-apoptotic mitochondrial membrane permeabilizing proteins of the Bcl-2 family, Bax and Bak, was decreased at 6 and 24 h. Neither the Ca^{2+} chelator BAPTA-AM nor the mitochondrial permeability transition pore inhibitor cyclosporin A altered the CTU-mediated decrease in ATP formation. Co-supplementation with the monounsaturated fatty acid oleic acid, which is essential for cardiolipin maintenance, prevented the CTU-mediated depletion of cardiolipin/phosphatidylglycerol, upregulation of endoplasmic reticulum stress genes, mitochondrial cytochrome c release, caspase-3/7 activation and annexin V/7AAD staining.
Discussion. The novel fatty acid bioisostere CTU has emerged as the first in a new class of agents with activity against cancer cells produced by targeting of the tumor cell mitochondrion and cardiolipin depletion. CTU-mediated apoptosis in MDA-MB-231 cells is independent of Bax and Bak and the mitochondrial permeability transition pore.

Choucair H et al (2016) ASCEPT 2016.¶

423 Anti-proliferative activity of novel ω-3 epoxy fatty acid analogues in MDA-MB-231 triple negative human breast cancer cells

Yassir Al-Zubaidi[1], Tristan Rawling[2], Kirsi Bourget[1], Nooshin Koolaji[1], Curtis Pazderka[2] and Michael Murray[1]. Discipline of Pharmacology, Univ of Sydney[1]; School of Mathematical and Physical Sciences, UTS[2], Sydney, NSW, Australia.

Introduction. Many experimental studies have shown that ω-3 polyunsaturated fatty acids reduce the risk of certain cancers. We recently synthesised a metabolically stable analogue of ω-3 epoxy eicosapentaenoic acid termed CTU that inhibits proliferation and activates apoptosis in highly metastatic MDA-MB-231 breast cancer cells (Murray et al, 2017). In this study, further CTU analogues were synthesised and tested for their anti-proliferative activity.
Methods. New CTU analogues termed TR16, CP19, CP21 and CP22 were produced by modifying the nature of the aromatic system in CTU. The viability of MDA-MB-231 cells was evaluated by ATP formation, cell cycle distribution was determined by flow cytometry, and immunoblotting was used to evaluate the expression of cyclin regulatory proteins.
Results. CP22 and CP21 were more effective than CTU and CP19 in decreasing ATP production in MDA-MB-231 cells compared to control (43±5.2%, 56±8.8%, 65±13% and 76±12.7%, respectively; 10 µM, 24 h); however, TR16 was inactive. Flow cytometry analysis showed a significant increase in the cell proportion in S phase and G2/M phase with CP22 (45.3 ± 5.2% and 21.1 ± 7%) and CP21 (27.9 ± 8% and 26.1 ± 2.7%) treatments relative to control ($P<0.05$). On the other hand, compared to control, a decrease in the cell population in G0/G1 phase was also noted with CP22 and, to a lesser extent, CP21, CP19 and CTU. Consistent with findings from flow cytometry, treatment of MDA-MB-231 cells with CP22, CP21, CP19 and CTU (10 µM, 24 h) produced decreases in cyclin D1 (to 6-fold, 5.9-fold, 3.2-fold and 3.7-fold of respective control) and CDK4 (to 6.4-fold, 2.9-fold, 2-fold and 1.9-fold of respective control) immunoreactive protein expression. In contrast, cyclin D1 and CDK4 expression were unaffected by TR16.
Discussion. CP22, CP21 and CP19 were more effective than CTU in impairing energy metabolism in MDA-MB-231 breast cancer cells and disrupting the cell cycle in S phase and G2/M phase. Additionally, the expression of cyclin D1 and CDK4 proteins was strongly down-regulated by CP22, CP21, CP19 and CTU, which may contribute to their anti-proliferative actions. These properties are promising for the development of novel anti-cancer therapeutics.

Murray M et al (2017) Biochem Pharmacol , 139:117.¶

424 Assessment of taste 1 receptor allosteric ligands for activity at metabotropic glutamate receptors

Amy NY Chen[1], Shane D Hellyer[1], Katie Leach[1], Karen J Gregory[1]. Drug Discovery Biology and Dept Pharmacol, MIPS, Monash Univ[1], Parkville, VIC, Australia.

Introduction. The Class C G protein-coupled receptors (GPCRs) include eight metabotropic glutamate receptor (mGlu) subtypes, Calcium-sensing receptors (CaSR) and taste 1 receptors. Class C GPCRs recognise a diverse array of ligands from ions (Mg^{2+}, Ca^{2+}, Gd^{3+}) to small molecules and proteins. Class C GPCRs, in particular $mGlu_2$ and $mGlu_5$, are attractive targets for a number of psychiatric and neurological disorders, for which the current therapeutic treatments are suboptimal and can often lead to side effects due to non-selectivity. Therefore, there is a great need to identify novel mechanisms of receptor activation. We hypothesised that taste 1 receptor ligands would have allosteric interaction with other Class C GPCRs.
Aims. We tested the hypothesis that taste 1 receptor allosteric ligands can also bind to and modulate activity of $mGlu_2$ and $mGlu_5$.
Methods. Functional effects of sweet proteins (thaumatin and monellin) and small molecules (NHDC, cyclamate and lactisole) were tested in HEK293A cells stably expressing $mGlu_2$ or $mGlu_5$ in LANCE cAMP accumulation and intracellular calcium (iCa^{2+}) mobilisation assays. Binding assays using the radiolabelled $mGlu_5$ allosteric ligand [^{3}H]mPEPy were employed in HEK293A-$mGlu_5$ cells to determine affinity.
Results. Monellin caused robust iCa^{2+} mobilisation in HEK293A-$mGlu_5$ cells. These effects were not evident in non-transfected HEK293A cells. Thaumatin and synthetic sweetener NHDC had no effect at either receptor. Lactisole and cyclamate, which interact with the 7 transmembrane spanning domain of taste 1 receptors, did not appreciably displace [^{3}H]mPEPy binding to $mGlu_5$.
Discussion. These results show that monellin is an allosteric agonist at the mGlu5 receptor. Sweet proteins extracted from plants have been shown to activate Class C G protein-coupled taste receptors through binding at the cysteine-rich domain, therefore, it is possible that monellin also recognises this cysteine-rich domain in $mGlu_5$. Future work will aim to identify the monellin binding site, which may lead to development of a novel class of $mGlu_5$ ligands with therapeutic potential.
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425 Small molecule inhibitors of Amyloid β and α Synuclein (αSA53T) protein aggregation

Sukanya Das[1], Tara L. Pukala[2], Ian F. Musgrave[1], Scott D. Smid[1]. Discipline of Pharmacology[1], Adelaide Medical School, Faculty of Health Sciences, The University of Adelaide, Adelaide, SA, Australia; School of Chemistry and Physics[2], Faculty of Sciences, The University of Adelaide, Adelaide, SA, Australia.

Introduction. Amyloid β (Aβ) and α Synuclein (αS) protein aggregation into amyloid fibrils is associated with the pathology of various neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) etc.
Aims. To understand and compare the effects of a diverse set of natural polyphenol compounds (honokiol, punicalagin, myricetin, luteolin, transilitin and semi-synthetic flavone 2-D08) and synthetic compounds selected through virtual screening, (dibenzyl imidazolidine and triazole acetamide derivatives) on Aβ and αS protein aggregation and neurotoxicity.
Methods. Thioflavin T fluoroscopic assay and transmission electron microscopy (TEM) were used to study inhibition of aggregation. Viability of Phaeochromocytoma (PC12) cells after exposure to either amyloidogenic protein or a combination of protein and aggregation inhibitors was measured by MTT assay. Molecular docking was used to understand the protein and small molecules interaction. For αS protein, its aggregation prone mutant αSA53T was expressed using *E. coli* BL21(DE3) cell line containing human αSA53T gene inserted into a pRSETB vector and purified following Volles and Landsbury method and size exclusion chromatography[1].
Results. Each of the polyphenols and two synthetic imidazolidine compounds demonstrated significant inhibition of both Aβ and αS protein aggregation. They also exhibited significant neuroprotection when cells were exposed to Aβ or prefibrilised αS. The predicted good binding from molecular docking was correlated with inhibition of both amyloidogenic protein aggregation.
Discussion. Together, these findings highlight the anti-aggregatory properties of a structurally diverse set of compounds, of both natural and synthetic origin, against pathological misfolded Aβ and αSA53T proteins. Such compounds could further inform the development of disease-modifying drugs against AD and PD.

Volles, P.T. (2007) Journal of Molecular Biology, 366: 1510-1522

426 Bias in fluorescence-based voltage-gated sodium channel assays

Jennifer R Deuis[1], Bryan Tay[1] & Irina Vetter[1,2]. Inst for Molecular Bioscience, Univ of Queensland[1], St Lucia, QLD, Australia; School of Pharmacy, Univ of Queensland[2], Woolloongabba, QLD, Australia.

Introduction. Voltage-gated sodium channels (Na_Vs) are key therapeutic targets for pain, epilepsy and cardiac arrhythmias, therefore high-throughput fluorescence-based assays are used to screen and characterise novel Na_V modulators. However, results obtained from fluorescence-based assays do not always correlate well with results obtained from conventional patch-clamp electrophysiology.
Aims. Systematically assess the effects of different Na_V channel modulators using fluorescence-based assays and patch-clamp electrophysiology to identify assay bias.
Methods. HEK293 or CHO cells heterologously expressing human $Na_V1.1$–1.8 (SB Drug Discovery; ChanTest) were used for functional assays. Changes in fluorescence were assessed using a FLIPR^{TETRA} (Molecular Devices), with commercial dyes that detect changes in membrane potential (FLIPR membrane potential red, Molecular Devices) or intracellular sodium ion influx (Asante NaTRIUM Green-2 AM, Abcam) used. Electrophysiology parameters were assessed using an automated whole-cell patch-clamp platform (QPatch-16, Sophion Bioscience).
Results. Fluorescence-based assays were able to detect Na_V channel activators and inhibitors with different binding sites and mechanisms of action. The EC_{50} values obtained from fluorescence-based assays for activators generally correlated well with EC_{50} values obtained from conventional patch-clamp, however the most robust responses were obtained from activators that caused persistent and/or tail currents (eg. veratridine, deltamethrin). The IC_{50} values obtained from fluorescence-based assays correlated well with conventional patch-clamp for pore blockers (eg. tetrodotoxin) but not for gating modifiers (eg. μ-theraphotoxin-Pn3a).
Discussion. While the endogenous activator of Na_V channels is voltage, fluorescence-based assays rely on using Na_V channel modulators to activate the channels, with the alkaloid veratridine (for $Na_V1.1$-1.7) or the pyrethroid deltamethrin (for $Na_V1.8$) commonly used. These Na_V channel activators likely stabilise different channel conformations or result in competitive binding, causing fluorescence-based assays to exhibit bias towards detection of pore blockers over gating modifiers. ¶

427 Nrf2 activators in medicinal plants of the Australian Aboriginal Dharawal people

Karthik Dhananjayan[1], Most Afia Akhtar[1, 2], Alejandra Rangel[1], Frances Bodkin[1], Ritesh Raju[1], Gerald Muench[1, 2]. Department of Pharmacology, School of Medicine, Western Sydney University[1], Campbelltown, New South Wales, Australia; National Institute of Complementary Medicine[2], Western Sydney University, Campbelltown, New South Wales, Australia.

Introduction. Nrf2 (nuclear erythroid 2-related factor 2) is a transcription factor which binds to the antioxidant response element (ARE) to regulate the expression of cytoprotective genes involved in detoxification, glutathione production and mitochondrial protection. Simultaneously failure of Nrf2 regulation can also exacerbate the production of pro-inflammatory markers via regulation of nuclear factor (NF)-κB due to oxidative stress (Bryan et al, 2013). Previously we have determined anti-inflammatory activity in the medicinal plants (Akhtar MA et al, 2016) of the Australian Aboriginal Dharawal people (collected from the Australian Botanic Gardens in Mount Annan); and currently we are investigating these plants for the presence of Nrf2 activators.
Aims. To identify whether extracts of medicinal plants of the Australian Aboriginal Dharawal people can activate Nrf2-mediated transcription.
Method. AREc32 cells (stably transfected with Nrf2 reporter gene (luciferase)) were activated with different concentration of ethanolic extracts of 15 selected plants in a dose dependent manner. After 24h of activation, the cell lysates were assayed for luciferase activity.
Results. Among 15 selected plants, *Pimelea linifolia* exhibited a 6-fold increase in Nrf2 activation, followed by *Acacia falcata* and *Hakea salicifolia* showing a 2-fold increase in comparison to non-activated cells.
Discussion. *Pimelea linifolia, Acacia falcata and Hakea salicifolia* extracts have shown a dose-dependent Nrf2 activation. Our future work will focus on isolation and structural identification of the active phytochemical constituents from these plants.

1. Bryan KH et al (2013) Biochem Pharmacol 85 :(6) 705-717.
2. Akhtar MA et al (2016) Evid Based Complement Alternat Med. 2016:1-8.

428 Phosphatase and tensin homolog (PTEN) silencing suppresses Ca^{2+} responses in MDA-MB-231 breast cancer cells.

Trin N Hua[1], Alice HL Bong[1], John J Bassett[1], Sarah J Roberts-Thomson[1], Gregory R Monteith[1,2]. School of Pharmacy. The University of Queensland[1], Brisbane, QLD, Australia; Mater Research, The University of Queensland[2], Brisbane, QLD, Australia.

Introduction. Phosphatase and tensin homolog (PTEN) is a gene that is mutated in many cancers and the loss of functional PTEN is associated with the activation of pathways that may promote proliferation, metastasis and loss of apoptotic sensitivity. Ca^{2+} signalling is a key regulator of events important in tumour progression (Monteith et al, 2017). Ca^{2+} signalling events may be altered as a consequence of PTEN loss, but this has not been fully explored in breast cancer cells (Bittremieux et al, 2016).
Aim. To assess the effects of PTEN loss on Akt phosphorylation and Ca^{2+} signalling in triple-negative MDA-MB-231 breast cancer cells stably expressing the GCaMP6m genetically-encoded Ca^{2+} indicator (GCaMP6m-MDA-MB-231).
Methods. MDA-MB-231 cells were treated with non-targeting (NT) or PTEN siRNA. Silencing efficiency was assessed using qPCR. Akt phosphorylation was assessed using immunoblotting with a phosphospecific antibody. For assessment of cytosolic free Ca^{2+} ($[Ca^{2+}]_{CYT}$) responses, fluorescence changes in response to Ca^{2+}-mobilising agents (ATP, trypsin and cyclopiazonic acid (CPA)) were assessed using a Fluorescence Imaging Plate Reader (FLIPR).
Results. siPTEN reduced PTEN mRNA levels and significantly increased levels of pAkt. Silencing of PTEN supressed increases in $[Ca^{2+}]_{CYT}$ elicited by the purinergic receptor activator adenosine triphosphate (ATP) (16.5% reduction at 100 µM) and the protease activated receptor trypsin (17.02% reduction at 100 nM). The loss of PTEN did not significantly alter $[Ca^{2+}]_{CYT}$ increases induced by the sarco/endoplasmic reticulum Ca^{2+}-ATPase inhibitor CPA.
Discussion. These studies suggest PTEN loss in triple negative breast cancer cells results in the suppression of some Ca^{2+} signalling events. This may be via a reduction in inositol 1,4,5-trisphosphate (IP_3) responses either through pAkt or other effects on IP_3 receptors (IP3Rs). These effects may lead to suppression of responses to apoptotic stimuli.

Monteith GR et al (2017) Nat Rev Cancer. 17:367-380.
Bittremieux M et al (2016) Biochim Biophys Acta. 1863:1364-78.¶

429 Comparison of analgesic and constipation profile of two G-protein biased endomorphin-2 analogue after intracerebroventricular administration in rats

Mohammad Z Imam[1,2], Andy Kuo[2], Sussan Ghassabian[2], Yunxin Cai[3], Tingyou Li[3], Maree T Smith[2,4]. School of Biomedical Sciences, Faculty of Medicine, The University of Queensland[1], Brisbane, QLD, Australia; Centre for Clinical Research, Faculty of Medicine, The University of Queensland[2], Brisbane, QLD, Australia; School of Pharmacy, Nanjing Medical University[3], Nanjing, Jiangsu, China; School of Pharmacy, The University of Queensland[4], Brisbane, QLD, Australia.

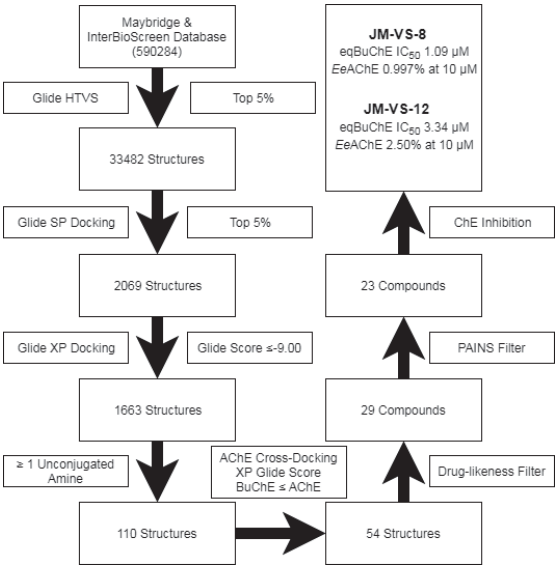
Introduction. Strong opioid analgesics are the mainstay for the clinical management of moderate to severe nociceptive pain. The analgesic effect of opioids are mainly mediated by the G-protein pathway of mu opioid receptor (MOPr). Opioid-related adverse effects such as constipation are thought to be mediated by the β-arrestin2 signalling pathway.
Aims. The aim of the present study was to evaluate and compare the analgesic and constipation profile of CYX-5 and CYX-6. These compounds are endomorphin 2 analogues. These compounds are G-protein biased MOPr agonists, delta opioid receptor (DOPr) antagonists and they lack β-arrestin2 recruitment.
Methods. Prior to experimentation, approval was obtained from the UQ Animal Ethics Committee. In anaesthetised male Sprague Dawley rats, an intracerebroventricular (i.c.v.) guide cannula was stereotaxically implanted. Five to 7 days later, each rat received a single i.c.v. bolus dose of either CYX-5 (3, 10, 20 nmol), CYX-6 (3, 10, 20, 30 nmol), morphine (100 nmol) or vehicle. Antinociception was assessed using the warm water tail flick test (52.5±0.5°C) and constipation was assessed using castor oil-induced diarrhoea and charcoal meal gut motility tests.
Results. Intracerebroventricular CYX-6 is ~ 5 times more potent than morphine in producing analgesia. The ED_{50} (95% CI) of i.c.v. CYX-6 for evoking antinociception in rats was estimated at 9.2 (6.8 to 12.6) nmol by nonlinear regression. CYX-5 was less effective in evoking analgesia. However, unlike morphine, CYX-6 did not alter stool consistency or gut motility even at higher doses. CYX-5 also did not affect the gut motility in rats.
Discussion. These results demonstrate that analgesia can be evoked without producing opioid-related gastrointestinal adverse effects. This in vivo profile of CYX-5 and CYX-6 suggests that highly selective MOPr agonists with G-protein bias may have benefit in dissociating analgesia from gastrointestinal adverse effects.

430 Structure-based virtual screening for the rapid discovery of selective butyrylcholinesterase inhibitors

Jared A. Miles[1], Girdhar Singh Deora[1], Marie-Odile Parat[1], and Benjamin P. Ross[1]. School of Pharmacy, The Univ of Queensland[1], Brisbane, QLD, Australia

Introduction. Alzheimer's disease (AD) is characterized by the progressive loss of cholinergic neurotransmission in the brain, and is symptomatically treated using acetylcholinesterase (AChE) inhibitor drugs. However, short-term benefit and high incidence of side effects limit the efficacy of these drugs. Recently, selective inhibitors of butyrylcholinesterase (BuChE) have been suggested as an alternative with superior efficacy and side effect profiles compared to AChE inhibitors, particularly in late-stage AD.

Methods. We used structure-based virtual screening (SBVS) to rapidly search two libraries containing over 590284 structures for inhibitors of BuChE. Additional *in silico* filtering was also employed to prioritize drug-likeness, selectivity for BuChE over AChE, and remove promiscuous inhibitors. The 23 compounds resulting from this workflow were screened *in vitro* for inhibition of eqBuChE and *Ee*AChE. Analogues of the top hits were also screened to examine structure-activity relationships.



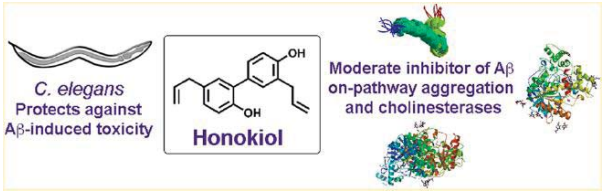
Results. From the initial 590284 input structures, the top 1663 compounds after SBVS went through additional filtering to yield 23 final hits. Of these, two compounds inhibited BuChE with low-micromolar IC_{50} values and showed significant selectivity for BuChE over AChE. Analogues of these hits, combined with virtual docking models, shed light on the structure-activity relationships.

Discussion. These results highlight the usefulness of SBVS as a tool for rapid drug discovery in AD, and provide two selective BuChE inhibitors which form a basis for the development of symptomatic treatments for late-stage AD.¶

431 Natural product honokiol reduces $A\beta_{42}$-induced toxicity in *Caenorhabditis elegans*, $A\beta_{42}$ fibrillation, cholinesterase activity, DPPH radicals, and chelates iron(II)

Jared A. Miles[1], Srinivas Kantham[1], Stephen Chan[1], Gawain McColl[2], Suresh Kumar Veliyath[1], Girdhar Singh Deora[1], Satish N. Dighe[1], Samira Khabbazi[1], Marie-Odile Parat[1], and Benjamin P. Ross[1]. School of Pharmacy, The Univ of Queensland[1], Brisbane, QLD, Australia. The Florey Inst, Univ of Melbourne[2], Parkville, VIC, Australia

Introduction. Honokiol is a neuroprotective natural product which has been proposed as a treatment for central nervous system disorders such as Alzheimer's disease (AD). There are many factors which contribute to the development of AD, including the progressive death of cholinergic neurons in the brain, accumulation and fibrillation of amyloid beta peptide (Aβ); and toxicity resulting from metal ions and oxidative stress.



Methods. We used transgenic *Caenorhabditis elegans* expressing $A\beta_{42}$ as an *in vivo* model for assessing the effect of honokiol against Aβ-induced toxicity. Additionally, we evaluated the *in vitro* ability of honokiol to inhibit $A\beta_{42}$ oligomerization and fibrillation; inhibit acetylcholinesterase and butyrylcholinesterase; scavenge 2,2- diphenyl-1-picrylhydrazyl (DPPH) radicals; and chelate iron(II).

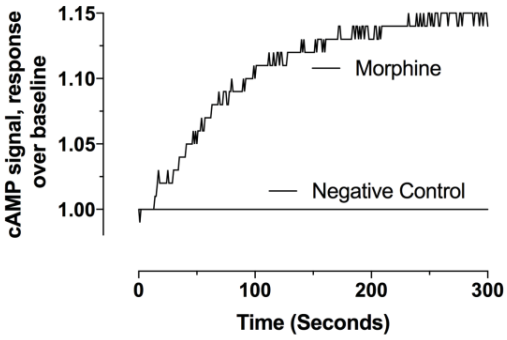
Results. Honokiol proved similar to resveratrol and (−)-epigallocatechin gallate (EGCG) at delaying $A\beta_{42}$-induced paralysis in *C. elegans*. However, honokiol has superior chemically stability relative to the highly unstable EGCG. We also showed that honokiol possesses moderate-to-weak activity to inhibit $A\beta_{42}$ aggregation and cholinesterase, scavenge DPPH radicals, and chelate iron(II).

Discussion. Considering these results, along with its drug-likeness and brain availability, honokiol may be a candidate for drug development and that the synthesis of analogues to further improve these properties should be considered.

432 Development and optimisation of a FLIPR high-throughput cAMP assay to screen for $G_{\alpha i}$ mediated GPCR modulators

Michael Morgan[1], Richard J Lewis[1], Irina Vetter[12]. Centre for Pain Research, Institute for Molecular Bioscience, The University of Queensland[1], Brisbane, QLD, Australia. The School of Pharmacy, The University of Queensland[2], Brisbane, QLD, Australia

Introduction. A number of cAMP assays are available to screen Gαi G protein-coupled receptor (GPCR) ligands, however they often entail multiple steps, require forskolin to activate cAMP production, lack cAMP kinetics data and can be labour intensive. We aimed to establish a high throughput assay for quick identification of $G_{\alpha i}$ GPCR modulators.



Methods. Human embryonic kidney cells stably expressing different opioid receptors (μ,κ or δ) were transfected with a fluorescent cAMP sensor (downward cADDIS cAMP sensor, Montana Molecular) and a mutant $G_{\alpha s}$ subunit. Cells were plated on a 384 well plastic bottom plate and allowed to adhere overnight. Opioid ligands were added to the wells by the automated FLIPR pipettor head and fluorescence measured and results.

Results. Activation of the opioid receptor resulted in a quick and sustained production of cAMP demonstrated by a dose-dependent increase in fluorescence, reaching maximal fluorescence after 3 minutes. While the dynamic range of the assay was relatively small, ligands displayed accurate and reproducible EC_{50} values and equivalent to other commercially available kits.

Discussion. The FLIPR cAMP assay provides a quick, simple method to determine activity of compounds at Gαi GPCRs and could be used for high-throughput screening of ligands.

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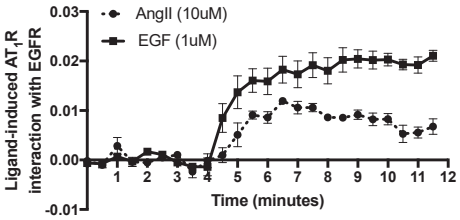
433 Development of a BRET based assay for AT_1R-EGFR transactivation: evidence for functional heteromers

Shannon L O'Brien[1], Elizabeth K Johnstone[2], Kevin D.G Pfleger[2], Walter G Thomas[1] School of Biomedical Sciences, Univ of Queensland, St Lucia, QLD, Australia; Molecular Endocrinology & Pharmacology, Univ of Western Australia, Nedlands, WA, Australia

Introduction. The Renin Angiotensin System (RAS) acts via the type 1 angiotensin receptor (AT_1R) to control cardiovascular physiology and pathophysiology. The actions of AT_1R in cardiac growth and remodelling involve a capacity to "transactivate" signalling pathways downstream of the Epidermal Growth Factor Receptors (EGFRs), but demonstrating this EGFR transactivation directly, in live cells, in real time has been challenging.



Aims. Identify and characterise the molecular, temporal and spatial aspects of AT_1R-EGFR transactivation

Methods. Bioluminescence Resonance Energy Transfer (BRET), GPCR-HIT assays and Bimolecular Fluorescence Complementation (BIFC) were used to functionally characterise the molecular basis of EGFR transactivation and AT_1R-EGFR complex formation.

Results. AngII and EGF stimulation resulted in recruitment of Grb2 to the EGFR, indicating EGFR transactivation. Moreover, BIFC revealed AT_1R and EGFR exist as heteromers at the membrane with GPCR-HIT data showing ligand stimulation further enhances AT_1R-EGFR complex formation.

Discussion. BRET is a valid tool to characterise transactivation in living cells. Data suggests that following AngII & EGF treatment a close complex forms between the two receptors, thus facilitating transactivation. The underlying mechanism driving AT_1R-EGFR complex formation forms part of ongoing investigations.

434 Consequences of pharmacological inhibition of store-operated calcium entry on calcium signalling in MDA-MB-468 breast cancer cells.

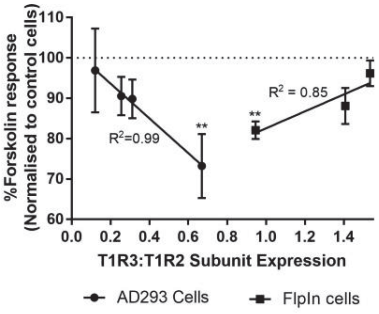
Greta XH Poo[1], Iman Azimi[1,2], Sarah J Roberts-Thomson[1], Gregory R Monteith[1,2]. School of Pharmacy. The University of Queensland[1], Brisbane, QLD, Australia; Mater Research Institute, The University of Queensland[2], Brisbane, QLD, Australia.

Introduction. Store-operated calcium entry (SOCE), describes the process whereby there is an influx of calcium ions (Ca^{2+}) after intracellular Ca^{2+} stores are depleted. A remodelling of the molecular components of SOCE is evident in breast cancers of the poor prognosis basal molecular subtype (McAndrew et al, 2011). However, pharmacological studies of this pathway in breast cancer cells have often used non-specific SOCE inhibitors, non-physiological mechanisms of calcium store depletion and just one basal breast cancer cell line - MDA-MB-231 (Yang et al, 2009).
Aims. To assess the effects of the selective SOCE inhibitors YM-58483 and Synta66 on calcium influx mediated by the Ca^{2+} store pump inhibitor cyclopiazonic acid (CPA), the purinergic receptor activator adenosine triphosphate (ATP), the protease-activated receptor-2 (PAR-2) activator trypsin and epidermal growth factor (EGF) in MDA-MB-468 basal breast cancer cells in the presence of extracellular Ca^{2+}.
Methods. MDA-MB-468 cells were loaded with the Ca^{2+} sensitive indicator Fluo-4 and cytosolic free Ca^{2+} levels ($[Ca^{2+}]_{CYT}$) were assessed during treatment with CPA, ATP, trypsin and EGF in the absence or presence of YM-58483 or Synta66 using a Fluorescence Imaging Plate Reader (FLIPR).
Results. CPA, ATP, trypsin and EGF exhibited $[Ca^{2+}]_{CYT}$ transients with different degrees of sustained Ca^{2+} influx. The effects of Synta66 and YM-58483 were greatest for CPA and ATP mediated Ca^{2+} influx. Sustained Ca^{2+} influx after stimulation was reduced by 35.1 and 35.5% for CPA (10 µM) and 52.4 and 48.6% for ATP (10 µM) by Synta66 and YM-58483, respectively.
Discussion. These studies define a role for SOCE as a consequence of activation in the regulation of sustained Ca^{2+} influx in MDA-MB-468 basal breast cancer cells.

McAndrew D et al (2011) Mol Cancer Ther. 10:448-60
Yang S et al (2009) Cancer Cell. 15:124-34¶

435 The sweet taste receptor: a novel target for drug discovery?

Susan Tan[1,2], Robert Healey[1,2], Pall Thordarson[2], Angela Finch[1]. School of Medical Sciences, UNSW Sydney[1], Sydney, NSW, Australia; School of Chemistry, UNSW Sydney[2], Sydney, NSW, Australia.



Introduction. Sweet taste receptors are expressed in many tissues throughout the body, and are implicated in obesity and diabetes. The canonical receptor is a heterodimer consisting of subunits T1R2 and T1R3 in a 1:1 ratio. However, in the pancreas and adipose tissue, the expression of these subunits has been shown to be unequal. It is essential to understand if this altered expression profile leads to changes in receptor function, so that this receptor may be harnessed as a novel drug target in the treatment of diabetes and obesity.
Aims. To examine the impact of altering subunit expression on receptor signalling and surface trafficking.
Methods. Heterologous expression systems were generated using either sequentially transfected AD293 cells, or the FlpIn system. Subunit expression was quantified by RT-PCR. Signalling through the Gi pathway was measured as a reduction in % forskolin response determined by cAMP assay using the BRET CAMYEL sensor. Surface trafficking was determined by biotinylation pull-down experiments.
Results. Subunit expression closest to 1:1 lead to the greatest functional responses to aspartame, as shown in the figure above. Expression of both sweet taste receptor subunits was found to be predominantly intracellular, and was not improved by 1:1 expression of both subunits.
Discussion. Unequal expression of the two sweet taste receptor subunits lead to an alteration in signalling profile – in this study, a reduction in Gi signalling. This suggests that the sweet taste receptor may either be non-functional, or signals through alternative pathways in tissues where there is unequal expression of subunits. Surprisingly, surface expression did not appear to correlate with functional response. More research is therefore needed to understand tissue-specific signalling profiles, to enable the development of the sweet taste receptor as a novel drug target.

436 Assessment of calcium responses induced by the transient receptor potential cation channel subfamily V member 4 (TRPV4) activator GSK1016790A in MDA-MB-468 breast cancer cells using automated epifluorescence microscopy.

Zara N Wagner[1], Iman Azimi[1,2], Johnathon J Bassett[1], Sarah J Roberts-Thomson[1], Gregory R Monteith[1,2]. School of Pharmacy. The University of Queensland[1], Brisbane, QLD, Australia; Mater Research Institute, The University of Queensland[2], Brisbane, QLD, Australia.

Introduction. The transient receptor potential cation channel subfamily V member 4 (TRPV4) is elevated in the basal molecular subtype of breast cancer (Peters et al, 2017). These breast cancers have poor prognosis and significantly overlap with the triple negative breast cancers. TRPV4 appears to contribute to the migration potential of breast cancer cells (Lee et al, 2017). However, the consequences of pharmacological activation of TRPV4 using the TRPV4 activator GSK1016790A have not been fully explored, particularly in the context of single cell Ca^{2+} imaging.
Aims. To assess temporal and spatial changes in cytoplasmic free Ca^{2+} ($[Ca^{2+}]_{CYT}$) induced by the TRPV4 activator GSK1016790A in MDA-MB-468 basal breast cancer cells.
Methods. MDA-MB-468 cells were plated onto 96-well microplates and loaded with the Ca^{2+} sensitive indicator Fluo-4 or Fura-2. Fluorescence changes induced by 0, 1 or 100 nM of GSK1016790A were detected using an automated epifluorescence microscope (ImageXpress). Image segmentation analysis was used to assess changes in $[Ca^{2+}]_{CYT}$ as assessed by Fluo-4, and ratiometric imaging was used to assess relative levels of $[Ca^{2+}]_{CYT}$ in Fura-2 loaded MDA-MB-468 breast cancer cells.
Results. MDA-MB-468 breast cancer cells exhibited spontaneous $[Ca^{2+}]_{CYT}$ oscillations. GSK1016790A at 100 nM induced pronounced, rapid and sustained increases in $[Ca^{2+}]_{CYT}$ in MDA-MB-468 breast cancer cells. Pronounced single cell heterogeneity was observed in $[Ca^{2+}]_{CYT}$ changes.
Discussion. These studies provide further evidence that MDA-MB-468 cells express functional TRPV4 channels and suggest that there may be significant heterogeneity in MDA-MB-468 breast cancer cell responses to TRPV4 activation.

Peters AA et al (2017) Oncogene (in press)
Lee WH et al (2017) Oncogenesis. 6:e338.¶

437 PAR_1 and PAR_2 open TRPV4 with conserved signalling pathways

Kirolos E Tadros, William G Darby, Owen L Woodman and Peter McIntyre. School of Health Biomed Sci, RMIT Univ, Bundoora, VIC, Australia

Introduction. We have previously shown that the pro-inflammatory G-protein coupled receptor, protease-activated receptor 2 (PAR_2) signals to and opens TRPV4 channels in HEK293 cells (Poole et al., 2013). We identified molecules which transduce signals from PAR_2 to TRPV4 using siRNA inhibition and identified signalling molecules which include heterotrimeric G-proteins, phospholipases and protein kinases (Darby et al., unpublished). In this study, we investigated whether any of the identified siRNA targets also transduce signals from PAR_1 to mediate TRPV4 opening.
Aims. To determine if PAR_1 and PAR_2-dependent opening of TRPV4 in HEK293 cells shares signalling mechanisms.
Methods. Parental HEK293 cells and HEK293 cells stably expressing human TRPV4 were transfected with Dharmacon SMARTpool siRNAs and each well was subsequently assayed for PAR_1-dependent opening of TRPV4 using a fura-2am fluorescence ratiometric intracellular calcium ($[Ca^{2+}]_i$) assay. Cells were injected with PAR_1 activating peptide (TFFLR-NH_2, 50 µM) followed by the selective TRPV4 agonist (GSK101067A, 30 nM), 85 s later. The area under curves from 50 – 90 s was compared using one-way ANOVA with Sidak's post hoc t-test.
Results. In parental HEK293 cells, PAR_1 activation transiently increased $[Ca^{2+}]_i$ (area = 12 ± 3). Functional expression of human TRPV4 caused a sustained increase of $[Ca^{2+}]_i$ (area = 43 ± 6) which was abolished by the TRPV4 antagonist (HC067047, 1 µM) (area = 9 ± 4). siRNA knockdown of $G\alpha_{13}$ and $G\gamma_8$ significantly ($p < 0.05$) inhibited PAR_1-dependent opening of TRPV4 reducing area by 52 ± 8% and 39 ± 7% respectively. Inositol-tetrakisphosphate 1-kinase (ITPK1), mitogen-activated protein kinase 13 (MAPK13) and lysine deficient protein kinase 4 (WNK4) also reduced area by 44 ± 12%, 69 ± 9% and 39 ± 9% respectively. Phospholipase A_2 group 4 (PLA_2G4) reduced the area by 54 ± 12%.
Discussion. Activation of GPCRs results in simultaneous activation of parallel signalling pathways. Therefore, inhibition of TRPV4 opening by a specific siRNA pool is an indication that the target protein contributes to PAR_1-dependent opening of TRPV4. Like PAR_2 receptors, PAR_1 receptors were found to couple to TRPV4 through heterotrimeric G-protein subunits, $G\alpha_{13}$ and $G\gamma_8$, PLA_2G4, and kinases ITPK1, MAPK13 and WNK4 in HEK293 cells.

Poole et al. (2013) J Biol Chem, 288:5790-5802¶

438 Neuronal calcium sensor-1 (NCS-1) in the regulation of calcium homeostasis and cell death in MDA-MB-231 basal breast cancer cells

Alice HL Bong[1], John J. Bassett[1], Sarah J Roberts-Thomson[1], Michael J. G. Milevskiy[2], Gregory R. Monteith[1,3]. School of Pharmacy, The University of Queensland[1], Brisbane, QLD, Australia; The Walter and Eliza Hall Institute of Medical Research[2], Melbourne, VIC, Australia; Mater Research, The University of Queensland[3], Brisbane, QLD, Australia.

Background: Altered calcium (Ca^{2+}) signalling in cancer cells may promote cancer hallmarks such as resistance to apoptosis. Proteins regulating these signals represent attractive therapeutic targets. Neuronal calcium sensor-1 (NCS-1) is associated with tumour aggression and poor prognosis in breast cancer patients. However, the characterisation of NCS-1 in breast cancer molecular subtypes, the effects of NCS-1 silencing on intracellular Ca^{2+} homeostasis in breast cancer cells and on the cytotoxic effect of the anti-cancer drug doxorubicin, remain unexplored.
Aim: To assess the expression of NCS-1 in public breast cancer datasets and assess the consequences of silencing NCS-1 on intracellular Ca^{2+} signaling and sensitivity to doxorubicin in the MDA-MB-231 basal breast cancer cell line.
Methods: The expression of NCS-1 in patient breast tumours was stratified by PAM50 molecular subtype and assessed using breast cancer public datasets. MDA-MB-231 cells stably expressing the GCaMP6m Ca^{2+} sensor were transfected with non-targeting control or NCS-1 siRNA. The effects of NCS-1 silencing on cytosolic Ca^{2+} in response to Ca^{2+}-mobilising agonists (ATP, trypsin and cyclopiazonic acid (CPA)) and on constitutive Ca^{2+} influx were measured using a Fluorescent Imaging Plate Reader (FLIPR). The sensitivity to doxorubicin (24 h) following gene silencing of NCS-1 was determined by propidium iodide staining.
Results: NCS-1 was expressed higher in basal molecular subtype breast cancers. Silencing NCS-1 did not alter cytosolic Ca^{2+} changes induced by ATP, trypsin or CPA treatment. However, NCS-1 silencing suppressed constitutive Ca^{2+} influx. NCS-1 silencing also promoted MDA-MB-231 cell death in combination with doxorubicin (1 µM) treatment.
Discussion: These results implicate NCS-1 in basal breast cancer, a subtype with poor prognosis. Indirect modulators of endoplasmic reticulum Ca^{2+} levels such as NCS-1 may alter constitutive Ca^{2+} influx pathways and influence processes important in cancer such as sensitivity to anti-cancer agents.
Monteith GR et al (2017) Nat Rev Cancer. 17:367-380.
Moore LM et al (2017) Mol Cancer Res. 15(7); 942–952¶

439 Understanding the physiological role of endogenous allosteric modulators in the muscarinic acetylcholine receptors

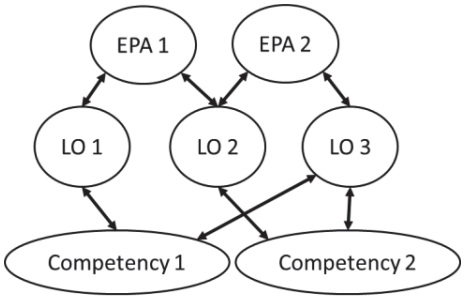
Ee Von Moo, Patrick M Sexton, Arthur Christopoulos and Celine Valant. Drug Discovery Biology, Monash Institute of Pharmaceutical Science, Monash University, Parkville, VIC, Australia.

Introduction. Allosteric binding sites on G protein-coupled receptor (GPCR) can be targeted by synthetic or natural (endogenous) molecules (van der Westhuizen et al., 2015). However, the (patho)physiological role(s) of many endogenous allosteric modulators remain poorly understood. One interesting example is major basic protein (MBP), a highly basic peptide that acts as a negative allosteric modulator (NAM) of acetylcholine (ACh) at airway M_2 muscarinic acetylcholine receptors (mAChR; Jacoby et al., 1993). We hypothesized that, in addition to MBP, other endogenous basic peptides, including the antimicrobial, LL-37, involved in chemotaxis, maturation of immune cells and apoptosis (Kahlenberg et al., 2013) could also interact allosterically with the M_2 mAChRs and have major physiological impacts.
Aims. To characterise the pharmacological properties and the putative (patho)physiological roles of LL-37 at mAChRs.
Methods. Using IMR-32, a native cell line endogenously expressing human M_2 mAChRs and mouse tissues predominantly expressing mouse M_2 mAChRs, we performed [^{3}H]NMS radioligand binding and [^{35}S]GTPγS turnover as a functional measure of receptor activation, to assess the allosteric effect of LL-37.
Results. LL-37 mediated a concentration-dependent partial inhibition of the antagonist [^{3}H]NMS binding in IMR-32 cells and mouse cardiac tissues (pK_B=4.7±0.3 and 5.6±0.5, respectively), a hallmark of allostery. Additionally, LL-37 also negatively modulated ACh-mediated G protein activation in mouse hypothalamus preparations.
Discussion. Our results suggest that LL-37 is a NAM of antagonist binding and agonist function at the M_2 mAChR. The M_2 mAChRs are highly expressed on both neuronal and non-neuronal cells, including immune cells and epithelial cells, and are known to be involved in their survival outcome. In the context of inflammation and cancer, when LL-37 is highly expressed, the antagonism of M_2 mAChR activity by the peptide could therefore have unappreciated (patho)physiological consequences.
van der Westhuizen ET al. (2015) J Pharm Exp Ther 353(2):246-60.
Jacoby et al. (1993) J Clin Invest 91:1314-1318.
Kahlenberg et al. (2013) J immunol 191(10):4893-901. ¶

440 Experiences in defining Entrustable Professional Activities to drive the learning of undergraduate pharmacy students

Hesham S Al-Sallami[1], Megan Anakin[1,2], Alesha Smith[1], Aynsley Peterson[1], Stephen B Duffull[1]. School of Pharmacy[1], University of Otago, Dunedin; Dunedin School of Medicine[2], University of Otago, Dunedin, New Zealand.

Introduction. Entrustable professional activities (EPAs) are discrete tasks or responsibilities that a trainee is entrusted to complete and document with appropriate supervision. EPAs (e.g. dispensing or treatment of a minor ailment) link directly to a work-based assessment framework and allow for a natural continuation of learning in pharmacy from an undergraduate student to an intern to a pharmacist. EPAs also map to learning outcomes, see figure, and therefore to professional competencies.



EPA = entrustable professional activity;
LO = learning outcome

Aims. To define entrustable professional activities appropriate for pharmacy undergraduate education.

Methods. A group of core and elective EPAs were identified using interviews with pharmacists, a survey of pharmacy services, and the pharmacy services stipulated by the Pharmaceutical Society and Pharmacy Council of New Zealand. For each EPA, one of five levels of attainment was assigned; where level 1 was "observation only" and level 5 "supervision provided by the student to more junior students".

Results. Nineteen core EPAs were defined. An example of a core EPA is dispensing which was assigned an attainment level of 4 (defined as "execution with post-hoc supervision"). Twenty-two elective EPAs were identified and were all assigned an attainment level of 1 or 2. An example is anticoagulation monitoring.

Discussion. EPAs are used extensively in medical education but not yet in pharmacy undergraduate programmes. They are a useful tool in the teaching and assessment of pharmacy services and professional competencies.

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441 Older people as university-based instructors to improve empathy and attitudes toward older people among first-year pharmacy students

Carmen Abeyaratne[1], J Simon Bell[1], Laura Dean[1], Sheryl Maher[1] Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University[1], Melbourne, VIC, Australia.

Introduction. There is increasing recognition of the need to provide comprehensive and holistic care for older people with multi-morbidity and polypharmacy (Mc Namara et al, 2017). Monash University began offering a 5-year vertically integrated MPharm program, in 2017, providing an opportunity to design a supported encounter with an older person for students. Professional Practice was one of three units of study taught within the first semester of the degree.

Aims. The objective of this education brief is to describe implementation of a workshop to improve first year pharmacy students' empathy and attitudes toward older people.

Methods. An eight item survey based on empathy and attitudes towards older people was developed. Students completed the survey instrument before and after the workshop. The 2-hour workshop required students to engage with older people as part of the Professional Practice course for first year undergraduate pharmacy students at Monash University, Melbourne, Australia.

Results. Engaging older consumers as university-based instructors for first year pharmacy students was associated with significant short-term improvements in three of the eight attitudinal items assessed. Following the workshop students' were more likely to report older people are pleasant to be with, more likely to understand what it feels like to have problems with aging, and less likely to believe older people become confused and less organised.

Discussion. A two-hour workshop involving older consumers as university-based instructors produced immediate improvements in self-reported attitudes towards older people. Engaging older people as university-based instructors for first year pharmacy students may be a successful strategy to develop positive attitudes, empathy and oral communication skills.

Mc Namara KP et al (2017) Age Ageing 46:291-9.

442 A digital portfolio: Learning gains and efficiencies for placements in new BPharm programme.

Lynne M Bye[1], Fiona M Spence[2]. School of Pharmacy, University of Auckland[1]. Learning Technology Unit, University of Auckland[2,] Auckland, New Zealand.

Introduction. The implementation of a new BPharm curriculum at the School of Pharmacy University of Auckland in 2016, presented an opportunity for significant change to experiential learning placements: amount of dedicated placement time; range of placement sites; use of digital technology.
Aims. To describe the key education principles that have informed the development an ePortfolio used by BPharm students during placement modules and report on initial learning from the implementation.
Methods. The placement team and a learning designer worked in partnership to develop an ePortfolio to guide student learning during placement modules and to assess competency of essential skills, knowledge and behaviours. Feedback was sought from key staff, students and preceptors to enable ongoing review and refinement of ePortfolio design and development.
Results. Education principles of alignment, relevance, scaffolding, Millers's Prism of Professional Competence[1] and Pharmacy Council of New Zealand competence standards have been applied in the designing of the ePortfolio. The design process resulted in student owned ePortfolio and website that bring together a comprehensive set of resources to support students before, during and after their placement modules. It has been designed to enable students to develop transferrable skills to support their transition to the pharmacy profession. Use of digital technology, in particular ePortfolio, has afforded efficiencies in terms of administration, submission and assessments for the placement modules in the new BPharm programme.
Discussion. The ePortfolio is used throughout the entire BPharm programme providing students with a longitudinal record of their learning in one ePortfolio. It provides a unique opportunity for students to draw on learning from across the curriculum and to progressively develop individualised learning and skill development from year to year.

Miller GE. The assessment of clinical skills/ competence/ performance. Acad Med (1990);65:s63-s67.¶

443 Education for vancomycin – what works?

Jane E Carland[1,2], Bethany Van Dort[1,3], Melissa T Baysari[2,4], Sophie L Stocker[1, 2], Richard O Day[1,2,3]
Dept of Clin Pharmacol and Toxicol, St Vincent's Hosp[1], Sydney, NSW; St Vincent's Clin School, Univ of New South Wales[2], Darlinghurst, NSW; School of Medical Sciences, Univ of New South Wales[3], Kensington, NSW; Australian Institute of Health Innovation, Macquarie Univ[4], North Ryde, NSW.

Introduction. Dosing and monitoring guidelines are readily available for vancomycin. However, hospital audits consistently show suboptimal vancomycin therapy (Davis et al., 2013). Few studies have examined the types, strengths and weaknesses of educational resources used to support vancomycin prescribing.
Aims. To explore the opinions and experiences of Australian educators on the methods used to educate health professionals about vancomycin in order to identify the most effective approach to education.
Methods. Health professionals involved in delivering antibiotic education to clinical staff were approached via email and invited to participate in a semi-structured interview. Questions focused on the use of educational resources and methods for vancomycin dosing and monitoring practices. Interviews were transcribed verbatim and analysed independently by two researchers for emerging themes.
Results. Pharmacists (n=18) and Infectious Disease physicians (n=6) were interviewed. The most frequent mode of vancomycin education reported was an annual lecture during junior staff orientation. This was in contrast to what educators viewed to be ideal education (one-on-one, case-based, tailored learning). Educators reported that different methods were likely to be effective for different healthcare professionals (e.g. doctors vs. nurses). Access to online resources (such as vancomycin.com.au and Qstream) and dosing calculators were also seen to enhance vancomycin education. Time constraints were a major limitation to clinical education, with development of readily accessible and efficient educational strategies a priority.
Discussion. Effective education was reported to be multimodal, including strategies such as academic detailing and interactive, problem based learning using case studies.

Davis *et al.* (2013) Pharmacotherapy 33:1256–1263.

444 Creating a labelling standard for compounded medicines – a learning task requiring higher order thinking skills

Stephen R Carter[1], Sarira El-Den[1] & Sarab Mansoor[2]. Faculty Pharmacy, Uni of Syd, Sydney, NSW, Australia[1]; School Sci & Tech, Univ New Eng, NSW, Australia[2]

Introduction. Involving students in authentic learning tasks which require high order thinking skills such as synthesis, design, evaluation and creation has been shown to engage students in more active and productive learning. A novel learning task was developed and integrated into the 3rd Year Dispensing Unit of Study. Groups of Bachelor of Pharmacy students were required to synthesise information from legislation, professional standards and research findings in order to create a "labelling standard" for producing and evaluating labels for compounded medicines.
Aims. The aim of this study was to explore students' perceptions of the newly developed learning task.
Methods. Students' perceptions were explored using focus group discussions conducted during the semester following the learning task. Thematic content analysis was used to explore and organise the findings. The Consolidated Criteria for Reporting Qualitative research (COREQ) guided the conduct, analysis and reporting of the study.
Results. Three focus groups were conducted over two weeks involving 25 students (11% of cohort). Two main themes were extracted. The first theme was perceptions of learning style. Students conveyed deep self-reflections about the benefit of "thinking outside the box", rather than answering questions in "recycled assignments". Not all students recognised the benefit of learning this way and some expressed a distinct distaste for the need to be creative in a pharmacy degree. When criticising the learning task, students focussed on the practical challenges. They cited problems with resource availability, lecturer guidance, clarity of the grading rubric, timing in relation to other assessments and aversion to group work. The second theme pertained to students' perspectives about the impact of their learning on how they labelled compounded medicines. While not universally reported, students recounted having better insight into consumer perspectives, legislative and professional guidance. Students recognised the benefit of having a written labelling standard for dispensing tasks, although its relevance to practice was questioned.
Discussion. Some pharmacy students embrace and thrive on creativity and critical analysis, however many do not expect their degree to include learning tasks which require synthesising information from a variety of resources to solve practical problems. Overall, students valued the resulting "labelling standard" and their constructive comments have informed modifications prior to integration into the curriculum. ¶

445 Nursing students are more reliant on ongoing assessment scores to succeed in pharmacology than paramedic or optometry students

Sheila A Doggrell and Sally Schaffer, Faculty of Health, Queensland University of Technology, Brisbane, QLD

Introduction. Ongoing assessment and examinations are often used to test different aspects of learning with examinations testing the assimilation of knowledge and ensuring that the students complete the work themselves. However, the proportional allocation of marks for ongoing assessment and examinations is often made on an arbitrary basis, and the consequences of this are not known.
Aim. The aim was to compare percentage marks and failure rates in ongoing assessment and examinations for the successful nursing, paramedic and optometry students completing a pharmacology unit in 2013/4/5.
Methods. In the unit, 40% of total marks were allocated to ongoing unsupervised assessment and 60% to examinations. The marks for each student who passed the ongoing assessment and exams were calculated as a percentage and compared by Students paired test. Students who achieved less than 50% in each component were considered to have failed the component; failure rates were compared by Odds ratio. In the Table below, significance is at *P < 0.05; the number of students is also indicated (n).
Results. Results for each year were similar. All student cohorts obtained significantly better marks in ongoing assessment than exams in the pharmacology unit. A higher percentage of nursing, than paramedic or optometry students, failed the ongoing assessment and exam components of the unit.

	Percentage Marks (number)		**Failure rates (percentage)**	
Student cohorts (2014)	Ongoing assessment	Exams	Ongoing assessment	Exams
Nursing	72.4 ± 0.5 (215)	57.7 ± 0.9 (215)*	18/215 (8.4%)	61/215 (28.4%)*
Paramedic	74.2± 1.1 (95)	66.1 ± 1.3 (95)*	1/95 (1.1%)	9/95 (9.5%)*
Optometry	84.4 ± 1.0 (50)	66.6 ± 1.8 (50)*	0/50 (0%)	2/50 (4%)

Discussion. The nursing students who passed the pharmacology unit were more reliant on scores obtained in ongoing unsupervised assessment. The nursing students, who passed the unit but not the examinations, may not have assimilated the necessary knowledge to continue in their courses. Additionally, some of the passing nursing students may have succeeded due to work done by others in ongoing assessment.¶

446 Do pharmacy students have different personal characteristics than other students?

James A Green[1], Carlo A Marra[1]. School of Pharmacy, University of Otago[1], Dunedin, New Zealand

Introduction. The personal characteristics of pharmacists will help shape the future of the profession, especially in determining whether students as future pharmacists will embrace advanced pharmacy roles. We consider three frameworks. Are their achievement goals motivated by internal standards (either striving for mastery or avoiding failure) or their performance relative to others (striving to beat others or avoiding failure)? How do they score on the five-factor model of personality (openness, conscientiousness, extraversion, agreeableness, neuroticism)? Do they prefer to make decisions based on rational deliberative processes, or experiential intuitive processes?
Aims. To determine the differences in trait characteristics between students entering the Otago pharmacy programme and students studying other subjects; and between students who apply only for pharmacy, versus those who apply for multiple health professional courses.
Methods. All second year students at the University of Otago were invited to take an online questionnaire, containing measures of the 'big five' personality traits, the Achievement Goals Questionnaire – Revised, and the Rational-Experiential Inventory, along with demographic variables.
Results. 565 students (97 pharmacy, 465 non-pharmacy) completed the survey, from an estimated 3536 invited (16% response rate). Relative to non-pharmacy students, pharmacy students were more motivated by achieving mastery, $p = .001$, $d = -.31$ [-0.53, -0.09] , but were lower on rational decision-making, $p = .019$), $d = 0.26$ [0.04, 0.48] and also experiential decision-making, $p = .03$, $d = 0.24$ [95% CI 0.02, 0.46]. Pharmacy students were slightly higher on Agreeableness, $p = .041$, $d = -0.23$ [-0.45, -0.01]. Students who applied for multiple health professional courses were more highly motivated by avoiding failure against their internal standards ('mastery avoidance') than students choosing pharmacy, $p = .003$, $d = 0.54$ [0.12, 0.97].
Discussion. Overall, pharmacy students had relatively similar characteristics to non-pharmacy students. However, there were some promising characteristics that may predict engagement with advanced pharmacy roles, including a higher focus on mastery, and higher agreeableness. Our future work will determine whether these are predictive of future role engagement. ¶

447 Student engagement in learning: learning space matters

James Blanchflower[1], Philip Poronnik[2] and Tina Hinton[1]. School of Medical Sciences (Pharmacology), The University of Sydney[1], Sydney, NSW, Australia; School of Medical Sciences (Physiology), The University of Sydney[2], Sydney, NSW, Australia.

Introduction. Course delivery in biomedical sciences at The University of Sydney relies on a mix of traditional, transmission-style (lecture), active learning, and laboratory-based activities. Research developing the active learning classroom (ALC) has sought to replace the outdated traditional model (TM) of education by changing pedagogy, room design and instructor/student interaction. Outcomes from many studies demonstrate greater student engagement in learning in active learning settings. Nonetheless, much of the literature fails to adequately define or operationalize proximal measures of engagement, and often relies heavily on subjective self-report of student experiences.
Aims. We aimed to develop a tool for student engagement in learning and to use this tool to evaluate student engagement across a range of learning spaces and learning activities.
Methods. Cognitive and social psychology were utilized to develop a model of engagement to predict behavioural phenotypes. The predictions were applied to both ALC and TM classrooms (n=50) to measure "on-target" and "off-target" student behaviours using observational coding. Participants were students aged 18-25 enrolled in biomedical science courses. A total of 21,826, (ALC=10,647, TM=11,509) behaviours were recorded and analysed across ALCs and TM settings.
Results. Analysis showed greater frequency of on-target behaviours, suggesting higher levels of engagement, in ALCs relative to TMs. Further trends in student behaviours from certain instructor interventions, environmental features, class scheduling and types of activity were found.
Discussion. Our findings inform physical, instructional, and social design decisions in biomedical curricula, and effective use of learning spaces.

448 Pilot study of a clinical pharmacology exam for medical students prior to hospital internship in Newcastle

Catherine J Lucas[1], David A Newby[1], Jennifer H Martin[1]. Discipline of Clinical Pharmacology, University of Newcastle[1], Newcastle, NSW, Australia.

Introduction. There is clear evidence that suboptimal prescribing is common, with errors attributable to a complex mixture of antecedent and contextual factors. New doctors are responsible for a large proportion of prescribing and are often underprepared and inadequately supported.
Aim. To evaluate the Prescribing Skills Assessment (PSA) test, adapted from the UK version for the Australian setting, as a summative tool for assessing medical student's ability to prescribe appropriately and safely.
Methods. Final-year medical students in the Joint Medical Program of the University of Newcastle and University of New England were invited to undertake the PSA - a two hour, computer-based, limited open book, pass/fail assessment of the skills, judgement and supporting knowledge related to prescribing medicines, based on eight competencies identified by the General Medical Council (including writing new prescriptions, reviewing existing prescriptions, calculating drug doses, identifying and avoiding both adverse drug reactions and medication errors and amending prescribing to suit individual patient circumstances). The content of each item is based on prescribing scenarios commonly encountered by junior doctors. Prior to the PSA students were able to complete example questions in order to familiarise themselves with the test format.
Results. Mean candidate score exceeded the pass mark by > 10%. Although the majority of candidates agreed that “the assessment was an appropriate test of the prescribing skills expected of a medical student upon graduation”, few candidates agreed that “my course prepared me for the content of the questions in this assessment”.
Discussion. The results of this pilot will be used to develop the PSA as a summative test of prescribing for use in future years of the Medical program. It will also stimulate improved education by helping to identify areas of teaching within the Medical program that require further development. Ultimately the use of the PSA will help improve the competence of junior doctors to prescribe, which will lead to better patient outcomes.

Dornan T, Ashcroft D, Heathfield H et al (2009) EQUIP study. London. General Medical Council.¶

449 Evaluation of a new integrated Master of Pharmacy curriculum

Rebecca H Roubin[1], Jane R Hanrahan[1], Faculty of Pharmacy, The University of Sydney[1], Sydney, NSW

Introduction. A new integrated Master of Pharmacy curriculum approaches the teaching of pharmacy from a more integrated perspective, rather than the previous discipline based approach. It is structured by themes and underpinned by a detailed set of learning outcomes, which describe the knowledge, skills and attitudinal milestones to be achieved each year and by the time of graduation.
Aims. This study aimed to examine the effectiveness of the new integrated Master of Pharmacy curriculum.
Methods. Unit of Study surveys (USS) collected feedback on the student experience at the unit of study level. Its content is aligned with items/scales of the national course-level survey, the SES. There are ten quantitative items and two open response items.
Results. USS results improved for the Master of Pharmacy overall compared to the previous discipline based approach. The combined USS mean score for first year, was 4.05 for core items 1-6 and 4.09 for overall items 1-10.
Discussion. The new integrated Master of Pharmacy curriculum demonstrated favourable results compared to the previous discipline based curriculum.

450 Development of a program wide pharmaceutical compounding strategy using the scaffold learning approach to improve student learning outcomes

Kristen Bremmell[1], Timothy Barnes[1], Bernard Hughes[1], Sanjay Garg[1], Desmond Williams[1], Elizabeth Hotham[1], Vijayaprakash Suppiah[1] School of Pharmacy and Medical Sciences, University of South Australia[1], Adelaide, SA, Australia.

Introduction. In our review of the Dosage Form Design courses, we realized that our Pharmacy students were not confident in undertaking extemporaneous compounding in Dosage Form Design 3 (DFD 3), a course taught in third year of the program in which expectations of the written and physical skills were high and tasks were assessed stringently. While students had spent time in the laboratory undertaking practical classes and aspects of Pharmacy practice in prior years, they struggled to combine the two skills.
Aims. The data and student feedback was pointing to two main problems. Hence we aimed to address the two main concerns by increasing students' prior exposure: 1. to compounding techniques. 2. to filling in batch sheets which form the record keeping component in the practical sessions.
Methods. Collectively, we decided to introduce the activity to students in a structured way, first familiarising them with the basic concepts in the first two years to develop the necessary laboratory skills and confidence required to perform the task individually in its entirety in the later years of the Pharmacy program. This scaffolding approach to the task was developed, extending throughout the four years of the Pharmacy program.
Results. Since changes in 2015, DFD3 has consistently had over 98% pass rate for the practical component, with more than 75 % of student attaining distinction and above for their practical component. In the third and fourth year practical classes, students exhibit more confidence, resilience and more independence. Lecturers have noticed that since the implementation of the changes, students have increasingly become independent learners.
Discussion. The scaffolding approach whereby we tailored our instruction by providing support incrementally improving a learners' ability to build on prior knowledge, as this was seen as an important learning approach for addressing this issue. By providing this support and development across the Pharmacy program, students have achieved a significantly enhanced ability and associated outcomes in pharmaceutical compounding. ¶

451 Gamification to enhance learning of difficult concept in Pharmacology

Lisa BG Tee, Petra Czarniak, Tin Fei Sim, Hilai Ahmadzai. School of Pharmacy, Curtin University, Perth, WA, Australia

Introduction. It is often challenging to engage students in learning difficult concepts in pharmacology as well as other pharmaceutical biology disciplines. Gamification, serious games and simulations are gaining popularity as new approaches to teaching and learning in higher education. Gamification has the potential in enhancing motivation and engagement and is used in pharmacology teaching.
Aims. To explore the use of gamification and game-based learning in pharmacology teaching with the aim to transform students' perceptions from 'pharmacology equals an extensive amount to know and remember' to 'pharmacology equals an interesting and essential subject that enhances competency in both clinical pharmacology and the prescription of medications'
Methods. A series of pharmacology games, including Drug Review Bingo, Speedy Drug Challenge block game, Pharmacology crossword puzzle and Speed Drug Dating were developed and used in Pharmacology teaching in the second and third year of the Bachelor of Pharmacy course. Collective and accumulative qualitative feedback were obtained through the University evaluation process, eVALUate, from 2012 to 2017. Students' perception on the benefits, favourite game(s) and areas for improvement were analysed using NViVo analysis.
Results. Based on the qualitative comments by students through eVALUate, Drug Review Bingo and the Speedy Drug Challenge Block game used as revision for each module of the pharmacology units were the two favourite tools perceived to enhance students learning. The usefulness of the Speed Drug Dating varied depending on the collaborative nature of the class in preparation of tasks before the activities. In classes where students came prepared, all comments indicated that it had been beneficial in fostering deep learning.
Discussion. Overall students commented that the various games were engaging, fun and improved their ability to understand more complex content of pharmacology and foster internalisation of knowledge allowing long term memory to occur more effortlessly.

452 Improving student engagement: utilising a wet pain practical

Waltraud Binder[1], Ross Grant[1,]. Dept Pharmacology[1], School of Medical Sciences, UNSW Sydney, NSW

Introduction. Practical classes provide a valuable technique based experience, which enhances the development of laboratory skills, reinforces lecture content and supports the development of critical reasoning. Students informally surveyed and on course CATEI indicated that they preferred 'wet practicals' to computer based and scenario based practicals.
Aims. To develop a new 'wet practical' conducive to clinical reasoning to replace a scenario based pain practical.
Methods. A practical which allowed the students to simply measure a pain response was developed. A pre-lab including a video demonstrating the procedure as well as a series of question that tested the student's comprehension was made available at the start of the class. In groups of 3, students were assigned as a subject, tester, or record keeper. Von Frey bristles were utilised to provide both a 'touch' and 'pain' response on the ventral side of the forearm. Control responses were obtained and tallied using a square grid, where students count the number of positive scores for each grid (maximum of 25). Two EMLA (eutectic mixture of local anaesthetics) patches (lignocaine and prilocaine) were applied on the opposite forearm for 30 and 60 minutes respectively. Scores were tallied in the same way as for controls and class data were collated (PHAR3251, practical manual).
Results. The outcome of this approach has been an observed improvement in comprehension of underlying theory (improved exam results). Students must successfully engage with the pre-lab and answer all questions correctly before they can proceed with the class. The class successfully combines the topical administration of drugs and the inhibition of pain in a wet practical where pain measurement is notoriously difficult to achieve. Student's comments (CATEI 2016) Best features of the course were: 'Labs support lectures well. Use of clinical examples are great.'; 'The labs allowed us to see how drugs worked first hand'. Students were in agreement with the question 'the course was effective for developing my thinking skills e.g. critical analysis, problem solving' (L&T agree 100% CATEI 2016).
Discussion. Providing the students with a wet practical, linked to their lecture component, where they can obtain 'hands on' experience has improved engagement and participation in practical learning. Improved their theoretical competence and allowed them to directly experience some of the difficulties/issues encountered when measuring pain. ¶

453 Demonstrating the ability to prescribe medicines: a multi-professional view

Lynda Cardiff[1], Charles Mitchell[1], Paul Bennett,[1] Robyn Nash[1], Lisa Nissen[1] School of Clinical Sciences, QUT[1], Brisbane, QLD, Australia

Introduction. An increasing number of Australian health professions have gained authority to prescribe medicines. Preparing students to competently prescribe medicines is challenging yet critical; as is the demonstration of ongoing fitness to prescribe.
Aim. To explore the opinion of a multi-professional cohort of clinicians, educators and regulators regarding key issues central to the development of a safe and effective prescribing workforce.
Method. An anonymous survey was available for completion using two formats: as part of a workshop conducted during a national conference and via email using an on-line format. Data generated from both sources were subsequently amalgamated and analysed.
Results. A total of 71 responses were received from a cohort who described their primary role as: practising clinician (31%), education and training (30%), accreditation and standards oversight (14%), policy and governance (21%). A further 8% were involved in professional development. Respondents represented a total of nine professions, including both established prescribing professions and those that currently do not prescribe medicines.
Respondents overwhelmingly agreed there is a need for a consistent approach to the demonstration of student prescribing competence, both within (92% agreed) and across (83% agreed) prescribing professions. A number of methods were proposed to provide an indication of prescribing ability. Direct observation of performance was frequently chosen as an effective method to demonstrate the ability to undertake many aspects of the prescribing process in the student context. The demonstration of ongoing fitness to prescribe was considered important by over 90% of respondents. A combination of assessment methods was considered most useful in this setting.
Discussion. The survey suggests that there is agreement between health professions that clear demonstration of prescribing ability is important, both at the time of initial achievement of prescribing authority and in an ongoing capacity. A number of methods were considered useful to assist with this process. Further development of appropriate competence assessment processes may positively impact the development and maintenance of a safe and effective prescribing workforce.

454 Does attending lectures matter when lecture recordings are available? Results for a preliminary study of nursing students in pharmacology

Sheila A Doggrell and Sally Schaffer, Faculty of Health, Queensland University of Technology, Brisbane, QLD

Introduction. Before the introduction of technology into teaching, it was assumed by many teachers that grades were related to lecture attendance; students who attended classes more frequently, obtained better grades. However, there have been no studies of the effects of lecture attendance on academic outcomes for nursing students in pharmacology. Also, the introduction of lecture recordings may have led to reductions in lecture attendance and/or better results for non-attending students.
Aims. To determine the effect of lecture attendance on academic outcomes in bioscience for nursing students provided with access to lecture recordings. The study was undertaken in 2013/4.
Methods. Prior to the start of lectures on gastrointestinal bioscience and/or microbiology anti-infectives, attending students provided their ID numbers upon submission of a short quiz, as part of another study. The academic outcomes for attending and non-attending students in the tutorial assessment (40%), examinations (60%), and final grade in pharmacology were compared by Student's unpaired t-test with *P < 0.05 (Table); the number of students is also indicated (n).
Results. The uptake of lecture recordings and lecture attendance was higher at the start than end of semester. Only a third of the nursing students attended the gastrointestinal and microbiology lectures late in the semester. Attending students obtained better outcomes in the tutorial assessment, examinations and final grade.

	Tutorial assessment - % mark		**Examinations - % mark**		**Grade**	
Year	Non-attending	Attending	Non-attending	Attending	Non-attending	Attending
2013	77.2 ± 0.7 (392)	80.6 ± 1.5 (50)	59.1 ± 0.7 (392)	66.0 ± 1.8 (50)*	4.8 ± 0.1 (392)	5.3 ± 0.1 (50)*
2014	75.9 ± 0.7 (308)	80.2 ± 1.9 (23)	57.4 ± 0.8 (308)	64.4 ± 2.9 (23)*	4.7 ± 0.1 (308)	5.3 ± 0.2 (23)*
Combined	76.6 ± 0.5 (700)	80.5 ± 1.2 (73)*	58.1 ± 0.5 (700)	65.3 ± 1.6 (73)*	4.8 ± 0.0 (700)	5.3 ± 0.1 (73)*

Discussion. This preliminary study suggests that nursing students attending lectures had better academic outcomes in pharmacology than those that did not attend lectures, and that it is still important to provide face-to-face lectures for these students.¶

455 Implementation of a consistent and structured approach to small class workshops: A case study in pharmacy education at Monash University.

Nilushi Karunaratne[1]. Faculty of Pharmacy and Pharmaceutical Science, Monash University[1], Melbourne, VIC, Australia.

Introduction. Small class teaching forms an essential part of the pharmacy education at Monash University. Traditionally, tutorials and workshops are delivered in conventional classroom settings, with variable timetable scheduling and rotating tutors. In addition, setup of teams for group activities is variable from session to session and variability also exists in the development of workshop materials and in their presentation. One of the key features of Monash University's new Bachelor of Pharmacy (Honours)/Master of Pharmacy degree (also known as the Vertical Integrated Master's or VIM) is the implementation of a consistent and structured approach to small class teaching.
Methods. Units within the VIM were structured to allow workshops to take place weekly on the same day, time, and location. A pool of experienced facilitators were sourced for each unit and underwent further training to effectively facilitate specifically within the VIM, and were rostered such that each small class engaged with the same facilitator throughout the semester. Within workshops, students were allocated into teams of 4-5 and these teams remained consistent throughout the semester. Workshops took place in newly designed technology-enhanced learning spaces featuring collaborative pods with whiteboard table surfaces, mobile computers on wheels (MCOWs) being accessible to each pod, and a master room allowing AV control of surrounding learning spaces enabled by a 'patch-in' system. Workshop materials were developed in line with a 'best practice' template which included having Monash branded PowerPoint presentation slides to visually guide students, a 'running time sheet' to aid facilitators to effectively manage a workshop session, and time dedicated for 'closing of the loop' at the conclusion of each workshop to tackle common misconceptions and to link concepts covered within the session to the profession of pharmacy.
Results. The combination of these improvements and best practices have been applied to over 90 workshop sessions across 2 semesters in the new VIM degree in 2017.
Discussion. Designing effective learning environments, providing students consistency in terms of timetabling, facilitator rostering and student grouping, together with improving instructional modalities has the potential to positively impact student-centered learning.

456 Practicing pharmacists' preferences for skills taught in an undergraduate pharmacy program

Alana Close,[1] Yejung Kim,[1] Catherine Lee,[1] Boss Katchapanan,[1] Neha Ramji,[1] Carlo Marra,[1] School of Pharmacy, University of Otago, Dunedin, NZ; Megan Anakin,[2] Dunedin School of Medicine, University of Otago, Dunedin, NZ; Robert Buckham,[3] Pharmaceutical Society of New Zealand, Wellington, NZ

Background: Pharmacy is a rapidly evolving profession and a broad range of skills is required for practicing pharmacy. As such, schools of pharmacy need to keep pace with changes in the profession to ensure that the skills that are being taught are in line with practice. The objective of this study was to determine practicing pharmacists' preferences for skills taught in an undergraduate pharmacy program.
Methods: A comprehensive search of the published and grey literature (including pharmacy web pages) resulted in the identification of 16 unique skills that were presented to practicing pharmacists in a Best Worst Scaling (BWS) choice experiment. The experiment was accompanied by The Change Readiness Questionnaire (CRQ) and questions to collect demographic and practice information from respondents. The Pharmaceutical Society of NZ sent a web-based link to the survey to all registered pharmacists and followed up two weeks later with a reminder. Standard descriptive analyses were used to characterize the sample and paired conditional logit was used to analyze the BWS choice data to generate the random utility values for each skill.
Results: At least some of the survey was answered by 388 pharmacists (10% response rate). Respondent demographics were similar to those of all registered pharmacists in NZ (67% female, mostly B.Pharm. educated, urban based, working in independent community pharmacies, and credentialed to provide various services). The most preferred skills to be taught were comprehensive disease management, medicine therapy assessment, medicine use review and dispensing; whereas, the least preferred skills were specialty compounding, independent prescribing, physical examination to assess and monitor drug therapies, and injections. Stratifying preferences by those within and outside the different domains of the CRQ (resourcefulness, optimism, adventurousness, drive, confidence, and tolerance for ambiguity) changed the magnitude but not the order of preferences for the skills.
Discussion: Practicing pharmacists provided distinct preferences for 16 skills that can be taught in a pharmacy undergraduate program. These skills encompass both traditional and advanced practices.¶

456.1 Developing a new unit in a new curriculum

Betty Exintaris. Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Melbourne, VIC, Australia.

Introduction. As of 2017, the Faculty of Pharmacy and Pharmaceutical Sciences at Monash University introduced a new Bachelor of Pharmacy (Honours)/Master of Pharmacy degree. The new degree seeks to equip graduates with the necessary skills and knowledge to lead practice in the ever-changing world of healthcare and medicine.
Aims. To develop a new, foundational, double credit point unit (How the Body Works).
Methods. The way in which the unit was to be delivered differed significantly from previous iterations of the unit. Firstly, the unit was a double credit point unit. Secondly the unit was delivered using a very structured approach: the 'DEAR' model. Briefly, on a weekly basis, for every 4 hours of pre-learning **D**iscovery (the information was presented in Moodle books, including revision questions), there were 4 hours of integrated lectures (students **E**xplored the discovery material using questions / scenarios posed by staff) and 4 hours of workshops (where students **A**pplied the information from discovery and the integrated lectures. Finally students were asked to continuously **R**eflect on their learning. An important aspect of the new unit was the focus on skill development. In How the Body works we focussed on communication and teamwork.
Results. As a team, we developed and delivered a dynamic unit incorporating the new teaching approach. Staff reported that students were better communicators and team players by the end of the unit. Exam and unit results were noticeably higher (~20%) than the previous year.
Given the new teaching approach, it could be anticipated that students would initially struggle with the concept of having to be prepared before class so that the integrated lectures and workshops were meaningful. This was also true of students who had transferred from the old course or another course and were therefore used to the 'old' style of teaching. It was not surprising that the overall unit evaluation result was lower than other years (~3.5/5 vs ~4.5/5). Students provided meaningful feedback by identifying areas which could be improved.
Discussion. Utilising a different teaching approach, we developed a new unit as part of the new Pharmacy curriculum which focuses on skill development. Qualitative data suggests that the students were noticeably better communicators and team players by the end of the unit. Exam results also demonstrated that the students performed comparably better than last year. Feedback obtained from staff and students will be used to further develop the unit.

457 Bleeding-related admissions in patients with atrial fibrillation receiving antithrombotic therapy: results from the Tasmanian Atrial Fibrillation (TAF) study.

Endalkachew Admassie[*1], Leanne Chalmers[2], Luke R. Bereznicki[1]. [1]Division of Pharmacy, School of Medicine, University of Tasmania, Tasmania, Australia. [2]School of Pharmacy, Curtin University, Western Australia, Australia.

Introduction. Limited data are available from the Australian setting regarding bleeding in patients with atrial fibrillation (AF) receiving antithrombotic therapy.

Aims. We aimed to investigate the incidence of hospital admissions due to bleeding and factors associated with bleeding in patients with AF who received antithrombotic therapy.

Methods. A retrospective cohort study was conducted involving all patients with AF admitted to the Royal Hobart Hospital, Tasmania, Australia, between January 2011 and July 2015. Bleeding rates were calculated per 100 patient-years (PY) of follow-up, and multivariable modelling was used to identify predictors of bleeding.

Results. Of 2202 patients receiving antithrombotic therapy, 113 presented to the hospital with a major or minor bleeding event. These patients were older, had higher stoke and bleeding risk scores, and were more often treated with warfarin and multiple antithrombotic therapies than patients who did not experience bleeding. The combined incidence of major and minor bleeding was significantly higher in warfarin- versus DOAC- and antiplatelet-treated patients (4.1 vs 3.0 vs 1.2 per 100 PY, respectively; p = 0.002). Similarly, the rate of major bleeding was higher in patients who received warfarin than in the DOAC and antiplatelet cohorts (2.4 vs 0.4 vs 0.6 per 100 PY, respectively; p = 0.001). In multivariate analysis, increasing age, prior bleeding, warfarin, and multiple antithrombotic therapy were independently associated with bleeding.

Discussion. The overall rate of bleeding in this cohort was low relative to similar observational studies. The rate of major bleeding was higher in patients prescribed warfarin compared to DOACs, with a similar rate of major bleeding for DOACs and antiplatelet agents. Our findings suggest potential to strategies to reduce bleeding include using DOACs in preference to warfarin, and avoiding multiple antithrombotic therapy in patients with AF.

458 Epicatechin's cardiovascular protective effects are mediated via opioid receptors and nitric oxide

Andrew Fenning[1], Kylie Connolly[1], Rebecca K Vella[1], Kirsty MacRae[1]; School of Health, Medical and Applied Sciences, Central Queensland University[1], North Rockhampton, QLD, Australia.

Introduction. Cardiovascular disease is the leading cause of mortality globally. Epicatechin has previously been shown to improve vascular responses and possess cardioprotective properties. However the mechanisms underpinning these cardiotropic outcomes are yet to be fully identified.
Aims. The aim of this study was to determine epicatechin's mechanism of action in the cardiovasculature.
Methods. The effects of epicatechin on isolated rat conduit and resistance arteries were investigated on resting tension and precontracted vessels both in the presence and in the absence of various antagonists. Changes in cardiac electrophysiology were assessed by microelectrode recordings from isolated left ventricular papillary muscles in the presence and absence of various antagonists.
Results. At resting tension, epicatechin alone did not affect the vasoreactivity of either conduit or resistance vessels. In noradrenaline pre-contracted thoracic aortic arteries and potassium chloride pre-contracted mesenteric vessels, epicatechin (10^{-9}M – 10^{-4}M) induced significant vasorelaxation. The addition of naloxone (10^{-5}M), N^{G}-nitro-L-arginine methyl ester (10^{-5}M), 4-aminopyridine (5mM) and verapamil (10^{-5}M) attenuated epicatechin-mediated vasorelaxation. No change in epicatechin-mediated vasorelaxation was observed with the addition of atropine (10^{-5}M). Epicatechin significantly improved cardiac electrophysiology by reducing the resting membrane potential, action potential amplitude and force of contraction that was mitigated following the addition of naloxone (10^{-5}M). Epicatechin significantly decreased the action potential duration at 20%, 50% and 90% of repolarisation and time to 90% relaxation of force that was unchanged following the addition of naloxone (10^{-5}M).
Discussion. These findings suggest epicatechin's vascular responses and cardioprotective effects are mediated through the opioid receptors, nitric oxide, potassium channel and calcium channel activation and highlight the importance of the endothelium/nitric oxide in epicatechin mediated vasorelaxation.¶

459 Exploiting E3-ubiquitin ligase mediated protein degradation pathways as new therapeutic target strategies for cardiovascular disease and beyond

Ingrid C. Gelissen[1], Shereen M Aleidi[1], Alryel Yang[1], Andrew J. Brown[2]. Faculty of Pharmacy, University of Sydney, NSW, Australia[1]; Biotechnology and Biomolecular Sciences, The University of NSW, Sydney, NSW, Australia[2].

Despite the longstanding success of the statins in controlling lipid levels, there is still significant residual cardiovascular risk in high-risk patients. Statins function by inhibiting cholesterol synthesis, which is subject to extensive feedback regulation. Another cholesterol related pathway considered for therapeutic targeting is upregulation of cholesterol export from cells via the ABC lipid transporters ABCA1 and ABCG1, which are essential for maintenance of cholesterol balance in macrophages and cells such as neurons and insulin-secreting beta cells. Cholesterol-filled macrophages are a first critical step in the development of atherosclerosis, and transcriptional upregulation of ABC transporter mediated cholesterol export has been exploited therapeutically with the development of LXR ligands. These have so far failed to reach the clinic due to side effects and new avenues to upregulate these transporters are of interest.
Here we describe how E3-ubiquitin ligase-mediated ABC transporter degradation may be exploited in order to upregulate these important lipid pumps. E3 ligases are enzymes that form the rate-limiting step in the protein ubiquitination cascade, which tags proteins with ubiquitin and sends them off for degradation. These ligases are becoming increasingly of interest as therapeutic targets in the cancer field. Using nano-liquid chromatography mass spectrometry, we identified three E3 ligases associated with human ABCG1, namely HUWE1, NEDD4-1 and HECTD1. siRNA silencing of HUWE1 and NEDD4-1 increased ABCG1 protein levels and cholesterol export activity from cells, while overexpression of these ligases showed the opposite effect in cells expressing ABCG1 and macrophages in culture (1). siRNA silencing of HECTD1 stabilised ABCA1 protein and increased cholesterol export activity in human macrophages (2). We are currently investigating whether these E3 ligases utilize co-factors in order to characterize these pathways in depth. These observations highlight a new role for E3 ligases in the regulation of cholesterol homeostasis, which may provide new avenues for therapeutic targeting in future.

Aleidi et al (2015) J Biol Chem 290:24604-13
Aleidi et al (under review)¶

460 Nattokinase: A promising alternative in prevention and treatment of cardiovascular diseases

Yiguang Lin[1], Hongjie Chen[2], Eileen McGowan[1]. School of Life Sciences, University of Technology Sydney[1], Broadway NSW Australia. Dept of TCM, 3rd Affiliated Hospital of Sun Yat-sen University[2], Guangzhou, China.

Introduction. Nattokinase (NK), the most active ingredient of Natto, possesses a variety of favourable cardiovascular effects and the consumption of Natto has been linked to the reduction of cardiovascular disease (CVD) mortality. However, the effect of NK on atherosclerosis in human has never been studied.

Aims. This study was designed to evaluate the efficacy of oral NK in the reduction of common carotid artery intimal medial thickness (CCA-IMT) and carotid artery plaque size, lowering blood lipids, and to explore the underlying mechanism of action of NK. We further explored NK's potential as an alternative treatment to Statin (ST) in the clinic.

Methods. All enrolled patients were randomly assigned to one of two groups, NK and ST. 26 weeks' treatment applied to both NK Group (NK were given at a daily dose of 6000 FU) and ST Group (treated with statin-simvastatin 20 mg daily). CCA-IMT, carotid plaque size and blood lipid of the patients were measured before and after treatment.

Results. A total of 90 patients were enrolled in the study and 81 patients (NK=43, ST=38) completed the study. Following the treatments for 26 weeks, there was a significant reduction in CCA-IMT and carotid plaque size in both groups compared with the baseline before treatment. The carotid plaque size and CCA-IMT reduced from 0.25±0.12cm^2 to 0.16±0.10cm^2 and from 1.15±0.12mm to 1.02±0.11mm, respectively. The reduction in the NK group was significantly more profound (P<0.01, 36.6% reduction in plaque size in NK group versus 11.5% change in ST group). Both treatments reduced total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG). While the reduction in both groups was shown to be statistically significant (P<0.01), the reduction of TC, LDL-C and TG in ST group was significantly greater (P<0.05). In addition, NK significantly increased the level of high-density lipoprotein cholesterol (HDL-C) (P<0.05), in contrast, HDL-C in the ST group did not change. The lipid lowering effect observed in the NK group was not corrected to the reduction of CCA-IMT and carotid artery plaque size.

Discussion. Our findings from this pioneer clinical study suggests that daily NK supplementation is an effective way to manage the progression of atherosclerosis and potentially may be a better alternative to statins which are commonly used to reduce atherosclerosis and further to prevent cardiovascular attack and stroke in patients. The mechanism underlying the reduction of carotid atherosclerosis by NK may be independent from its lipid-lowering effect, which is different from that of statins. Together with the long history of natto consumption in Asia and its favourable effects on CVD, the findings further support that oral NK administration can be used as an alternative in the prevention and treatment of CVD. ¶

461 Gaps in anticoagulation knowledge in patients with atrial fibrillation

Kehinde O Obamiro, Leanne Chalmers, Kenneth Lee, Bonnie J Bereznicki, Luke R Bereznicki. Pharmacy, School of Medicine, University of Tasmania, Hobart, TAS, Australia.

Introduction. Knowledge regarding oral anticoagulant (OAC) therapy can influence treatment outcomes in patients with atrial fibrillation (AF). The relationships between anticoagulant knowledge, treatment expectations, convenience and satisfaction, health information overload and medication adherence have not been adequately studied in patients with AF.

Aims. To measure the level of anticoagulation knowledge in patients with AF taking OACs, investigate the association between patient-related factors and anticoagulation knowledge, and compare these results in patients taking warfarin and direct acting oral anticoagulant (DOACs).

Methods. Participants were recruited for an online survey via Facebook. Survey components included the Anticoagulation Knowledge Tool, the Perception of Anticoagulant Treatment Questionnaires (assessing treatment expectations, convenience and satisfaction), a modified Cancer Information Overload scale and the Morisky Medication Adherence Scale. Treatment groups were compared and predictors of OAC knowledge were identified.

Results. Participants taking warfarin had a higher knowledge score compared to those taking DOACs (n =386, 73.4 ± 13.2 vs 65.7 ± 13.7, p<0.001). Advancing age, type of OAC, health information overload and ease of OAC use (treatment expectation) were significant predictors of knowledge. Treatment expectations, including the belief that OAC treatment would cause bleeding side effects, varied significantly between participants taking warfarin and DOACs (4 vs 3, p = 0.011).

Discussion. The study identified knowledge gaps in patients taking OACs, and these deficiencies appear to be greater in participants taking DOACs. Knowledge assessment should be integrated within patient counselling sessions to help identify and resolve knowledge deficits. The relationship between these patient-related factors and treatment outcomes is an important area for further research.

462 Phosphoinositide 3-kinase p110 gene delivery limits cardiac remodelling and inflammation in a pre-clinical model of type 2 diabetes

Darnel Prakoso[1,2], Miles J De Blasio[1,2], Helen Kiriazis[1], Hongwei Qian[1], Minh Deo[1], Edwina Jap[1], Kate L Weeks[1], Laura J Parry[2], Xiao-Jun Du[1], Paul Gregorevic[1], Julie R McMullen[1], Rebecca H Ritchie[1,3]. Baker Heart and Diabetes Institute[1], Melbourne, VIC, AUS; School of BioSciences[2] and Dept of Pharmacology and Therapeutics[3], University of Melbourne, Melbourne, VIC, AUS.

Introduction. Diabetic cardiomyopathy in both type 1 (T1D) and type 2 diabetes (T2D) is characterised by cardiac inflammation, remodelling and dysfunction, with diastolic dysfunction preceding systolic dysfunction. Phosphoinositide 3-kinase (PI3K)-p110α is cardioprotective in type 1 diabetes but its effectiveness in the more prevalent T2D is unknown.
Aim. To test the hypothesis that PI3K gene therapy rescues diabetic cardiomyopathy in a preclinical model of T2D.
Method. T2D was induced in 6wk-old male mice by low dose streptozotocin (55mg/kg/day i.p. for 3 days) combined with high-fat diet for 24wks. After 18wks of diabetes, diastolic dysfunction was confirmed by echocardiography. A single i.v. injection of recombinant adeno-associated virus (rAAV6)-caPI3K ($2x10^{11}$vg) or null vector was then administered, and mice were followed for a further 8wks (n=8-12/group).
Results. Diabetes induced increases in cardiac inflammatory markers tumor necrosis factor-α and NF-κB, which was not observed in rAAV6-caPI3K-treated T2D mice (↓53±11%, ↓15±6% vs null-treated-T2D, respectively; both P<0.05). Cardiac interstitial and perivascular fibrosis induced by T2D were also significantly reduced (to baseline levels) in rAAV6-caPI3K-treated T2D mice (↓67±16%, ↓49±17% vs null-treated-T2D, respectively; both P<0.05). rAAV6-caPI3K also reduced expression of cardiac pro-fibrotic genes in T2D, including connective tissue growth factor, transforming growth factor-β and tissue inhibitor of metalloproteinase-2 (reduced by 49±16%, 43±10% and 45±13% vs null-treated-T2D, respectively, all P<0.05). These cardioprotective actions of PI3K gene therapy were accompanied by improvements in LV diastolic (isovolumic relaxation time, ↓12±5% vs null-treated-T2D and e'/a', ↑44±10% vs null-treated-T2D; both P<0.05) and systolic function (fractional shortening: ↑31±8% vs null-treated-T2D, P<0.05).
Conclusion. This study is the first to demonstrate that PI3K gene delivery rescues T2D cardiomyopathy and limits the associated cardiac remodelling and inflammation.¶

463 Targeting Annexin-A1 to treat diabetic cardiomyopathy

Jesse Walsh[1,2], Chengxue Helena Qin[2], Minh Deo[2], Helen Kiriazis[2], Daniel Donner[2], Xiao-Jun Du[2], Marianne Tare[1,3], Rebecca Ritchie[2, 3]. Depts of Physiol and Medicine, Monash Univ[1,3], Clayton, VIC, Australia; Baker Heart and Diabetes Institute[2], Melbourne, VIC, Australia.

Introduction: Inflammation plays an important role in the progression of many diabetic complications, including diabetic cardiomyopathy.
Aim: To test the hypothesis that the anti-inflammatory protein Annexin-A1 mimetic, Compound17b (Cmpd17b) attenuates markers of diabetic cardiomyopathy in Type 1 Diabetes (T1D).
Methods: Diabetes was induced in 6wk-old C57/Bl6 male mice using streptozotocin (55mg/kg i.p. /day, 5 days). After 8 weeks, diabetic mice were randomly allocated to receive either Cmpd17b (50mg/kg/day i.p) or its vehicle for 8 weeks, prior to echocardiography and tissue collection in anaesthetized mice using ketamine/xylazine (60/6mg/kg i.p.).
Results: As shown in the table, diabetic mice exhibited significant hyperglycaemia and diabetic cardiomyopathy. Cmpd17b tended to limit hypertrophic β-myosin heavy chain gene expression (p<0.05) and cardiac fibrosis (p<0.05) in diabetic mice.
Conclusion: Annexin-A1 mimetics such as Cmpd17b may be potential interventions for the treatment of diabetic cardiomyopathy.

Results (mean±SEM)	Non-diabetic mice	Diabetic + Vehicle mice	Diabetic + Cmpd17b mice
n	10	9	11
Body weight (g)	30.2 ± 0.7*	22.9 ±1.2	22.1 ± 0.8
Blood Glucose (mM)	8.7 ± 0.4*	31.7 ± 0.7	32.1± 0.8
LV β-myosin heavy chain expression(fold)	1.0 ± 0.2	6.6 ± 1.6*	3.8 ±0.7#
LV CD68 expression (fold)	1.0 ± 0.2	0.5 ± 0.1*	0.3 ± 0.05
LV Pro-collagen 3 expression (fold)	1.0 ± 0.1	0.9 ± 0.2	0.4 ± 0.1#
LV Total Collagen (%)	0.20 ± 0.04	0.60 ± 0.20*	0.30 ± 0.10#
LV Function: E/A	1.9 ± 0.2	1.4 ± 0.1*	1.6 ± 0.1

*p<0.05 versus non diabetic sham, #p<0.05 versus diabetic vehicle One way ANOVA followed by *post hoc* Newman-Keuls test.

464 β-Ile^5-Angiotensin II as a novel treatment for cardiac fibrosis

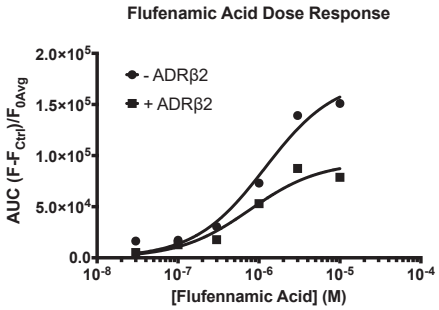
Yan Wang[1], Mark P Del Borgo[2], Marie-Isabel Aguilar[2], Kate M Denton[3] Chrishan S Samuel[1], Robert E Widdop[1], Departments of [1]Pharmacology, [2]Biochemistry & Molecular Biology, [3]Physiology, and Biomedicine Discovery Institute, Monash University, Clayton VIC, Australia.

Introduction. Excessive collagen accumulation results in organ fibrosis culminating in end-organ failure, for which new treatments are needed. A beta-isoleucine substitution to angiotensin II (β-Ile^5-Ang II) exhibits high selectivity for type 2 receptors (AT_2R) which counter-regulates pathophysiological effects induced by type 1 receptors (AT_1R).
Aims. To determine the anti-fibrotic effects of β-Ile^5-Ang II in vitro and in experimental models of fibrosis.
Methods. Human cardiac fibroblasts (HCF; ScienCell) were treated with recombinant human transforming growth factor beta-1 (TGF-β1) (5ng/ml) ± β-Ile^5-Ang II (10-1000 nM) and incubated for 72 hours. Fibrosis and collagen turnover were assessed by Western blotting using extracted protein. Male FVB/N mice were subjected to an 8-week model of high salt (HS; 5% diet)-induced cardiac fibrosis. From weeks 5-8, mice (n=5-8/group) were treated with β-Ile^5-Ang II (75pmol/kg/min) ± PD123319 (AT2R antagonist; 1mg/kg/day) or A779 (MasR antagonist; 1mg/kg/day) via osmotic pumps. Cardiac inflammation, fibrosis and collagen turnover were measured and compared with normal salt (NS)-fed mice.
Results. β-Ile^5-Ang II caused dose-dependent reductions in TGF-β1-stimulated collagen-I, alpha-smooth muscle actin (α-SMA; marker of myofibroblast differentiation) and tissue inhibitor of metalloproteinase (TIMP)-1 in HCF (all $P<0.05$, n=4-6). HS generally increased cardiac inflammation (F4/80 and phosphorylated-IkB levels) and cardiac fibrosis (left ventricular interstitial fibrosis measured by picrosirius red-staining), which was associated with increased myofibroblast differentiation (α-SMA) and TGF-β1 (all $p<0.05$ vs NS group). β-Ile^5-Ang II significantly reversed HS-induced cardiac inflammation (F4/80, phosphorylated-IkB) and cardiac fibrosis (picrosirius red, α-SMA and TGF-β1; all $p<0.05$ vs HS group). The anti-fibrotic and anti-inflammation effects caused by β-Ile^5-Ang II were abolished by PD133319 and A779 in combination.
Discussion. The novel peptide β-Ile^5-Ang II exerts anti-fibrotic and anti-inflammatory effects via the stimulation of both AT_2R and MasR; associated with inhibiting collagen production and enhancing collagen degradation. ¶

465 Functional regulation of bitter taste receptors (T2Rs) by β2-adrenergic and M2 muscarinic acetylcholine receptor

Jilai Zhao[1], Conor J Bloxham[1], Simon R Foster[2], Brooke Purdue[1] & Walter G Thomas[1]. School of Biomed Sci, Univ of Queensland[1], Brisbane, QLD, Australia; Dept of Drug Design and Pharmacol, Univ of Copenhagen[2], Copenhagen, Demark.

Introduction. G protein-coupled receptors (GPCRs) are key mediators of cardiac physiology and targeted for therapeutics. The ectopic expression of bitter taste receptors (T2Rs) in heart was first reported by the Thomas Laboratory. Stimulation of T2R14 in human right atrial tissue with bitter ligands produces a dramatic cardiodepressant effect, but it is not known whether the actions of T2R14 are modulated by other GPCRs related to cardiac contractility, principally the adrenergic and muscarinic receptors.
Aims. To determine the effect of co-expressing and activating the β2-adrenergic receptor and the M2 muscarinic receptor on the activation of the T2R14 bitter receptor.



Methods. AD293 cells were transfected with T2R14, chimeric G protein $G\alpha_{16/gust44}$, and the Ca^{2+} sensor GCaMP5. Ligand stimulated intracellular Ca^{2+} was measured by fluorescence imaging via an automated fluorometric plate reader. Fluorescently tagged T2Rs were used in confocal imaging studies, focusing on the expression and localisation of T2Rs.
Results. The co-expression of the β2-adrenergic receptor significantly reduced T2R signalling in response to flufenamic acid (see figure). Conversely, an increase in T2R function was observed when co-expressed with the cardiac parasympathetic regulator, M2 muscarinic acetylcholine receptor. These changes did not involve alterations in the expression and cellular localisation of T2R14. Pre-treatment with adrenergic/muscarinic ligands did not affect subsequent activation of the T2R14.
Discussion. Co-expression of T2Rs with the adrenergic and muscarinic receptors alters their responsiveness and efficacy to bitter ligands, leading to consequent effects on cardiomyocyte contractility. Ongoing investigations are probing the mechanism involved.

466 Gene therapy targeting the hexosamine biosynthesis pathway (HBP) attenuates markers of diabetic cardiomyopathy in a mouse model of type-2 diabetes (T2D)

Charles Cohen[1,3], Miles De Blasio[3], Darnel Prakoso[3], Minh Deo[3], Helen Kiriazis[3], Xiao-Jun Du[3], Paul Gregorivic[3], Hong-Wei Qian[3], Barbara Kemp-Harper[1], Rebecca Ritchie[2,3].
Dept. of Pharmacology[1], Dept. of Medicine[2] Monash University, Clayton, VIC; Heart Failure Pharmacology Laboratory[3], Baker Heart and Diabetes Institute, Prahran, VIC.

Introduction. Diabetic cardiomyopathy is characterized by left ventricular (LV) diastolic dysfunction, and cardiac remodelling. The nutrient-sensing HBP has been implicated diabetic cardiomyopathy. The final product of the HBP, 'O-GlcNAc' glycosylates proteins via the enzyme O-GlcNAc transferase (OGT), altering their function. O-GlcNAcylation is reversed by O-GlcNAcase (OGA). Sustained O-GlcNAcylation in diabetes impairs LV function.
Aim. To determine if rAAV6-human-OGA (hOGA) gene therapy improves diabetic cardiomyopathy in T2D mice *in vivo.*
Methods. 6-week-old male FVB/N mice were randomised into citrate vehicle control, or T2D induced by low-dose streptozotocin (STZ, 3x55mg/kg, i.p) and high-fat-diet (HFD, n=22). After 18-weeks untreated diabetes, rAAV6-hOGA or null-vector-rAAV6 ($2x10^{11}$ vector genomes, i.v.) was administered to diabetic mice (n=11/group). Citrate controls received null-vector (CIT-Null, n=5). Diastolic function was measured by Doppler echocardiography at 6, 24, and 32-weeks-of-age in mice under anaesthesia (Ketamine/Xylazine/Atropine, 60/6/0.6 mg/kg, i.p.) and blood glucose levels measured fortnightly. Eight-weeks after gene therapy, mice were euthanised and tissues collected.
Results. Blood glucose, HbA1c, bodyweight and fat mass of diabetic mice were elevated compared to citrate controls ($P<0.05$). Echocardiography indicated a reduced E/A ratio at 18-weeks diabetes ($P<0.05$), however this was not improved 8-weeks post hOGA-rAAV6. LV collagen deposition was increased in STZ-HFD-Null mice ($P<0.05$) and was attenuated by hOGA ($P=0.05$). LV CTGF expression in STZ-HFD-Null was elevated compared to CIT-Null. hOGA-rAAV6 reduced LV OGT expression ($P<0.0001$) and endogenous LV OGA expression. Augmented pan O-GlcNAcylation in T2D was attenuated by rAAV6-hOGA ($P<0.01$). No changes in cardiomyocyte hypertrophy or ROS-generation were evident.
Conclusions. hOGA-rAAV6 gene therapy reduces fibrosis and total O-GlcNAcylation associated with diabetic cardiomyopathy in T2D, but neither cardiomyocyte hypertrophy, ROS-generation, nor cardiovascular function *in vivo* were protected at this dose.¶

467 Blood pressure lowering post-stroke; a review of the evidence supporting recommendations of draft Clinical Guidelines for Stroke Management 2017

Fahmida Ilyas[1], Genevieve M Gabb[1,2], General Medicine, Royal Adelaide Hospital, Adelaide, SA, Australia[1] ; Discipline of Medicine, University of Adelaide, Adelaide, SA, Australia[2]

Introduction. An 88-year-old normotensive woman collapsed with hypotension after initiation of guideline directed blood pressure lowering therapy (BPLT) following a haemorrhagic stroke. Hypotension is the most frequent precipitant for Medical Emergency Team calls within hospitals. When developing guidelines, selection of evidence from a defined clinical population is recommended and appropriate (National Institute for Health and Care Excellence). Updated draft Clinical Guideline for Stroke was available for public consultation in 2016.
Aim. To review the public consultation draft stroke guideline, particularly in relation to recommendation for blood pressure lowering post-stroke.
Method. Recommendations for blood pressure lowering post-stroke were identified. References were reviewed and classified according to study design, inclusion of post-stroke population and evidence for efficacy and safety.
Results. The draft stroke guideline recommended, "All stroke and TIA patients, regardless of baseline blood pressure, should have long term blood pressure lowering therapy initiated or intensified, unless contraindicated by symptomatic hypotension" with five supporting references. Two were intervention based (BPLT) meta-analysis, where a specific patient population was not defined, one was a post hoc analysis of a randomized controlled trial, one was an open label randomized trial that found no difference in outcome with varying blood pressure thresholds and another was a review and meta-analysis of blood pressure lowering post-stroke that included studies where blood pressures up to 160 mmHg were considered normal.
Discussion. The evidence base supporting recommendations in the draft stroke guideline included meta-analysis of intervention based studies (BPLT) rather than studies in post-stroke populations. Clinical relevance to post-stroke populations is uncertain. Robust evidence of benefit for BPLT post-stroke for all patients, irrespective of blood pressure was lacking. Guidelines should be based on evidence derived from appropriate clinical populations.

468 Resveratrol shows neuronal and vascular-protective effects in older, obese, streptozotocin-induced diabetic rats

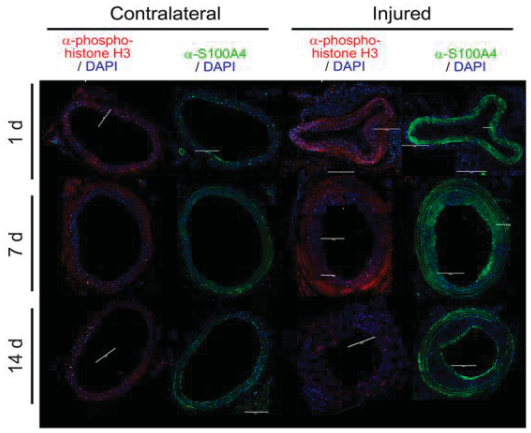
Jordon C Irwin[1], Hnin E Phyu[1], Rebecca K Vella[1], Andrew S Fenning[1]. School of Health, Medical and Applied Sciences, Central Queensland University[1], North Rockhampton, QLD, Australia.

Introduction. Old, obese streptozotocin-induced (STZ) diabetic rats can provide a disease model of type 1 diabetes mellitus with some aspects of type 2 diabetes mellitus and metabolic syndrome. While the cardioprotective effects of resveratrol in young STZ rats are well-established, the effectiveness of this polyphenol antioxidant compound in maintaining cardiovascular health in old, obese STZ animals remains largely unknown.
Aims. The aim of this study was to determine whether resveratrol, when administered at a dose that can be reasonably obtained through supplementation, could prevent the development of cardiovascular complications in older, obese, diabetic rats.
Methods. Diabetes was induced in 6-month old, obese, male Wistar rats via a single intravenous dose of STZ (65 mg/kg). Randomly selected animals were administered resveratrol (2 mg/kg) via oral gavage daily for 8 weeks. Changes in body mass, blood glucose levels, food intake and water consumption were monitored as indicators of diabetes. Vascular reactivity, left ventricular function and tactile allodynia were assessed at the end of the treatment period.
Results. Resveratrol therapy significantly improved tactile allodynia as well as vascular contractile and relaxation functionality in diabetic rats ($P < 0{\cdot}05$). There was no significant effect of resveratrol on left ventricular compliance or heart rate. Similarly, plasma glucose concentrations, water consumption and body mass were not significantly affected by resveratrol administration in diabetic animals.
Discussion. Resveratrol-mediated improvements in vascular and nerve function in old, obese, diabetic rats were associated with its reported antioxidant effects. Resveratrol did not improve cardiac function nor mitigate the classic clinical symptoms of diabetes mellitus (i.e. hyperglycaemia, polydypsia and a failure to thrive). This suggests that supplementation with resveratrol at a dose achievable with commercially available supplements would not produce significant cardioprotective effects in individuals with diabetes mellitus.¶

469 The microRNA miR-124 inhibits vascular smooth muscle cell proliferation by targeting S100 calcium-binding protein A4 (S100A4)

Hyun Kook, Nakwon Choe. Dept Pharmacol, Chonnam National University Medical School, Hwasun, South Korea

S100 calcium-binding protein A4 (S100A4) induces proliferation and migration of vascular smooth muscle cells (VSMCs). We aimed to find the microRNA regulating S100A4 expression. S100A4 transcripts were abruptly increased in the acute phase of carotid arterial injury at 1 day but gradually decreased at 7 and 14 days. Bioinformatics analysis revealed that *miR-124* targeted S100A4. VSMC survival was attenuated by *miR-124 mimic* but increased by *miR-124 inhibitor*. *miR-124* was decreased immediately after carotid arterial injury but dramatically increased at 7 and 14 days. *miR-124 inhibitor*-induced cell proliferation was blocked by *S100A4 siRNA*, whereas *miR-124*-induced cell death was recovered by S100A4. *miR-124* is a novel regulator of VSMC proliferation and may play a role in the development of neointimal proliferation.



Choe et al., FEBS Lett 591: 1041-52, 2017¶

470 The role of phospholipase A_2 in the cardiovascular effects of *Pseudechis australis* snake venom

Amna Mazeh, Sanjay N Panday, Christine E Wright. Dept of Pharmacol and Therapeutics, Univ of Melbourne, Parkville, VIC, Australia.

Introduction. Phospholipase A_2 enzymes (PLA_2s) are abundantly present in snake venoms and cause the anticoagulant and myotoxic effects of *Pseudechis australis* (*P. australis*) venom (Hart et al, 2014). LY315920 has been shown to be a potent inhibitor of PLA_2s (Schevitz et al, 1995) and thus provides a valuable tool to assess the role of these enzymes.
Aims. To assess the cardiovascular effects of *P. australis* snake venom in isolated cardiac and vascular tissues *in vitro* and to determine the role of PLA_2s in these effects.
Methods. In organ baths, the inotropic and chronotropic effects of the venom (0.01-30 µg/mL) were assessed in the rat isolated left and right atria, respectively, in the absence or presence of LY315920 (1.0 µM). Using myography, in U46619 pre-contracted rat small mesenteric arteries (221-400 µm i.d.) venom-induced (0.3 or 1.0 µg/mL) vasorelaxation was assessed in the absence or presence of LY315920 (1.0 µM).
Results. In left and right atria *P. australis* venom caused positive inotropic and chronotropic effects with similar EC_{50} values of 1.3±0.2 (n=14) and 1.2±0.2 µg/mL (n=12), respectively. LY315920 (1.0 µM) pre-treatment significantly inhibited both inotropic and chronotropic effects, right-shifting the curves. The resulting EC_{50} values were 11.5±0.9 µg/mL (n=9; P<0.001) in the left atria and 5.5±1.0 µg/mL (n=6; P<0.001) in the right atria. In the mesenteric arteries, *P. australis* venom (0.3 and 1.0 µg/mL) caused a transient relaxation with a decrease of pre-contractile tone of -68±7% (n=5) and -33±7% (n=15), respectively; the lower concentration of venom caused a significantly greater relaxation (P=0.017). LY315920 (1.0 µM) pre-treatment significantly inhibited the vasorelaxation caused by venom 0.3 µg/mL and 1.0 µg/mL by 87% (n=7; P=0.003) and 67% (n=9; P=0.035), respectively.
Discussion. This study suggests that PLA_2s in *P. australis* venom contribute significantly to the venom-induced inotropic and chronotropic effects, and vasorelaxation in mesenteric arteries. The venom concentration-independent vasorelaxant responses require further investigation.

Hart AJ et al (2014) Clin Toxicol 52:604-610
Schevitz RW et al (1995) Nat Struct Biol 2:458-465¶

471 Endotoxin tolerance-like response in human abdominal aortic aneurysm (AAA) macrophages

Lara T. Meital[1], Mark Windsor[1], Alesiya Maynard[1], Maria Perissiou[1], Rebecca Magee[2], Karl Schulze[3], Digby Krastins[1], Peter Young[1], Pankaj Jha[2], Jill O'Donnell[2], Steven Coverdale[4], Kim Greaves[4], Tom G. Bailey[1], Jonathan Golledge[5], Christopher D. Askew[1], Fraser D. Russell[1]
Univ. of the Sunshine Coast[1], Maroochydore, QLD, Australia; Dept. of Surgery, Sunshine Coast University Hospital[2], Birtinya, QLD, Australia; Sunshine Vascular[3], Buderim, QLD, Australia; Sunshine Coast University Hospital, Univ. of the Sunshine Coast and Univ. of Queensland[4], Birtinya, QLD, Australia; College of Medicine and Dentistry, James Cook Univ. and Dept. of Vascular and Endovascular Surgery, Townsville Hospital[5], Townsville, QLD, Australia.

Introduction. Macrophages are involved in the pathogenesis of AAA. Endocytosis of lipid rafts reduces the expression of Toll-like receptor 4 (TLR4) on macrophage membranes, reducing responsiveness to bacterial lipopolysaccharide (LPS) (Józefiwsju et al., 2017). Prior exposure of macrophages to LPS leads to attenuated cytokine production (eg Tumor necrosis factor-α; TNF-α), on subsequent exposure; a phenomenon called endotoxin tolerance.
Aim. To investigate whether human AAA macrophages exhibit endotoxin tolerance after LPS exposure.
Methods. Blood-derived macrophages were obtained from men with small (<5.5 cm) AAA (75±6 yr, n=19) and age-matched non-AAA male controls (72±5 yr, n=36). Cells were incubated in culture with 0.1 µg/mL LPS for 24 or 28h. Biomarkers of inflammation were determined by ELISA, and distribution of lipid rafts by confocal microscopy.
Results. The LPS-stimulated release of inflammatory biomarkers (8-isoprostane, TNF-α, interleukin-6) from macrophages was significantly lower in AAA compared to non-AAA participants. Protein expression of TLR4 was significantly reduced in AAA compared to non-AAA macrophage lysates. Lipid rafts were localised to the membrane of non-stimulated macrophages from n=3/3 control participants. Lipid raft internalisation was observed in LPS-stimulated macrophages from n=3/3 control, and in non-stimulated macrophages from n=5/10 AAA participants.
Discussion. This refractoriness of AAA macrophages to an LPS stimulus is reminiscent of endotoxin tolerance. Internalisation of lipid rafts in some AAA participants may contribute to the apparent endotoxin tolerance-like response. Reduced responsiveness to TLR4-activators may increase risk of infection and non-resolving inflammation.

Józefiwsju et al. (2017) Cellular Immunology 312:42-50¶

472 β_3-Adrenergic Receptors in the Rat Cremaster Muscle Artery

Samantha L Saunders, Fiona C Britton, Sarah E Wright, Shaun L Sandow, Timothy V Murphy.
Department of Physiology, School of Medical Sciences, University of New South Wales, Sydney, NSW, 2052, Australia.

Introduction. The β_3-adrenergic receptor (β_3-AR) was first isolated and cloned in 1989. There exists evidence of this receptor having a role in the cardiovascular system, as seen in various studies undertaken in the heart and vasculature. Its role in the microvasculature in particular however, remains elusive.
Aims. This project aims to determine β_3-AR expression and function in the rat cremaster muscle artery.
Methods. Cremaster muscle arterioles were isolated from adult male Sprague Dawley rats. Immunofluorescence and PCR techniques were used to assess β_3-AR expression. Functional studies were performed using pressure myography (70 mm Hg). Concentration-response curves were obtained using a variety of β-AR agonists and antagonists. The data was analyzed by means of two-way ANOVA, followed by Sidak's Multiple Comparisons Test, using GraphPad Prism v7.0.
Results. The β_3-AR agonists, CL-316,243 and mirabegron alone had no effect on basal myogenic tone of the arteries. Another β_3-AR agonist, SR-586,11A, caused a dilation of 5813% from baseline when administered alone (EC_{50} = -6.0 0.8, n = 5). In the presence of the β_1/β_2-AR antagonist, nadolol (10 µM), both CL-316,243 and mirabegron caused vasodilation (EC_{50} = -8.5 9.9, n = 5 and EC_{50} = -8.4 2.3, n = 3 respectively), which was blocked by the β_3-AR antagonist L-748,337 (1 µM). The potency of SR-586,11A was enhanced in the presence of nadolol (EC_{50} = -8.6 6.8, n = 3, $P < 0.05$) and responses to SR-586,11A were also prevented by L-748,337. Vasodilation induced by the non-selective β-AR agonist, isoprenaline was abolished by nadolol, but was not altered by L-748,337. CL-316,243 (1 µM) was shown to attenuate dilation induced by the endothelium dependent vasodilator, ACh (EC_{50} = -5.9 0.4, n = 5), compared to control (EC_{50} = -6.9 0.2, n = 5).
Conclusions. β_3-AR causing vasodilation are masked when the β_1-AR and β_2-AR are fully functional. β_3-AR may also inhibit endothelium-dependent vasodilation.¶

473 The association between short sleep duration and BMI in Australian Indigenous children

Melissa Deacon-Crouch[1], Isabelle Skinner[2], Joseph Tucci[1] and Timothy Skinner[2]
[1] Pharmacy & Applied Sciences, LIMS, La Trobe University, Vic, Australia; [2] Psychological and Clinical Sciences, Charles Darwin University NT Australia.

Associations between short sleep duration and obesity and the relationship between obesity and chronic illness are well documented. Obese children are likely to become obese adults. To date there is a paucity of information regarding sleep duration and quality for Indigenous Australian people. It may be that poor quality, short sleep is contributing to the gap in health outcomes for Indigenous people compared with non-Indigenous Adults and Children. This study sought to investigate the possibility that poor sleep quality may be contributing to health outcomes for Indigenous children by exploring associations between sleep duration and BMI.
Methods: Participants: 1253 children aged 7 – 12 years in Wave 7 of the national Longitudinal Study of Indigenous Children survey. Interviewers asked primary carers about children's sleep times. Body mass index (BMI) was derived from measurements of children made by researchers.
Results: Regardless of age, relative socioeconomic disadvantage and level of remoteness, unhealthy weight was associated with less sleep duration than healthy weight for Indigenous children.
Conclusion: The relationship between short sleep duration and BMI in Indigenous children has important implications for their future health outcomes. Both overweight conditions and short sleep are established modifiable risk factors for metabolic dysfunction and other chronic illnesses prominent in the Indigenous population. It is important to consider strategies to optimise both for Indigenous children in an attempt to help "close the gap" in health outcomes and life expectancy between Indigenous and non-Indigenous people.

474 Vascular effects of Australian brownsnake venoms (*Pseudonaja* spp.): the role of secretory phospholipase A_2s

Nhi T Vuong, Christine E Wright. Dept of Pharmacol and Therapeutics, Univ of Melbourne, Parkville, VIC, Australia

Introduction. The World Health Organisation recognised snakebite management as a public health crisis and listed envenomation as a neglected tropical disease in 2017. While antivenoms exist for most venomous snake species, reports of their high cost, scarcity and ineffectiveness have grown considerably over the years. Many toxic effects of snake venoms may be caused by secretory phospholipase A_2s (sPLA$_2$s), therefore inhibition of this enzyme family may have therapeutic potential for the treatment of snakebite (Lewin et al, 2016).
Aims. The aims were to assess the role of sPLA$_2$s in the vascular effects of four different brownsnake venoms (*Pseudonaja* spp.) and to test the effectiveness of treatment with LY315920, a potent inhibitor of sPLA$_2$s.
Methods. Rat isolated small mesenteric arteries (i.d. 250–350 µm), mounted in myographs, were either pre-contracted with U46619 (for relaxation studies) or electrically-stimulated (for sympathetic nerve responses). Crude venom from *P. affinis*, *P. inframacula*, *P. mengdeni* or *P. textilis* was added (30 µg/ml). In separate experiments, arteries were pre-treated with LY315920 (1 µM) before additions of snake venoms.
Results. All venoms elicited significant relaxation from the pre-contractile tone (–63-93% tone, n=6-10; P<0.0001); only *P. mengdeni* and *P. textilis* venoms were inhibited by LY315920 (48±11%, n=9; P=0.0007, and 66±23%, n=7; P=0.017, of relaxation by venom alone, respectively). The venoms, with the exception of *P. mengdeni* (22±17%, n=6; P=0.12), inhibited sympathetic nerve stimulation by 38-56% compared with the control group. Only *P. inframacula* and *P. textilis* venoms were affected by LY315920 (inhibition 58±18%, n=9; P=0.0046 and 77±25%, n=6; P=0.011, respectively). LY315920 did not inhibit the relaxation or sympatholytic effects caused by *P. affinis* venom (P>0.05).
Discussion. These results suggest that sPLA$_2$s in the venom of these snake species (with the exception of *P. affinis*) from the same genus (*Pseudonaja*) contribute to vascular relaxation as well as inhibition of sympathetic nerve stimulation via pathways yet to identified. Furthermore, the treatment with LY315920 showed that a sPLA$_2$ inhibitor may offer an effective alternative in the treatment of snake envenomation.

Lewin et al (2016) Toxins 8:248. ¶

475 Delineating the signal transduction pathways by which relaxin mediates its anti-fibrotic actions in human cardiac fibroblasts.

Chao Wang, Caitlin V Lewis, Zihui Wei, Robert E Widdop, Barbara K Kemp-Harper, Chrishan S Samuel. Biomedicine Discovery Institute and Department of Pharmacology, Monash University, Clayton, VIC 3800, Australia.

Introduction. The ovarian and cardiovascular hormone, relaxin, mediates its anti-fibrotic effects via Relaxin Family Peptide Receptor 1 (RXFP1)/angiotensin II type 2 receptor (AT_2R) heterodimers (Chow B et al., Kidney Int 2014, 86:75-85) and inhibition of TGF-β1 expression and activity. Currently, the extent to which relaxin signals through AT_2R-dependent mechanisms and the TGF-β1/NADPH oxidase (NOX) axis remains unknown.
Aims. To determine whether relaxin mediates its anti-fibrotic effects via modulation of 1) AT_2R-dependent phosphatase activity and/or 2) specific NOX isoforms that are expressed by primary human cardiac fibroblast (HCFs).
Methods. HCFs (fetal ventricular and atrial fibroblasts; ScienCell, USA) were screened by real-time and/or Western blotting for their ability to express the AT_2R-dependent tyrosine (SHP-1, SHP-2), serine/threonine (PP2A) and MAP kinase (MKP-1) phosphatases as well as NOX1, NOX2, NOX4 and NOX5. HCFs were also stimulated with TGF-β1 (5ng/ml) and treated with human recombinant relaxin (RLX; 16.8nM = 100ng/ml) or the AT_2R-agonist, Compound 21 (C21; 1µM), in the absence or presence of the PP2A inhibitor, okadaic acid (10nM) for 72 hrs. Known end-points of RLX activity: phosphorylated (p-)ERK1/2, p-nNOS, α-SMA (myofibroblast differentiation) and collagen I were then assessed by Western blotting. The effects of RLX (5 or 16.8nM) or C21 (1 or 5µM) on NOX4 mRNA and protein as well as amplex red-hydrogen peroxide (H_2O_2) levels after 72 hrs were also determined (all 3-4 separate times in duplicate).
Results. HCFs were found to express the PP2A and MKP-1 phosphatases, and predominantly expressed NOX4 mRNA and protein in comparison to NOX1, NOX2 and NOX5. TGF-β1 stimulation of HCFs significantly increased NOX4 mRNA and hydrogen peroxide levels (both p<0.05 vs unstimulated cells), while RLX or C21 normalised the TGF-β1-stimulated H_2O_2 levels (both p<0.05 vs TGF-β1) without affecting NOX4 expression. RLX or C21 also significantly increased p-ERK1/2 and p-nNOS, but decreased α-SMA and collagen I expression by HCFs; while the anti-fibrotic effects of either therapy were abrogated by co-administration of okadaic acid (all p<0.05 vs RLX or C21 alone).
Discussion. RLX appears to mediate its anti-fibrotic effects in HCFs via AT2R-dependent PP2A phosphatase activity but not via modulation of NOX4 expression, strengthening the finding that it can signal through RXFP1/AT_2R dimers.

476 Targeting IRAP: A Novel Treatment to Stabilize Existing Abdominal Aortic Aneurysms

Kaki Fan[1], Robert Widdop[1], Ekaterina Salimova[2], Siew Yeen Chai[3] & Tracey Gaspari[1]. Dept of Pharmacol, Monash University[1], Clayton, VIC, Australia; ARMI, Monash University[2], Clayton, VIC, Australia; Dept of Physiol, Monash University[3], Clayton, VIC, Australia.

Introduction. Abdominal aortic aneurysm (AAA) is a degenerative disease with no pharmacological treatment available to prevent progression or risk of rupture. Preliminary evidence from our laboratory indicated inhibition/deficiency of the enzyme, insulin regulated aminopeptidase (IRAP) prevented AAA formation in angiotensin (Ang) II-infused mice, indicating IRAP may be a novel target in treatment of AAA.
Aim. To determine if the IRAP inhibitor, HFI-419 can stabilize established AAA in Ang II-infused apolipoprotein E deficient (ApoE KO) mice.
Methods. 12 week old male ApoE KO mice were infused with Ang II (1000ng/kg/min) for 6 weeks to induce AAA. Once presence of established AAA was confirmed mice were randomized to receive either vehicle or HFI-419 (500ng/kg/min; s.c.) from weeks 2-6. Ultrasound imaging (to measure aortic diameter and area) and systolic blood pressure (SBP; tail cuff method) measurements were performed fortnightly to track AAA development and SBP changes
Results. Two-week infusion of Ang II induced aneurysm formation in >90% of all mice. Co-infusion of HFI-419 with Ang II significantly reduced aneurysm area and diameter in the absence of any effect on SBP. Immunohistochemistry analyses confirmed increased expression of IRAP in proximal aorta and AAA sections taken from Ang II infused mice whilst IRAP inhibition tended to reduce IRAP expression. HFI-419 treatment attenuated elastin degradation which was correlated with reduced matrix metalloproteinase (MMP)-9 and macrophage expression in AAA sections.
Discussion. Inhibition of IRAP significantly reduced progression of established AAA, although underlying protective mechanisms are still under investigation. This study highlights the potential of inhibiting IRAP as a novel therapy for treatment of AAA
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477 Comparing the anti-fibrotic effects of emerging treatments: Serelaxin and the IRAP inhibitor, HFI-419 to a clinically-used ARB and ACE inhibitor in a high salt-induced mouse model of kidney disease.

Matthew Shen, Adithya Shastry, Yan Wang, Tracey A. Gaspari, Robert E. Widdop, Chrishan S. Samuel. Biomedicine Discovery Institute and Department of Pharmacology, Monash University, Clayton, VIC 3800, Australia.

Introduction. Fibrosis is a hallmark of chronic kidney diseases and its inability to resolve causes severe organ dysfunction and end-organ failure. The limited anti-fibrotic efficacy of current therapies suggests a need for alternative treatments.
Aims. To compare the anti-fibrotic effects of serelaxin (human recombinant relaxin; RLX) and HFI-419 to the AT1 receptor blocker, Candesartan cilexetil (CAND) or ACE inhibitor, Perindopril (PERIN) in a murine high salt (HS) diet-induced model of kidney disease.
Methods. 8-10 week male C57Bl/6J mice were subjected to 8-weeks of HS (5% NaCl) diet-induced renal injury. From weeks 5-8, sub-groups (n=4-8) were treated with either vehicle, RLX (0.5mg/kg/day), HFI-419 (0.72mg/kg/d), CAND (2mg/kg/day) or PERIN (4mg/kg/d). Each drug dose used had previously demonstrated anti-fibrotic efficacy in other experimental models. Mice maintained on a normal salt (NS) diet (0.5% NaCl) for 8-weeks were used as controls. Various measures of renal inflammation and fibrosis as well as plasma urea levels were evaluated.
Results. HS diet-fed mice were associated with significantly increased renal inflammation, TGF-□1 expression levels, myofibroblast differentiation, glomerulosclerosis, interstitial fibrosis, TIMP-1 levels and vascular rarefaction (determined by morphometry of Masson's trichrome- or immunohistochemically-stained sections and/or Western blotting), total kidney collagen concentration (hydroxyproline analysis) and plasma urea compared to that measured from NS diet-fed counterparts (all $P<0.01$ vs NS group). RLX or HFI-419 significantly reduced most measures of HS-induced renal fibrosis and plasma urea levels back to that measured in mice fed the NS diet (all $p<0.05$ vs HS group). RLX or HFI-419 demonstrated similar, if not greater, anti-fibrotic effects compared to that offered by PERIN, but which also reduced blood pressure, body weight and worsened plasma urea levels at the dose used ($p<0.01$ vs HS group). CAND, however, did not demonstrate any marked anti-fibrotic effects in the model/organ studied.
Discussion. RLX or HFI-419 offers improved anti-fibrotic efficacy and renoprotection compared to CAND and safer anti-fibrotic efficacy compared to PERIN in the setting of HS-induced kidney damage.¶

478 Systemic and cardiac-selective targeting of histone deacetylase 4 (HDAC4) to limit diabetic cardiomyopathy

Andrew M. Willis[1,2], Mitchel Tate[1], Miles J. De Blasio[1], Darnel Prakoso[1], Minh Deo[1], Helen Kiriazis[1], Xiao-Jun Du[1], Paul Gregorevic[1], Hong-Wei Qian[1], Marianne Tare[3], Rebecca H. Ritchie[1,3]. Baker Heart and Diabetes Institute[1], Melbourne, VIC; Dept. of Physiology[2] and Dept. of Medicine[3], Monash University, Clayton, VIC.

Introduction: Diabetic cardiomyopathy is characterised by left ventricular (LV) diastolic dysfunction and structural changes, including cardiomyocyte hypertrophy and interstitial fibrosis. Epigenetic modifications, such as histone deacetylation, have been implicated in the molecular pathways that drive structural changes in this setting. HDAC4 is associated with the pathological cardiac remodelling similar to that observed in diabetic cardiomyopathy.
Aims. To determine whether inhibiting HDAC4, via a cardiac-selective approach using adeno-associated virus (AAV), or globally (by tasquinimod), ameliorates diabetic cardiomyopathy in a murine model of type-1 diabetes (T1D).
Methods: T1D was induced in 6 week old male FVB/N mice with streptozotocin (5 days, 55mg/kg/d or vehicle, i.p.). Echocardiography was performed at 6 (baseline), 14 (pre-treatment), and 22 (endpoint) weeks of age in anaesthetised mice (ketamine/xylazine/atropine, 60/6/0.6 mg/kg). The first approach utilised cardiac-selective rAAV6-dnHDAC4 ($2x10^{11}$ genomes or null vector). The second approach utilised tasquinimod (10mg/kg/d or vehicle administered via daily i.p.). Both approaches commenced after 8 weeks of diabetes with a follow-up period of 8 weeks.
Results: Blood glucose and HbA1c levels were increased with diabetes ($P<0.0001$). Diabetes reduced heart mass, however rAAV6-dnHDAC4 significantly increased LV mass compared to untreated diabetes ($P<0.05$). Diabetes-induced prolongation of isovolumetric relaxation time and increased LV connective tissue growth factor (CTGF) gene expression; both were attenuated by rAAV6-dnHDAC4 ($P=0.08$ and $P<0.05$, respectively) in T1D mice. Treatment with rAAV6-dnHDAC4 also blunted the diabetes-induced expression of hypertrophic genes including B-type natriuretic peptide (BNP) and β-myosin heavy chain (β-MHC, both $P<0.05$). Treatment with tasquinimod ameliorated diabetes-induced LV diastolic dysfunction with improved E/A and e'/a' in comparison to untreated diabetes (both $P<0.01$) and a reduction in deceleration time ($P<0.01$). Diabetes increased LV BNP gene expression ($P<0.05$) and superoxide levels ($P<0.001$) both of which were reduced by treatment with tasquinimod (both $P<0.05$).
Conclusions: Inhibition of HDAC4 attenuates characteristics of diabetic cardiomyopathy including cardiomyocyte hypertrophy, fibrosis, superoxide generation and LV diastolic dysfunction, in a model of T1D.¶

479 Role of TRPC3 in endothelium-dependent vasodilation of rat mesenteric arteries

Sarah E Wright and Timothy V Murphy. Dept of Physiol, Sch of Med Sci, UNSW Sydney, Sydney NSW, Australia.

Introduction. Endothelium-dependent dilation (EDD) of arteries is an important auto-regulatory function of the microvasculature. Previous studies suggested a role for transient receptor potential canonical-3 channels (TRPC3) in EDD (Senadheera et al., 2012) using pyrazole-3, a TRPC3 blocker with poor selectivity (Schleifer et al., 2012).
Aims. The present study further examined the role of TRPC3 in both agonist and flow-stimulated EDD of arteries utilizing a new, more selective TRPC3 blocker, pyrazole-10 (PYR10; Schleifer et al., 2012).
Methods. Cumulative stimulus-response curves to ACh (1 nM/L - 10 µM/L) or intra-luminal flow (0-20µL/min) were performed in isolated, pressurized (60 mmHg), phenylephrine-constricted rat mesenteric arteries. Data is presented as % maximum dilation from baseline.
Results. In control arteries, increasing flow caused dilation, with peak dilation observed at 14uL/min (17.2 ± 3.2%, n=6). The flow-mediated dilation (FMD) was not altered by inhibition of nitric oxide (NO) synthase and guanylate cyclase using a combination of L-NAME (100 µM) and ODQ (10 µM). In the presence of PYR10 (1 µM), some FMD persisted at low flow rates (<10 µl/min), but at flow ≥12µL/min significant flow-induced constriction of vessels was observed (max constriction -21.8 ± 10.5% $P\leq0.05$, n=4). ACh caused a concentration-dependent dilation of mesenteric arteries (pEC_{50} = 7.63 ± 0.09, max 95.1 ± 2.6%, n = 4). The ACh-induced dilation was inhibited by PYR10 (max 51.0 ± 1.5%, $P<0.05$, n = 4). The combination of L-NAME, ODQ and PYR10 further reduced ACh-induced dilation (max 10.0 ± 1.1%, $P<0.05$, n = 4). PYR10 did not alter phenylephrine-induced vasoconstriction of the arteries.
Discussion. These studies support a role for TRPC3 in mediating both agonist- and flow-induced EDD of rat mesenteric arteries. TRPC3 appears to be coupled to non-NO-dependent signaling pathways, presumably involving endothelium-derived hyperpolarization of vascular smooth muscle.

Schleifer H, *et al.* (2012). Br J Pharmacol 167**:** 1712-1722.
Senadheera S, , *et al.* (2012). Cardiovasc Res 95**:** 439-447.

480 An investigation of the vascular effects of Sailuotong, a standardised Chinese herbal formula, for vascular dementia

Seungyeon Yeon[1], Dennis Chang[1], Hosen Kiat[1,2,3], Alan Bensoussan[1] and Sai Wang Seto[1].
[1]NICM, School of Science and Health, Western Sydney University[1], Campbelltown, NSW, Australia. [2]Faculty of Medicine, University of New South Wales, NSW, Australia. [3]Faculty of Medicine and Health Sciences, Macquarie University, NSW, Australia

Introduction. Sailuotong (SLT) is standardised three-herb formulation consisting of *Panax ginseng C A Mey*, *Ginkgo biloba L* and *Crocus sativus L* for the management of vascular dementia (VaD). Although SLT has been shown to increase cerebral blow flow in animal and clinical studies, the direct effects of SLT on vascular reactivity have not investigated.
Aims. To examine the vasodilatatory effects of SLT and its underlying mechanisms of action in rat isolated tail artery.
Methods. Male, 250-300g Wistar Kyoto (WKY) rat-tail artery was isolated for isometric tension measurement.
Results. Cumulative administration of SLT (0.1 – 5000 µg/mL) caused a concentration-dependent relaxation in phenylephrine-preconstricted tail artery. Pre-incubation of endothelium nitric oxide synthase inhibitor (N-nitro-L-arginine methyl ester, L-NAME; 20 µM) did not inhibit the SLT-induced vasodilatation. In contraction experiments, SLT (10, 100 and 1000 µg/mL) significantly attenuated phenylephrine (0.001 to 10 µM)- and KCl (10 – 80 mM)-induced contraction. In Ca^{2+}-free solution, SLT (5000 µg/mL) markedly suppressed Ca^{2+}-induced (0.001 – 3 mM) vasoconstriction in both phenylephrine (10 µM) and KCl (80 mM) stimulated tail arteries.
Discussion. Putting these together, our results suggested that SLT induces relaxation of rat isolated tail arterial rings through an endothelium-independent pathway, involving blockade of extracellular Ca^{2+} influx.¶

481 Clinically actionable CYP450 pharmacogenotypes relevant to analgesics used for alleviating rheumatoid arthritis pain in community-dwelling older Australians.

Thilani H Dias[1], Mohitosh Biswas[1], Nilofar Daneshi[1], Elizabeth Holliday[2], Stephen Hancock[2], Karen Kerr[1], Irene Munro[1], John Attia[2], Rodney Scott[1] and Liz Milward[1] School of Biomed Sci and Pharmacy, The University of Newcastle[1], Newcastle, NSW, Australia; School of Med and Public Health, The University of Newcastle[2], Newcastle, NSW, Australia.

Introduction. Genomic polymorphisms altering metabolic activity of isoforms of cytochrome P450 (CYP) enzymes may lead to heterogeneity in patient responses to analgesics ranging from therapeutic failure to drug toxicities (Ting and Schug, 2016). Pre-emptive array-based analysis of such pharmacogenotypes has potential for optimizing therapeutic outcomes while reducing unnecessary costs associated with adverse drug reactions (Van Driest SL et al, 2014).
Aims. To assess prevalence of clinically actionable polymorphisms with strong or moderate level evidence for opioids and non-steroidal anti-inflammatory drugs in 2121 Australians aged 55 years or older from the Hunter Cohort study.
Methods. Clinical actionability and risk level (medium- or high-risk) of drug-gene interactions with strong evidence (codeine-*CYP2D6*; rs28371705, rs28371725, rs28735595 and tramadol-*CYP2D6*; rs28371705) or moderate evidence (oxycodone-*CYP2D6*; rs28371705 and celecoxib-*CYP2C9*; rs1057910) were assessed from the Pharmacogenomic Knowledge Database, Clinical Pharmacogenomic Implementation Consortium or FDA recommendations using self-reported medication data and genotyping by Affymetrix Kaiser Axiom arrays or imputed from reference panels.
Results. One third of participants (33%, 698/2121; 95% CI: 31%–35%) had at least one medium- or high-risk clinically actionable genotypes of the *CYP2D6* or *CYP2C9* gene variants studied. In total 2% (47/2121; 95% CI: 1.6%–2.2%) were homozygous for strongly or moderately evidenced high risk actionable SNPs of *CYP2D6* or *CYP2C9* and were also considered as poor metabolizers. About 1% (20/2121, 95% CI: 0.5%–1.4%) of participants with actionable genotypes were exposed to codeine or celecoxib. Conversely, about 17% (44/256, 95% CI: 13%–22%) of participants taking these medications had at least one relevant actionable genotype.
Discussion. At least 3 in 10 participants have an actionable genotype and over 10% of those on analgesics have at least one actionable genotype that would prompt a change of standard therapy according to current international therapeutic guidelines. Taking genotype into account may provide better therapeutic outcomes for arthritis patients.
Ting S and Schug S (2016) J Pain Res 9:49-56 Van Driest SL et al (2014) Clin Pharmacol Ther 95:423-31¶

482 Cytochrome interactions between lumacaftor and ivacaftor undergoing Orkambi cystic fibrosis therapy

Elena K. Schneider[1], Jian Li[2†], Tony Velkov[1†*]
[1]Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences; Monash University, Parkville, VIC 3052, Australia; [2]Monash Biomedicine Discovery Institute, Department of Microbiology, Monash University, Clayton, VIC 3800, Australia.

Ivacaftor (Kalydeco) and ivacaftor-lumacaftor (Orkambi) combination are two new breakthrough cystic fibrosis (CF) drugs that directly modulate the activity and trafficking of the defective CF transmembrane conductance regulator-protein. However, there is still a dearth of understanding on the pharmacology of ivacaftor and lumacaftor. Since release of Orkambi several red-flags have been raised that highlight the clinical efficacy maybe be limited due to antagonistic drug-drug interactions e.g. cytochrome P450 interactions. For the cell-free CYP inhibition studies, P450-Glo luminescence assays have been used to measure the cytochrome P450 activity of ivacaftor, its major metabolites and lumacaftor at 10 µg/mL. Chloramphenicol, a known CYP3A4 inducer at 10 µg/mL was employed as a positive control. Ivacaftor-carboxylate (RLU = 274 394.4) and lumacaftor (RLU = 304 899.45) produced higher response luminescence units (RLU) than Chloramphenicol (RLU = 248 319.4). Interestingly, hydroxymethyl-ivacaftor (RLU = -1 368.895) and ivacaftor (RLU = 153 564.4) caused a decrease in RLU compared to the control. This would suggest potential antagonistic drug-drug interactions between lumacaftor and ivacaftor are at play where the former induces the metabolism of the latter. Overall, these factors maybe compounding together to limit the clinical efficacy of Orkambi therapy. This is clearly an important issue that requires attention given the modest benefits to the patient may not justify the high cost of therapy.

483 The role of efflux transporters in the transfer of drugs from mother to breastfed infant via breastmilk.

Hilai Ahmadzai[1], Lisa BG Tee[1], Andrew Crowe[1] School of Pharmacy, Curtin University, Bentley, WA, Australia.

Introduction. Although breastfeeding is advocated as the best nutritional start for an infant, there is always concern regarding the transfer of medications from mother to their breastfed baby via milk. Although most drugs are compatible with breastfeeding, cases of toxic drug exposure have been reported. This is thought to be due to active transport mechanisms whereby efflux transporter proteins expressed in the epithelial cells of the mammary gland actively secrete drugs into milk. An example of such efflux transporters is the breast cancer resistance protein (BCRP) which is strongly induced during lactation and this could result in contamination of milk with the substrates of this transporter which may place any suckling infant at risk of toxicity.
Aim. The objective of this study was to investigate the changes in the expression of four ATPase Binding Cassette (ABC) transporters namely BCRP, MDR1, MRP1 and MRP2 in the lactating human mammary epithelial cells at various time points during lactation and to explore whether cells derived from breastmilk can be used to develop an individualised, non-invasive model to predict drug transfer from mother to baby via breastmilk.
Methods. Milk samples were collected from nursing mothers at various times starting at one month post-partum (intended at 1, 3, 5, 9 and 12 months) until a maximum of 12 months post-partum or cessation of breastfeeding. Gene expression of the transporters was tested at both the mRNA (qRT-PCR) and protein levels (immunostaining). Cells obtained from breastmilk were isolated and successfully grown in culture using specialised media.
Results. Breastmilk derived cell gene expression of these transporters varied widely amongst participants. Our results indicate that there was a strong trend showing a monthly increase of +2.24 in MRP2 ($p=0.0002$), and a weaker (but significant) increase in MDR1 (+0.17 per month; $p=0.0102$). There was no evidence of a change in BCRP or MRP1 over time. The expression of these transporters also varied significantly in cultured cells compared to fresh cells.
Discussion. Our results show that the expression of some ABC transporters is stage dependent in humans and may exhibit some interpersonal variability.

484 Silencing *ABCC2* transporter gene enhances oxaliplatin chemo-sensitivity in colorectal cancer cells

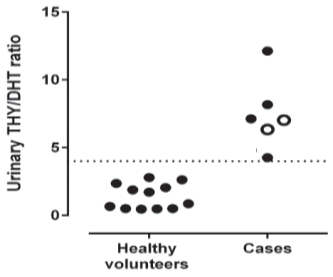
Riya Biswas[1], Fabrice Merien[1, 2], Jun Lu[1, 4], Mark McKeage[3], Yan Li[1, 4]. School of Science, AUT[1], Auckland, NZ; AUT-Roche Diagnostics Laboratory[2], Auckland, NZ; Dept of Pharmacol and Clin Pharmacol, Univ of Auckland[3], Auckland, NZ; School of Interprofessional Health Studies, AUT[4], Auckland, NZ

Introduction. Oxaliplatin as a first-line treatment for colorectal cancer has greatly contributed to improving patient outcomes. However, a member of the ATP-binding cassette (ABC) transporter superfamily, ABCC2, has been suggested to confer oxaliplatin resistance by pumping oxaliplatin out of cells.
Aims. To observe the effects of small interfering RNA (siRNA) targeting *ABCC2* gene in Caco-2 cells and interaction of ABCC2 with oxaliplatin.
Methods. Caco-2 cells were transfected with three different siRNAs of *ABCC2* and scramble-sequence negative control siRNA. *ABCC2* mRNA expression levels were measured by quantitative real time PCR. Flow cytometry was used to analyse the cellular accumulation of ABCC2 substrate, 5(6)-carboxy-2', 7'-dichlorofluorescein (CDCF). MTT ((3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide) assay was undertaken to determine oxaliplatin sensitivity and half-inhibitory concentration (IC_{50}) of oxaliplatin was calculated.
Results. The *ABCC2* mRNA expression significantly decreased by 60% after siRNA transfection. The cellular CDCF accumulation significantly increased by 33%±7.0% ($P < 0.05$), 53%±3.7% ($P< 0.001$) and 45%±4.5% ($P<0.001$) in ABCC2-silencing Caco-2 cells compared with control. The IC_{50} values of oxaliplatin in transfected Caco-2 cells were decreased to 7.7±0.1 µM ($P < 0.05$), 8.4±0.2 µM ($P < 0.05$) and 7.0±0.9 µM ($P< 0.05$) compared with a control value of 13.83±1.5 µM.
Discussion. Our study provided the evidence that ABCC2 was identified as a targetable factor and transfection of *ABCC2* by siRNA, enhanced sensitivity of Caco-2 cells to oxaliplatin. Thus, silencing of *ABCC2* gene may reverse oxaliplatin resistance in colorectal cancer.¶

485 Raised urinary excretion of thymine following an oral load is a marker for severe fluoropyrimidine toxicity

John Duley[1], Catherine Shannon[2], Ross Norris[3], Marion Harris[4], Nuala Helsby[5], Bruce Charles[1], Leslie Sheffield[6]. Pharmacy, Univ. of Qld[1], Brisbane, QLD, Aust; Medical Oncology, Mater Research Inst.[2], Brisbane, QLD, Aust; Pharmacology, Univ. of NSW[3], Sydney, NSW, Aust; Monash Health[4], Melbourne, VIC, Aust; Medical Sciences, Univ. of Auckland[5], New Zealand; MyDNA Life Aust P/L[6], Melbourne, VIC, Aust.

Introduction. Cancer chemotherapy continues to rely heavily upon 5-fluorouracil (5FU) and its prodrug capecitabine. Serious adverse effects have focussed dihydropyrimidine dehydrogenase (DPD), but this accounts for only about one-third of observed toxicity. The majority of 5FU toxicity remains unexplained.
Aim. To compare retrospective oral thymine (THY) loading of six cancer patients who had suffered severe 5FU toxicity, with a control range.
Methods. The THY oral loading regimen was published previously for twelve healthy volunteers (Duley et al, 2016). Briefly, after a light breakfast a 250 mg capsule of powdered THY was swallowed with tap water. Patients provided a pre-dose urine, then post-dose urines up to 5 hours. Urine THY and its catabolite dihydrothymine (DHT) were assayed.



Results. The figure shows the ratios of THY:DHT excreted in urine by the six patients, compared to twelve healthy volunteers. The mean (range) of urine THY:DHT for healthy subjects was 1.34 (0.36 - 2.84). Of the patients, two were later confirmed DPD-deficient carriers, with ratios of 6.35 and 6.93 respectively (unfilled symbols). The other four patients ranged from 4.8 - 12.1. Using a nominal THY:DHT ratio cutoff of 4 for healthy volunteers, all six patients had elevated urinary THY:DHT, post-THY load.
Discussion. Oral THY loading appears to provide a means of evaluating fluoropyrimidine sensitivity in cancer patients that is superior to other reported methods. Our trial in six cancer patients, who had suffered 5FU toxicity, found DPD deficiency in two of the patients. Three of the four other patients appeared to have an augmented thymine uptake phenotype. PK-based THY testing may facilitate prediction of the majority of cases of fluoropyrimidine sensitivity, until the pharmacogenetic factors are fully comprehended. A prospective trial is being undertaken in NZ.
Ref. Duley JA et al (2016) Eur J Pharm Sci 81:36-41¶

486 The ethics of direct-to-consumer pharmacogenomic screening in primary care

Suzanne L Harvey (BPharm(Hons) candidate), Adam La Caze
School of Pharmacy, University of QLD, Brisbane, QLD, Australia

Background: Direct-to-consumer pharmacogenomic screening is currently available in primary care through community pharmacies and general practice (e.g. https://www.mydna.life). Screening involves testing for an array of single nucleotide polymorphisms commonly implicated in variation in drug response. While the genetic contribution to pharmacodynamics and pharmacokinetics is increasingly well understood for many drugs, direct-to-consumer pharmacogenomic screening raises a number of ethical questions. A key ethical consideration is whether there is sufficient evidence for the benefit of these tests.
Aim: Assess the appropriateness of direct-to-consumer pharmacogenomic screening in primary care.
Method: The evidence for the benefit of direct-to-consumer pharmacogenomic screening is assessed by examining the evidence for screening in relation to common treatments such as warfarin and antidepressants. Pharmacogenomic studies for these medications are reviewed to identify challenges in applying the information provided in the literature to direct-to-consumer pharmacogenomic screening.
Results: The warfarin and antidepressant cases highlight a number of challenges for determining the clinical utility of direct-to-consumer pharmacogenomic screening. Specifically, the complexity of the contribution that genetic variation makes to other clinical variation; the methodological weaknesses of the studies conducted; limited frameworks for clinical implementation and weak measures for improved patient outcomes. [1,2]
Conclusion**:** The translation of pharmacogenomic research to the day-to-day management of patients has a number of opportunities, but also some challenges. More discussion is needed on how the current evidence base may be used to implement direct-to-consumer pharmacogenomic screening appropriately.

1. Alcalde MG, Rothstein MA. Pharmacogenomics: Ethical concerns for research and pharmacy practice. American Journal of Heal-System Pharmacy. 2002;59(22):2239–40.
2. Ma JD, Lee KC, Kuo GM. Clinical application of pharmacogenomics. Journal of Pharmacy Practise. 2012;25(4):417–27.

487 Therapeutic drug safety, important to 'Close the Gap' for Aboriginal and Torres Strait Islanders: an illustrative case of phenytoin hypersensitivity syndrome.

Fahmida Ilyas1, Andrew A Somogyi2, Genevieve Gabb1. Internal Medicine, Royal Adelaide Hospital, Adelaide, SA, Australia, Discipline of Pharmacol, Univ of Adelaide2, Adelaide, SA, Australia.

Introduction. Australian Indigenous populations have high burdens of disease and consequent medication exposure. The evidence base for drug efficacy and safety in this population is limited (Thynne, Gabb 2016). Early identification of specific adverse drug reactions and strategies to mitigate risk in this population are important to 'Close the Gap'.
Aims. To describe a clinical case of a severe phenytoin hypersensitivity syndrome in a 30 year old Aboriginal woman.
Methods. Clinical case report of phenotypic features, cytochrome P450 and HLA testing.
Results. A 30 year old Aboriginal woman presented with six months of odynophagia, intermittent diarrhoea and 50 kilogram weight loss with a desquamating, ichthyoid rash, most severe on the palms and feet. She had been commenced on phenytoin six months previously following seizures. She had been reviewed by her general practitioner, as well as 3 speciality services (gastroenterology, cardiology, intensive care) without a diagnosis. Investigations revealed eosinophilia, acute kidney injury with electrolyte disturbance, vitamin and mineral deficiencies and abnormal liver function with cholestasis. A clinical diagnosis was made of drug rash with eosinophilia and systemic symptoms (DRESS) secondary to phenytoin and phenytoin was ceased. Cytochrome P450 testing was positive for CYP2C9*3 denoting a poor metaboliser, and HLA testing was positive for HLA-B*56-02 previously associated with phenytoin hypersensitivity in Aboriginal Australians (3 cases, 2 fatal) (Harding et al, 2012). This patient survived and recovered over the next twelve to 18 months.
Discussion. This case illustrates the importance of clinical recognition of adverse drug reactions in Aboriginal and Torres Strait Islanders; the relevance of personal genomic information that may contribute to risk and that phenytoin DRESS HLA is different to Caucasians and Asians. An organised pro-active approach to therapeutic drug safety in the indigenous Australians may assist in closing the gap in health outcomes for this population.

Thynne T, Gabb G (2016) MJA 2014:16-17
Harding DJ et al (2012) Aust Med J 197:411-4¶

488 Physiologically based pharmacokinetic modelling of atomoxetine in the different *CYP2D6* genotypes

Se-Hyung Kim, Young-Hoon Kim, Ji-Young Byeon, Choong-Min Lee, Eui-Hyun Jung, Won-Ki Chae, Choon-Gon Jang, Seok-Yong Lee, School of Pharmacy, Sungkyunkwan University, Suwon 16419, Republic of Korea

Atomoxetine is a norepinephrine reuptake inhibitor indicated in the treatment of attention deficit hyperactivity disorder. It is primarily metabolised by CYP2D6 to its equipotent metabolite, 4-hydroxyatomoxetine, which promptly undergoes further glucuronidation to an inactive 4-HAT-O-glucuronide. Clinical trials have shown that decreased CYP2D6 activity leads to substantially elevated atomoxetine exposure and more adverse reactions. The aims of this study were to analyse the pharmacokinetics of atomoxetine and to develop a pharmacologically based pharmacokinetic (PBPK) model of atomoxetine in different *CYP2D6* genotypes. A single 20 mg dose of atomoxetine was given to 19 healthy Korean individuals with *CYP2D6*wt/*wt* (**wt = *1* or **2*) or *CYP2D6*10/*10* genotype. Based on the results of this pharmacokinetic study, a PBPK model for *CYP2D6*wt/*wt* individuals was developed. This model was scaled to those with *CYP2D6*10/*10* genotype, as well as *CYP2D6* poor metabolisers. We validated this model by comparing the achieved pharmacokinetic parameters with diverse results from the literature. The presented PBPK model describes the pharmacokinetics after single and repeated oral atomoxetine doses with regard to *CYP2D6* genotype and phenotype. This model could be utilized for identification of appropriate dosages of atomoxetine in patients with reduced CYP2D6 activity to minimize the adverse events, and to enable personalised medicine.¶

489 No significant effect of *CYP3A*, *ABCB1*, *POR* and *NR1I2* polymorphisms on acute rejection and nephrotoxicity in the first 3 months post kidney transplantation in patients receiving tacrolimus

Rong Hu[1], Daniel T Barratt[1], Janet K Coller[1], Benedetta C Sallustio[1,2], Andrew A Somogyi[1]. Disc of Pharmacology, Univ of Adelaide[1], Adelaide, SA; Dept of Pharmacology, Queen Elizabeth Hospl[2], Adelaide, SA.

Introduction. Tacrolimus is a first line immunosuppressant used after kidney transplantation but with extensive inter-individual variability in PK and PD. Low or high tacrolimus concentrations are associated with acute rejection and nephrotoxicity, respectively. SNPs in its major metabolising enzyme (*CYP3A4/5*), P-glycoprotein efflux transporter (*ABCB1*), their expression regulator Pregnane X Receptor (*NR1I2*), and cytochrome P450 reductase (*POR*), have been studied for their effects on tacrolimus PK (Hesselink et al, 2014; Kurzawski et al, 2017). However, there are few studies on their effects on PD, especially in the first 3 months post-transplantation when acute rejection occurs more frequently.
Aims. To investigate the impact of *CYP3A4/5*, *ABCB1*, *NR1I2* and *POR* SNPs on acute rejection and nephrotoxicity in kidney transplant patients receiving tacrolimus in the first 3 months post-transplant.
Methods. A total of 165 kidney transplant recipients and 129 donors were included in this study. Biopsy- or clinical observation-confirmed acute rejection, delayed graft function (DGF) and eGFR data were collected from case notes. Acute rejection and DGF were analysed as binomial outcomes (Y/N) while eGFR (unit: ml/min/1.73m^2) as continuous variables. Genotyping was performed for: *CYP3A5*3*; *CYP3A4*22*; *ABCB1* 61A>G, 1199G>A, 1236C>T, 2677G>T, 3435C>T; *POR*28*; and *NR1I2* 8055 C>T, -25385C>T, 63396C>T. Recipient and donor genotype and predicted *ABCB1* haplotype (PHASE) differences in recipients with acute rejection and DGF in 3 months post-transplant, and 1- and 3-month log-transformed eGFR, were tested by χ^2 or Fisher's exact tests, and linear mixed effects models, respectively.
Results. No recipient or donor genotypes/haplotypes had a significant effect on occurrence of acute rejection (P>0.2), DGF (P>0.1), or eGFR (P>0.02) after adjusting for multiple testing (False discovery rate (α=0.05), P=0.002).
Discussion. Tacrolimus metabolism- and transport-related genetic factors do not significantly affect acute rejection or nephrotoxicity in the first 3 months post kidney transplantation.

[1] Hesselink D.A. et al. (2014) Clin Pharmacokinet, 53(2): 123-39.
[2] Kurzawski M. et al. (2017) Pharmacogenet Genomics. 2017;27(10):372-7.¶

490 *ABCB1* pharmacogenetics in Papua New Guinea HIV/AIDS patients and association with efavirenz CNS/Psychiatric adverse effects

Helena Van Schalkwyk[1], Joseph Tucci[2], Paul Pumuye[3], Daniel Barratt[1], Andrew A Somogyi[1] Disc Pharmacol, Univ Adelaide[1], Adelaide, SA; Dept of Pharmacy & Applied Science, La Trobe Univ[2], Bendigo, Vic; School of Medicine and Health Sciences, Univ Papua New Guinea[3], Boroko, Papua New Guinea.

Introduction. Papua New Guinea (PNG) has the highest prevalence of HIV/AIDS in the Pacific with efavirenz as the main treatment. *ABCB1* encodes the P-glycoprotein efflux transporter which is important for drug disposition, and *ABCB1* genotype has been linked to efavirenz CNS/Psychiatric adverse effects (Dickinson et al., 2016). However, nothing is known about key *ABCB1* SNPs in the PNG population. We hypothesised that *ABCB1* genetics would be associated with efavirenz CNS/Psychiatric adverse effects in PNG HIV/AIDS patients.
Aims. To determine the frequency of *ABCB1* 61A>G, 1199G>A, 1236C>T, 2677G>T and 3435C>T SNPs and haplotypes in PNG HIV/AIDS patients receiving efavirenz and examine genotype/haplotype differences in the incidence of CNS/Psychiatric adverse effects.
Methods. Demographic and clinical data, including CNS/Psychiatric adverse effects, and saliva were collected from 51 PNG HIV/AIDS patients. Salivary DNA was genotyped for *ABCB1* SNPs and allele frequencies compared to other populations (Caucasian, East Asian, African) (Auton et al., 2015). *ABCB1* haplotypes were inferred by PHASE. Incidence of CNS/Psychiatric adverse effects was compared between *ABCB1* genotypes and haplotypes by Fisher's exact tests.
Results. PNG HIV/AIDS patients have a high frequency of 1236T (82%), 2677T (62%) and 3435T (66%) alleles compared to other populations (14-63%, 0-13% and 15-52%, respectively). No variant alleles were observed for 61A>G and 1199G>A. There were no significant genotype/haplotype differences in CNS/Psychiatric adverse effects ($p>0.15$).
Discussion. PNG HIV/AIDS patients exhibit very high frequencies of key *ABCB1* SNPs which may have important implications for P-glycoprotein substrate drugs in this population. However, no significant association with efavirenz adverse effects was detected in this small study, and larger studies incorporating efavirenz PK are required.

Dickinson et al. (2016) Clin Pharmacokinet 55:861-873.
Auton et al. (2015) Nature 526:68-74.¶

491 Therapeutic drug monitoring of voriconazole

Kanika Chaudhri[1,2], Jane E Carland[1,3], Sophie L Stocker[1,3], Kenneth M Williams[1,2], Garry G Graham[1,2] & Deborah JE Marriott[4], Richard O Day[1,2,3]. Dept of Clin Pharmacol and Toxicol, St Vincent's Hosp[1], Darlinghurst, NSW; School of Med Sci, Univ of NSW[2], Kensington, NSW; St Vincent's Clin School, Univ of NSW[3], Kensington, NSW. Dept Clin Microbiol & Infectious Diseases, St Vincent's Hosp[4], Darlinghurst, NSW.

Introduction. Voriconazole is used to treat invasive fungal infections. It is an ideal candidate for therapeutic drug monitoring (TDM) as it has non-linear PK, a narrow therapeutic index and large inter-patient variability. Guidelines for both voriconazole dosing and TDM (target trough concentrations 1-5 mg/L) are available.
Aims. To examine voriconazole dosing and monitoring at St Vincent's Hospital and determine compliance with guidelines.
Methods. A retrospective audit (1st Jan to 31st Dec 2016) of voriconazole dosing and TDM was undertaken. Patient demographics, voriconazole dosing history and plasma concentrations were collected from medical records. Voriconazole trough concentrations were predicted using a Bayesian dose prediction software (DoseMe, Brisbane).
Results. Serum samples (n=417) were collected from 94 patients during 127 courses of therapy. For po therapy, the first and second loading doses and initial maintenance dose were concordant with guidelines in 20%, 17% and 86% of courses, respectively. For iv therapy, the first and second loading doses and initial maintenance dose were concordant with guidelines in 22%, 26% and 42% of courses, respectively. The most commonly prescribed dose was 200 mg. Voriconazole concentrations were obtained for 104/127 therapies. There was marked variability in the timing of the first serum sample in the course of therapy (median: before 5th dose, range: before 1st – 22nd dose). Of the first serum samples collected, 24% were "true" trough concentrations (median: 1.7 mg/L, range: 0.1 – 4.3 mg/L). Approximately 80% of the predicted trough concentrations were within the target range; 20% were <1 mg/L. Only one of the courses with sub-therapeutic predicted trough concentrations had a dose increases.
Discussion. Compliance with voriconazole guidelines was poor. Further, when trough concentrations were outside the guideline recommended therapeutic range no change was seen in dosing. The disparity between voriconazole prescribing and monitoring observed implies a need for improved guidance for clinicians to optimise patient outcomes. Bayesian dose prediction software has the potential to support TDM for voriconazole.

492 Antithrombotic drug-drug interaction alerts in MedChart™

Amanda Crawford[1], Paul Chin[1,2], Matt Doogue[1,2]. Department of Medicine, University of Otago[1], Christchurch, NZ; Department of Clinical Pharmacology, Canterbury District Health Board[2], Christchurch, New Zealand

Introduction. Concomitant use of two antithrombotic medications (antiplatelets or anticoagulants) is associated with increased risk of bleeding. Public hospitals in Christchurch, NZ use MedChart™, a computerised physician order entry system that has been locally configured with prescribing alerts that trigger against antithrombotic drug-drug interactions (DDIs).
Aims. To evaluate the rate of antithrombotic DDI alerts and prescriber responses to these alerts.
Methods. MedChart™ alert data from 1 August to 31 December 2016 were extracted and rates of antithrombotic DDI alerts were determined. A subset of the alerts were reviewed in detail. Analysis of prescription changes attributed to the alert and issues contributing to alert fatigue were also performed.
Results. During the study period 1011 antithrombotic DDI alerts were recorded (mean 7 per day) corresponding to an alert rate of 48/10,000 total prescriptions. Oral anticoagulant-oral antiplatelet alerts comprised of 62% (624/1,011) of these DDI alerts. Of 280 alerts assessed, 81% (228/280) were 'clinically appropriate'. Prescribers changed antithrombotic prescriptions within 30 minutes of triggering DDI alerts on 28% (79/280) of occasions. The combination of enoxaparin and dabigatran was associated with 34 alerts, of which 88%(30/34) were 'clinically appropriate' and 74% (25/34) were associated with a change in antithrombotic prescription within 30 minutes of the alert firing.
Discussion. Targeted clinical decision support can reduce high risk prescribing. However, even carefully constructed alerts targeting the highest risk prescribing has specificity considerably below 100%. It is important to assess temporally proximal changes to prescriptions following an alert, and not just focus on the decision at the point of the alert. This data will inform further development of clinical decision support.

493 Prescribing based on the effective dose 50 (ED50)

Simon B Dimmitt[1], Hans G Stampfer[2], Jennifer H Martin[3]. Division of Internal Medicine[1] and Psychiatry[2], University of Western Australia; School of Medicine and Pharmacology,[3] University of Newcastle, NSW.

Introduction. Undesirable on- and off-target effects of pharmacotherapy are mostly dose-related. The prescriber may avoid these with knowledge of a drug's effective dose 50 (ED50), which can be defined as the mean population dose necessary to achieve half of the maximum possible drug effect (Emax). ED50 may be based on receptor occupancy or effect, clinical surrogates or outcomes and can guide dose optimisation.
Aims. To provide an ED50 reference for routine cardiovascular drugs, to facilitate optimal prescribing.
Methods. Clinical studies which addressed dose response were sought through best Reviews and PubMed.
Results.

	ED50 (mg)	Approved doses (mg)	Approved doses as a ratio of ED50
LDL-lowering Rx			
Simvastatin	15	5 - 80	0.3 - 5.3
Pravastatin	40	10 - 80	0.25 - 2
Atorvastatin	2	10 - 80	5 – 40
Ezetimibe	0.3	5 - 10	17 - 33
PLATELET ANTI-AGGREGANT Rx			
Aspirin	40	50 - 100	1.2 - 2.5
Clopidogrel	30	75	2.5
ANTIHYPERTENSIVE Rx			
Hydrochlorothiazide	10	12.5 - 25	1.2 - 2.5
Metoprolol	30	50 - 100	1.6 - 3.3
Amlodipine	2	5 - 10	2.5 – 5
(T2DM: Metformin	2000	500-2000	0.25 – 1.0)

Discussion. ED50 centres a drug's dose response curve for a population. Benefits plateau above ED50, whilst a variety of adverse events continue to increase. Mid-range low density lipoprotein (LDL) concentrations and blood pressure (BP) correlate with cardiovascular outcomes but total mortality at low LDL and BP plateaus and may increase related to adverse events. Benefit and risk of a drug should be established by commencement at ED50 and careful measurement of the clinical effects with titration down if not tolerated and up to achieve required efficacy.¶

494 'Mrs Have-A-Chat': Pilot study showing that following up an "AdherenceCheck" every two weeks for 9 months improves the management of medicines in the older-aged living in a rental retirement village

Sheila A Doggrell[1], Morna Atkinson[1], Kaileen Lynch[1] and Vincent Chan[2]. Faculty of Health, Queensland University of Technology[1], Brisbane, QLD and School of Health and Biomedical Sciences[2], RMIT, VIC

Introduction. We have shown that the older-aged living in a low socioeconomic, rental retirement village have a low adherence to medicines and a poor understanding of their illnesses (Doggrell & Kairuz, 2012), and that this is not improved by an "AdherenceCheck, which was based on the "MedsCheck" (Doggrell, 2017).
Aims. The aim was to determine whether following up an AdherenceCheck every two weeks for 9 months had any effect on the ongoing management of medicines by the older-aged living independently in a rental retirement village.
Methods. After we assessed the management of medicines by the older-aged living in the village, using semi-structured interviews, we delivered to each of them a personalized "Action Plan" to help them manage their medicines. Then, we followed-up 2 weekly with phone calls or visits to discuss the Action Plan. Nine months later we reassessed their management of medicines.
Results. The 27 participants at the rental retirement village had a mean age of ~80 years, 59% were non-adherent or at risk of being nonadherent, and only 33% had a good knowledge of their medicines/illnesses. After 9 months, 9 participants were lost to the study: 6 had left the village, 2 withdrew, and 1 had died. Of the remaining 18 subjects; at baseline, 50% were nonadherent and 31% had a good knowledge of their medicines/illnesses. After the 9 months of follow-up, only 17% participants remained nonadherent, and 57% had a good knowledge of their medicines/illnesses.
Discussion. The management of medicines by the older-aged living in a low socioeconomic rental retirement villages is poor, and there is evidence from this pilot study, that following up an AdherenceCheck/Action Plan every two weeks for 9 months improves this.

Doggrell SA, Kairuz T. (2012) J Pharmac Pract Res 42:208-12.
Doggrell SA. (2017) Int J Clin Pharmac 39:443-9.

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495 Making Adverse Drug Reactions Visible

Matthew Doogue[1,2], Richard McNeill[2], Mary Young[2], John Wilkinson[2], Sandra Pugh[2], Valya Sylevych[2], Chris Warren[2], QianYi Chua[2], Niall Hamilton[2], Ignatius Chua[2], Heather Isenman[2], Murray Barclay[1,2], Paul Chin[1,2]. Department of Medicine, University of Otago[1]; Clinical Pharmacology, Canterbury District Health Board[2], Christchurch, New Zealand.

Introduction. Adverse drug reactions (ADRs) cause harm to patients and add unnecessary costs to the health system. Every patient admitted to hospital has their ADR history recorded on the medication chart. Every patient discharged from hospital has diagnoses coded, including ADRs, using the "International Statistical Classification of Diseases and Related Health Problems" (ICD-10). However, this information is of variable quality and under used in patient care.
Aims. To increase the accessibility and utility of ADR data. To describe the incidence and prevalence of ADRs in a tertiary hospital.
Methods. Stakeholder user requirements were established. An ADR incidence dashboard of ADR coding data extracted from hospital coding data was developed. An ADR prevalence dashboard of patient ADR histories extracted from the ePrescribing software was developed. The ADR dashboards were evaluated by clinical governance groups. Canterbury District Health Board (CDHB) data were evaluated using the dashboards. One year of coding data and 3 months of prescriptions were examined.

	Incidence (new ADRs)	Prevalence (n=4,421)
Total ADRs	4,427 per year (7.6 per 100 admissions)	8,643
ADRs to Penicillin	201 per year	1,293
Anaphylaxis to penicillin	11 per year	98

Results. The incidence of coded ADRs at CDHB is 7.6% of admissions. The prevalence of ADRs in CDHB inpatients is 50% with a median of 1 ADR per patient (range 1-21). Penicillin antibiotics is the most prevalent class of drugs with ADRs. Non-drug reactions were 8.8% of ADR entries in electronic medication charts.
Discussion. Clinical dashboards were successfully developed to provide access to ADR data. Limitations include inconsistent taxonomies between data sources and non-coded text fields (e.g. the reactions recorded in the prescribing software). The dashboards allow rapid interrogation of hospital ADR data including time trend and data quality. The next step is implementation of these tools in clinical practice to improve the veracity of ADR diagnoses.

496 Severe cutaneous adverse reactions and the (in)accuracy of medicines information sources.

Matthew Doogue[1,2], Marie-Claire Morahan[2], Elle Coberger[2], Paul Chin[1,2]. Department of Medicine, University of Otago[1]; Clinical Pharmacology, Canterbury District Health Board[2], Christchurch, New Zealand.

Introduction. In the preparation of New Zealand consumer medicines information (CMIs) we find frequent inconsistencies in adverse drug reactions (ADRs) recorded in commonly used sources of medicines information. Severe cutaneous adverse reactions (SCAR) is the most feared type of ADR. The drugs causing SCAR have been systematically identified by the RegiSCAR group (www.regiscar.org) and this has been used as the definitive source to inform our CMIs (www.mymedicines.org.nz/cdhb). Incorrect warnings about SCAR in medicines information can lead to incorrect clinical decisions.
Aim. To evaluate the accuracy of medicines information sources' warnings of potential severe cutaneous adverse drug reactions.
Methods. For medicines in the MyMedicines database, we defined their SCAR risk using RegiSCAR publications. We compared this list with the SCAR ADRs recorded in four widely used sources of medicines information: Micromedex®, Lexidrugs®, the New Zealand manufacturer's product information (PI) and the New Zealand Formulary (NZF).
Results. There were 41 medicines in the MyMedicines database causally associated with SCAR. Of these 37, 34, 32 and 34 had SCAR warnings in Micromedex®, Lexidrugs®, the PI and the NZF, respectively – true positives. Of 321 medicines not causally associated with SCAR 24, 30, 25 and 18 had SCAR warnings in Micromedex®, Lexidrugs®, the PI and the NZF respectively – false positives.
Discussion. ADRs are inconsistently recorded in medicines information. The limited clinical data at the time of registration results in under-recording of ADRs. Conversely, medico-legal caution and failure to control for placebo data results in over-recording of ADRS. Consideration of individual ADRs across all drugs lead to more accurate risk assessment than consideration of all ADRs in individual drugs. For most ADRs there is an existing body of literature that can be used to provide more accurate risk assessments than are currently provided.¶

497 Peri-operative medication dosing in obese elective surgical patients: a systematic review of clinical studies

Zahid Hussain[1], Colin Curtain[1], Corinne Mirkazemi[1], Syed Tabish R. Zaidi[1]
[1] Division of Pharmacy, School of Medicine, University of Tasmania, Hobart, TAS, Australia.

Introduction. Despite an increasing number of obese patients requiring elective surgery, there is a lack of guidelines about medication dosing in such patients.
Aims. To systemically review the dosing and outcomes of peri-operative medications used in obese elective surgical patients, and develop practical dosing recommendations for commonly used medications.
Methods. Medical subject headings and general key words were used to systematically search multiple databases (PubMed, EMBASE, Cochrane Library and CINAHL). Studies comparing the dosing of medications in obese patients undergoing surgery were included if they had a non-obese control or comparative dosing scalar group.
Results. Thirty-three studies of six drug classes were include; anaesthetics (n=6), muscle relaxants (n=10), neuromuscular reversal agents (n=3), analgesics (n=2), antibiotics (n=5), and anticoagulants (n=7). A variety of dosing scalars and/or recommendations were identified. Ideal body weight was the preferred dosing scalar for non-depolarizing muscle relaxants, and neuromuscular reversal agents. For anaesthetic agents, lean body weight was used for induction of anaesthesia and total body weight was preferred for the maintenance of anaesthesia. Total body weight was found to be suitable for dosing muscle relaxants whereas corrected or ideal body weight were suitable weight scalars for dosing morphine. The standard 2 g dose of cefazolin appeared effective in the prevention of surgical site infections. For anticoagulants, body mass index stratified dosing of enoxaparin appeared effective for venous thromboembolism prevention.
Discussion. Limited data suggest that clinicians should consider each class of medication when selecting a dose for obese surgical patients. Routine use of fixed dosing regimen is likely to under- or overdose obese patients thus predisposing them to adverse drug events or treatment failure leading to patient harm.

498 Audit of Individual Patient Use Applications for High Cost Medicines at a Tertiary Hospital

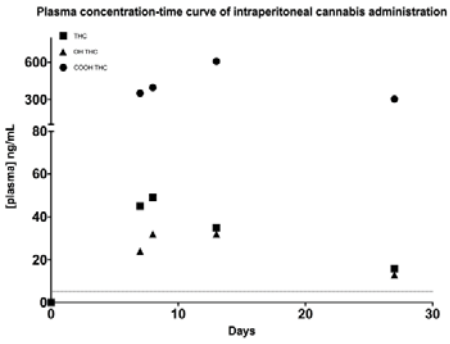
Joshua M. Inglis[1], Gillian E. Caughey[1], Sepehr Shakib[1,2]. Clinical Pharmacology Department, Royal Adelaide Hospital[1], Adelaide, SA; Discipline of Clinical Pharmacology, School of Medicine, University of Adelaide[2], SA.

Introduction: High-cost medicines are often used for rare diseases and non-approved indications. Clinicians in South Australia must apply to their Drug and Therapeutics Committee (DTC) for individual patient use (IPU) of medicines which exceed >$10,000 per treatment course.
Aims: To examine the characteristics of IPU applications for high-cost medicines at a large teaching hospital.
Methods: We conducted a retrospective audit of IPU applications for high-cost medicines between January 2015 and December 2015 at the Royal Adelaide Hospital, South Australia. Information obtained included the medicine name, approval status, cost, level of evidence to support the application and nominated monitoring outcome. Monitoring outcomes were categories into subjective and objective and a judgment made on whether a third party could determine the efficacy of the funded treatment from the patient's medical records using the information provided.
Results: A total of 87 IPU applications were examined. All except one (n=86, 98.85%) of these applications were approved resulting in an annual cost of $1,339,203. The most common high-cost medicines were rituximab (n=33, 37.93%), abacavir/dolutegravir/lamivudine (n=10, 11.49%), infliximab (n=8, 9.20%) and posaconazole (n=5, 5.75%). Half of all applications (n=45, 51.72%) provided no supporting evidence and when evidence was included it was often NHMRC Level III or below (n=28, 32.18%). Of all applications, approximately half (n=41, 47.13%) proposed an objective monitoring outcome but very few (n=8, 9.20%) contained sufficient information for a third party to make a determination from the patient's medical records on whether the approved medicine had been efficacious. For renewal applications, the efficacy of the previously funded treatment course was described in over half of all cases (n=15, 68.18%).
Discussion: This study confirms the considerable cost associated with funding high-cost medicines. Applications were often based on low levels of evidence, making it difficult to assess the benefit and cost-effectiveness of funding these treatments. Furthermore, the monitoring outcomes provided are rarely objective or evaluable, posing challenges for auditing the efficacy of the course being funded. These findings have informed change to the IPU application process for clinicians seeking funding for high-cost medicines at our institution.¶

499 Cannabinoid toxicity post human intraperitoneal injection

Catherine J Lucas[1], Jennifer H Martin[1], Stephanie E Reuter[2], Peter Galettis[1]. Discipline of Clinical Pharmacology, University of Newcastle[1], Newcastle, NSW, Australia; School of Pharmacy and Medical Sciences, University of South Australia[2], City, SA, Australia.

Introduction. Medicinal cannabis is able to be prescribed under the provision of a controlled drug in the Australian Poisons Standard. However, multiple laws must be navigated in order for patients to obtain access and imported products can be expensive. Dose-response information for both efficacy and toxicity pertaining to medicinal cannabis is lacking. The pharmacokinetics of cannabis administered by traditional routes has been described but to date, there is no literature pertaining to pharmacokinetics of an intraperitoneal cannabinoid emulsion.



Case description. A cachectic 56-year-old female with stage IV ovarian cancer and peritoneal metastases presented to hospital with fevers, abdominal distension and severe pain, vomiting, anorexia, dehydration and confusion. The patient reported receiving an intraperitoneal injection, purported to contain 12 g of mixed cannabinoid (administered by a deregistered medical practitioner) two days prior to presentation. Additionally, cannabis oil oral capsules were administered in the hours prior to hospital admission.
Results. THC concentrations were consistent with the clinical state but not with the known pharmacokinetics of cannabis nor of intraperitoneal absorption. THC concentrations at the time of presentation were predicted to be ~ 60 ng/mL. Evidence suggests that blood THC concentrations > 5 ng/mL are associated with substantial cognitive and psychomotor impairment. The predicted time for concentrations to drop < 5 ng/mL was 49 days post administration.
Discussion. The unusual pharmacokinetics of the case suggest that there is a large amount unknown about cannabis pharmacokinetics. The pharmacokinetics of a large amount of a lipid soluble compound given intraperitoneally gave insights into the absorption and distribution of cannabinoids, particularly in the setting of metastatic malignancy.¶

500 Clinical relevance of drug-drug interaction alerts

Sylvain M M Meslin[1,2], Melissa T Baysari[1,3], Wu Y Zheng[1,3], Ric O. Day[1,2]. Clinical Pharmacology & Toxicology, St Vincent's Hospital[1], Sydney, NSW; School of Medical Sciences, UNSW[2] Sydney, NSW Australia; Australian Institute of Health Innovation, Macquarie University[3], Sydney, NSW, Australia.

Introduction. Computerised alerts trigger at the point of prescribing to warn prescribers that a drug-drug interaction (DDI) may occur. Although useful in principle, users become desensitised to DDI alerts due to the high number being triggered (Van der Sijs *et al.* 2006)
Aims. To evaluate the potential alert burden and clinical relevance of severe DDI alerts if they were to be enabled in a Sydney hospital.
Methods. Firstly, alert burden was measured by identifying how often DDI alerts would hypothetically be triggered in the system if alerts were operational. Secondly, drug pairs that triggered alerts in the hospital system were entered common DDI compendia to determine the severity of the interaction. Thirdly, a subset of patient cases was presented to an expert panel to determine the perceived clinical relevance of DDI alerts.
Results. In total, 40% (31/78) of patient admissions would experience at least one severe DDI alert. On average, these admissions would have triggered 4.7 DDI alerts. The most frequently triggered DDI alert was between "opioid agonists and opioid antagonists" (25% of all alerts). There was poor agreement between the compendia on what constituted a severe DDI (Fleiss' kappa= -0.01). The expert panel determined the relevance of DDI alerts is dependent on the context, for example, the patient's age and lab results would be important for determining when certain alerts fire.
Discussion. Context factors such as age and lab data should be used to ensure alerts only trigger when relevant to the patient and clinician.

Van der Sijs H (2006) J Am Med Inform 13:138-147

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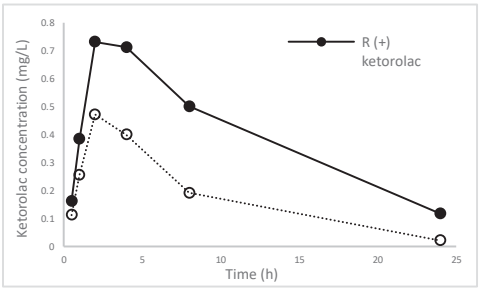
501 A chiral UHPLC-MS/MS method to investigate the pharmacokinetics of enantiomeric ketorolac in human plasma

Yarmarly C. Guerra Valero[1], Usha Gurunathan[2], Jason A Roberts[1,3], Jeffrey Lipman[1,4], Steven C Wallis[1], Suzanne L Parker[1]. Burns, Trauma and Critical Care Research Centre, Univ of Queensland Centre for Clinical Research[1], Brisbane, QLD; Dept of Anaesthes & Perfusion Services, Prince Charles Hosp[2], Brisbane, QLD; Dept of Pharm, Royal Brisbane & Women's Hosp[2], Brisbane, QLD; Dept of Intensive Care Med, Royal Brisbane & Women Hosp[3], Brisbane, QLD.

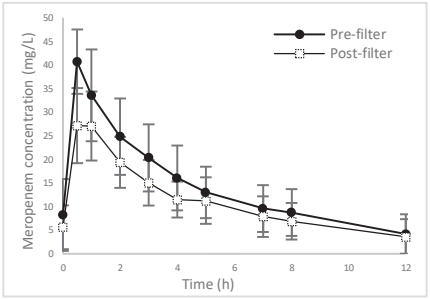
Introduction. Ketorolac tromethamine is used for joint infiltration by orthopaedic surgeons as part of multimodal analgesia. Ketorolac is a racemic mixture of S (-) ketorolac and R (+) ketorolac enantiomers, with the S (-) isomer providing pharmacological activity.
Aims. Establish a simple and validated LC-MSMS method for the determination of S (-) ketorolac and R (+) ketorolac in plasma, suitable for application to a clinical PK study.
Methods. Plasma samples were collected from patients receiving intra-articular ketorolac during total knee or total hip replacement surgery. 100 µL of plasma was extracted using an acetonitrile protein precipitation method, followed by a dichloromethane wash to remove unwanted lipophilic compounds. A chiral Phenomenex Lux Cellulose-3, 50 x 2mm (3µm) column separated S (-) and R (+) ketorolac and the internal standard, [$^2H_4$]-ketorolac. Quantitation was performed using a Shimadzu UHPLC-MSMS 8030+ with electrospray ionisation, using an SRM at 256>>105 (reference ion 256>>77).



Results. The assay met the requirements for a bioanalytical method validation for the measurement of S (-) ketorolac and R (+) ketorolac in plasma across the concentration range of 0.02 to 5 mg/L. Precision was within 10% and accuracy within 3% for both S (-) and R (+) ketorolac. The figure shows the ketorolac PK profiles for a patient undergoing total hip replacement, with maximum concentrations (C_{max}) of 0.47 mg/L for S (-) ketorolac and 0.73 mg/L for R (+) ketorolac, minimum concentrations (C_{min}) were 0.021 mg/L for S (-) ketorolac and 0.117 mg/L for R (+) ketorolac.
Discussion. This accurate and rapid method for the quantification of the enantiomers, (S)-ketorolac and (R)-ketorolac, in plasma has been successfully validated and applied to clinical samples from a PK study of patients undergoing total hip or knee replacement surgery.

501.1 A suite of LC-MSMS assays to investigate the pharmacokinetics of meropenem in critically ill patients receiving renal replacement therapy

Yarmarly C. Guerra Valero[1], Jason A Roberts[1,2], Jeffrey Lipman[1,3], Steven C Wallis[1], Suzanne L Parker[1]. Burns, Trauma and Critical Care Research Centre, Univ of Queensland Centre for Clinical Research[1], Brisbane, QLD; Dept of Pharm, Royal Brisbane & Women's Hosp[2], Brisbane, QLD; Dept of Intensive Care Med, Royal Brisbane & Women Hosp[3], Brisbane, QLD.



Introduction. Maximising effectiveness of and limiting resistance to meropenem requires an understanding of the patient group. Patients requiring renal replacement therapy may experience sub-optimal antibiotic exposures as meropenem is largely renally excreted and recommended dosing regimens have not been validated in these patients.
Aims. To establish validated LC-MSMS methods for bioanalysis of meropenem in plasma, renal replacement therapy effluent (RRTE) and urine, for a clinical PK study [Roberts et al, 2016].
Methods. 10 µL of plasma, RRTE and urine from critically-ill patients undergoing RRT and receiving meropenem were treated with acetonitrile. Meropenem and the internal standard, [$^2H_6$]-meropenem were separated using a SeQuant zic-HILIC 2.1 x 20 mm (5.0µm) column. Quantitation was performed using Shimadzu Nexera 8030+ LC-MSMS, equipped with an electrospray ionisation source, monitoring SRM 383.5>>68 (ref 383.5>>141) for meropenem, and 390>>147 (ref 390>>68) for [$^2H_6$]-meropenem
Results. The assays using microsample volumes for each matrix met requirements for a bioanalytical method validation over the concentration range of 0.2 to 100 mg/L in plasma and RRTE, and 20 to 10,000 mg/L for urine. The figure presents the pre- and post-filter plasma results from three ICU patients on RRT receiving IV meropenem b.i.d. Maximum concentrations (C_{max}) were 37.4 ± 3.2 mg/L for plasma, 18.3 ± 1.6 mg/L for RRTE and 926 ± 532 mg/L for urine.
Discussion. Application of this method may lead to improved clinical study participation for patients with challenging phlebotomies or where the collection of small volumes of sample can reduce the burden of study participation. This suite of methods has been successfully used in a multinational clinical PK trial.
Roberts et al (2016) BMC Infect Dis 16:103

502 Current antimicrobial stewardship (AMS) practices in the Australian community pharmacies

Tasneem Fatima Rizvi, Angus Thompson, Mackenzie Williams, Tabish R Zaidi, Division of Pharmacy, School of Medicine, Faculty of Health, University of Tasmania, TAS, Australia

Introduction**.** Increasing antimicrobial use is one of the modifiable causes of antimicrobial resistance (AMR) that is expected to claim 10 million human lives by 2050. Though the majority of antimicrobials are prescribed in community, little is known about the antimicrobial stewardship (AMS) practices in the Australian pharmacies. Therefore, we report the development, validation and piloting of the first Australian survey to measure the current AMS practices. Method. A questionnaire to measure community pharmacists' current practices of AMS and perceived importance, barriers and facilitators to participate in AMS initiatives was developed based on a literature review and expert opinion. A convenience sample of 140 community pharmacists was selected who were invited to complete the online survey. Cronbach's alpha and exploratory factor analysis (EFA) were used to measure the reliability and validity of the questionnaire, respectively. Results. 85 out of 140 (61%) pharmacists responded to the survey. The majority of the pharmacists were female practicing in metropolitan areas. EFA identified three components confirming a single factor solution for the three scales. Cronbach's alpha for each scale is; perceived importance 0.65, barriers 0.82 and facilitators 0.68. The majority of respondents require better access to patient records (92%), guidelines (62%) and training (52%) to enable their participation in AMS initiatives. The majority of respondents (54%) agreed that GPs are more receptive of a change in dose or duration of an antibiotic recommendation but less receptive if a change in antibiotic choice is recommended (63%). Discussion. A reliable and valid tool was developed to measure community pharmacists' perceptions of AMS that can be used to conduct larger national and international studies. Tasmanian pharmacists were more willing to participate in AMS initiative if additional training, access to locally developed antibiotic guidelines and better access to patients' clinical data is provided to them.
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503 Inappropriate drug prescribing in elderly hospitalised patients with falls and fractures

N Soerjadi[1], W Srikusalanukul[1], A Fisher[1,2]. Dept of Geriatric Medicine, The Canberra Hospital[1], Canberra, ACT, Australia; Australian National University Medical School[2], Canberra, ACT, Australia.

Introduction. Falls and osteoporotic fractures are two major health problems in the elderly. Medications significantly contribute to both risks and prevention of these serious complications.
Aims. To investigate the prevalence of prescribing potentially inappropriate, especially psychoactive, medications and prescribing omissions (especially anti-osteoporotic drugs) in older patients with falls and fractures.
Methods. Data on medications used, demographics and comorbidities were collected in two cohorts of elderly patients (≥ 60 years): 587 medical (mean age 85.7±6.9 years, 63.6% female) and 854 orthogeriatric patients with non-vertebral fractures (mean age 78.10±9.51 years, 73.0% female). In medical patients risk of osteoporosis was estimated (Osteoporosis Self-assessment Tool, OST). The appropriateness of medication use was assessed by Beers Criteria 2015.
Results. Amongst medical patients, there were 137 (23.3%) with history of falls and 98 (16.7%) with previous fractures. At admission, 55 (40.1%) of fallers and 23 (23.5%) of patients with fractures have been using at least one of the following classes of medications known to be associated with falls and fractures: antidepressants (selective serotonin reuptake inhibitors, tricyclics), benzodiazepines or antipsychotics (haloperidol, risperidone, olanzapine, quetiapine). High risk of osteoporosis (OST<-3) was found in 352 (66.9%) patients, 122 (34.7%) of whom were receiving falls-risk medicines, but only 66 (18.8%) have been prescribed anti-osteoporotic drugs (bisphosphonates, denosumab). OST<-3 was significantly and independently associated with age >75 years (OR 15.0, 95%CI 6.05-37.21, p<0.001), history of fractures (OR 2.5, 95%CI 1.23-4.90, p=0.011) and falls (OR 1.9, 95%CI 1.09-3.44, p=0.024). Anaemia (haemoglobin<120g/L), mostly iron deficient, was found in 72 (52.6%) fallers and 54 (55.1%) patients with fractures, but iron supplements were used only by 8.3% and 13.0%, respectively; at discharge the prescriptions improved minimally. Among orthogeriatric patients, prior to admission, 239 (28.0%) were using falls-risk medicines, 620 (72.6%) were anaemic, but only 139 (16.3%) received anti-osteoporotic drugs and only 41 (6.6%) anaemic individuals were prescribed iron supplements.
Discussion. Deprescribing potentially inappropriate drugs and rationale use of anti-osteoporotic and anti-anaemic therapies is essential for prevention falls and fractures in the elderly.

504 A time and motion study of phlebotomists' work

Sophie L Stocker[1, 2], Vasu Mehndiratta[1], Melissa T Baysari[1, 3], Mirela Prgomet[3], Graham Jones[5], Jane E Carland[1, 2], Richard O Day[1, 2, 5]. Dept of Clin Pharmacol and Toxicol, St. Vincent's Hospital[1], Darlinghurst, NSW; St. Vincent's Clinical School, Univ of NSW[2], Kensington, NSW; Aus Institute of Health Innovation, Macq Univ[3], North Ryde, NSW; Sydpath[4], Sydney, NSW; School of Med Sci, Univ of NSW[5], Kensington, NSW.

Introduction. Therapeutic drug monitoring (TDM) involves adjusting drug dosage regimens according to circulating concentrations of the drug. Critical to this process is obtaining blood samples (usually collected by phlebotomists) at the appropriate time in the dosing interval. Due to the busy nature of the clinical setting, TDM samples are often collected at the incorrect time. No research has explored phlebotomists' work and their role in the TDM.
Aims. To collect time and motion data on the work of phlebotomists and to explore the opinions and experiences of phlebotomists about their working environment.
Methods. Observational time and motion data of ward phlebotomists (n=5, 45 hours) was collected using the Work Observation Method by Activity Timing (WOMBAT) software. Descriptive statistics were used to determine the proportion of total observed time spent on tasks. Participating phlebotomists also partook in a focus group.
Results. Phlebotomists predominantly spent time collecting blood (54%), in professional communication (15%) and in transit (15%). Phlebotomists spent 14% of their time multitasking and were interrupted every 19 minutes. Social activities, including lunch and bathroom breaks, accounted for 13% of their time. Phlebotomists raised concerns about their high workload, predominately attributed to understaffing and patient care tasks beyond blood collection, which contributed to physical fatigue and stress.
Discussion. Phlebotomists spent the majority of their time in blood collection. Professional communication was also an important component of their daily tasks and was most commonly associated with multitasking and interruptions. This finding was recognised by the phlebotomists. Phlebotomists displayed similar multitasking to nurses (14% vs 12%) however had a much more frequent interruption rate (19 mins vs 49 mins)[1]. The heavy workload experienced by the phlebotomists contributes to the difficulty of collecting TDM samples at regimented times. Increasing the number of ward phlebotomists and/or recruiting a dedicated TDM phlebotomist may help overcome this challenge.
[1]Westbrook J (2009) Int J Med Inform 78:S25-33¶

505 Impact of deprescribing interventions in older hospitalised patients on prescribing and clinical outcomes: a systematic review of randomised trials

Janani Thillainadesan[1], Danijela Gnjidic[2], Sarah Green[3], Sarah N Hilmer[1,4]. Dept of Aged Care, Royal North Shore Hosp, Sydney, NSW[1]; Fac of Pharmacy, Univ of Sydney, Sydney, NSW[2]; Pharmacy Dept, Royal North Shore Hosp, Sydney, NSW[3]; Kolling Institute, Univ of Sydney, Sydney, NSW[4].

Introduction. Polypharmacy and potentially inappropriate medications (PIMs) are prevalent in older inpatients, and are associated with adverse drug reactions, falls, confusion, hospitalisation, and death. Deprescribing is one intervention to reduce polypharmacy and PIM use.
Aims. To investigate the efficacy of deprescribing interventions to reduce PIMs and impact on clinical outcomes in older inpatients.
Methods. MEDLINE, Embase, Informit, International Pharmaceutical Abstracts, Scopus, PsycINFO, Cochrane Central Register of Controlled Trials, and CINAHL were searched for randomised controlled trials (RCTs) in English from 1996 to April 2017. Two researchers independently screened retrieved articles. RCTs reporting on deprescribing interventions to reduce PIMs in older hospitalised adults were eligible. Data was extracted and study quality of all included RCTs was assessed. The primary outcome of interest was reduction in PIMs. Where available other clinically relevant outcomes were assessed.
Results. Nine RCTs (n=2522 subjects) met the inclusion criteria. A high risk of bias was present among the studies. Deprescribing interventions were either pharmacist-led (n=4), physician-led (n=4), or multidisciplinary team-led (n=1). Six studies used an explicit tool to identify PIMs. In terms of the primary outcome, 7 of the 9 studies reported a statistically significant reduction in PIMs in the intervention group. There was significant heterogeneity in outcome measures and reporting. Other reported clinical outcomes included impact on drug related problems, health related quality of life (n=2), mortality (n=3), hospital readmissions (n=4), falls (n=3), and functional status (n=2). The results were mixed with most reporting no statistically significant difference between control and intervention groups.
Discussion. The available evidence suggests that deprescribing interventions are feasible and safe in older adults in hospital, and are efficacious at reducing PIMs. However, the current evidence is limited and of low quality. High quality RCTs with clinical outcomes relevant to older adults are required.

506 A Multicentre Open-Label Pharmacokinetic-Pharmacodynamic Study of Febuxostat in Patients with Chronic Gout

Bishoy Kamel[1,2], Garry G Graham[1,2], Kenneth M Williams[1,2], Sophie L Stocker[2,3], Jane E Carland[2,3], Kevin D Pile[4], Louis E McGuigan[5], Ian J Portek[6], Neil W McGill[7], Richard O Day[1,2,3]. School of Med Sc, Univ of New South Wales[1]; Dept of Clin Pharmacol and Toxicol, St Vincent's Hosp[2]; St Vincent's Clin School, Univ of New South Wales[3]; Dept of Med, Western Sydney Univ[4]; Dept of Rheum, Narrabri Hosp[5]; Dept of Rheum, St George Hosp[6]; Dept of Med, Univ of Sydney[7].

Introduction. There are conflicting data concerning the effect of renal function on the pharmacokinetics and response to febuxostat (Fbx).
Aims. To explore relationships between the concentrations of serum urate (SU) and plasma Fbx in patients with chronic gout and examine the influence of renal function on the plasma concentrations of Fbx and the efficacy of Fbx.
Methods. Baseline demographics including SU and serum creatinine concentrations were collected. Plasma Fbx concentrations and SU were measured at four times during long term treatment with Fbx over the dosage interval (24 h). Data is presented as mean ± S.D.
Results. Chronic gout patients (20 males, 6 females) were recruited. The duration of Fbx treatment (40-120 mg/day) was 6 weeks to 66 months. Baseline SU and eGFR were 0.59 ± 0.09 mmol/L and 61 ± 24 mL/min, respectively. Fbx 40 (n=8), 80 (n=17) and 120 (n=5) mg/day achieved similar reductions of SU; 0.34 ± 0.09, 0.36 ± 0.11 and 0.31 ± 0.07 mmol/L, respectively. Target SU ≤ 0.36 and ≤ 0.30 mmol/L were achieved by 90% (24/26) and 77% (20/26) of patients, respectively, with Fbx doses of up to 120 mg/day. At Fbx 80 mg daily, the reduction in SU was 0.37 ± 0.09 and 0.34 ± 0.13 mmol/L in patients with eGFR < 60 (n=9) and ≥ 60 (n=8) mL/min, respectively. At Fbx dosage of 80 mg daily, trough concentrations of Fbx were significantly higher in patients with eGFR < 60 mL/min (0.17 ± 0.11) than those with eGFR ≥ 60 mL/min (0.03 ± 0.01) (P= 0.009). Renal function had no significant effect on peak Fbx concentrations. There was a 50-fold fluctuation in plasma Fbx over 24 h while SU did not fluctuate significantly over this time.
Discussion. Higher trough Fbx concentrations in patients with eGFR < 60 mL/ min may be due to the retention of Fbx-glucuronide and the subsequent regeneration of the parent drug. Renal function does not influence the hypouricaemic response to Fbx. We suggest that the small fluctuation in SU over 24 h is due to the long half-life of urate (20 to 30 h). A larger sample size is required to confirm present results. The small fluctuation in plasma urate over 24 h is due to long half-life of urate and possibly prolonged hypouricaemic effects of Fbx.

1. Mayer MD et al (2005) Am J Ther 12(1):22-34.
2. Hira D et al (2015) J Pharmacology 96(1-2):90-8.
3. Becker MA et al (The CONFIRMS trial) (2010) Arthritis Res Ther 12(2):R63.

508 The perceived impact of medicines, foods and substances taken by mother on their breastfed baby.

Hilai Ahmadzai[1], Lisa BG Tee[1], Andrew Crowe[1] School of Pharmacy, Curtin University, Bentley, WA, Australia.

Introduction. It has been shown that the types and rate of adverse drug reactions (ADRs) experienced by breastfed infants whose mothers are taking medications has not been well defined and are notoriously under reported. Those that are reported often have crucial information missing which makes it difficult to draw valid conclusion mainly due to a lack of a standardized reporting system.
Aim. The objective of this study was to ascertain whether the breastfed baby of a nursing mother experienced any ADRs due to the medications taken by the mother and the impact of such a reaction on the continuation of breastfeeding and/or mother's treatment.
Methods. This study was conducted as an anonymous online survey consisting of 42 questions divided into 6 sections. Data was collected over a period of 6 months. Data was analysed using SPSS software.
Results. A total of 360 responses were obtained. Approximately 40% of the breastfeeding mothers surveyed indicated that they took one or more medication(s) while breastfeeding. About one third of the respondents indicated that they were concerned about the transfer of medications to their baby. An ADR in the breastfed baby led to discontinuation of treatment in 20 women and cessation of breastfeeding in another 8 women. Only 2 reports of an adverse drug reaction was confirmed to have been reported by the healthcare professional to a regulatory body.
Discussion. Medication use in breastfeeding is quite prevalent and consequently the occurrence of ADRs in the breastfed infant is also possible. An adverse drug reaction in a breastfed baby can lead to treatment discontinuation for the mother or cessation of breastfeeding, with neither being ideal. However, the identification of ADRs in breastfed infants and reporting of these ADRs is likely to be understated.
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509 The effect of deprescribing after chronic polypharmacy on locomotor activity and cognition in a preclinical model

Swathi Ekambareshwar[1,2], John Mach[1,2,3], Gizem Gemikonakli[1,2], Jennifer Debenham[1,2], Caitlin Logan[1,2], David G. Le Couteur[1,4] & Sarah N. Hilmer[1,2,3]. Univ of Sydney, Sydney, NSW[1]. Kolling Institute, Sydney, NSW[2]. Royal North Shore Hosp, Sydney, NSW[3], Concord Hospital, Sydney, NSW[4]

Introduction. Two-thirds of Australians over the age of 75 are prescribed 5 or more drugs concurrently (polypharmacy). Clinical observational studies have shown polypharmacy and increasing exposure to anticholinergic and sedative effects, which can be measured using Drug Burden Index (DBI), are associated with adverse geriatric outcomes, including falls, frailty and cognitive impairment. In older people, interventional studies of deprescribing (withdrawal of medications) are logistically difficult to conduct. A preclinical model to test the effects of deprescribing would help to provide evidence as to the safety and efficacy of deprescribing for global health outcomes.
Aim. To determine the effects of deprescribing on locomotor activity and cognition after chronic exposure of ageing mice to polypharmacy regimens with increasing DBI.
Methods. From 12 to 21 months of age, male C57BL/6 mice were given control diet or feed containing therapeutic doses of commonly used medications. Polypharmacy treatment groups included zero DBI (simvastatin, metoprolol, omeprazole, paracetamol, irbesartan), low DBI (simvastatin, metoprolol, omeprazole, paracetamol, citalopram) and high DBI (simvastatin, metoprolol, oxybutynin, oxycodone, citalopram). The single drugs from the high DBI group were also administered as monotherapy. At 21 months, half of the animals in treatment groups had medications deprescribed (n=14-20 per group). The open field and Barnes Maze were performed at 21 and 24 months.
Results. Preliminary results are shown for a subgroup of the cohort (n=9-12 per group). Deprescribing the high DBI with polypharmacy regimen and citalopram resulted in locomotor activity improvement ($P<0.005$ and $P<0.05$ respectively) when compared to mice that continued treatment. Non-significant improvements in short and long term memory were seen in mice deprescribed the high DBI polypharmacy regimen when compared to those that continued treatment ($P<0.3$).
Discussion. This is the first reported pre-clinical model to examine the safety and efficacy of deprescribing. Our preliminary results show deprescribing medications in the absence of disease does not appear to be harmful and could improve outcomes. Completion of the study is required to confirm these findings in a larger sample.

510 A simple, sensitive and rapid LC-MS/MS method for the simultaneous measurement of anthracyclines, cyclophosphamide and taxanes in breast cancer patient samples

Peter Galettis[1,2,3], Madhu Garg[2,3,4], Jennifer Schneider[2,3,5], Stephen Ackland[2,3,4,5], Jennifer Martin[1,2,3]. Discipline of Clin Pharmacol, Univ of Newcastle[1], Callaghan NSW, Hunter Medical Research Institute[2], New Lambton Heights NSW, Hunter Cancer Research Alliance[3] NSW, Medical Oncology, Calvary Mater Newcastle[4], Waratah NSW, Discipline of Pharmacy and Experimental Pharmacology, Univ of Newcastle[5], Callaghan NSW

Introduction. Tailoring drug dose for anticancer drugs is known to provide better outcomes by maximising drug benefit and minimising toxicity, especially in patients with altered phenotypes such as obesity, advanced age or organ dysfunction. Dose individualization with chemotherapies has been shown to improve patient outcomes and minimise adverse events, yet dose individualization is a challenging task, methodologically and practically. New simple, sensitive, rapid and reproducible methods to simultaneously measure drugs levels in small volumes of patient samples are needed to make it convenient and practical for patients and clinicians.
Aims. To develop a simple, sensitive and rapid LC-MS/MS method for the simultaneous measurement of anthracyclines, cyclophosphamide and taxanes in small volumes of blood samples.
Methods. Deuterated internal standards in acetonitrile are added to small volumes of blood samples (10-50µl) for extraction. Chromatographic separation is achieved using a Kinetex C18 50 x 2.1mm, 1.7µm column with gradient elution of mobile phase starting at 20% acetonitrile with 0.1% formic acid. The compounds are detected by a triple quadruple mass spectrometer (Shimadzu 8060), operating in positive electrospray. Total run time is 5.0 min.
Results. The method is linear over a range of 1–500ng/mL for doxorubicin, epirubicin, docetaxel and paclitaxel, 0.1-50µg/mL for cyclophosphamide covering the expected concentrations in patient samples. Inter-assay precision is between 1 - 15% and inter-assay bias is between -11 – 9% for all compounds. Intra-assay precision was between 0.4 - 6% and intra-assay bias was between -5 – 11% for all compounds.
Discussion. An LC–MS/MS method for determination of anthracyclines, cyclophosphamide and taxanes in very small volumes of blood was developed and validated. This methodological improvement will facilitate personalised dosing of chemotherapy for each patient to provide the best response and reduced side effects. Methods can be adapted for a variety of agents, including novel targeted anticancer therapies.¶

511 Relationship between plasma dolutegravir concentration and cause of anti- HIV therapy discontinuation

Kato M[1], Togami H[1], Fukushima N[1], Kawaguchi S[1], Hirano A[1], Matsumoto S[1], Yokomaku Y[1], Takahashi M[2].
Dept of Pharmacy, National Hosp Organization Nagoya Medical Center[1], Nagoya, Japan; Dept of Pharmacy, National Hosp Organization Suzuka National Hosp[2], Suzuka, Japan

Introduction. Dolutegravir (DTG) is a second-generation HIV-1 integrase inhibitor that is high potent against both wild-type and drug-resistant HIV-1 strains. DTG has a good toleration, few drug interactions, minimal drug resistance and once-daily dosing for treatment-naive patients. Therefore, DTG is approved for use in a broad population of HIV-infected patients. However, there are few data for reasons of DTG discontinuation during antiretroviral therapy.
Aims. In this study, we intended to investigate major causes of DTG discontinuation and relationship with plasma DTG concentrations.
Methods. We examined 656 HIV-1-infected patients (male:female=604:52) who were treated with DTG containing regimen from 2014 to 2016, retrospectively. All patients had been administered with 50mg DTG once daily in combination with other antiretrovirals. Plasma DTG concentrations were determined by our developed LC-MS method. Adverse events were assessed by laboratory data and interview at outpatient clinic.
Results. In 656 patients, 149 patients were therapy-naïve and 507 patients were therapy-experienced for HIV. Of 656 patients, 17 patients (male:female=15:2) discontinued DTG, and switched from DTG to other antiretrovirals. The reasons of DTG discontinuation were adverse events (15 patients), drug interactions (1 patients), and pregnancy (1 patient), respectively. The median duration of DTG administration was 40 weeks (2-77 weeks). The adverse events were rash (7 patients), CNS side effects (3 patients), vomiting (1 patients), diarrhea (1 patient), ALT/AST elevation (1 patient), arthralgia (1 patient), and renal dysfunction (1 patient), respectively. The plasma DTG concentrations were significantly higher (2.5-fold) in patients who had adverse events than in those with no events.
Discussion. These findings suggest that we have to pay attention for rash and CNS side effects during DTG containing antiretroviral regimen, especially. As the patients with adverse events had higher DTG plasma concentrations, Therapeutic drug monitoring for DTG will be useful for preventing various adverse events.

512 Preclinical models to understand the risks of single and multiple concurrent medicines in old age

John Mach[1,2,3], Caitlin Logan[1,3], Doug Drak[1,3], Gizem Gemikonakli[1,3], Swathi Ekambareshwar[1,3], Jennifer Debenham[1,3], Alice E Kane[3,4], Susan Howlett[4], Rafael de Cabo[5], David G Le Couteur[3,6]& Sarah N Hilmer[1,2,3]. Kolling Institute, Sydney, NSW[1]. Royal North Shore Hosp, Sydney, NSW[2]. Univ of Sydney, Sydney, NSW[3]. Dalhousie University, Halifax, Canada[4]. National Institute on Aging, National Institute of Health, Maryland, USA[5]. Concord Hospital, Sydney, NSW[6].

Introduction. Chronic medication use is common in older people. Older people, particularly those with polypharmacy (use ≥ 5 drugs) for multi-morbidity, are rarely included in clinical trials to determine efficacy and safety. Observational studies indicate polypharmacy and increasing Drug Burden Index (DBI: measures total anticholinergic and sedative medication exposure) are associated with impaired physical function in older people. Preclinical models of clinically relevant drug exposures in ageing would be useful to screen for adverse geriatric outcomes prior to marketing.
Aim: To develop a preclinical mouse model to determine whether chronic use of therapeutic drugs (monotherapy or polypharmacy) and/or increasing DBI exposure impair translatable functional outcomes in ageing.
Methods: From 12 months of age, male C57BL/6 mice were fed control diet or feed/water containing therapeutic doses of study drug(s). We tested regimens of five drugs that had Zero DBI (simvastatin, metoprolol, omeprazole, paracetamol, irbesartan), Low DBI (simvastatin, metoprolol, omeprazole, paracetamol, citalopram), High DBI (simvastatin, metoprolol, oxybutynin, oxycodone, citalopram) and single drugs from the High DBI regimen as monotherapy. Functional tests are performed every 3 months throughout life. Power calculations estimate that a sample size of 10-12 per group is required to detect changes in functional measures with treatment.
Results. For the subgroup of animals with data currently available after 6 months of treatment (age 15 and 18 months), compared to control, measures of spontaneous activity in the open field (distance and midzone entries), grip strength (wire hang), nesting scores and frailty score were reduced in the Low DBI, High DBI and citalopram groups (n=25-40, $p<0.05$). Compared to control, muscle endurance (rotarod) was significantly reduced in Low DBI and citalopram after 6 months of treatment (n=25-40, $p<0.05$).
Discussion: We have developed a preclinical model that can detect impaired functional outcomes following chronic treatment with polypharmacy regimens or monotherapy in ageing mice. These methods can be applied to determine and understand mechanisms and reversibility of the risks of medicines to global health outcomes in old age. ¶

513 Prevalence and prediction of adverse drug reactions in older inpatients with hyperpolypharmacy

Patrick W Sutton[1], Rayan Nahas[1], Slade Matthews[1], Peter Carroll [1], Lisa Kouladjian O'Donnell[1] ,Danijela Gnjidic[1] , Emily Reeve [1] , Terry Finnegan[1] ,Jenny Crane[1], Phillip Hoyle[1], James Hardy[1], Kathyrn Sutton[1] ,Fiona Robinson[1], & Sarah N Hilmer[1] ,Kolling Institute, Royal North Shore Hospital[1] Sydney , New South Wales, Australia

Introduction. Adverse drug reactions (ADRs) in hospital carry serious health consequences and increase the burden on the health care system. As the risk of ADRs increases with old age and the number of medications, older patients with hyperpolypharmacy (taking 10≤ medications), are at particularly high risk. Additional clinical and pharmacological risk assessments could help prioritise inpatients for medication review to prevent potentially avoidable ADRs.
Aims. To determine the prevalence of ADRs in older inpatients with hyperpolypharmacy and explore potential predictors for identifying patients who are most likely to have an ADR in hospital.Methods. Patients >65 years with hyperpolypharmacy on admission were recruited prospectively from a tertiary referral teaching hospital in Sydney, Australia. Data collected included gender, age, current medications, Reported Edmonton Frail Scale and Charlson Comorbidity Index. ADRs were detected by review of medical records, assessed for causality using the Naranjo criteria, and classified by drug class. Data was verified by a multidisciplinary panel. T-tests were used to compare clinical characteristics and medication use between patients who did and did not have an ADR.
Results. Sixty nine patients were recruited with a median age of 78 years with 56.5% being female .Preliminary results showed 22.1% of inpatients had an ADR during their admission. Average Naranjo rating for each of the experienced ADRs was 6.9 ± 0.4, with an average of 3.4± 0.2 unknown factors, where a score of 5-8 is probable. Of the 23 ADRs, drug classes responsible were antibiotics (26.1%), diuretics (26.1%), cardiac drugs (21.7%), opioids (8.7%), anticonvulsants (8.7%), and anticoagulants (8.7%).There was no significant difference in frailty, comorbidity index or measures of medication exposure, between patients with and without an observed ADR in hospital. However, those who experienced an ADR in hospital had a significantly longer length of stay (11.1 verses 5.7 days, P<0.05).
Discussion. ADRs in hospital were common in this high risk group. Average Naranjo ratings suggest probable causality but assessment was limited by a high prevalence of unknown factors. Preliminary results show no significant association of patient and medication characteristics with ADRs for older patients with hyperpolypharmacy in the acute setting. Future studies will need to investigate larger sample sizes to confirm these findings. ¶

514 Pharmacometrics to address weaknesses in Australian medical countermeasure product development

Thomas M Polasek[1,2], Felicia Pradera[3], Shane Seabrook[4], Kashyap Patel[1], Emily J Wodward[5], Craig R Rayner[1,6]
d3 Medicine, A Certara Company[1], Melbourne, VIC, Australia; Dept of Clinical Pharmacology, Flinders University[2], Adelaide, SA, Australia; Defence Science and Technology Group, Dept of Defence[3], Melbourne, VIC, Australia; Commonwealth Science and Industrial Research Organisation[4], Melbourne, VIC, Australia; Synchrogenix, A Certara Company[5], Nashville, TN, USA; Monash Institute of Pharmaceutical Sciences, Monash University[6], Melbourne, VIC, Australia.

Introduction. Medical countermeasure (MCM) products are defined as diagnostics, vaccines and therapeutics for the protection of personnel against chemical, biological and radiological (CBR) threats, and emerging infectious diseases.
Aims. To understand Australia's MCM product development capability and capacity and to identify new opportunities in the ecosystem for pharmacometrics.
Methods. An electronic survey of 145 questions was conducted together with 30 min minute structured interviews. Surveys were analysed using descriptive statistics. Technology readiness level (TRL)-guided 'impressions' of capability and capacity were established, de-identified, and presented using heat maps (individual) and summarized (national).
Results. There were 131 completed surveys. Two-thirds identified their primary and secondary positions on the MCM product development value chain as 'translational research/pre-clinical research'. The greatest concentration of activity was at TRL4 and earlier. Late-phase capabilities (i.e., clinical development and manufacturing) were weaker, and very few respondents identified market access as their primary position (5/131). Interviews were conducted with 49 of the survey respondents (37%). Interviews confirmed strong BSL2/3+ *in vitro* capabilities but minimal GxP examples in DMPK, immunoassay, bioanalysis, PD or safety. *In vivo* GLP-compliant non-clinical services had limited diversity and availability. The 2 areas of MCM product development that could benefit most from increased pharmacometrics were non-clinical *in vivo* PK ± PD and toxicology studies (e.g., to replace/inform studies in larger animals that require high level containment, ABSL3/4) and early clinical development (e.g., phase 1 and phase 2a/b).
Discussion. Australia has a dispersed, relatively small but experienced discovery and development community. Pharmacometric approaches could be utilized more broadly to address capability and capacity gaps in the Australian MCM product development ecosystem.¶

515 Intravesical mitomycin C enhances spontaneous phasic contractile activity in the murine bladder

Eliza West[1], Russ Chess-Williams[1], Catherine McDermott[1]. Centre for Urology Research, Faculty of Health Sciences and Medicine, Bond University[1], Robina, QLD, Australia.

Introduction. Mitomycin C (MMC) is the most common cytotoxic drug used for intravesical bladder cancer treatment, but 34.5% of patients experience urological adverse effects including increased urinary frequency, urgency and pain. The effects of MMC on normal bladder function are poorly understood and there are currently no proven treatment options to manage these side effects.
Aims. This study aimed to determine the effects of intravesical MMC on normal murine bladder function 7-days following treatment.
Methods. Aged female C57/BL6JArc mice (Age 36 weeks, n=4 per group) were randomly allocated into 2 experimental groups (Saline/Control or MMC) and given a 1-hour intravesical treatment with saline or MMC (1mg/mL). After 7 days, a whole bladder preparation was used to assess spontaneous contractile activity, and intravesical pressure changes in response to bladder filling (30µl/min), electrical field stimulation (EFS: 1,5,10, 20Hz) and pharmacological agents.
Results. Spontaneous phasic contractile activity was observed in saline treated bladders with a frequency of 2.5±0.29 contractions/min and amplitude of 0.11±0.1 mmHg. Spontaneous activity was increased in MMC treated bladders with a 1.7-fold increase in frequency (4.25±0.48 contractions/min, $p<0.05$) and 3.4 fold increase in the amplitude (0.36±0.13 mmHg, $p>0.05$) of phasic contractions. Pressure responses to EFS, the muscarinic agonist carbachol, the purinergic agonist α,βmATP and the β-adrenoceptor agonist isoprenaline were unchanged by MMC treatment.
Discussion. An increase in the rate and amplitude of spontaneous non-voiding bladder contractions may explain the increased frequency and urgency in patients following treatment with MMC.

516 The influence of perioperative opioids on cancer metastasis

Nan Xie[1], Nicholas Matigian[2], Kim-Anh Lê Cao[2], Kye Gregory[3], Tharindu Vithanage[3], Zeyad D. Nassar[1], Peter Cabot[1], David Sturgess[3], Paul N. Shaw[1], Marie-Odile Parat[1]. School of Pharmacy, The University of Queensland[1], St Lucia, QLD, Australia, The University of Queensland Diamantina Institute, Translational Research Institute[2], Brisbane, QLD, Australia. Mater Research Institute (MRI-UQ), The University of Queensland[3], Brisbane, QLD, Australia.

Introduction. The possibility that opioids can modulate the tumour microenvironment and thereby influence tumour growth and metastasis is of intense interest. The μ-opioid receptor (MOR) and toll-like receptor-4 (TLR4) can be activated by opioids or their metabolites, are expressed on cancer cells as well as tumour-associated cells, and control signalling pathways that play a key role in modulating cancer metastasis. In this study, we quantified the ability of opioids and their metabolites, present in clinical samples, to activate the MOR and TLR4. We also evaluated the effect of opioid administration to patients, on their circulating proteolytic profile.
Aim. The research aims to elaborate upon the potential interplay between opioid analgesia and tumour metastasis through MOR, TLR4, and matrix degradation.
Methods. Plasma samples were collected from 60 patients undergoing elective lower limb joint replacement pre-operatively and at 3, 6 and 24 h after the surgery. Plasma was also collected from 10 healthy volunteers. Opioid administration was recorded and converted into morphine IV equivalents. AlphascreenTM cyclic AMP (cAMP) assay and MOR-overexpressing HEK293 cells were employed to quantify MOR activation. Cells engineered to express TLR4 and co-receptors essential for TLR4 activation (HEK-Blue™ hTLR4) were utilised to measure TLR4 activation. Circulating matrix metalloprotease (MMP) and Tissue Inhibitor of Matrix Protease (TIMP) activities were assessed by zymography and reverse zymography, respectively.
Results. Post-operative plasma samples displayed MOR activation potential and, the ability to inhibit LPS-induced TLR4 activation. These samples also displayed altered circulating matrix-degrading enzymes activity potential.
Discussion. Evaluating the effect of perioperatively administered opioids on circulating parameters likely to affect the biology of cancer cells and other prominent tumour-associated cells is a novel and promising approach to understanding whether perioperative analgesia of cancer surgery patients can influence the risk of long term metastasis or recurrence.¶

517 Simultaneous determination of adalimumab and infliximab in human serum by liquid chromatography/tandem mass spectrometry

Mei Zhang* [1,2], Grant A Moore [2], Matthew P Doogue [1,3] & Murray L Barclay [1,3,4] Department of Medicine, University of Otago - Christchurch [1]; Toxicology, Canterbury Health Laboratories [2], Department of Clinical Pharmacology, Christchurch Hospital [3], Department of Gastroenterology, Christchurch Hospital [4], Christchurch, New Zealand

Introduction. Adalimumab and infliximab are monoclonal antibody biologic drugs that work against tumour necrosis factor alpha (TNF-α) and are used to treat autoimmune diseases. Pharmacokinetic studies and therapeutic drug monitoring of adalimumab and infliximab in patients require a well validated analytical method to analyse the concentrations of adalimumab and infliximab in serum.
Aims. The objective of this work was to develop and validate a simple and sensitive LC-MS/MS method for the simultaneous determination of adalimumab and infliximab in human serum.
Methods. The method was based on a combination of trypsin digestion of serum and LC-MS/MS analysis of unique peptides produced by trypsin digestion of the therapeutic monoclonal antibody drugs. Serum samples were processed by denaturation, reduction, alkylation and trypsin digestion to break down proteins into peptides. Digests were injected into the LC-MS/MS system. The tryptic peptides were separated under gradient elution using an analytical column. The mass spectrometer was operated in the positive ion mode. The tryptic peptides that are unique for adalimumab and infliximab were utilized for their quantification.
Results and Discussion. For both adalimumab and infliximab, standard curves were linear over the concentration range 1.0 to 100 mg/L (r > 0.99) in serum, biases were <±10%, and intra- and inter-day coefficients of variation (imprecision) were <10%. The limit of quantification was 1.0 mg/L in serum. The assay has been successfully tested to monitor adalimumab and infliximab concentrations in patients on adalimumab or infliximab.¶

518 Ibuprofen in Infants younger than 6 Months: What is the Efficacy and Safety Profile?

Victoria C. Ziesenitz[1,2], , Andreas Zutter[3], Thomas O. Erb[3], Johannes N. van den Anker[1,4]. Paed Pharmacol and Pharmacometrics, Univ of Basel Children's Hosp[1], Basel, Switzerland; Paed Cardiol, Univ Children's Hosp[2], Heidelberg, Germany; Paed Anaesth, Univ of Basel Children's Hosp[3], Basel, Switzerland; Clin Pharmacol, Children's Natl Health Syst[4], Washington, DC, USA

Introduction. Ibuprofen is a non-steroidal anti-inflammatory drug frequently administered to children of various ages for relief of fever and pain and is approved as over-the-counter medication in many countries worldwide. Although there is extensive data on its efficacy and safety in children and adults, there are divergent dosing recommendations for analgesia and treatment of fever in infants, especially in the age group between 3 and 6 months of age.
Aims. To assess the safety and efficacy profile of ibuprofen in this age group in an attempt to optimise pain and fever management.
Methods. A comprehensive PubMed search was conducted in order to identify publications concerning the use of ibuprofen in infants younger than 6 months of age. Identified studies were reviewed so that only those presenting original clinical data regarding the pharmacokinetics, safety or efficacy of ibuprofen in this age group are included.
Results. The literature search identified 5 pharmacokinetic and 10 efficacy and safety studies which met the review inclusion criteria. Eligible PK studies presented data of 243 children, which included at least 18 infants under the age of 6 months. Eligible efficacy and safety studies contained data of 39,234 children including minimum 207 children younger than 6 months. The most common underlying pathological condition was fever. The most common clinical setting was outpatient care.
Discussion. Based on the current evidence, short-term use of ibuprofen is considered safe in infants older than 3 months of age having a body weight of more than 5-6 kg when special attention is given to the patient's hydration. Ibuprofen should be prescribed based on body weight using a dose of 5-10 mg/kg. This dose can be administered 3-4 times a day resulting in a total daily dose of maximally 30-40 mg/kg. The rectal route has been shown to be less reliable because of erratic absorption, especially in young infants. Since most efficacy and safety data have been derived from paediatric trials in infants with fever, future studies should focus on the efficacy of ibuprofen in young infants with pain.¶

519 The Safety and Pharmacokinetics of Metformin in Heart Failure

Gina Chowdhury[1], Felicity C Smith[1], Peter S Macdonald[2], Jane E Carland[1], Sophie L Stocker[1], Shaun S Kumar[3], Jerry R Greenfield[4], Kenneth M Williams[1], Garry G Graham[1], Richard O Day[1]. Dept of Clin Pharmacol, St. Vincent's Hosp, School of Med Sci, Univ of NSW[1], Sydney, NSW, Australia; Heart Transplant Unit, St Vincent's Hosp[2], Sydney, NSW, Australia; Div Clin Pharmacol, Dept Ped, Univ of Utah[3], UT, USA; Dept Endocrin, St Vincent's Hosp[4], Sydney, NSW; St Vincent's Clinical School, Univ of NSW[5], Kensington, NSW

Introduction. Metformin, a type II diabetes (T2DM) drug, is contraindicated in heart failure (HF) in Australia due to a perceived increased risk of lactic acidosis. The safety of metformin in HF, described in epidemiological studies, has facilitated approval of its use in HF patients in the US, UK, Canada and New Zealand. Detailed prospective data on the safety and PK of metformin is required to confidently remove this contraindication in Australia.
Aim. To explore the safety and PK of metformin in HF patients and compare with healthy subjects (Timmins et al, 2005) and T2DM patients without HF (T2DM Control) (Duong et al, 2013)
Methods. This cross-sectional study consisted of two cohorts of HF subjects; those with T2DM receiving metformin (n=10), and those without T2DM and metformin naïve (n=26). Biochemical parameters (including lactate, anion gap and bicarbonate) and plasma metformin concentrations were determined. Metformin PK parameters were determined using NONMEM.
Results. In HF patients with T2DM, plasma lactate, anion gap and bicarbonate concentrations did not correlate with plasma metformin concentrations. The apparent CL of metformin (37 ± 17 L/h) was similar to the T2DM patients (49 ± 26 L/h), but significantly lower than healthy subjects (75 ± 14 L/h; $p < 0.05$). The peripheral V was significantly lower in HF patients compared to healthy subjects ($p = 0.04$). Lactate concentrations of HF patients without T2DM (1.5 ± 0.7 mmol/L) were significantly lower than in T2DM patients with or without HF (1.9 ± 0.9 mmol/L; $p < 0.05$).
Discussion. The PK of metformin in T2DM HF patients are similar to those in T2DM patients without HF. Additionally, hyperlactatemia was not associated with HF patients both with and without T2DM. These results provide the support for a larger interventional study with metformin in HF patients.
Duong JK et al (2013) Clin Pharmacokinet 52:373-384
Timmins P et al (2005) Clin Pharmacokinet 44: 721-729¶

520 The Safety of Metformin in Haemodiafiltration

Felicity C Smith[1,2], Timothy J Furlong[3], Jerry R Greenfield[4], Sophie L Stocker[1,5], Jane E Carland[1,5], Garry G Graham[1,2], Kenneth M Williams[1,2], Richard O Day[1,5]. Dept of Clin Pharmacol, St. Vincent's Hospital[1], Sydney, NSW; School of Med Sci, Univ of NSW[2], Kensington, NSW; Dept of Nephrol, St. Vincent's Hospital[3], Sydney, NSW; Dept Endocrin, St. Vincent's Hospital[4], Sydney, NSW; St. Vincent's Clinical School, Univ of NSW[5], Kensington, NSW.

Introduction. The cardioprotective effects of the anti-hyperglycaemic agent metformin may be of great benefit to patients with type 2 diabetes mellitus (T2DM) and end-stage kidney disease (ESKD) who require haemodiafiltration (HDF). Metformin is extensively cleared from plasma during HDF (Smith et al, 2016). This indicates that metformin may be safely given to these patients if administration matches extraction during HDF, thereby preventing metformin accumulation and lactic acidosis. Further studies are required to confirm this.
Aims. To monitor the safety of metformin in patients with T2DM and ESKD undergoing HDF.
Methods. Patients received metformin (IR, 250 mg) after each HDF session (thrice weekly; 750 mg/week) for 6 months. Regular blood samples were collected prior to the start of HDF to monitor safety parameters (plasma lactate <5 mmol/L, plasma metformin <5 mg/L). Metformin concentrations were quantified by HPLC.
Results. Plasma lactate concentrations remained below 5 mmol/L in all patients (n=7) for the duration of treatment. Plasma metformin concentrations remained below 5 mg/L, except for 2 occasions in Patient 3 (max=5.3 mg/L). Unfortunately, Patients 1 and 6 passed away from cardiac events in the fourth month of the study. The study was subsequently ceased by local governance. No safety data from these patients was suggestive of lactic acidosis.
Discussion. Cardiovascular disease is the leading cause of death in HDF patients. Additionally, there is no evidence to date that associates metformin with an increased risk of cardiovascular events. Prior to study cessation, all data collected supported the safety of metformin in HDF. This information, particularly given the safety data collected from Patients 1 and 6, suggests it is unlikely that metformin contributed to these deaths. Regardless, further studies are required to investigate any potentially deleterious interactions between metformin and the rapid shifts in biochemistry and body fluid that take place during HDF.
Smith F et al (2016) Am J Kidney Dis 68:990-992¶

521 Discharge summaries: an untapped resource for optimising Adverse Drug Reaction identification

Frida Djukiadmodjo[1], Jane Booth[2], Claire Keith[2], Christopher O'Callaghan[1], Albert Frauman[1]. Dept of Clinical Pharmacology and Therapeutics, Austin Health[1], Heidelberg, VIC; Dept of Pharmacy, Austin Health[2], Heidelberg, VIC.

Introduction. Adverse drug reactions (ADRs) are the most common type of iatrogenic injury and cause substantial morbidity, mortality and financial costs. Most pharmacovigilance systems are based on voluntary reports, however under-reporting is a well-recognised limitation. In December 2016, a complementary pathway was introduced for generating ADR reports using International Statistical Classification of Diseases (ICD-10) coding data from electronic discharge summaries.
Aims. To determine the effect of the introduction of a clinical coding surveillance system on the identification of ADRs, considering differences in reaction severity and patient follow-up.
Methods. All encounters at our health service coded with ICD-10 codes Y40-Y59 were captured by the clinical coding surveillance system as potential ADR reports. These reports are reviewed by a multi-disciplinary committee which assigns ratings of causality and severity and decides whether any follow-up is required. ADR data from before (pre-intervention period) and after the introduction of coding surveillance (post-intervention period) were compared.
Results. Two six-month periods were compared. In the pre-intervention period, 104 ADRs were reported by clinicians. In the post-intervention period, 281 ADR notifications were generated and of these, 109 reports were from clinicians, 113 were from coding and 59 were detected in both systems. The review of this volume of ADR notifications was possible because of the use of electronic medical records in our organisation. The proportion of reactions rated as at least "moderate" severity was the same for both periods (78.9% vs. 82.6%; difference 3.7%; 95% CI -6—13.4%; p=0.49). There was no difference in the proportion of reactions that resulted in an ADR Committee intervention (55.8% vs. 48.0%; difference 7.8%; 95% CI -4.1—19.6%; p=0.22).
Discussion. Clinical coding surveillance complements the existing voluntary reporting process by providing valuable information which would otherwise has been missed. The additional detection of ADRs of at least moderate severity by this process may impact patient morbidity and safety. This could have system-wide implications for the uptake of pharmacovigilance in hospital systems.

522 GLP-1-induced anorectic and emetic responses are mediated via exendin (9-39)-sensitive mechanisms in *Suncus murinus*

Sze Wa Chan[1], Zengbing Lu[1,2], John A Rudd[2]. School of Health Sciences, Caritas Institute of Higher Education[1]; Brain and Mind Institute and School of Biomedical Sciences, The Chinese University of Hong Kong[2], Hong Kong SAR, China.

Introduction. GLP-1 receptor agonists can be associated with nausea, emesis and reduced appetite in man. Our previous studies showed that the GLP-1 receptor agonists, GLP-1 (7-36) amide and exendin-4, inhibited feeding and water intake, and induced emesis in *Suncus murinus*.
Aims. In the present study, we examine if the action of GLP-1 (7-36) to induce emesis and inhibit feeding are mediated via central GLP-1 receptors using the potent GLP-1 receptor antagonist, exendin (9-39).
Methods. *Suncus murinus* were anaesthetised with sodium pentobarbitone (40 mg/kg, i.p.) and then stereotaxically implanted with a guide cannula into the lateral ventricle and allowed a 7-days recovery before experimentation. Animals were fasted 12-h prior to administration of drugs. On the day experimentation, they were administered exendin (9-39) (30 nmol, i.c.v.), or saline (5 µl i.c.v.) 15 min prior to GLP-1 (7-36) (3 nmol, i.c.v.), or saline (5 µl, i.c.v.). Food and water consumption and behaviour were measured for 1-h.
Results. GLP-1 (7-36) inhibited food and water intake ($P<0.001$) and induced emesis in 1 out of 6 animals. GLP-1 (7-36) also reduced significantly the distance moved when compared with the control group ($P<0.05$) and increased the duration of lying flat behaviour ($P<0.001$). Exendin (9-39) antagonized the effect of GLP-1 (7-36) on feeding and drinking, and lying flat behaviour ($P<0.01$). None of the animals pretreated with exendin (9-39) exhibited emesis.
Discussion. The data suggests that the action of GLP-1 (7-36) in the brain is probably mediated via GLP-1 receptors. The studies were fully supported by a grant from the Research Grants Council of the Hong Kong SAR, China (Project no. UGC/FDS11/M02/15).
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523 Polyphenol reversal of amyloid-induced neurite dysfunction

Mirabel Alonge[1], Ian F Musgrave[2]. Dis of Pharmacol, Adelaide Medical School, Univ of Adelaide[1-2], Adelaide, SA, Australia.

Introduction. The amyloid beta protein (Aβ) that accumulates in Alzheimer's disease induces neuronal death and neurite dysfunction. Potential anti-amyloid drugs have typically been tested for their ability to prevent cell death, but not reversal of neurite dysfunction. One such compound is epigallocatechin gallate (EGCG) due to its neuroprotective effects that reduce and prevent amyloid beta (Aβ) induced toxicity and cell death. Current research with EGCG primarily focusses on prevention of cell death in late stages of the disease while EGCG's potential to reduce or even prevent Aβ toxicity at the earlier stage of the neuronal dysfunction, has been largely ignored.
Aims and Hypotheses. This research aims to test EGCG's potential to prevent or reverse Aβ-induced neurite dysfunction and to test whether this can be achieved at lower concentrations than what is needed to prevent cell death. It is hypothesised that EGCG will prevent Aβ from hindering axonal growth and neurite development and stimulate the repair of dysfunctional neurites.
Methods. PC-12 Ordway cells were grown in Roswell Park Memorial Institute medium, under standard conditions. These cells were passaged every 3-4 days. Cells were then either plated into 96 well plates or onto coverslips in six well plates. Cell death was monitored in 96 well plates using the MTT assay. Cells on coverslips were exposed to Aβ (100nmol/L and 1µmol/L) and EGCG (20nmol/L and 200nmol/L) during development and differentiation for 7 days (O'Neil et al, 2016). Neurite number and length were initially counted manually and will be analysed later by image J.
Results. Preliminary results show that Aβ stops neurite formation at concentrations much lower than those that produce cell death (100nmol/L vs 1µmol/L). EGCG did not have any adverse effect on neurite outgrowth and we expect it will reverse the neurite dysfunction caused by Aβ.
Discussion. The finding that Aβ is more potent on neurite formation suggests that early intervention with Anti-amyloid drugs may be more effective than later. Compounds such as, EGCG may potentially slow the progression of the disease if used early.

O'Neil K et al (2016) Basic Clin Pharmacol Toxicol 120(4): 390-397¶

524 Endosomal trafficking kinetics of orexin receptors as measured by BRET trafficking assay.

Natasha C Dale[1,2], Kevin DG Pfleger[1,2,3], Elizabeth KM Johnstone[1,2]. Mol Endocrinol and Pharmacol, Harry Perkins Inst of Med Res[1], Nedlands, WA; Centre for Med Res, Univ of Western Australia[2], Crawley, WA; Dimerix Ltd[3,] Nedlands, WA.

Introduction. Studies of the two orexin G protein-coupled receptor (GPCR) subtypes (OXR1 and OXR2) report differences in temporal interactions with β-arrestin-ubiquitin complexes, with OXR1 exhibiting transient interactions and rapid recycling relative to OXR2 (Dalrymple et al, 2011). These differing kinetics are likely reflected in divergences in spatial and temporal endosomal trafficking, however, no such comparative study has yet been conducted.
Aims. To investigate the temporal and spatial aspects of OXR1 and OXR2 trafficking.
Methods. Trafficking kinetics were investigated using a novel trafficking assay (Lan et al, 2012; Tiulpakov et al, 2016) with bioluminescence resonance energy transfer (BRET) technology. This assay allows temporal and spatial trafficking of a protein of interest to be observed through proximity to tagged compartment marker proteins. This assay was also used to construct dose-response curves.
Results. Statistically significant differences in BRET signals between OXR1 and OXR2 were observed in response to stimulation with 1 µM orexin A (OxA) for proximity to Rab4 (early endosome to recycling), Rab5 (early endosome) and Rab11a (recycling endosome) (Two-way repeated measures ANOVA of plateau, n=5, $p<0.05$). OXR1 exhibited an increased signal relative to OXR2 with Rab4, and a decreased signal relative to OXR2 with Rab5 and Rab11a.
Discussion. Subtle differences in the endosomal trafficking kinetics of OXR1 and OXR2 have been observed. These results increase our understanding of the molecular characteristics of OXR1 and OXR2, further illustrating molecular differences between the orexin receptor subtypes.

Dalrymple MB et al (2011) J Biol Chem 286:16726-16733.
Lan TH et al (2012) Traffic 13:1450-1456.
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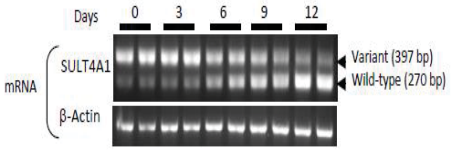
525 Splicing regulation and function of cytosolic sulfotransferase: SULT4A1

Misgana Idris, Neville J Butcher, Rodney F Minchin. Laboratory for Molecular and Cellular Pharmacology, School of Biomedical Sciences, University of Queensland, Brisbane, QLD, Australia

Introduction. In many tissues and cell lines, Sulfotransferase 4A1 (SULT4A1) is transcribed as an aberrant splice variant that does not translate into a functional protein. By contrast, neuron- and enterocyte-like cells splice SULT4A1 pre-mRNA into the protein coding wild type transcript. SULT4A1 protein is also known to regulate other co-expressed paralogue sulfotransferases (SULTs).



SULT4A1 switching pattern in SH-SY5Y cells with 12 days of RA treatment

Aims. To decipher the splicing events dictating the preferential expression of SULT4A1 protein and to understand the mechanisms of SULT4A1 regulation of other SULTs.
Methods. Human neuroblastoma cell lines SH-SY5Y and SK-N-MC were used as models in this study. Differentiation of cells was with 10 µM retinoic acid (RA) up to 14 days. A minigene splicing assay using a series of deletions and site-directed mutagenesis of SULT4A1 intronic sequences 5' and 3' of exon 6 were used to map splicing factor binding sites identified by bioinformatics. Expression patterns of endogenous SULTs and splicing factors were profiled by Western blot and semi-quantitative RT-PCR. SULTs activities were monitored using HPLC and MS techniques.
Results. Minigene deletion assays and overexpression assays in SH-SY5Y cells identified Muscleblind-like proteins (MBNL) and CUG-BP and ETR-3-like factor (*CELF*) proteins as potential regulators of SULT4A1 splicing. In line with SULT4A1 switching, increased nuclear translocation of MBNL proteins and cytosolic retention of CELF proteins were seen in SH-SY5Y cells with RA treatment. It was also found that SULT4A1 protein targets other co-expressed SULTs to the autophagosomal degradation pathway in SK-N-MC cells.
Discussion. The pattern of their intracellular compartmentalisation following RA-induced neuronal differentiation suggested MBNLs as primary regulators of SULT4A1 splicing, at least in this cell model. Our results also demonstrated the central role of SULT4A1 protein in modulating the function of other SULTs by influencing their stability in vivo. ¶

526 Diverse approaches to understand functional pharmacology- examples of the serotonin 5-HT1B and 5-HT2A receptors

Amber Ko[1], Thierry Jolas[2], Chantal Rein[2], Sandrine Guyonnet[2], Jacques Migeon[1], Elsa Liu[1], Tsui-Hwa Lin[1], Ying-Chieh Wu[1], Shiuh-Jen Teng[1], Benoit Fouchaq[2]. EPDS[1], Taipei, Taiwan; EPDS[2], Celle L'Evescault, France.

Introduction. Serotonin (5-hydroxytryptamine, or 5-HT) receptors mediate a wide range of physiological processes in the central and peripheral nervous systems. The serotonin receptor family is composed of both G-protein coupled receptors (GPCRs) and ligand-gated ion channel (LGIC) superfamilies. Serotonergic dysfunction has been implicated in many neuropsychiatric disorders. Due to the extensive distribution of serotonin receptors in the CNS and periphery, a complete understanding of the selectivity and the pharmacological actions of compounds of interest is critical.
Aims. In this poster, we present two examples involving the 5-HT1B and 5-HT2A receptor sub-types to demonstrate how the use of diverse pharmacology platforms can provide a more precise evaluation of compound/receptor interactions.
Methods. In the example of 5-HT1B receptor, we modulated the cAMP assay conditions to quantify reference compounds-induced changes of cAMP production. In the example of 5-HT2A receptor, we applied GTPgammaS, IP1 and calcium flux methods to detect % response or % inhibition patterns and potency changes of a series of reference compounds.
Results. In the example of 5-HT1B receptor, an increase of Na^+ in the assay buffer decreases constitutive activity in cellular models. It decreases agonist potency without affecting antagonist IC50s. In the example of 5-HT2A receptor, full or partial agonist-induced response patterns and potency vary by assay types whereas antagonists potency are relatively consistent among the three assay types and inverse agonism can only be revealed by GTPgammaS method.
Discussion. In order to have a complete understanding of the selectivity and the pharmacological actions of compounds of interest, an appropriate screening platform is extremely important in drug discovery. This poster shows the importance of carefully selecting models as pharmacological tools. A complete scanning of references in diverse formats to select ideal screening tools is also suggested to prevent assay type-dependent bias.
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527 Statins exhibit diverse effects on behaviour and cytokine levels in an in vivo model of LPS-induced neuroinflammation

McFarland AJ[1,2,3], Anoopkumar-Dukie S[1,2,3], Davey AK[1,2,3], Lau B[4], Arora DS[1,2,3†]. School of Pharm & Pharmacol, Griffith Univ, Gold Coast, QLD, 4222, Australia; Quality Use of Medicines Network[2], QLD, Australia; Menzies Health Institute Queensland[3], QLD, Australia; Hong Kong Polytechnic Univ[4], Hung Hom, Hong Kong

Introduction. The effect of statins in the CNS has received much attention in recent years, with recent *in vitro* studies implicating the reduction of neuroinflammation as a potential protective mechanism associated with statin use. Despite this, there is a lack of *in vivo* studies which explore the relationship with statins and neuroinflammation; hence many aspects of statins' effects, including comparisons between individual statins and the differences between short-term and long-term administration, remain unclear.
Aims. To compare the short-term and long-term effects of atorvastatin (ATO), pravastatin (PRA), rosuvastatin (ROS), or simvastatin (SIM) on lipopolysaccharide (LPS)-induced neuroinflammation *in vivo*.
Methods. C57BL/6J male mice were randomly assigned to one of seven groups (n=6). Each group received either saline or statin (equivalent max. human daily dose) over 3 or 21 days. At 24 h post-final treatment, 1.5 mg/kg LPS from *E. coli* (055:B5) was used *i.p.* to induce neuroinflammation and behavioural despair. Behavioural assays (open field test, forced swim test, tail suspension test) were performed within 3 h of LPS. Animals were sacrificed by cervical dislocation 3 h post-LPS. Serum & brain samples were tested for TNF-α and IL-1β concentrations by ELISA.
Results. After 3 days, PRA, ROS, and SIM (but not ATO) improved at least one aspect of LPS-induced behavioural deficit in the OFT, FST and TST ($P<0.05$). Only ROS showed improvement in all 3 tests ($P<0.05$). PRA, ROS and SIM decreased serum TNF-α ($P<0.01$). While 3 day ATO did not affect behaviour, it reduced brain IL-1β and TNF-α ($P<0.05$). After 21 days all statins improved behaviour vs. LPS, which correlated with reduced brain IL-1β ($P<0.01$). PRA decreased brain IL-1β to below baseline. Brain TNF-α only reduced in ATO, ROS and SIM ($P<0.05$).
Discussion. Our findings are the first *in vivo* evidence which support the notion that the neurocognitive effects of statins could be non-equivalent across the class. PRA, ROS & SIM reduced LPS behavioural deficit at 3 days, while ATO only showed significant effect at 21 days. Differences between behaviour and cytokine release profile statins may suggest anti-neuroinflammatory mechanisms differ between statins, and require further investigation. ¶

528 The role of caveolae in glioblastoma invasiveness

Wenjun Pu[1], Zeyad Nassar[2], Samira Khabbazi[1], Nan Xie[1], Marie-Odile Parat[1]. School of Pharmacy, the University of Queensland[1], Brisbane, QLD, Australia; Adelaide Medical School, The University of Adelaide[2], Adelaide, SA, Australia.

Introduction. Glioblastoma (GBM) is the most common brain cancer. The average survival time for most patients is approximately one year after diagnosis. A major feature of GBM that contributes to its poor prognosis is its high invasiveness. Caveolae are plasma membrane subdomains that participate in numerous biological functions. Caveolin-1 and polymerase I and transcript release factor (PTRF) are both necessary for caveola formation. We hypothesized that high expression of caveola-forming proteins in GBM promotes invasiveness *via* modulation of the production of matrix-degrading enzymes.
Aims. (i) to investigate the relationship between mRNA expression of caveola-forming proteins and GBM aggressiveness in patients and (ii) to compare the proteolytic profile and invasion *in vitro* among GBM cell lines expressing, of devoid of, caveolin-1 or PTRF.
Methods. The mRNA expression of caveola-forming protein in GBM samples, and survival after stratifying patients according to caveolin-1 or PTRF expression, were analyzed from TCGA and REMBRANDT databases. The proteolytic profile of different cell lines was investigated using zymography and real-time qPCR. The knockdown of caveola-forming proteins was performed using small interfering RNA (siRNA) transfection. Invasion through basement membrane-like protein was investigated *in vitro* using Transwell™.
Results. Expression of both caveolin-1 and PTRF was increased in GBM compared to normal samples. High expression of caveola-forming proteins was associated with lesser survival time. GBM cell lines that formed caveolae expressed more urokinase-type plasminogen activator (uPA) and matrix metalloproteinases-2 (MMP-2) than GBM cells devoid of caveolae. Conversely, knockdown of caveolin-1 or PTRF in GBM cells decreased the expression of uPA and/or MMP-2.
Discussion. Caveolae may modulate GBM cell invasion by regulating uPA and MMP-2 expression. ¶

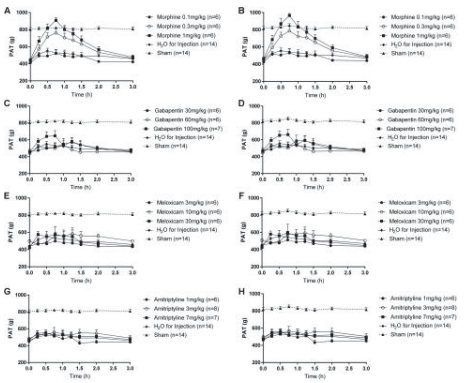
529 Air on a G-String: Guanine Oxidation as a Stress Sensor in Relation to Depression and Neurological Disorders

Tim Shaw[1,3], Andrew Peel[2,3]. Victorian Infectious Diseases Reference Laboratory, The Peter Doherty Institute Melbourne, VIC, Australia [1]; Scram Software Melbourne, VIC, Australia [2]; NucleopharmGT, Melbourne, VIC, Australia[3].

Introduction. Aberrant BDNF (Brain-Derived Neurotrophic Factor) signalling has been implicated in depression and neurological disorders that are often associated with chronic inflammation and stress. Expression of the BDNF gene is up-regulated by H_2O_2, a ubiquitous signalling molecule. BDNF signalling stimulates the Keap1-Nrf2 transcription factor system, the master regulator of oxidative stress responses, which creates a pair of regulatory feedback loops. The guanine (G)-rich BDNF promoter has the potential to form G-quadruplexes (GQs). GQs are stacks of two or more sets of four co-planar Gs that usually exist in dynamic equilibrium with alternative stem-loop (SL) structures. Guanine (G) is the most readily oxidised of the canonical nucleobases, 8-oxoG being a major product. Oxidation of G residues can act as a molecular switch by changing the equilibrium between GQ and SL structures, which results in the recruitment of proteins that couple DNA damage repair to transcriptional responses. Re-setting molecular switches requires repair of oxidative 8-oxoG "lesions", which in this context are increasingly being recognised as epigenetic markers[1,2].
Methods and Aim. Various bioinformatics resources that are freely accessible *via* the internet were used to identify and analyse regulatory elements in the BDNF, Keap-1 and Nrf-2 genes, as well as other genes that are involved stress responses and maintenance of the intracellular G nucleotide pool, with the aim of devising a theoretical model.
Results. The BDNF proximal promoter contains a poly G tract homologous to putative redox-sensing poly G tracts that are located promoters of key stress response genes, most notably SOD2 (mitochondrial Superoxide Dismutase). G-rich sequences with the potential to form GQs in competition with alternative SL structures were identified in promoters of all relevant genes. Testable dynamic interaction models were generated from this information.
Discussion. BDNF expression is predicted to be controlled at the transcriptional level by an oscillatory redox sensing system involving cycles of G oxidation and repair-coupled transcription driven by GQ-SL transitions, for which the intracellular ratio of oxidised:reduced G derivatives is critical. The system is robust due to complex feedback and internal redundancy, but must fail when its capacity to remove 8-oxoG and/or supply (d)GTP is exceeded.
Fleming AM et al (2017) PNAS 114:2604-2609.B 2. Fleming AM & Burrows CJ (201) DNA Repair 56:75-83.¶

530 Behavioural, pharmacologic and histologic characterisation of a rat model of mechanical low back pain

Thomas S W Park[1], Andy Kuo[1], Maree T Smith[1,2]. CIPDD, The Univ of Queensland[1], Brisbane, QLD, Australia; School of Pharmacy, The Univ of Queensland[2], Brisbane, QLD, Australia.



Introduction. Low back pain (LBP) is a common health problem affecting humans globally. Hence, I have used behavioural, histological and pharmacological methods to characterise an optimised rat model of mechanical LBP established at the CIPDD.[1]
Aims. To use behavioural, histological and pharmacological methods to characterise our new rat model of mechanical LBP.
Methods. Ten small punctures (0.5 mm o.d.; 2 mm deep) were induced in the L4/L5 and L5/L6 intervertebral discs (IVDs). Sham rats had the same surgery but there was no IVD puncture. Pressure algometry thresholds (PATs) at L4/5 and L1 were assessed. Additionally, paw withdrawal thresholds (PWTs) were measured in the bilateral hindpaws using calibrated von Frey filaments. PATs and PWTs were measured at weekly intervals until study completion. Dosing solutions of morphine (0.1, 0.3, and 1.0 mg/kg; sc), gabapentin (30, 60, and 100 mg/kg; ip), amitriptyline (1, 3, and 7 mg/kg; ip), meloxicam (3, 10, and 30 mg/kg; ip) and vehicle (2 mL/kg; ip) were administered to rats by the first person and testing was undertaken in a 'blinded' manner by the second person. Both LBP and sham rats were also characterised using histologic methods.
Results. Mechanical hyperalgesia developed progressively at L4/L5 and L1 in LBP-rats but not sham-rats. Importantly, PWTs remained unaltered for the study period. Histological analysis of the IVDs from LBP-rats showed an apparent loss of sharp boundaries between the nucleus pulposus and annulus fibrosus. In LBP-rats, single bolus doses of morphine produced dose-dependent relief of primary and secondary mechanical hyperalgesia in the lumbar axial deep tissues at L4/L5 and L1, respectively, whereas gabapentin, amitriptyline, meloxicam and vehicle were inactive.
Discussion. We have characterised a new rat model of chronic mechanical LBP using behavioural, pharmacologic and histologic methods.
[1]Muralidharan A, Park TSW et al (2017) Front Pharmacol 8:493¶

531 Morphine dosing affects development of antinociceptive tolerance and motor behaviour

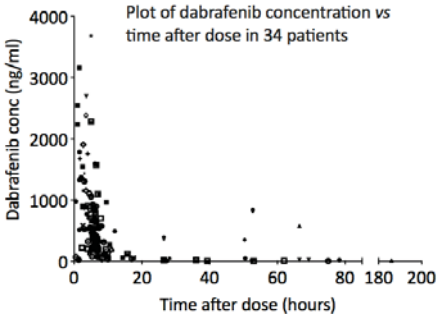
Alok K Paul[1], Nuri Gueven[1], Nikolas Dietis[1,2]. Division of Pharmacy, School of Medicine, University of Tasmania[1], Hobart, TAS, Australia; Medical School, University of Cyprus[2], Nicosia, Cyprus.

Introduction. Clinical development of antinociceptive tolerance after repeated administration morphine limits its chronic use. Despite growing knowledge about the molecular mechanisms of morphine tolerance, we know little about the influence of dosage regimen in its development.
Aims. We hypothesized that morphine dose, as well as dose increments, contribute to tolerance development. In addition, morphine-induced behavioural changes also might follow similar pattern of antinociception and tolerance.
Methods. Four groups of male Sprague Dawley rats received different daily doses of intermittent subcutaneous morphine for 14 days. After the development of antinociceptive tolerance, different increments of morphine doses were administered until tolerance redeveloped (Group A: 2.5 (b.i.d) $\rightarrow$ 5 $\rightarrow$ 10 mg/kg/day, Group B: 5 (b.i.d.) $\rightarrow$ 10 mg/kg/day, Group C: 5 (b.i.d.) $\rightarrow$ 15 mg/kg/day and Group D: 10 (b.i.d.) $\rightarrow$ 20 mg/kg/day). Antinociceptive responses were measured daily by tail-flick and hot-plate assays pre-treatment and at various post-treatment time-points. Motor behavioural effects were also measured using automated open-field paradigm and visual observations.
Results. Animals treated with lower starting-doses of morphine developed antinociceptive tolerance faster than those started on higher doses. Higher starting-doses and higher dose-increments after tolerance development resulted in more sustained antinociception and delayed the re-development of tolerance. These results were replicated by both anti-nociceptive assays and are therefore not assay-specific. The kinetics of morphine-induced motor suppression and desensitization were similar to those of antinociception and antinociceptive-tolerance respectively.
Discussion. These results suggest that morphine dosing regimen in rats significantly influences the manifestation of antinociceptive tolerance and the total antinociception (Paul et al., 2017). Our results also indicate that repetitive morphine dosing leads to desensitization of motor suppression in all major motor-behavioural parameters and manifests desensitization in conjunction with antinociceptive tolerance. Therefore, our results highlight that an optimized morphine dosing strategies can delay antinociceptive tolerance and reduce behavioural adverse effects.
Paul AK et al (2017) Neuropharmacology 121:158-166

532 Pharmacokinetics and metabolism of dabrafenib and trametinib in BRAF V600E/K metastatic melanoma

Hannah Y Kim[1], Xiaoman Liu[1], Janna K Duong[1], Georgina V Long[2,], Maria Gonzalez[2], Alexander M Menzies[2], Alan V Boddy[1]. Faculty of Pharmacy, Univ of Sydney[1], Sydney, NSW, Australia. Melanoma Institute Australia and School of Medicine, Univ of Sydney[2], Sydney, NSW, Australia.

Introduction. Combination of BRAF inhibitor, dabrafenib and MEK inhibitor, trametinib (CombiDT) has improved survival outcomes compared with chemotherapy or BRAF inhibitor monotherapy in advanced BRAF V600E/K melanoma. However, the use of CombiDT has a high incidence of pyrexia, causing treatment delays (Menzies, 2015). The pharmacokinetics and metabolism of dabrafenib and trametinib may give clues relating to side effects such as pyrexia.



Aims. To measure plasma drug concentrations of dabrafenib and trametinib in melanoma patients treated with CombiDT.

Methods. Patients treated with CombiDT were recruited onto Neo Adjuvant Combi Trial (protocol ID: 200332). Their plasma samples were analysed for drug and metabolite concentrations using LC-MS. Standard plasma solutions were made for the range of 1ng/ml to 1000ng/ml for dabrafenib and 1ng/ml to 100ng/ml for trametinib. Vemurafenib was used as an internal standard.

Results. A total of 198 samples from 34 patients were analysed. Dabrafenib (4.0-3680ng/ml) and trametinib (1.0-66.2ng/ml) concentrations were measurable in 151 samples. Three dabrafenib metabolites (carboxy-, hydroxyl- and N-desmethyl-dabrafenib) were also measurable and showed a high degree of inter-patient variation.

Discussion. An analytical method was successfully established to measure dabrafenib, trametinib and metabolite concentrations. Further analysis using absolute metabolite concentrations, or more likely parent drug-metabolite ratio, may provide useful information regarding PK associations with toxicities such as pyrexia.

Menzies AM et al (2014) Annals of Oncology 26: 415–421.

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533 Optimisation of a meropenem plus tobramycin combination dosage regimen against hypermutable and non-hypermutable *Pseudomonas aeruginosa via* the hollow-fibre infection model and mechanism-based modelling

Rajbharan Yadav[1], Vanessa E Rees[1,,2], Kate E Rogers[1,,2], Phillip J Bergen[2], Tae Hwan Kim[3], Beom Soo Shin[3], Antonio Oliver[4], Jurgen B Bulitta[5], Roger L Nation[1], Cornelia B Landersdorfer[1,2]. Drug Deliv, Dispos and Dynamics[1], Centre for Medicine Use and Safety[2], Monash Univ, Parkville, VIC, Australia; School of Pharmacy, Sungkyunkwan Univ[3], Gyeonggi-do, Korea; Hospital Son Espases[4], Palma de Mallorca, Spain; Dept of Pharmaceutics, Univ of Florida[5], Orlando, FL, USA.

Introduction. Hypermutable *Pseudomonas aeruginosa* are prevalent in patients with cystic fibrosis and rapidly become resistant to antibiotics when used as monotherapy. Antibiotic combinations are currently chosen empirically.

Aims. To optimise a combination dosage regimen against hypermutable and non-hypermutable strains utilising the dynamic hollow-fibre infection model (HFIM) and mechanism-based modelling (MBM).

Methods. The PAO1 wild-type strain and its isogenic hypermutable PAOΔ*mutS* strain ($MIC_{meropenem}$ 1.0mg/L, $MIC_{tobramycin}$ 0.5mg/L, for both) were assessed using 96h static concentration time-kill studies (SCTK) and 10-day HFIM studies (inoculum ~$10^{8.4}$ cfu/mL). MBM of SCTK data was performed in S-ADAPT to predict expected HFIM outcomes. Regimens studied in the HFIM were: meropenem 1g 8-hourly (0.5h infusion), meropenem 3g/day continuous infusion, tobramycin 10mg/kg 24-hourly (1h infusion) and both combinations; meropenem regimens delivered the same total daily dose. Time-courses of total and less-susceptible populations and MICs were determined.

Results. For PAOΔ*mutS* in the HFIM, all monotherapies resulted in rapid regrowth to >$10^{8.7}$ cfu/mL with near complete replacement by less-susceptible bacteria by day 3. Meropenem 8-hourly with tobramycin caused >7-log_{10} bacterial killing followed by regrowth to >6-log_{10} cfu/mL by day 5 and high-level resistance ($MIC_{meropenem}$ 32mg/L, $MIC_{tobramycin}$ 8mg/L). Continuous infusion meropenem with tobramycin achieved >8-log_{10} bacterial killing without regrowth. For PAO1, meropenem monotherapies suppressed bacterial growth to <4-log_{10} over 7-9 days, with both combination regimens achieving near eradication.

Discussion. As predicted by the MBM, an optimised meropenem plus tobramycin regimen was required to achieve synergistic killing and resistance suppression against the hypermutable *P. aeruginosa* strain when subjected to human pharmacokinetics in the HFIM, whereas both combination dosage regimens resulted in near eradiation of the non-hypermutable *P. aeruginosa* strain.¶

534 Evaluation of optimised piperacillin plus tobramycin combination dosage regimens against *Pseudomonas aeruginosa* (Pa) for patients with altered pharmacokinetics *via* the hollow fibre infection model and mechanism-based modelling

Rajbharan Yadav[1], Kate E. Rogers[1,2], Phillip J. Bergen[2], Jürgen B. Bulitta[3], Carl M. J. Kirkpatrick[2], Steven C. Wallis[4], David L. Paterson[5], Roger L. Nation[1], Jeffrey Lipman[4], Jason A. Roberts[4] and Cornelia B. Landersdorfer[1,2]. Drug Deliv, Dispos and Dynamics[1], Centre for Medicine Use and Safety[2], Monash Univ, Parkville, VIC, Australia; Dept of Pharmaceutics, University of Florida[3], Orlando, FL, USA; Burns, Trauma Crit Care Res Centre[4], Cent for Clin Res[5], Univ of Queensland, Brisbane, Australia.

Introduction. Augmented renal clearance (ARC) in critically-ill patients can result in suboptimal drug exposures and potential treatment failure.
Aims. This study aimed to design and evaluate optimised combination dosage regimens of piperacillin (PIP) and tobramycin (TOB) against a Pa clinical isolate in the hollow fibre infection model (HFIM) for patients with ARC.
Methods. We studied clinically relevant PIP and TOB concentrations, alone and in combinations in *in vitro* static concentration time-kills (SCTK), against a Pa clinical isolate at two inocula ($10^{5.7}$ and $10^{7.5}$ cfu/mL) over 72h. We optimised PIP + TOB regimens *via* mechanism-based modelling (MBM) of SCTK data. The effect of optimised PIP (4g q4h, 0.5h infusion) plus TOB (5 mg/kg q24h, 7 mg/kg q24h and 10 mg/kg q48h as 0.5h infusions) regimens on bacterial killing and regrowth was evaluated in the HFIM for patients with ARC (creatinine clearance 250 mL/min) over 8 days.
Results. PIP monotherapy (4g every 4h) in the HFIM provided 2.4 $\log_{10}$ killing at 13h followed by rapid regrowth at 24h with resistance emergence. TOB monotherapies displayed rapid initial killing (≥5 $\log_{10}$ at 13h) followed by extensive regrowth. The PIP + TOB dosage regimens were synergistic and provided ≥5 $\log_{10}$ killing with resistance suppression over 8 days in the HFIM.
Discussion. Optimised PIP + TOB regimens provided significant bacterial killing and suppressed resistance emergence as predicted by MBM, and therefore translated well from SCTK to the dynamic HFIM. This highlights the utility of MBM to select optimised regimens that maximise bacterial killing and minimise resistance emergence against Pa, an especially important finding given that Pa can rapidly develop MDR. Thus, these regimens are highly promising for effective and early treatment, even in the near-worst case scenario of ARC.¶

535 High-throughput assay for simultaneous quantification of the plasma concentrations of Omeprazole, Dextromethorphan, Midazolam, Losartan and their metabolites using liquid chromatography/tandem mass spectrometry (LC-MS/MS)

Santosh KS Adiraju[1, 3], Kiran Shekar[2], John F Fraser[2], Maree T Smith[1, 4], Sussan Ghassabian[1]
[1]Centre for Integrated Preclinical Drug Development, Centre for Clinical Research, University of Queensland (UQ), Brisbane, QLD, [2]Critical Care Research Group, Adult Intensive Care Services, The Prince Charles Hospital, Brisbane, QLD, [3]School of Biomedical Sciences, UQ, Brisbane, QLD, [4]School of Pharmacy, UQ, Brisbane, QLD.

Changes in pharmacokinetics of critical medications administered during surgeries involving cardiopulmonary bypass (CPB) have been reported. The impact of CPB on the activities of cytochrome P450 (CYP) enzymes is the key factor requiring further investigation. The rate of metabolism of dextromethorphan (DXM) to dextrorphan (DXR), midazolam (MDZ) to α-hydroxy midazolam (α-HM), omeprazole (OME) to 5-hydroxy omeprazole (5-HO) and Losartan (LOS) to EXP-3174 (EXP) are specific measures of *in vivo* CYP 2D6, 3A4, 2C19 and 2C9 activities, respectively. The aim of the study was to develop and validate a sensitive LC-MS/MS method to measure the concentrations of analytes of interest in plasma samples collected from patients to study the impact of CPB on the activities of major CYPs. Methods: To aliquots of human plasma (100 µL), internal standards (OME-d3 (10 ng/ml), DXM-d3 (50 ng/ml), LOS-d4 (40 ng/ml) and α-HM-d4 (10 ng/ml), 100 µL) and 10% methanol (MeOH) in 75mM ammonium acetate (AA) (pH=7, 100 µL) were mixed and loaded on solid phase extraction cartridges (Waters Oasis® HLB) which were then washed using 5% MeOH in 75mM AA pH=7 before elution with 20% propanol in MeOH. The samples were dried under the stream of nitrogen and reconstituted in 200 µL of 10% MeOH in AA pH=7. The mobile phase comprised 0.1% formic acid in water and 0.1% formic acid in acetonitrile with a flow rate of 0.4 mL/min using a 6.5 min run time. A C-18 XTerra® analytical column (Waters) was used and detection was performed using a QTrap 5500 mass spectrometer (AB SCIEX) with both positive & negative electrospray ionization. Results: The method demonstrated acceptable within-run and between-run precision and accuracy for all analytes of interest quality control samples (n=6, at 3 different days). Analytes were stable for 48 h in the autosampler, after 3 freeze-thaw cycles and after 6h at room temperature. The recovery was 88.6%-114.4% for all the analytes. Discussion: The fully validated high-throughput LC-MS/MS assay method using small volume of patients' blood (200 µL) in a relatively short run time met all validation requirements based on 2012 EMEA guideline on Bioanalytical method validation.¶

536 The influence of sampling time on estimated tobramycin exposure in cystic fibrosis patients

Yanhua Gao[1], Stefanie Hennig[1,2], Michael Barras[1,2] .[1]School of Pharmacy, University of Queensland, Brisbane, QLD, Australia, [2]Princess Alexandra Hospital, Brisbane, QLD, Australia.

Introduction. Current practice favours using the log-liner regression (LLR) method to estimate exposure (AUC) and subsequent dose adjustment of tobramycin in patients with cystic fibrosis (CF). This requires a minimum of two blood samples. Bayesian forecasting (BF) methods have been shown to be more accurate and precise in estimating the AUC; however the best sampling times for either method are unknown.
Aims. To investigate the influence of sampling time on the precision and accuracy of tobramycin exposure estimation and to determine the best sampling times.
Methods. Adult patients with CF, treated with once daily IV tobramycin, were intensively sampled to measure serum concentrations over one 24-hour dosing interval (50, 70, 100, 160, 280, 520 and 640 mins post-dose) to determine true exposure. AUCs were estimated using both LLR and BF methods with all combinations of sampling time points; 21 combinations per patient. All estimated AUCs were compared against the true exposure. The relative prediction errors (RE) were calculated, standardised to the true exposure.
Results. Twelve patients, with a median age and weight of 25 years and 66.5 kg respectively, contributed 84 tobramycin concentrations - a total of 504 estimated AUC combinations (LLR and BF methods). The average RE ranged from -35.4% to 34.5% for the LLR method and from -17.6% to 5.7% for the BF method. The most precise sampling time combinations were 100mins and 520mins for the LLR method and 70mins and 160mins for the BF method.
Conclusions. Sampling times markedly influence the precision and accuracy of AUC estimates and vary between methods. Overall, the change of sampling time impacts more on the precision and accuracy of AUC estimation with the LLR method. ¶

537 Tumour expression of copper transporters in colorectal cancer patients

Haigang Cui [1,2], Anna Zhang[2], Louise Nott[2], Dominic Geraghty[2], Nuri Guven[2], Johnson J Liu[1]. Dept of Pharmacol, School of Medical Sciences, Univ of New South Wales[1], Sydney, NSW; School of Medicine, Univ of Tasmania, Hobart, TAS[2]

Introduction. Human copper transporters have been implicated in the transport of platinum-based anticancer drugs, including hCTR1, ATP7A and ATP7B. We have previously shown the positive contribution of hCTR1 to cellular uptake of oxaliplatin in hCTR1-overexpressing colorectal cancer cells, and the enhancement of oxaliplatin cytotoxicity by Cu chelators via hCTR1-mediated transport mechanism. However, information on endogenous expression of Cu transporters in tumour tissues of colorectal cancer is limited, but of clinical importance.
Aims. To quantify tumour expression of Cu transporters in tumour and matched normal colonic tissues of colorectal cancer patients.
Methods. Colorectal cancer patients were recruited based on pre-set eligibility criteria. Tissue specimens were collected to prepare paraffin-embedded sections for standard DAB immunohistochemistry. A semi-quantitative analysis was performed on de-convoluted DAB-stained images to measure histogram profile, score and percentage of positive hCTR1, ATP7A and ATP7B immunostaining.
Results. Eight patients aged 74 (65-86) had primary cancer at sigmoid, caecal and right colon. The immunoreactivity of hCTR1, ATP7A and ATP7B was limited to the adenocarcinoma. The percentage of hCTR1 positive staining in tumour tissues was 35 ± 4.9%, 41 ± 2.9%, 45 ± 1.8%, 74 ± 4.5, 53 ± 2.9% and 56 ± 3.7% in six patients. Higher tumour hCTR1 expression was detected than normal tissue in 2/6 cases. ATP7B immunostaining in tumour tissues was 69 ± 2.5%, 65 ± 1.4%, 55 ± 4.1%, 73 ± 4.3, 63 ± 4.5%, 69 ± 2.1% in six colorectal cancer patients. Higher tumour ATP7B expression was than normal tissue in 4/6 cases. ATP7A immunostaining in tumour tissues was 53 ± 1.9%, 40 ± 7.9%, 57 ± 3.5%, 55 ± 6.1, 62 ± 3%, 64 ± 5.4%. Higher ATP7B expression was detected in tumour than normal tissue in 2/6 cases.
Discussion. Cu transporters hCTR1, ATP7A and ATP7B are expressed in tumour tissues of colorectal cancer. There is no significant difference in hCTR1 or ATP7A expression between tumour and normal tissues in the majority of cases. ATP7B expression is lower in tumour tissues in most cases. Interpatient variability of expression of these transporters implies varying Cu demand and disposition in colorectal cancer, therefore, personalised strategy is needed for targeting Cu transporters. Supported by Royal Hobart Hospital Research Foundation and Cancer Council Tasmania.¶

538 Investigating the optimal initial dose of gentamicin in paediatric oncology patients considering efficacy and reduction in renal function

Carolina C Llanos-Paez[1], Christine E Staatz[1], Stefanie Hennig[1]. School of Pharmacy, The University of Queensland[1], Brisbane, Queensland, Australia.

Introduction. Selection of an optimal initial dose of gentamicin in paediatric oncology patients is challenging with patients often receiving long courses of this agent on multiple occasions, increasing the risk of nephrotoxicity.
Aims. This study aimed to estimate an optimal initial dose of gentamicin targeting specific efficacy endpoints while minimising the risk of renal function reduction.
Methods. Individual's gentamicin exposure was predicted using a population pharmacokinetic model[1] and bacterial killing was predicted using a semi-mechanistic pharmacodynamic model[2]. A utility function balancing probability of efficacy after the first dose and extent of reduction in renal function on day seven, if this dose was repeated daily for 7 days, was implemented in NONMEM® software. Different efficacy targets were considered: A maximal gentamicin concentration (C_{max}) to bacteria minimum inhibitory concentration (MIC) ratio of ≥ 10 and an area under the concentration-time curve from 0 to 24 hours post-dose (AUC_{24}) to MIC ratio of ≥ 70 – 100; and bacterial count reduction of 2-log_{10} Colony Forming Unit (CFU)/mL at 24-hours post-dose.
Results. An estimated initial dose of gentamicin of 7.1 mg/kg for bacteria with an MIC of 0.5 mg/L, 9.5 mg/kg for an MIC of 1 mg/L, 10.8 mg/kg for an MIC of 2 mg/L and 14.6 mg/kg for an MIC of 4 mg provided ≥ 75% probability of achieving C_{max}/MIC ≥ 10 and AUC_{24}/MIC ≥ 70 – 100. With an estimated dose of 12.8 mg/kg, 81.7% of patients achieved a 2-log_{10} bacterial count reduction at 24-hours post-dose. Under these different dosing scenarios reduction in renal function ranged on average from 6.9% to 14.5% on day seven.
Discussion. An initial gentamicin dose of 7.5 mg/kg/24 hours given in clinical practice may not achieve adequate efficacy for microorganisms with a MIC > 0.5 mg/L. With the highest dose estimated in this study (14.6 mg/kg/24 hours), 63.2% of patients had some reduction in their renal function on day seven. Therapeutic drug monitoring is recommended to individualised treatment after a high initial dose to ensure efficacy and minimize toxicity.

1. Llanos-Paez C.C (2017) AAC 61(8)
2. Mohamed A.F (2012) AAC 56(1):179-88.¶

539 Interaction of mangosteen extract and alpha mangostin with metformin in diabetic rats: PK/PD studies

Mirawati Tjakkudu[1,3], Sukmadjaja Asyarie[1], Neng F Kurniati[2], Lucy Sasongko[1]. Department of Pharmaceutics[1], Department of Pharmacology & Clinical Pharmacy[2], Institut Teknologi Bandung, Bandung, Indonesia; Faculty of Pharmacy, Universitas Muslim Indonesia[3], Makassar, Indonesia.

Introduction. Diabetes mellitus (DM) is a metabolic disorder disease and the first choice drug for type 2 diabetes is metformin. Nowadays, combining drugs with herbs becomes more popular, including for diabetic treatment. Mangosteen pericarp containing α-mangostin is one herb that shown antidiabetic effect.
Aims. To evaluate the pharmacokinetic and pharmacodynamics (PK/PD) interactions of mangosteen extract (ME) and α-mangostin (AM) with metformin (MFN) when used simultaneously in alloxan induced diabetic male rats.
Methods. Studies were performed on 5 groups of diabetic male rats (n = 5 for each group). Group I, II and III were single dose groups and given MFN (100 mg/kg BW), α-mangostin (37.2 mg/kg BW) and ME (248 mg/kg BW), respectively. Group IV and V were combination groups and given MFN & AM and MFN & ME, respectively, and group VI served as a control. MFN and AM levels in plasma were determined by HPLC and plasma glucose levels were determined by the GOD-PAP method. PK profiles and parameters of MFN and AM were calculated, % blood glucose decrease were calculated and dose-response curves were made.
Results. PK profiles of MFN followed 2 compartment model from either single or combination administrations, so did the AM from pure AM or EM administrations. Surprisingly, AM plasma levels could not be measured when AM given in combination with MFN (Group IV & V), while PD effects were observed. Based on AAC_{0-12}, MFN did not show significant change ($p>0.05$) in PD effects when combined with pure AM (Group IV vs I), interestingly significant changes ($p<0.05$) were observed when combined with EM (Group V vs I). AAC_{0-12} of Group IV and V increased when compared to Group II and III, these showed that AM increased the effects of MFN although the AM plasma concentrations could not be detected.
Discussion. Combination of MFN and EM showed a better hypoglycemic effects when compared to combination of MFN and AM, this could be due to other constituents in the extract that produced a potent hypoglycemic effects than AM itself. The current findings might lead to a benefit in using the mangosteen extract than the pure alpha mangostin.¶

540 Early prediction of chemotherapy efficacy in liver cancer cells by specific ROS levels

Haotian Yang[1], Haolu Wang[1], Michael S Roberts[1,3], Xiaowen Liang[1]. Therapeutics Research Centre, The University of Queensland Diamantina Institute, Faculty of Medicine, The University of Queensland[1], Brisbane, QLD, Australia; School of Pharmacy and Medical Science, University of South Australia[2], Adelaide, SA, Australia

Background: Liver cancer is the second most common cause of death from cancer worldwide. The most common type of primary and secondary liver cancer is hepatocellular carcinoma (HCC), and colorectal cancer liver metastases (CLM), respectively. Current assessments of chemotherapy responses for liver cancer require weeks to months, causing delay in instituting alternative chemotherapy regimens. Thus, there is an urgent need to predict the chemotherapy response at an early stage to improve liver cancer prognosis. It is known that levels of cellular reactive oxygen species (ROS) correlate with the aggressiveness of tumour cells and prognosis of patients. Cancer cells with increased endogenous ROS stress are more sensitive to anticancer agents and high levels of ROS generated by chemotherapeutic agents can induce cell death. Hence, ROS levels before and after chemotherapy in cancer cells can be an early indicator of treatment efficacy, which has the potential to shed new light on the chemotherapy.
Methods: In this study, the specific ROS (H_2O_2) levels were monitored and quantified before and after various concentrations of oxaliplatin in human colorectal cancer cells (HCT116) and mouse HCC cells (Hepa1-6). After different time points (30mins, 1, 2, and 3 hrs) post treatment by oxaliplatin, specific ROS detection probe (CM-H2DCFDA) was added to cells for detecting ROS levels by confocal microscopy (Olympus FV3000) at the excitation of 490 nm and emission wavelength of 520-560 nm. The fluorescence intensity of single cell in each group was measured and quantified by Image J. In the meantime, the viability and proliferation of these cells treated by the same concentrations of oxaliplatin were measured by MTT cell proliferation assay. Finally, the changes of specific ROS levels was correlated to cell viability after chemotherapy.
Results and conclusion: H_2O_2 levels of HCT116 cells was significantly increased from 1 hrs after oxaliplatin treatment compared to control untreated group, while Hepa1-6 did not show obvious increase of H_2O_2 levels after oxaliplatin treatment. In addition, the higher levels of H_2O_2 within cells in 3 hrs correlated well with greater inhibition of oxaliplatin after 24 hrs. These results indicated oxaliplatin has better treatment response in HCT116 cells, and ROS levels could be an indicator for early prediction of chemotherapy efficacy in CLM.¶

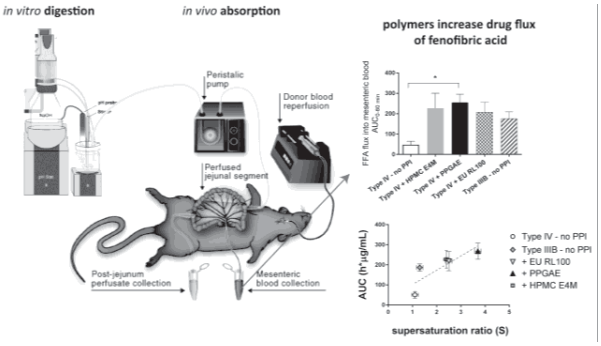
541 Drug delivery to the intestinal lymphatics enhances the immunosuppressant effects of mycophenolic acid in mice.

Ruby Kochappan[1,2], Sifei Han[1,2], Luojuan Hu[1,2], Timothy Quach[2,3], Danielle Senyschyn[1,2], Enyuan Cao[1], Given Lee[1,2], Fern Lim[2,3], J.S. Simpson[2], Justine Mintern[4], Natalie L Trevaskis[1], Christopher J.H. Porter[1,2]. [1] Drug Deliv Dispos and Dyn, [2]ARC CoE in Bio Nano Sci and Tech, [3]Med Chem, Monash Inst of Pharm Sci, Melbourne, VIC, Australia, [4]Biochem and Mol Bio, Bio21 Instit, Univ of Melbourne, Melbourne, VIC, Australia.
Introduction: The lymphatic vessels that drain the intestine, the gut associated lymphoid tissue (GALT) and the mesenteric lymph nodes (MLN) are central to gut immune surveillance. The intestinal lymphatics also serve to transport dietary lipids (triglycerides, TGs) from the gut to the systemic circulation (Trevaskis et al 2015).
Aim: To evaluate the pharmacodynamic benefit of targeting an immunomodulatory agent (mycophenolic acid, MPA) to gut lymphatic immune cells by mimicking the endogenous transport pathway of TGs into the lymph. This was achieved via the design of a TG mimetic prodrug of MPA (MPA-2-TG) (2) to target lymphocytes in intestinal lymph.
Methods: The intestinal lymph transport of MPA and MPA-2-TG, was assessed after intraduodenal infusion, by cannulating the mesenteric lymph duct of anaesthetised mice (100 mg/kg ketamine and 10 mg/kg xylazine, ip). Immunosuppression was studied by adoptive transfer of dye labelled CD8+ T cells, purified from lymph nodes (LN) from OT 1 mice, into syngeneic mice fed 50 mg ovalbumin (OVA). Mice were then administered MPA or MPA-2-TG (50 mg/kg) twice daily for 3 days. At the end of the treatment, T cell proliferation in mesenteric and peripheral LNs was evaluated using flow cytometry.
Results: The lymphatic uptake of MPA-2-TG (17.3 % dose) was higher than MPA (0.14 %). MPA-2-TG treatment significantly reduced the proliferation of CD8+ T cells in the MLN, with most dye labelled cells (~80%) being found in generation 4 or lower after OVA stimulation. In contrast, MPA had no significant effect on cell replication.
Discussion: Targeting lymphocytes in intestinal lymph, via the use of a lipid-mimetic prodrug significantly enhanced the immunosuppressive effects of MPA. This approach may have the potential to enhance the pharmacodynamic benefit of other drugs, such as cytotoxic or immunomodulators that act within the mesenteric lymphatics and MLN.

1. Han S et al (2014) J Control Release 177:1-10.
2. Trevaskis NL et al (2015) Nat Rev Drug Discov 14:781-803.¶

542 Polymer precipitation inhibitors can maintain drug supersaturation and increase in vivo absorption from lipid-based formulations

Estelle Suys[1,2], David K. Chalmers[3], Colin W. Pouton[1], Christopher J.H. Porter[1,2]. [1]Drug Delivery, Disposition and Dynamics, [2]ARC Centre of Excellence in Convergent Bio-Nano Science and Technology and [3]Medicinal Chemistry, Monash University, Melbourne, VIC, Australia



Introduction. Lipid-based formulations (LBFs) have emerged as a promising formulation strategy to overcome the issue of solubility-limited absorption, thereby improving the oral bioavailability of poorly water-soluble drugs (PWSDs). After oral dosing, supersaturation often arises with the potential for drug precipitation. To stabilize the metastable supersaturated state, polymer precipitation inhibitors (PPIs) may be added to LBFs to inhibit drug precipitation, potentially resulting in increased drug absorption.
Aims. The current project is exploring the solubility-supersaturation-absorption relationship when using PPIs in LBFs, by measuring drug flux in an *in vivo* experimental model.
Methods. A coupled *in vitro* digestion - isolated rat jejunum model, has been employed to evaluate in real time the impact of PPIs on drug flux. Fenofibrate and saquinavir were chosen as model PWSDs.
Results. Addition of selected PPIs prolonged supersaturation and led to increases in fenofibric acid absorption of up to ~ 4-fold. Reasonable correlation was evident between the degree of supersaturation and drug flux suggesting that increases in the intraluminal free drug fraction were driving increased absorption.
Discussion. This work demonstrates the utility of the coupled *in vitro* digestion-*in vivo* absorption model in developing a better understanding of drug absorption from polymer-containing LBFs. The data suggest that PPIs can support prolonged drug supersaturation and that this results in improved absorptive drug flux *in vivo*.¶

543 The effects of aging on polarization in collagen sandwich-cultured hepatocytes.

Sun Woo Sophie Kang[1,2], Dong Fu[3], David G. Le Couteur[1,2] and Victoria C. Cogger[1,2]. Aging and Alzheimers Institute, ANZAC Research Institute, Concord Clinical School/Sydney Medical School[1], Concord, NSW, Australia; Charles Perkins Centre, University of Sydney[2], Sydney, NSW, Australia; UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill[3], NC, United States of America.

Introduction. Hepatocytes have a unique polarized phenotype where apical domains of adjacent cells make up a tubular structure, known as bile canaliculus. This polarized morphology is important for hepatocyte function and viability. Loss of polarity can result in excessive accumulation of bile, toxins and metabolites that can lead to hepatocellular damage such as seen in drug-induced hepatotoxicity and liver diseases such as cholestasis, fibrosis and cirrhosis. Ageing is associated with increased susceptibility to impaired hepatic function, which can increase the risk of adverse drug reactions that are associated with hepatotoxicity and liver disease. However, the effect of ageing on hepatocyte polarization is unknown. Using collagen sandwich cultures of hepatocytes, we compared the reestablishment of hepatocyte polarization in isolated hepatocytes from young and old mice.
Methods. Hepatocytes were freshly isolated from young (3 months) and old (24 months) C57BL6 male mice and cultured in a collagen sandwich configuration. Polarization was assessed every 12 hours over 72 hours using lipid droplet staining and immunofluorescence of apical protein ATP-binding cassette sub-family B member 1 and tight junctional protein Zonula occludens-1. ATP levels were also quantified.
Results. Immunofluorescence revealed that hepatocytes from old mice polarized at a faster rate than young hepatocytes. Furthermore, there were significantly more and larger lipid droplets in the hepatocytes of old mice from the beginning of hepatocyte polarization. Lipid droplets remained large in old hepatocytes after 60 hours even after the formation of the bile canalicular network. In young mice, the reduction of lipid droplet numbers was evident after 24 hours. Polarization is an energy-dependent cellular process. ATP levels rapidly peaked within 24 hours in old hepatocytes whereas in young hepatocytes levels increased more slowly and peaked after 48 hours.
Discussion. Hepatocytes from old mice polarize and accumulate ATP more rapidly than young hepatocytes. These changes might contribute to age-related changes seen in hepatic function and susceptibility to drug-induced hepatotoxicity and liver diseases such as fatty liver. ¶

544 Tachykinin NK_2 receptor expression in the human colon; an insight into the influence of gender, age and disease

Stelina Drimousis, Irit Markus, Tim Murphy, Lu Liu. School of Medical Sciences, UNSW Sydney, Sydney, NSW, Australia.

Introduction. Neurokinin A (NKA) released from enteric neurons contracts intestinal smooth muscle via tachykinin NK_2 receptors (NK_2R). We have previously reported gender differences in the abundance of [^{125}I] NKA binding sites, and in the potency of the NK_2R antagonist ibodutant, in control human colonic smooth muscle (Burcher et al., 2008, Drimousis et al., 2016). We have also shown that NK_2R mRNA expression is downregulated, and contractility to NKA is reduced in the colonic smooth muscle of patients with diverticular disease (DD) (Burcher et al., 2008, Liu et al., 2011).
Aims. This study aimed to determine the existence of any gender differences in the cellular distribution and density of the NK_2R in the human colon in control and DD.
Methods. In human colon specimens, fluorescent immunohistochemistry and Western blot were conducted to localise and quantify the NK_2R protein expression.
Results. NK_2R immunoreactivity was densely expressed in the colonic smooth muscle layer, where it is colocalised with cell markers for smooth muscle (α-smooth muscle actin), nerve cell bodies (Hu), neurons (β-tubulin) and glial cells (S100). There were no obvious differences between genders, and between control and DD. NK_2R protein expression in control colonic smooth muscle was slightly higher in females compared to males (P = 0.066). While no age-related differential expression was observed in males, there was an increased expression with age in females (r = 0.61, $*P$ = 0.010), which was particularly noticeable in specimens older than 50 years of age compared to younger ones ($*P$ = 0.0485). There was a significant increase in NK_2R protein expression in DD muscle (1.3 fold higher than its age- and gender-matched control counterpart, $***P$ = 0.0005).
Discussion. Increased NK_2R protein expression arises in females at the average onset of menopause, suggesting that sex hormones may influence NK_2R expression. In DD, negative feedback may explain the discrepancies between NK_2R mRNA and protein levels.

Burcher E et al. (2008) J Pharmacol Exp Ther 324:170-8
Drimousis S et al. ASCEPT-MPGPCR conference abstract, 27-30 Nov 2016, Melbourne
Liu L et al. (2011) Neurogastroenterol Motil 23:475-83¶

545 Antibiotic Guidelines for Urinary Tract Infections (UTI) and Hospital Length of Stay

PK Loh[1], Catherine Bassett[2]. Dept Geriatric Medicine, Royal Perth Hospital[1], Perth, WA, Australia; Medical School, Uni Notre Dame[2], Fremantle, WA, Australia.

Introduction. UTIs and pyelonephritis accounted for 73300 separations Australia wide and 7365 hospitalizations across WA hospitals in 2014 to 2015. This in an audit of inpatient antibiotic treatment and its potential effect on hospital average length of stay (ALOS).
Aims. To determine whether compliance with antibiotic stewardship guidelines impacts on ALOS for patients treated for kidney and urinary tract infections with catastrophic or severe case complexity by the Department of Geriatric Medicine at a major metropolitan tertiary hospital.

Table 1. Antibiotic Prescribing and Compliance with Guidelines

	Number of cases (total n=20)	Percent of total cases (%)
Antibiotic compliant with guidelines	11	55%
Antibiotic not compliant with guidelines	9	45%
Total	20	100%
Reasons for non compliance		
Incorrect drug	2	10%
Incorrect drug combination	3	15%
Incorrect dose	1	5%
Incorrect frequency	2	10%
Total	8	40%

Methods. Audit medical records of patients discharged between 1st July 2016 and 30th December 2016 in Geriatric Medicine at Royal Perth Hospital for ICD-10-CM primary diagnosis of Australian Refined Diagnosis Related Group (AR-DRG) L63A: Kidney and Urinary Tract Infections with Catastrophic or Severe Case Complexity. Review the compliance of antibiotic prescription with "Therapeutic Guidelines: Antibiotic Guidelines".
Results. There were 20 admissions. 6 males (30%) and 14 females (70%), ages ranging from 65 to 98 years of age, 70% were over the age of eighty. Urinary catheter in situ on admission was 4 out of 20, 2 were male and 2 were female. 19 patients had a mid-stream urine collected during their admission. 13(68.4%) had their specimen collected before commencing their first dose of antibiotics. Of these 13, 9 had a pathogen identified and antibiotic sensitivity confirmed (69.2%). For the 6 specimens collected after commencing antibiotics, 3 had a pathogen identified and antibiotic sensitivity confirmed (50%). There was no significant difference between compliant vs noncompliant groups (Table 1) for ALOS variance (p=0.38). There was a significant difference in LOS variance (p=0.03) for parenteral vs oral antibiotic used between the 2 groups.
Discussion. In a group of older patients with multiple comorbidities and social issues non-medical factors play a significant role in ALOS. However, the use of oral vs parenteral antibiotics compliant with therapeutic guidelines for severe kidney infections or UTIs have an effect on ALOS for the older patients. ¶

546 Age-related variations in porcine bladder responses to clinical antimuscarinics.

Eleanor West, Russ Chess-Williams, Christian Moro. Bond University Centre for Urology Research, Faculty of Health Sciences and Medicine, Bond University, Gold Coast, QLD, Australia.

Introduction. Of all patients prescribed antimuscarinic therapy for overactive bladder, those aged under 60 are more likely to discontinue treatment earlier than their older counterparts. The cause of this reduced adherence to treatment regimens is unclear, however may be attributed to either lifestyle changes or age-related physiological changes, with the latter being of particular interest.
Aims. This project aims to investigate the influence of ageing on contractile responses of the urinary bladder detrusor and U&LP (urothelium and lamina propria) tissue layers in response to clinically prescribed antimuscarinics.
Methods. Porcine U&LP or detrusor strips from either juvenile bacon-pigs or aged sows were mounted in gassed Krebs-bicarbonate solution at 37°C and carbachol concentration-response curves were recorded in the presence and absence of selective muscarinic antagonists. Data obtained was analysed using paired Student's *t*-tests, with $P<0.05$ being significant.
Results. Aged U&LP demonstrated a greater contraction to carbachol, with peak contractions of 7.49±0.84g being reached at 78mM (n=8) compared to juvenile tissue at the same concentration 4.50±0.63g (78mM, n=7). Aged detrusor also exhibited a heightened contraction to carbachol (21.55±2.48g, 780mM, n=8) than the juvenile samples (14.85±2.90g, 78mM, n=8). In both detrusor and U&LP tissues, the presence of 4-DAMP (10nM, n=8), oxybutynin (1µM, n=7) and tolterodine (1µM, n=8) significantly inhibited the contraction to carbachol ($P<0.05$ for all), and this inhibition was more effective in aged samples, when compared to juveniles ($p<0.05$ for all).
Discussion. A greater response to carbachol was observed in aged U&LP and detrusor tissues, compared to younger samples. 4-DAMP, oxybutynin and tolterodine inhibited these contractions to carbachol, with an increased effectiveness in inhibiting responses of aged tissue compared to juvenile samples. This suggests that the observed increased persistence for overactive bladder treatment regimes in older adults may be attributed to a heightened effectiveness of antimuscarinic therapy.

547 Histamine receptors as regulators of urothelial and detrusor contractile activity

Zane Štromberga, Russ Chess-Williams, Christian Moro. Bond Centre for Urology Research, Gold Coast, QLD, Australia; Bond University.

Introduction. The mechanisms underlying bladder contractile disorders, such as overactive bladder, are not fully understood. It is apparent that acetylcholine release is involved, however, other mediators and regulator chemicals may also have a potential influence. As such, there is a particular interest in isolating which receptors, other than muscarinic, are involved in modulating spontaneous contractile activity. Aims. This study aimed to identify the specific influence of the H1, H2, H3 and H4 histamine receptors on urothelial and lamina propria (U&LP) contractile activity. Methods. Strips of porcine U&LP and detrusor were mounted in gassed Krebs-bicarbonate solution at 37°C and responses to histamine obtained in the absence and presence of selective antagonists. Data analysis of the responses was performed using paired Student's *t*-tests. This project was supported by the Australian Bladder Foundation.

		ΔTension (g)		ΔFrequency (cpm)		
Antagonist	Conc.	Absence	Presence	Absence	Presence	n
Pyrilamine	30nM	0.47±0.11	0.11±0.08*	1.32±0.38	0.01±0.21*	8
Cimetidine	1µM	1.32±0.56	1.84±0.65*	1.48±0.63	1.41±0.94	8
Thioperamide	1µM	1.20±0.29	1.75±0.29*	1.49±0.63	1.76±0.58	6

Results. The table shows U&LP responses to 100µM histamine in the absence and presence of selective antagonists. The U&LP contracted in the presence of histamine by 1.14±0.3g and the frequency of spontaneous contractile activity was increased by 1.53±0.38 cycles min-1 (cpm, 100µM, n=26). Pyrilamine (30nM, H1 antagonist) inhibited these contractile responses ($p<0.01$, n=8) and increases in spontaneous contractions ($p<0.01$, n=8). In the presence of cimetidine (1µM, H2 antagonist) maximal contractions to histamine were enhanced ($p=0.05$, n=10). Although thioperamide (1µM, H3 and H4 antagonist) initially showed a significant increase in contractions ($p=0.03$, n=6), selective antagonism revealed no influence of H3/H4. In detrusor preparations, H1 receptors were responsible for the majority of the contraction to histamine ($p<0.05$, n=8), with no influence from antagonism of H2,H3 or H4. Discussion. Histamine produces both a contractile and relaxation response in the U&LP. The contraction appears mediated by the H1 receptor, while relaxation is mediated by the H2 receptor. Preliminary data presents these receptors as potential targets in future therapeutic treatments for overactive bladder or other bladder contractile diseases. ¶

548 β-adrenoceptors in the urinary bladder vasculature

Damian Nilsson[1], Donna J Sellers[1], Russ Chess-Williams[1]. Centre for Urology Research, Faculty of Health Sciences and Medicine, Bond University[1], Gold Coast, QLD, Australia

Introduction. Ischaemia of the bladder has been suggested to play a role in the etiology of bladder dysfunction (Bayrak et al., 2015). Mirabegron, the newest treatment available to treat bladder dysfunction, mediates relaxation via an action on β_3-adrenoceptors in the bladder detrusor smooth muscle (Igawa & Michel, 2013). Whether this action on β_3-adrenoceptors is also seen in the bladder vasculature is unknown.
Aims. The aim of this study was to investigate whether β3-adrenoceptors are involved in relaxation of the bladder vasculature.
Methods. Rings of superior vesical artery (SVA) from 6-month old pigs were mounted in organ baths. Tissues pre-contracted with KCl (60mM) were relaxed with a β-adrenoceptor agonist, either isoprenaline (non-selective), salbutamol (β_2), CGP-12177A (partial β_3) or mirabegron (β_3), in the presence of phentolamine (10µM) and L-NNA (100µM). Isoprenaline relaxations were also performed in the presence of the β-adrenoceptor antagonists propranolol (non-selective), CGP-20712A (β_1 selective), ICI-118, 551 (β_2 selective) and SR-59230A (β_3 selective).
Results. Isoprenaline relaxed the SVA with high potency (pEC_{50} 7.6±0.14, n=6) and a maximum relaxation of 57.1±3.2% of the KCl pre-contraction. Salbutamol, CGP12177A and mirabegron also induced relaxations with high potency (pEC_{50} 7.45±0.2, 7.94±0.18 and 7.93±0.16 respectively), although maximum relaxations were significantly ($P<0.05$) smaller than for isoprenaline (salbutamol, 23.7±1.9%; CGP12177A, 20.3±1.2%; mirabegron, 20.7±1.1%; n=7). Propranolol (10 & 100nM), CGP-20712A (3µM), ICI-118, 551 (3nM) and SR59230A (10nM) antagonised isoprenaline relaxations with high affinity (pKB 9.52, 9.26, 8.28, 12.14 and 8.87 respectively, n=3-6).
Discussion. This study demonstrates that all three β-adrenoceptor subtypes mediate relaxation of the superior vesical artery and confirms that β3-adrenoceptors are present within the bladder vasculature. Mirabegron can relax these blood vessels and this action may contribute to the efficacy of this new treatment for bladder dysfunction.

Bayrak S et al. (2015) Naunyn-Schmiedeberg's Arch Pharmacol. 388: 47-54.
Igawa Y & Michel M (2013) Naunyn-Schmiedeberg's Arch Pharmacol. 386: 177-183¶

549 Ethanol as an intravesical vehicle: effects on bladder function

Katrina Smith[1], Catherine McDermott[2], Russ Chess Williams[3] .[1,2,3] Centre for Urology Research, Bond University, Gold Coast, QLD, Australia.

Introduction. Capsaicin is usually dissolved in 30% (v/v) ethanol when used intravesically to treat some refractory bladder conditions. Previous work examining capsaicin in the bladder using 30% ethanol as a vehicle control reported that the ethanol was just as irritating as the treatment.
Aims. Our objective was to investigate the effects of luminal ethanol on bladder function.
Methods. 30% ethanol (in 0.9% saline) was applied to the luminal surface of porcine bladders for 30 minutes. Matched control tissues (treated with 0.9% saline) were also assessed. Treatment medium was assayed for ATP and Ach release, contractile responses of isolated tissue strips were recorded and tissues were compared histologically.
Results. Histological examination revealed significant thinning of the urothelium occurred after treatment (control =69.4±6.36µm v 30%=13.3±1.51µm, n=6, $p<0.0001$). Treatment medium contained significantly enhanced urothelial ATP (control=0.01±0.004µM v 30%=1.68±0.22µM, n=8, $p<0.0001$) and depressed Ach release (control=2.61±0.40µM v 30%=0.24±0.22µM, n=8, $p<0.0001$). Maximal contractile responses to carbachol were significantly greater in urothelial (control=31.33±2.74mN v 30%=41.14±3.47nN, n=7, $p<0.046$) and detrusor tissues (control=66.91±4.06mN v 30%=92.81±2.13mN, n=7, $p<0.0002$) treated with 30% ethanol. Neurogenic responses were significantly larger at maximum stimulation (control=56.93±9.99mN v 30%=119.10m±16.31mN, n=7, p= <0.006).
Discussion. Based on our study, 30% ethanol used as a vehicle produces significant urothelial damage, altered release of mediators and enhanced contractile activity. The damage and enhanced activity should be taken into consideration as part of treatment side effects.

550 Prazosin but not tamsulosin sensitises PC-3 and LNCaP prostate cancer cells to docetaxel

Briohny H Spencer[1,2,3], Catherine M McDermott[4], Russ Chess Williams[4], David Christie[1,2,5], Shailendra Anoopkumar-Dukie[1,23], [1]School of Pharmacy & Pharmacology; Griffith University, Gold Coast Campus, Gold Coast, QLD 4222, Australia, [2] Quality Use of Medicines Network, Griffith University, Gold Coast Campus, Gold Coast, QLD 4222, Australia, [3] Menzies Health Institute Queensland, G40 Griffith Health Centre, Gold Coast campus, Griffith University QLD 4222, Australia, [4] Centre for Urology Research, Faculty of Health Sciences and Medicine, Bond University, Robina, QLD 4229, Australia, [5] Genesis Cancer Care, Southport , QLD Australia.

Introduction: Docetaxel is currently the first-line chemotherapeutic agent available for the treatment of patients with advanced prostate cancer. While docetaxel has been shown to modestly improve survival times for patients; they also experience significant docetaxel-induced toxicities. If treatment failure occurs there is currently no effective alternative and therefore there is an urgent need for adjunct therapies. Some quinazoline-based α1-adrenoceptor (ADR) antagonists have previously been shown to have cytotoxic actions in prostate cancer cells, but there is no research into their effects on docetaxel-induced toxicity.
Aims: The aim of this study was to determine if the quinazoline ADR, prazosin altered sensitivity of prostate cancer cells to docetaxel *in vitro*.
Methods: PC-3 and LNCaP cells were pre-treated (1hr) with prazosin (30µM) or tamsulosin (30µM), followed by docetaxel (12.5µM to 100µM, 24hrs). Docetaxel-induced toxicity was measured in terms of changes in cell proliferation (resazurin reduction), autophagy (monodansylcadaverine staining) and apoptosis (caspase-3 activity) and the production of reactive oxygen species (2'7'-dichlorofluorescein diacetate fluorimetry).
Results: Prazosin sensitised both cell lines (PC-3 and LNCaP) to docetaxel-induced toxicity. This effect appears to be mediated by autophagy and may also involve apoptosis. These sensitising effects of prazosin appear to be largely independent of reactive oxygen species production. In contrast, tamsulosin did not effect docetaxel-induced toxicity.
Discussion: We have shown, for the first time, that prazosin increases docetaxel-induced toxicity in PC-3 and LNCaP cells. Prazosin may therefore offer a viable treatment option in combination with docetaxel in metastatic prostate cancer.
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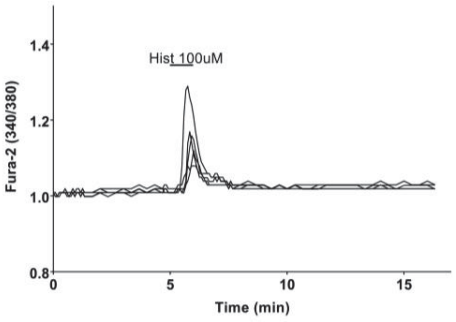
551 Purinergic P2X7 receptor antagonist A804598 reduces the damage induced by acrolein in *ex-vivo* porcine bladders

Zhinoos Taidi[1], Kylie Mansfield[2], Lu Liu[1]. School of Medical Sciences, UNSW Sydney[1], Sydney, NSW, Australia; School of Medicine, University of Wollongong[2], Wollongong, NSW, Australia

Introduction. Cyclophosphamide (CYP) is an antineoplastic agent commonly used in chemotherapy. Acrolein, the highly toxic metabolite of CYP, excretes into urine causing severe bladder cystitis. The purinergic P2X7 receptor (P2X7R) has recently come into attention for its role in inflammation. P2X7R is highly expressed by many immune cells and regulates the expression and secretion of various cytokines such as IL-1β and TNF-α.
Aims. In this study, we aimed to develop an *ex-vivo* model of urothelial inflammation by perfusing porcine bladders with acrolein, and to determine if urothelium inflammation affects bladder activities. We also aimed to investigate if P2X7 antagonism can protect against acrolein-induced inflammation and damage in the bladder.
Methods. The whole bladders (n=9) from 2 month-old porcine were placed in 100-ml organ baths containing Krebs-Henseleit solution maintained at 37°C and perfused for 4 hours with carbogenated RPMI culture media (in the presence or absence of 0.05% acrolein) via a fine tube that was inserted into the bladder from urethral orifice. After 4 hours perfusion, each bladder was dissected into intact, detrusor and mucosa strips and their contractility in response to acetylcholine (ACh) were measured. Histology staining was performed to determine the degree of tissue damage.
Results. ACh contracted intact, detrusor and mucosa strips in a concentration-dependent manner in fresh and perfusion control bladders. In acrolein-treated strips, the contractile responses to ACh were significantly diminished in intact strips and completely abolished in mucosal strips. Pre-treating bladders with the P2X7R antagonist A804598 (at 10 µM for 1 hour) significantly reversed acrolein-induced reduction in response to ACh. The histology staining showed that acrolein caused substantial damage to the urothelial and suburothelial layers.
Discussion. In this study, we have established an *ex-vivo* inflammatory model in the porcine bladder, which is a good model for the study of the human bladder. The damage to the muscle bundles and myofibroblasts in the mucosa layer by acrolein is likely to account for the reduced contractile response of the intact and mucosa strips to ACh. The protective effect of A804598 has provided strong evidence that P2X7R plays an important role in bladder inflammation and indicated that an inhibition of P2X7R activities could be a pathway for the treatment of bladder inflammation, and could potentially be co-administered with CYP for chemotherapy.¶

552 Histamine receptor (Hrh) subtypes mediate bladder afferent sensitivity in mice

Ashlee Caldwell[1], Luke Grundy[1,2], Andelain Erickson[1], Grigori Rychkov[2], Stuart Brierley[1,2]. Dept of Medicine, Univ of Adelaide[1], Adelaide, SA; Dept of Hum Physiol, Flinders Univ[2], Bedford Park, SA.



Introduction: Pelvic pain conditions such as overactive bladder syndrome and interstitial cystitis are associated with enhanced bladder sensation, leading to the symptoms of frequency, urgency and pain. Histamine, released from activated mast cells, is a key mediator of neurogenic inflammation and pain in the bladder and other visceral organs. However, the exact role and distribution of histamine receptor subtypes (Hrh1-4) in bladder sensory structures is unknown.
Aims: To determine the expression and function of histamine receptors in bladder sensory structures.
Methods: RT-PCR was performed on primary urothelial cells and mucosal and detrusor layers of mouse bladders. Retrogradely labelled bladder DRG neurons from mice were isolated and dissociated for single-cell RT-PCR and calcium imaging. *Ex-vivo* bladder afferent recordings determined bladder mechanosensitivity.
Results: RT-PCR revealed mRNA expression of Hrh1-3 in dissociated urothelial cells, and 10-fold higher expression in bladder mucosal and detrusor tissue. Hrh4 mRNA expression was 1000-fold lower in both cells and tissues. Single cell PCR data identified Hrh1 mRNA expression in 29% of bladder afferent neurons whilst histamine (100µM) induced significant calcium transients in 18% of bladder DRG neurons. Histamine (300µM) perfused into the bladder lumen induced mechanical hypersensitivity to bladder distension versus saline ($p<0.01$, n=6) which was attenuated by Hrh1 antagonist pyrilamine (100uM) and completely abolished by combined Hrh1 and Hrh4 antagonists.
Discussion: Histamine receptors are present and functional in bladder sensory structures, and their activation is able to induce calcium transients in isolated bladder neurons and enhance bladder mechanosensitivity to distension. This work provides valuable insight into the action of histamine, and the role of histamine receptors in the bladder, unravelling potential mechanisms of pelvic pain pathology.¶

553 Characterization of Na_v Channels in Colon-Innervating Dorsal Root Ganglion Neurons in Mice

Andelain Erickson[1,3], Sonia Garcia-Caraballo[1,3], Joel Castro[1,3], Luke Grundy[1,3], Grigori Rychkov[1], Richard Lewis[2], Irina Vetter[2], Glenn King[2] and Stuart M. Brierley[1,3], Discipline of Medicine, SAHMRI, University of Adelaide[1], SA, AUSTRALIA, Institute for Molecular Bioscience, University of Queensland[2], St Lucia, QLD, AUSTRALIA, Visceral Pain Research Group, Human Physiology, Flinders University[3], Adelaide, SA, AUSTRALIA.

Chronic visceral pain is a poorly managed symptom of functional and inflammatory gastrointestinal disorders and there is a lack of analgesics that are efficacious without gastrointestinal side effects. Voltage-gated sodium (Na_v) channels regulate action potential generation and cell membrane excitability in sensory neurons, and they are implicated in several pain or loss-of-pain phenotypes in humans, which has inspired investigation into the therapeutic potential of Na_v channel modulation. In this study, we show that Na_v channels and their auxiliary β-subunits are abundantly expressed in dorsal root ganglia (DRG) neurons at thoracolumbar (TL) and lumbosacral (LS) levels from C57BL/6J mice, and heterogeneously expressed in colon-innervating DRG neurons. Using retrograde labeling and whole-cell patch clamp electrophysiology, we found that colonic TL and LS neurons exhibited comparable peak sodium current densities (TL: –894 pA/pF, n = 23; LS: –883 pA/pF, n = 14), however, colonic TL neurons were significantly less excitable compared to colonic LS neurons (rheobase: TL: 183 pA, n = 32; LS: 85 pA, n = 22. p = 0.0143). The Na_v channel blocker tetrodotoxin (TTX, 100 nM) significantly increased the minimum current required to fire an action potential in colonic TL and LS neurons, however, sodium current densities in colonic TL neurons were less affected by TTX compared to colonic LS neurons (TL: 50% reduction, n = 14; LS: 70% reduction, n = 8).

In conclusion, voltage-gated sodium channels and auxiliary β subunits are highly abundant in whole DRG and colonic DRG from T10–S1 spinal levels. However, TTX-S channels may have differing contributions to colonic DRG neurons innervating the thoracolumbar versus lumbosacral regions, which may underlie their differing functions.

554 Pharmacological effects of a jungle ginger on rat prostatic smooth muscle

Eunice NN Su[1,3], Jamie S Simpson[2], Philip Thompson[2], Sabatino Ventura[1], Drug Discovery Biology[1] and Medicinal Chemistry[2], Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC, Australia. Sarawak Biodiversity Centre, Kuching, SWK, Malaysia[3]

Introduction. Jungle ginger has been traditionally used by Sarawak natives to treat urological disorders. Since drugs that relax prostatic smooth muscle are used to manage urinary symptoms associated with urological disorders.
Aims. To assess the pharmacological effects of a jungle ginger on prostate contractility and to isolate its bioactive components.
Methods. This is original work reporting the biological effects of jungle ginger on isolated rat prostate contractility. Jungle ginger rhizome, roots, leaves and stem were harvested from Sarawak. Extracts of dried and ground plant materials were extracted using water at room temperature. Activity of these extracts was evaluated pharmacologically by assessing their effects on contractions of isolated rat prostate gland maintained in a modified Krebs solution at 37ºC and bubbled with carbogen gas. Nerve mediated contractions were evoked electrically (0.1-20 Hz, 0.5 ms pulse duration, 60 V) while direct muscle stimulation was achieved by application of the exogenously administered agonists. Pharmacological tools were used to identify mechanisms of action.
Discussion. Jungle ginger rhizome ($p=0.0004$, n=6), root ($p<0.0001$, n=6) and stem ($p=0.0057$, n=6) extract inhibited electrical field stimulation (EFS) induced contractions of rat prostatic smooth muscle, while leaf extract did not exhibit bioactivity ($p=0.0988$, n=6). Contractions mediated by exogenous administration of noradrenaline (1 nM-1 mM, n=6), acetylcholine (1 nM-1 mM, n=6) or ATP (0.3 uM-1 mM, n=6) were not inhibited by rhizome extract. Tyramine (10 nM-0.1 nM) induced contractions were also not effected by the rhizome extract (n=4). EFS-induced contractions were still attenuated by the rhizome extract in the presence of prazosin (300 nM, n=6), suramin (30 nM, n=6), yohimbine (1 µM, n=6), idazoxan (1 µM, n=6), propranolol (1 µM, n=6), atropine (1 µM, n=6), methysergide (1 µM, n=6), mepyramine (1 µM, n=6), hexamethonium (10 µM, n=6), desipramine (100 nM, n=6), 8-phenyltheophylline (10 µM, n=6), and AH6809 (10 µM, n=6). Jungle ginger rhizome, stem and root extracts inhibit contractility of rat prostatic smooth muscle by an indirect prejunctional mechanism that inhibits exocytotic release of neurotransmitter.¶

555 Inhibition of human $Ca_V3.2$ channels by synthetic cannabinoid MDMB-CHMICA *in vitro*

Chris Bladen[1], Marina Santiago[1], Mitchell Longworth[2] Michael Kassiou[2], Sam Banister[3], and Mark Connor[1]. Dept of Biomedical Sciences, Macquarie University[1], Sydney, NSW, School of Chemistry, University of Sydney[2], Sydney, NSW, 2006, Dept of Pathology, Stanford University School of Medicine[3], Stanford, CA 94305, USA

Introduction. Methyl-2-[[1-(cyclohexylmethyl)indole-3-carbonyl]amino]-3,3-dimethylbutanoate (MDMB-CHMICA) is a synthetic cannabinoid associated with severe adverse effects including dozens of deaths (EMCDDA, 2016). We have recently shown that MDMB-CHMICA has a higher efficacy and 20-fold greater *in vitro* potency as a CB1 agonist than the psychoactive ingredient of cannabis, ∆9-tetrahydrocannabinol (Banister et al, 2016). The CB1 potency and efficacy may underlie some of the severe hallucinogenic and psychotomimetic effects of the drug, however, the mechanisms responsible for other symptoms such as heart arrhythmias and peripheral toxicity remain to be established.
Aims. Cannabinoids directly interact with several ion channel classes, and the aim of this study was to explore whether MDMB-CHMICA interact with human T-type calcium channels ($hCa_V3.2$), which are known to regulate rhythmicity in the heart and the brain (Catterall et al, 2008).
Methods. Whole-cell voltage clamp recordings were made from HEK293 cells expressing $hCa_V3.2$.
Results. When cells were stepped from a holding potential of -100 mV to a test potential of -30 mV, MDMB-CHMICA rapidly blocked $hCa_V3.2$ with an IC_{50} of 1.5 ± 0.2 µM (n=6 cells per point). When applied at a concentration of 1 µM, MDMB-CHMICA did not significantly affect the half-activation potential of $hCa_V3.2$ (-42 ± 1 mV in control, -43.3 ± 1 mV in drug) and had no obvious effects on channel kinetics (n=6).
Discussion. This is the first report of illicit synthetic cannabinoid inhibition of human T-type calcium channels. The mechanisms underlying synthetic cannabinoid toxicity are not firmly established, but many of the most severe symptoms, including arrhythmia, seizures and low blood pressure have been associated with altered $hCa_V3.2$activity (Catterall et al, 2008).

Banister SD et al, (2016) ACS Chem Neurosci 7: 1241-1254.
Catterall WA et al (2008) J. Neurosci 28:11768 –11777
European Monitoring Centre for Drugs and Drug Addiction (2016) EMCDDA–Europol Joint Report on a new psychoactive substance: MDMB-CHMICA.

556 Potential role of herb-herb interactions in hepatotoxicity

Susan M Britza[1], Ian F Musgrave[1], Roger W Byard[2, 3]. Dept of Pharmacol, Univ of Adelaide[1], Adelaide, SA, Australia; Dept of Pathol, Forensic Science SA[2], Adelaide, SA, Australia; Dept of Pathol, Univ of Adelaide[3], Adelaide, SA, Australia.

Introduction. Despite the unknown safety of many complementary medicines, use of products continues to increase. Approximately 20% of all drug-induced hepatotoxicity cases have been linked to herbal medicines; a significant proportion of which are multi-herb traditional Chinese medicines (TCMs). Commonly perceived as natural, hence safe, TCMs are often taken with other non-prescribed substances; hence, it is imperative a causal relationship between adverse events and herbs is established. Currently, research focusses on herb-drug interactions, neglecting herb-herb interactions. A recent case of fatal hepatotoxicity was believed to be due to pharmacokinetic interactions between the Psoralea corylifolia toxic component, psoralen, a CYP3A4 inhibitor, astragaloside IV (AST-IV), from Astragalus propinquus, and Atractylodes macrocephala, atractylenolide I (ATR-I), shown to increase Astragalus glycoside levels.
Aims. To establish CYP functionality and metabolic competency in our cell models with paracetamol and CYP inducers, rifampicin and phenobarbital, and to investigate the individual and combined toxicity of active components listed.
Methods. Psoralen and related chemicals, coumarin and 8-methoxypsoralen (8-MOP), were utilized in interaction experiments due to limited availability of psoralen. Psoralen, coumarin, 8-MOP, AST-IV and ATR-I were individually assessed for toxicity in model liver (HepG2) and intestinal epithelial (Caco2) cells. Following these experiments, combinations of the compounds were investigated. Cell viability was determined using colorimetric assays.
Results. Cell viability was significantly decreased with coumarin ($p=0.0002$; $n=5$) and 8-MOP ($p=0.002$; $n=5$) in HepG2 cells, and psoralen in HepG2 ($p<0.0001$; $n=8$) and Caco2 cells ($p<0.0001$; $n=5$). No significant effect was observed with AST-IV or ATR-I ($p<0.0001$; $n=8$), but they were toxic when combined (0.1mM AST-IV, 0.3mM ATR-I) in both cell lines ($p<0.05$; $n=3$). Previously non-toxic 0.2mM coumarin and 8-MOP decreased cell viability combined with AST-IV ($p<0.05$; $n=3$) and ATR-I ($p<0.05$; $n=3$) in both models. In three-component interactions, all combinations were no more toxic than two-component interactions ($p>0.05$; $n=3$).
Discussion. For the first time, this study showed that some major herbal components can be studied in relevant tissue culture models. Our results demonstrate that herbal components have the potential to produce severe toxic effects when combined in high, but plausible, concentrations.

557 QSAR models define Molecular Initiating Events for multiple AOPs

Davy Guan[1], Slade Matthews[1]. Pharmacoinformatics Laboratory, Discipline of Pharmacology, The University of Sydney[1], Sydney, NSW, Australia

Introduction. Molecular Initiating Events (MIE) comprise the first component of an Adverse Outcome Pathway (AOP), defining the interaction(s) between the chemical properties of a xenobiotic and a biological target that is mechanistically linked to an adverse outcome. This enables the application of Quantitative Structure Activity Relationship (QSAR) methodologies to predict potential MIEs for untested chemicals, which is essential to the practical regulatory use of AOP frameworks. Contemporary QSARs use multitask machine learning algorithms (MTML) which feature multiple prediction outputs to utilise salient information shared between similar tasks. This enhances performance, however, the capability of MTML techniques to model weakly related endpoints has not been studied.
Aims. This project investigates the performance of MTML QSAR in the prediction of *in vitro* assay results screening for endocrine disruption, steatosis, skin sensitization, and cardiac arrhythmia MIEs.
Methods. A 25293-structure dataset was collated from existing Tox21 (endocrine disruption, n=8014) and SkinSensDB (skin sensitization, n=402) datasets, in addition to searching public databases for nuclear receptor agonists (liver steatosis, n=7682) and hERG inhibitors (cardiac arrhythmia, n=9195). Single task and MTML algorithms modelled the 25 classes of this dataset to determine the effect of multitask learning for weakly related endpoints.
Results. Initial results with a Multitask Deep Neural Network model found 0.83±0.01, 0.79±0.04, 0.67±0.12, and 0.90 Mean (±SEM) AUC for predicting endocrine disruption, steatosis, skin sensitization, and hERG inhibition assay results in the external validation dataset, compared to a baseline Logistic Regression model which found 0.81±0.02, 0.64±0.08, 0.62±0.04, and 0.87 Mean (±SEM) AUC for those respective assays.
Discussion. MTML QSAR models feature enhanced prediction performance for weakly related outcomes, however, the results show the magnitude of this effect is highly variable. While this project is still ongoing, the degree of similarity between MIEs may determine the magnitude of performance enhancement. The current results show QSARs support the practical application of AOP paradigms with enhanced predictive performance for similar and distinct chemical domains.
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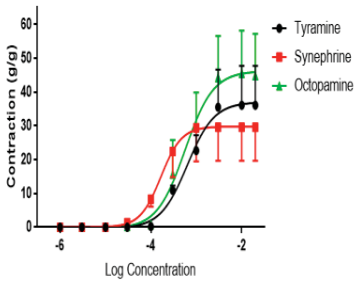
558 Functional Evaluations of Synephrine and Octopamine - Stimulants in Pre-Workout Supplements

Andy H W Koh [1], Russ Chess-Williams [1] and Anna E Lohning [1]. Faculty of Health Sciences and Medicine, Bond University[1], QLD, Australia

Introduction. Pre-workout supplements usually contain stimulatory botanical extracts for improved athletic performance. The rise in popularity of these supplements correlates with increased adverse health reports (Eudy et al, 2010). The biogenic amines synephrine and octopamine - found in plant extracts can increase blood pressure. However, the mechanisms involved in the vascular effect of these biogenic amines have not been fully established.



Aims. The purpose of this study was to evaluate whether vasoconstrictions were caused by synephrine and octopamine acting as indirect sympathomimetic agents (releasing the neurotransmitter, noradrenaline (NA)) - similar to tyramine, or whether these amines act directly on α- adrenoceptors.

Methods. The responses to synephrine and octopamine were investigated *in vitro* in rings of inferior mesenteric arteries of pigs.

Results. Synephrine (pEC50= 3.78 ± 0.21; *n=6*) was a more potent vasoconstrictor (*p<0.05*) than octopamine (pEC50= 3.25 ± 0.21; *n=6*). After depleting NA from the tissues, the maximum response for synephrine decreased by 67% (*p<0.05*), and its potency decreased (pEC50= 3.56 ± 0.18; *n=4*). However, neither the maximum contraction for octopamine nor its potency were affected by NA depletion (pEC50= 3.48 ± 0.26; *n=4*).

Discussion. The vasoconstriction induced by synephrine involves an indirect sympathomimetic pathway, whereas octopamine is likely a direct agonist at vascular α-adrenoceptors. These stimulants coupled with caffeine and strenuous exercise could explain the increase in adverse cardiovascular-related reports. Although synephrine is somewhat regulated in Australia, octopamine is an unregulated substance that is increasingly added to commercially available pre-workout supplements. Understanding the effects of these amines could lead to regulations of dietary supplement to protect vulnerable consumers.

Eudy AE et al (2013) Am J Health-Syst Ph, 70:577-588

559 The immunomodulation of dynorphin 3-14 on lipopolysaccharide-activated toll-like receptor 4 signalling pathway

Siti Sarah F Rahiman[1,4], Michael Morgan[2], Paul Gray[3], Paul N Shaw[4] & Peter J Cabot[4]. School of Pharmaceutical Sciences, Universiti Sains Malaysia[1], PENANG, Malaysia; Institute for Molecular Bioscience, The Univ of Queensland[2], Brisbane, QLD; School of Medicine, The Univ of Queensland[3], Brisbane, QLD; School of Pharmacy, The Univ of Queensland[4], Brisbane, QLD.

Introduction. In inflamed tissue, immune-derived dynorphin 1-17 (DYN 1-17) opioid peptide undergoes rapid metabolic degradation, producing a wide range of fragments with immunomodulatory functions. Dynorphin 3-14 (DYN 3-14) was found to be the most stable and prevalent fragment, however, there is little known of its cellular effects.

Aims. This study aims to investigate the presence of DYN 3-14 following biotransformation of DYN 1-17 in human inflamed tissues and to determine its effects on the LPS-activated toll-like receptor (TLR4) signalling pathway.

Methods. DYN 1-17 was incubated with human inflamed nasal tissue explants and its biotransformation was examined using LC-MS. The translocation of nuclear factor-kappaB/p65 (NF-κB/p65), the release of interleukin-1beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) were assessed in differentiated LPS-induced THP-1 cells treated with DYN 3-14. The involvement of DYN 3-14 on TLR4 activation was also examined using HEK-Blue™–hTLR4 cells stimulated with LPS.

Results. Incubation of DYN 1-17 with human inflamed tissues revealed that DYN 3-14 was one of the major hydrolysis fragments produced throughout the incubation period. Furthermore, DYN 3-14 inhibited LPS-induced NF-κB/p65 nuclear translocation (P<0.05) and differentially modulated the pro-inflammatory cytokines by inhibiting IL-1β and paradoxically augmenting TNF-α release (P<0.05). Intriguingly, DYN 3-14 showed significant concentration-dependent attenuation of TLR4 activation in HEK-Blue™-hTLR4 cells, albeit 300-fold lower than the potent TLR4 antagonist, LPS-RS.

Discussion. The abundant production of DYN 3-14 in human inflamed tissue homogenates highlights a rationale for its activity during an inflammatory response. Further observations reveal a mechanistic insight into the inhibition of NF-κB/p65 translocation and modulation of IL-1β and TNF-α release *via* the TLR4 pathway, following incubation of human activated macrophages with DYN 3-14. These findings thereby describe a potential role for DYN 3-14 as an antagonist at TLR4 and for its involvement in the regulation of inflammatory signals through a non-opioid mechanism in inflammation. ¶

560 Intranasal delivery of the TLR7 agonist, imiquimod, protects against influenza A virus-induced morbidity in mice

Jonathan R. Erlich[1], Eunice E. To[1,2], Raymond Luong[1,2], Felicia Liong[1], Keshia Hendricks[2], Steven Bozinovski[1], John J. O'Leary[3], Doug A. Brooks[4], Ross Vlahos[1], Stavros Selemidis[1,2]. [1]School of Health and Biomedical Sciences, RMIT University Bundoora, VIC, Australia; [2]Dept of Pharmacology, Monash University, Clayton, VIC, Australia. [3]School of Medicine, Trinity Translational Medicine Institute, Trinity College Dublin, Ireland. [4]School of Pharmacy and Medical Sciences, Sansom Institute for Health Research, University of South Australia, Adelaide, 5001, Australia.

Introduction. Influenza is a significant global burden with 5 million cases per year, 10% of which are fatal and thus, there is an urgent need for new therapeutics (WHO factsheet, 2017). Toll like receptor 7 (TLR7) is a pattern recognition receptor, which drives a powerful anti-viral signalling pathway that helps clear virus infections.
Aim. To determine the effect of the TLR7 agonist imiquimod on lung inflammation, oxidative stress and antibody production caused by influenza A virus (IAV) infection in mice.
Methods. Saline or imiquimod (50μg/mouse) was delivered intranasally to anaesthetised (inhaled isoflurane; 3%) male C57BL/6J mice one day prior to infection with a low (10^3PFU/mouse), moderate (10^4PFU/mouse) or high dose (10^5PFU/mouse) of the mouse adapted Hong Kong X31 (x-31) virus strain and everyday thereafter until mice were culled day 3 (d3) or 7 (d7) post-infection for analysis. Bronchoalveolar lavage (BAL) was performed to assess airways inflammation, and oxidative burst by L-012 enhanced chemiluminescence. In addition, BAL fluid and serum was used to determine antibody titres. The lungs were harvested and used to assess inflammation (H&E staining) and pro-inflammatory cytokine gene expression by qPCR. Bodyweights were recorded daily during the experimental process.
Results. Imiquimod significantly suppressed body weight loss caused by IAV infection with a maximum reduction of ~60% starting from day 4 (10^3 PFU/mouse, n=7-13, $p<0.001$). At d3 post infection, imiquimod treatment caused a significant reduction (~50-60%) in airway and peri-bronchial inflammation and BALF neutrophil populations (10^5 PFU/mouse, n=8-15, $p<0.01$) but had no effect on macrophage and lymphocyte populations, and the oxidative burst. TNF-α and IL-6 mRNA expression was supressed by ~60% ($p<0.01$ and $p<0.05$, respectively). Day 7 showed a modest but significant increase in IgE, IgM, IgG1, and IgG2a ($p<0.05$) in BALF following imiquimod treatment.
Discussion. Our findings highlight an exciting potential of imiquimod as a therapeutic option for the treatment of influenza disease.

561 IRAK3 modulates NFκB through its guanylate cyclase activity

Lubna A. Freihat, David T. Manallack, Janet I. Wheeler, Helen R. Irving. Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences - Monash University, 381 Royal Parade, Parkville, VIC 3052, Australia.

Introduction. Interleukin-1 receptor associated kinase 3 (IRAK3) acts as a negative regulator of inflammation. The role of IRAK3 is critical to maintaining homeostasis in the innate immune response and in preventing the development of autoimmune diseases. It is involved in various inflammation-associated disorders such as lung injury, metabolic syndrome and tumour growth. Prior studies identified IRAK3 as a potential novel guanylate cyclase (GC) catalyzing cyclic guanosine monophosphate (cGMP) synthesis. IRAK3 is predicted to be a mammalian representative of a new class of GCs containing a GC centre encapsulated within the kinase domain. (Freihat et al., 2014).
Aims. To investigate if IRAK3 is capable of generating cGMP and if modifying the GC centre modulates the downstream signaling pathways.
Methods. GC activity was assessed using the GE Amersham cGMP enzyme immunoassay kit. HEK BLUE hTLR4 cells containing a SEAP reporter system were transfected with either IRAK3 or IRAK3 mutant constructs, effects on NFκB activity in the presence of lipopolysaccharide (LPS) and cGMP were investigated.
Results. Recombinant IRAK3 protein produced significant amounts of cGMP in vitro, whilst the IRAK3 GC mutant did not. Overexpression of IRAK3 in HEK BLUE hTLR4 cells significantly reduced LPS induced, NFκB activation. Whereas IRAK3 GC mutants with reduced cGMP-generating capacity failed to inhibit LPS induced NFκB activity. The presence of cell-permeable cGMP restored IRAK3 function and significantly reduced NFκB activity in IRAK3 mutants with reduced cGMP-generating capacity.
Discussion. Low levels of cGMP are important for IRAK3 action and these findings are providing insight into the hidden functions of IRAK3 and may assist in explaining its selectivity and functionality in the inflammatory signalling cascade. Understanding how this novel GC function impacts the anti-inflammatory effect of IRAK3 is likely to be important when targeting this protein in different disease states.

Freihat, L., Muleya, V., Manallack, D.T., Wheeler, J.I., and Irving, H.R. (2014). Biochemical Society Transactions *42*, 1773-1779.¶

562 Pharmacological characterisation of small molecule C5aR1 inhibitors in primary human macrophages

Xaria X. Li[1], Daniel E. Croker[1], Richard J. Clark[1] Trent M. Woodruff[1]. School of Biomedical Sciences, The University of Queensland[1], Brisbane, QLD, Australia

Introduction. The complement system is an essential component of innate immunity. The complement factor C5a is a core effector protein that exerts potent proinflammatory and immunomodulatory functions through its major receptor C5aR1. Over-activation of the C5a-C5aR1 axis has been implicated in a plethora of acute and chronic diseases, propelling the development of therapeutic inhibitors of C5aR1. Despite a number of these inhibitors being developed, to date, no systematic pharmacological characterisation of these compounds has been reported in human immune cells.
Aims. To compare the antagonistic potency and duration of inhibition of selected C5aR1 inhibitors against C5a-mediated cytokine release and phospho-ERK1/2 signalling respectively in primary human macrophages *in vitro*.
Methods. The peptidic (PMX53, PMX205, JPE1375) and non-peptide (W54011, NDT9513727) C5aR1 inhibitors were profiled in human monocyte-derived macrophages (HMDMs). IL-6 and IL-10 release in the co-presence of LPS was quantified using ELISA. Time-lapse pERK1/2 activity was examined using a AlphaLISA-based kit.
Results. The peptidic compounds were significantly more potent than the non-peptide small molecules in inhibiting the immunomodulatory effect of C5a. The rank order of potency was JPE1375 > PMX53 > PMX205 > NDT9513727 > W54011 for both IL-6 and IL-10 assays. In the wash-off study for pERK1/2 activity, PMX53 and JPE1375 possessed significantly longer duration of antagonistic activity ($t_{1/2}$ > 24 h) compared to the remaining inhibitors ($t_{1/2}$ ~ 5 h).
Discussion. The peptidic C5aR1 inhibitors are more effective at inhibiting C5aR1-mediated immunomodulatory effects in primary human immune cells, possibly due to their prolonged duration of receptor antagonism. The peptidic inhibitors may thus represent more ideal clinical drug candidates due to their potent and prolonged antagonistic activities. ¶

563 Chemical profile and anti-cancer potency of *Dendrobium* species from China and Australia

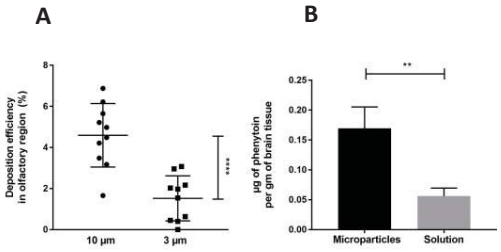
I Gusti Surya Trapika[1], Suet Yee Sara Tang[1], Jun-Lae Cho[1], Kong M Li[2], Guoyi Ma[3], George Q Li[1]. [1]Faculty of Pharmacy, The University of Sydney, NSW 2006, Australia; [2]Discipline of Pharmacology, The University of Sydney, NSW 2006, Australia; [3]The National Center for Natural Products Research, The University of Mississippi, University, MS 38677, USA

Introduction. Some species of the *Dendrobium* and their chemical compounds especially bibenzyl derivatives have been reported to have anti-cancer activity. However, there are limited studies of chemical compounds and bioactivities of Dendrobium species from Australia. The aim of this study was to compare chemical profile and to explore anti-cancer potency of Dendrobium species from China and Australia.
Methods. Stems of *Dendrobiums* including twelve species commonly used in Chinese medicines from China and three species from Australia were extracted with pure ethanol and analyzed by TLC. Cytotoxicity and anti-proliferative activity assays were conducted with MTT and Incucyte method in LNCap cells.
Results. TLC profile indicated that each species has different chemical profile, and some compounds are likely common to all species tested. Only *D. chrysotoxum* contained erianin in high concentration. The ethanol extract, *D. chrysotoxum* showed the strongest cytotoxic activity against LNCap cells while *D. kingianum,* one of Australian species showed mild inhibitory activity with IC_{50} 67.8µg/mL and 36.5µg/mL at 24 and 72 hours respectively.
Discussion. Bibenzyl in *Dendrobium* are useful for quality standardization of *Dendrobium,* and contribute to cytotoxic effect of *Dendrobium*. Further study is needed to confirm active compounds and their potency.

Wang H et al (2016) Cell Death Dis 7:e2247
Ho C-K et al (2003) Cancer Investigation 21(5):729-36¶

564 Olfactory targeted mucoadhesive microparticles for enhanced brain uptake of phenytoin

Sasi Bhushan Yarragudi, Anita Barzegar-Fallah, Richard N Prentice and Shakila B Rizwan, School of Pharmacy, University of Otago, Dunedin, New Zealand.



Introduction: Targeting and retention of drug in the olfactory region (OR) remain major challenges in nose-to-brain drug delivery and are a consequence of the geometrical complexity and rapid mucociliary clearance in the nasal cavity. Recently, we have developed a microparticle formulation that can address both these challenges by its specific size (10 µm) and mucoadhesive nature respectively (1).
Aims: Current study aims to package the poorly soluble anticonvulsant drug phenytoin into this microparticle formulation and determine its brain uptake after intranasal administration.
Methods: Spray drying parameters were optimised to produce 10 µm-sized phenytoin containing mucoadhesive microparticles with the naturally occurring polymer tamarind seed polysaccharide. Size, mucoadhesion and powder characteristics were investigated by laser diffraction texture-analysis, and X-ray diffraction respectively. A 3D-printed human nasal replica cast was used to study the deposition of microparticles in the OR. Male Wistar rats (3/group) were anesthetized (5% isoflurane) and phenytoin microparticles or solution was administered (~4 mg/kg) intranasally. Rats were sacrificed and tissues analyzed for phenytoin content by HPLC.
Results: A high entrapment of phenytoin (91% ± 4, n=5), in microparticles was achieved and the microparticles were amorphous. Microparticles demonstrated high mucoadhesion compared to phenytoin powder (n=3; $P<0.01$). Microparticles 10 µm in size showed significantly greater deposition (Fig. Panel A) in the OR (n=10; $P<0.001$) compared to 3 µm particles. The amount of phenytoin per gm of brain tissue administered as microparticles was significantly higher (Fig. Panel B) than the solution ($P< 0.05$).
Discussion: Phenytoin can be packaged into tailor-made 10 µm mucoadhesive microparticles to improve the olfactory deposition and retention and subsequent uptake into the brain. Furthermore, these amorphous microparticles can aid in solubility enhancement of phenytoin. Studies are underway to determine the efficacy in rat-seizure model.

(1). Yarragudi S B et al (2017) Carbohydrate Polymers 163: 216–226¶

565 Synthesis and characterization of a smart inulin hydrogel system for colon targeted drug delivery

Franklin Afinjuomo[1] Thomas Barclay[1], Yunmei Song[1], Sanjay Garg[1] Centre for Pharmaceutical Innovation and Development (CPID), School of Pharmacy and Medical Sciences, University of South Australia, SA

Introduction. Australia and New Zealand have the highest incidence of colorectal cancer in the world[1] and the incidence amongst young adults is increasing globally. Unfortunately, most chemotherapies for colorectal cancer use non-selective systemic delivery of the toxic drugs, resulting in significant side effects. Therefore, the development of a targeted drug delivery system for colon cancer treatment using oral administration is highly desirable.
Aims. To develop a smart inulin hydrogel that combines both pH and colonic bacteria dependent triggers for colon targeted drug delivery.
Methods. Inulin was crosslinked with dianhydrides via an esterification reaction. The physicochemical properties of the hydrogels were evaluated using Fourier-Transform Infrared Spectroscopy (FT-IR), mechanical analysis and equilibrium swelling tests. The loading of 5-fluorouracil (5-FU) into the hydrogel and subsequent *in-vitro* drug release in media mimicking both the conditions of the gastrointestinal tract and the colon was evaluated using HPLC as was the degradability of the hydrogel using inulinase.
Results / Discussion. FTIR was used to confirm the formation of the new hydrogel with new bands for the ester bonds and carboxylic acid groups observed. The hydrogel shows excellent water swelling following second order kinetics with water diffusion having a non-Fickian pattern. Increase gel strength with increase in crosslinker ratio. 5-FU was absorbed into swollen hydrogels at loadings of 8 and 18.1% dependant of crosslink density, having entrapment efficiencies 14.0 and 31.42% respectively. The *in-vitro* release studies showed a controlled release pattern with about 70 % release in the pH conditions of the colon. Furthermore, release of fructose from the hydrogel demonstrates degradability of the hydrogel by colon specific microbes.
Conclusion. These findings show that this hydrogel is a promising drug carrier for colon-specific drug delivery.

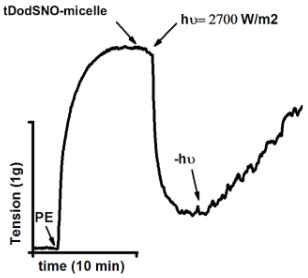
Reference

1. Boyce et al. Young-onset colorectal cancer population-based study. MJA, 2016;205(10):465-70. ¶

566 Induction of localized vasodilation and hyperpermeability using a novel nitric oxide donor nanoparticle.

Houman Alimoradi[1], Khaled Greish[2], Ivan Sammut[1], Anita Barzegar-fallah[1], Gregory I Giles[1]. [1]Department of Pharmacology and Toxicology, University of Otago, Dunedin, Otago, New Zealand. [2]Aljawhara centre for molecular medicine, Arabian Gulf University, Manama, Kingdom of Bahrain.

Nitric oxide (NO) donors can enhance drug targeting towards specific body compartments, especially for the uptake of nano-sized particles and proteins, and this has great potential in the treatment of many diseases such as solid tumours and central nervous system (CNS) disease. The main limitation, however, is controlling release of nitric oxide in target tissues. Hence, we have developed photoactive nanoparticles (NPs) by encapsulation of a bulky, hydrophobic and stable s-nitrosothiol, tert-dodecane s-nitrosothiol (tDodSNO), into polystyrene maleic acid which releases NO in a controlled manner. The NPs in the absence of irradiation had a $t_{1/2}$ of approximately 100 h, while photoactivation (cold light with the intensity of 2700 W/m^2) decreased this to just 4 min.



Theoretically NPs avoid metabolic breakdown of the s-nitrosothiol as well as trans-nitrosation reactions with other proteins, thereby inhibiting unspecific vasodilation and vascular hyperpermeability. To examine the effect of NPs on vasodilation, rat aortic rings were constricted with phenylephrine and then the vasoconstriction properties of different concentrations of NPs, in presence or absence of photoactivation, were assessed. The micellar system significantly relaxed the aortic rings only in the presence of photoactivation (graph inset). In addition, a rat mesenteric bed assay was used to determine the ability of the NPs to induce localized vasodilation when stimulated by light, as quantified by Evans blue dye leakage and florescent microscopy of mesenteric windows. Photo-irradiation of the NPs led to a significant increase in the dye extravasation compared with control NPs ($p< 0.01$), showing that photoactivation can control the release of NO in a target tissue and thereby cause localized vasodilation and hyperpermeability. In conclusion, tDodSNO-NPs are a novel form of NO donor, whose NO release characteristics can be modulated by photoactivation. They cause controllable and localized vasorelaxation and hyperpermeability, and therefore can potentially be used for tumour therapy and CNS disorders.¶

567 Scarring in horses – is there a way to objectively quantify an equine scar?

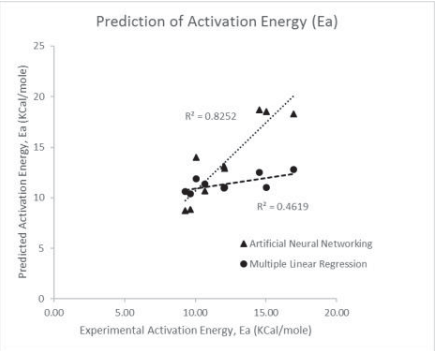
Selena M Boyd[1,2], Kathryn J Steadman[1], Lisa M Nissen[2], Paul C Mills[3]. School of Pharmacy, University of QLD[1], Brisbane, QLD; School of Clinical Sciences, Queensland University of Technology[2], Brisbane, QLD; School of Veterinary Science, University of QLD[3], Brisbane, QLD, Australia.

Introduction. When a large wound on a horse heals it tends to develop inferior quality scar tissue. This scar tissue is fragile, easily damaged, stiff and cosmetically unappealing. While there have been numerous studies that have reviewed and tested measuring devices in humans for scar assessment, there have been no studies in horses. In order to effectively evaluate and monitor scar reduction treatments quantitative measurement modalities are needed.
Aims. To test the validity and reliability of the equipment used to quantify scars in humans, in horses.
Methods. A research study using different equipment to test horses' scars for flexibility, size and thickness was conducted. A cutometer, the gold standard for measuring pliability of human skin and scar tissue had the intra- and inter-rater reliability measured to ensure its validity in horses. The Silhouette Star, a laser beam wound camera was used to calculate the surface area of the scars and was compared for accuracy with the old method of using a tracing. Finally, ultrasound was compared to punch biopsy for measuring the epidermal, dermal and total thickness of the scar.
Results. The cutometer was reliable for measuring the pliability of some scars and normal skin however it was unreliable for severe scars due to a ceiling effect when rigid tissue was encountered. There was a low intra-rater reliability due to the difficulty relocating the device to the same measurement spot and the high sensitivity of the device. The Silhouette Star was not comparable to the tracing method for accuracy. The punch biopsy provided more information at a histological level than the ultrasound but was an invasive procedure and quite dangerous when trying to sample hind limbs.
Discussion. Objective scar measurement tools allow the accurate and reproducible evaluation of scars, which is important for both clinical and scientific use. However, no studies had been conducted to date to evaluate horse scars or validate equipment used for this purpose in humans and translate this to horses. Equipment validation is important in order to effectively evaluate and monitor scar reduction treatments in the future.

568 Prediction of skin permeation based on solute properties using machine learning and statistical tools

Hanumanth Srikanth Cheruvu[1], Yousuf H Mohammed[2], Azadeh Alinaghi[1], Jeff E. Grice[2], Lorraine Mackenzie[1], Michael S. Roberts[1,2]. [1]School of Pharmacy and Medical Sciences, University of South Australia, Basil Hetzel Institute for Translational Health Research, Adelaide, SA; [2]Therapeutics Research Centre, Diamantina Institute, University of Queensland, Translation Research Institute, Brisbane, QLD, Australia.

Introduction. The mechanism by which many solutes penetrate through the main human skin physical barrier, the stratum corneum, after topical application is currently poorly understood. Imaging, kinetic, quantitative structure –permeation relationships and computational dynamic studies suggest that pathways for transport include: directly through the corneocytes; between the corneocytes through the intercellular lipids; and via appendages, with deeper layers offering significant resistance for lipophilic solutes.
Aims. In this work, we used solute skin permeability coefficients determined at different temperatures to derive the thermodynamic parameters associated with their penetration. We then derived quantitative solute structure – human skin permeation relationships for these properties using both machine learning and statistical analysis.
Methods. Activation energy (Ea) and entropy (ΔS) for permeation were derived from literature and our own permeation data at different temperatures and related to solute physicochemical properties, including solute lipophilicity, molar volume and solubility). Artificial neural networking (ANN) was used for training and validation, with confirmatory statistical analyses using multiple linear regression (MLR) and multivariate analyses.
Results. Fig. 1 shows that the predicted Ea based on ANN better described the experimental data (r^2=0.82) than a MLR analysis (r^2=0.46). Solute molar volume and polarity were found to be the main determinants for Ea.
Discussion. Multiple linear regression is widely used to study quantitative solute structure – human skin permeation relationships. This work suggests that machine learning better predicts Ea. Our next step is to apply its findings in the better understanding of skin permeation mechanisms for different solutes.



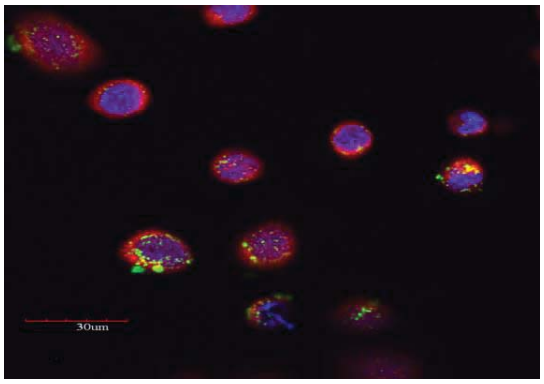
569 Quality of levofloxacin tablets: in vitro dissolution testing and content evaluation

Ensieh Izadi, Long C. Ming, Rahul P. Patel, Syed Tabish R. Zaidi. Pharmacy, School of Medicine, University of Tasmania, Hobart, TAS, Australia.

Introduction. Levofloxacin is a broad spectrum antibiotic and used empirically to treat community acquired or nosocomial pneumonia. Low quality levofloxacin tablets can lead to treatment failure or bacterial resistance; hence the pharmaceutical evaluation of products available in the market should be conducted regularly.
Aims. To compare the *in vitro* dissolution and content uniformity of different brands of levofloxacin tablets manufactured and sold in India, Iran and Pakistan.
Methods. Innovator and generic brands of immediate release levofloxacin 500mg tablets were purchased from the authorized medicine wholesaler located at India, Iran and Pakistan as well as Australia. A total of 13 brands were tested for content uniformity and dissolution. For content uniformity analysis, levofloxacin tablets were dissolved in sufficient amount of 10% acetic acid which later was diluted prior to HPLC analysis. For dissolution, the tablets were added to Simulated Gastric Fluid prepared according to United State Pharmacopeia (USP) and sample was taken at 5,10,15,20,30,45, 60 and 90 minutes. *In vitro* dissolution data were collected with a Erweka USP 2 apparatus (37°C, 900ml, 50 rpm) The absorbance of all sample were measured at 270nm. Triplicate were used and each sample was tested twice. Dissolution profile comparison was performed using similarity factor (f_2) with $f_2 \geq 50$ indicate similarity.
Results. All the generic and brand-name levofloxacin passed content uniformity test stipulated by United State Pharmacopeia (USP) (specification: 90% to 110%). In term of ddissolution testing, 11 brands showed more than 80% dissolution within 30 minutes except two brands sourced from Pakistan.
Discussion. The content uniformity and weight uniformity of the levofloxacin brands from Iran, India and Pakistan were in accordance to USP standard. However, the dissolution profile of these brands were different, as indicated by the f_2 similarity factor. Levofloxacin is a Biopharmaceutics Classification System Class 1 compound characterised by high solubility and high permeability. Literature has not reported any risk of bioequivalence for levofloxacin tablets produced using different manufacturing methods. Clinically, levofloxacin has a wide therapeutic index and good oral bioavailability. Even though the tested levofloxacin tablets sourced from local suppliers exhibited different *in vitro* dissolution profiles versus the reference product, the potential effect on the *in vivo* performance will be minimal.

570 Evaluation of PLGA nanoparticles (NPs) uptake using Caco-2 cell monolayers

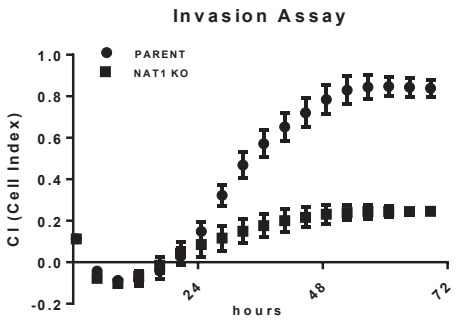
Yongzhi Zhou, Danhui Li, Jingyuan Wen. School of Pharmacy, University of Auckland, Auckland, New Zealand.



Introduction. PLGA NPs are solid colloidal particles made of biodegradable polymer. Therapeutic agents can be adsorbed to the surface or entrapped in the particles. PLGA NPs are suitable for delivering small molecular weight drugs by either localised or targeted delivery to the tissue of interest. Caco-2 cell is the most commonly used as in vitro cellular model for the studies of drug transport, uptake, metabolism and toxicity.
Aims. To investigate the uptake of PLGA NPs by Caco-2 cells.
Methods. A fluorescent material (FITC) was conjugated to PLGA using modified carbodimide method. Then FITC-labelled PLGA were prepared by the modified water-in-oil-in-water emulsion solvent evaporation technique. The lyophilized FITC-PLGA NPs were added to Caco-2 cells and the uptake of the NPs by the cells was investigated by fluorescence spectrophotometer and confocal laser scanning microscopy (CLSM).
Results. The uptake of PLGA NPs by Caco-2 cells seems to be mediated by endocytosis. Caco-2 cells took up PLGA NPs via a saturable, and temperature dependent process. The rate and extent of cellular uptake of PLGA NPs are mainly affected by particle size and hydrophilicity of particle surface. A decrease in particle size or particle surface hydrophilicity led to an increase in cellular uptake. The enhanced uptake is a consequence of better particles-cells interaction resulting in higher endocytotic uptake and/or higher retention time of NPs in cells. The CLSM image indicates that NPs were adsorbed on the cell membrane and a few of them were clearly localised in cytoplasm. The results are promising as they indicate that PLGA NPs of small particle size with hydrophobic surface may be employed as a drug delivery system for oral delivery of therapeutic agents to improve the drug bioavailability via oral administration.

571 Human NAT1 regulates invasion of MDA-MB-231 breast cancer cells by modulating the expression of MMPs

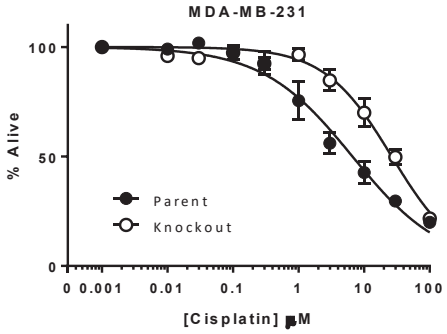
Peng cheng Li, Rodney F Minchin, Neville J Butcher. School of Biomed Sci, Uni of Queensland, Brisbane, QLD, Australia.



Introduction. Recent studies suggest that the phase II drug metabolising enzyme, arylamine N-acetyltransferase 1 (NAT1), may be important in cancer cell biology. To investigate its role in cancer cell invasion, NAT1 was knocked out in the highly invasive breast cancer cell line MDA-MB-231 using CRISPR technology. Matrix metalloproteinases (MMPs) are an important family of zinc-dependent endo-proteinases that degrade the extracellular matrix and promote cell invasion. They are secreted as latent pro-MMPs that are then activated by plasmin or other MMPs.
Aims. To determine the effect of NAT1 KO on 1) the ability of MDA-MB-231 cells to invade in vitro, 2) MMP gene expression.
Methods. Invasion and migration assays were performed using the ACEA xCELLigence system and Matrigel-coated membranes. Invadopodia degradation assays were performed on fluorescein-conjugated gelatin-coated coverslips and visualised by confocal microscopy. MMP gene expression was quantified by real-time RT-PCR and protein expression in cells and growth medium was determined by Western blot.
Results. Although cell migration was not different, NAT1 KO cells had a reduced ability to invade compared to parent cells. The gene expression of some MMPs changed significantly upon NAT1 KO, with MMPs 2, 7 and 9 all increasing, while MMP1 decreased. In addition, treatment of parent cells with the histone deacetylase inhibitor trichostatin A, indicated that these changes were associated with altered histone acetylation. Western blot of culture medium from NAT1 KO cells showed that MMP9 was significantly increased compared to parent cells, while MMP1 was significantly decreased compared to parent cells. MMPs 2 and 7 were not detectable for either NAT1 KO or parent cells.
Discussion. NAT1 KO cells have increased MMP9 expression, but unexpectedly, a reduced ability to invade in vitro. From Western blots, the size of the secreted MMP9 protein suggested that it is the latent pro-form of the protein in NAT1 KO cells. Further studies are required to explain this observation, as well as to determine the mechanism by which loss of NAT1 leads to changes in MMP gene and protein expression.¶

572 Effect of N-acetyltransferase 1 on the sensitivity of chemotherapeutics in breast cancer

Courtney E McAleese, Neville J Butcher, Rodney F Minchin. Sch of Biomed Sci, Uni of Queensland, Brisbane, QLD, Australia.



Introduction. Arylamine *N*-acetyltransferase 1 (NAT1) is a phase II drug-metabolising enzyme that acetylates drugs and carcinogens and has been associated with increased risk for some types of cancer. More recently, it has been linked to cancer cell growth and survival, as well as other characteristics of cancer progression, such as resistance to chemotherapeutics.

Aim. To determine if altering NAT1 levels in cancer cells can modulate their sensitivity to chemotherapy agents.

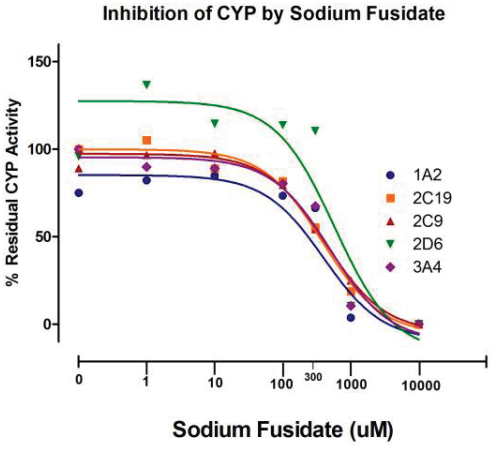
Methods. CRISPR technology was used to knockout NAT1 in the breast cancer cell lines MDA-MB-231 (ER-) and T47D (ER+). Cytotoxicity assays were performed using CyQuant NF Cell Proliferation Assay Kit following drug treatments of 72 hr.

Results. No change in toxicity was observed in the NAT1 KO with metformin, venetoclax, gemcitabine, etoposide and 5-FU. MDA-MB-231 NAT1 KO cells showed an increased resistance to cisplatin toxicity compared to parent cells (IC_{50} 26.6 ± 2.7 µM and 6.6 ± 0.9 µM, respectively), as was the case for T47D NAT1 KO cells (IC_{50} 26.7 ± 3.6 µM and 2.3 ± 0.4 µM, respectively). Similar results were found in both cell lines with daunorubicin. Combining multiple chemotherapeutics did not improve the sensitivity. No difference in cisplatin toxicity was seen between the parent and NAT1 KO in HT-29, 22RV1 and HeLa cell lines.

Discussion. Cisplatin has been shown to inhibit NAT1 irreversibly by binding to its catalytic cysteine. This inhibition occurred in a dose-dependent manner in-vitro but did not inhibit the enzyme significantly in cells. It is suspected that the NAT1-cisplatin interaction may have a role in the sensitivity of cells to the chemotherapeutic. However, the mechanism is not well understood and is still under investigation.

573 An Investigation of Sodium Fusidate and Recombinant Cytochrome P450 Enzymes Inhibition *In-Vitro*

John Mishriky[1], Jacqueline Balassone[1], Zenah Bashour[1], Simranjit Kaur[1], Vini Raman[1], Robel Getachew[1], Narin Osman[1], Daniel Guidone[2], Vincent Chan[1], and Peter J. Little[1,3]. School of Health and Biomedical Sciences[1], RMIT University, Bundoora, VIC, Australia; Pharmacy Services[2], Alfred Health, Melbourne, VIC, Australia; School of Pharmacy[3], The University of Queensland, Woolloongabba, QLD, Australia.



Introduction. Sodium fusidate is an antimicrobial agent that is used in the treatment of staphylococcal infections. Several case reports have noted a drug interaction between sodium fusidate and CYP3A4 metabolised statins, leading to statin toxicity. It is unclear whether sodium fusidate has the potential to cause interactions with other cytochrome P450 enzymes.

Aims. To investigate the effects of sodium fusidate on recombinant cytochrome P450 enzymes (1A2, 2C9, 2C19, 2D6 and 3A4) *in-vitro*.

Methods. A range of sodium fusidate concentrations (0.1µM, 1µM, 10µM, 100µM, 300µM, 1000µM and 10000µM) were tested to examine its activity on rCYP1A2, rCYP2C9, rCYP2C19, rCYP2D6 and rCYP3A4 using a luminescent assay with a luciferin substrate.

Results. Sodium fusidate inhibited all enzymes at tested concentrations which are relevant to those likely to be achieved in clinical practice. Further, sodium fusidate was found to be a time-dependent inhibitor of all the tested isoenzymes, with the exception of rCYP2C9.

Discussion. These findings suggest that there is a potential for sodium fusidate to cause drug interactions when used with other agents that are substrates for rCYP1A2, rCYP2C9, rCYP2C19, rCYP2D6 or rCYP3A4. Understanding the basis of this potential drug interaction will assist in safer use of sodium fusidate in clinical practice.

574 Physiologically-based IVIVC compared with conventional IVIVC for predicting in vivo pharmacokinetics of crushed paracetamol mixed with thickened fluids for swallowing disorders.

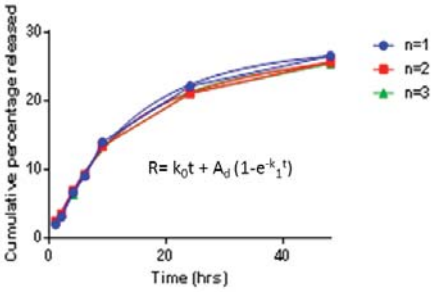
C. Radhakrishnan[1,2], Lisa M Nissen[3], Julie A Y Cichero[1], Aaron Baysingh[1], Kathryn J Steadman[1]. School of Pharmacy, The University of Queensland[1], Brisbane, QLD; 4am Software[2], Brisbane, QLD, Australia; School of Clinical Sciences, Queensland University of Technology[3], Brisbane, QLD, Australia.

Introduction. The aim of the study is to compare a conventional deconvolution method using *in vitro – in vivo* correlation (IVIVC) and a mechanistic physiologically-based *in vitro – in vivo* correlation (PB-IVIVC). The test product was crushed paracetamol tablets mixed with thickened water.
Methods. *In vitro* dissolution was performed in simulated gastric fluid using USP apparatus. *In vivo* PK parameters were calculated from salivary concentrations following a single 1 g dose in 20 adults. Conventional deconvolution IVIVC was performed using Level A correlation with Winnonlin®. Physiologically-based pharmacokinetic (PBPK) deconvolution was performed using the PK-Sim® model. The % prediction error (%PE) was calculated for AUC and C_{max} for the observed and predicted concentrations using the formula below. FDA guidelines recommend %PE < 15%.
Results. PB-IVIVC produced %PE < 15% for both AUC and C_{max}. The error associated with conventional IVIVC was higher than 15% for these parameters.
Discussion. The PB-IVIVC method includes corrections for *in vivo* dissolution, permeation, gut-wall metabolism and first-pass liver metabolism, while the conventional method does not separate the multiple mechanisms involved in the process of drug absorption. Incorporating these adjustments allowed PB-IVIVC to predict the *in vivo* profile more accurately than conventional IVIVC.

575 Release of somatostatin monomers from self-assembled hydrogels

Uma Rai[1], Thilini Thrimawithana[1], Celine Valery[2], Simon Young[1]. Discipline of Pharmacy, RMIT University[1],Bundoora, VIC, Australia; Discipline of Pharmaceutical Sciences[2], RMIT University, Bundoora, VIC, Australia.

Introduction. Somatostatin-14 self-assembly has been demonstrated by in aqueous media (van Grondelle et al, 2007). Nanofibril self-assembly can be altered by the presence of electrolytes. While the reversibility of nanofibril formation has been demonstrated in the presence of heparin, an aggregation inducer (Anoop et al, 2014) there is currently no published data on the rheology and release kinetics of somatostatin hydrogels.



Aims. This study aims to investigate the release of monomers of somatostatin at higher concentrations that form a physical hydrogel in aqueous media and in the presence of electrolytes.
Methods. Rheological characterization of the somatostatin hydrogels was performed to determine a relationship between the viscoelasticity of the hydrogels and the release of somatostatin monomers. Transmission electron microscopy (TEM) was performed to characterise the morphology of the nanofibrils. Release of monomers was assayed by UV spectroscopy and fitted to a hybrid dual-order release model.
Results. This study showed that release of somatostatin monomers followed a two exponential release model. Somatostatin gels in water demonstrated relatively rapid release, which correlates to the lower storage modulus (G').

Anoop, A. et al, (2014) *J Biol Chem*, *289* (24), 16884-903
van Grondelle, W. et al,(2007) *J Struct Biol, 160* (2), 211-23
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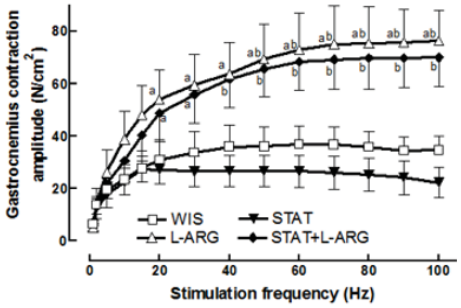
576 L-arginine protects skeletal muscle against statin-induced myopathy.

Kimberly Ryan[1], Rebecca Vella[1], Jordon Irwin[1] & Andrew Fenning[1], School of Medical and Applied Sciences, CQUniversity[1], Rockhampton, QLD, Australia.



Introduction. Statin-induce myopathy (SIM) is reported to occur in 1 out of 10 000 statin users and be associated with high doses. Increases in inflammation, nitric oxide levels, mitochondrial dysfunction and reactive oxygen species are hypothesized as contributing factors for its development. Current literature indicates that L-arginine (L-arg) may be beneficial in protecting against such factors due to its antioxidant and vasodilatory effects.
Aims. To investigate whether the co-administration of L-arginine prevents the development of statin-induced damage to skeletal muscle.
Methods. 10-12 week old female Wistar rats were randomly assigned to one of four treatment groups; control (CON), SIM (80mg/kg/day of simvastatin), control+L-arg (L-arg; 100mg/kg/day) and SIM+L-arg (SIM+L-arg). After two weeks of treatment organ mass, muscle mass and serum samples were collected. Three skeletal muscles (gastrocnemius, soleus and tibialis anterior) were tested using electrical field stimulation to assess contractility and functionality while serum samples were analysed for biochemical markers of skeletal muscle damage.
Results. Improvements in skeletal muscle contractility and function from L-arg treatment was noted in gastrocnemius, soleus and tibialis anterior muscles compared to SIM treatment. The administration of L-arg to SIM animals attenuated serum albumin and significantly reduced creatinine levels (SIM+L-arg 30.29 ±1.48µmol/L; SIM 38.33 ±1.69µmol/L). Reductions in body mass after L-arg treatment (SIM+L-arg -1.19 ±6.72%; SIM 6.14 ±4.35%) and significantly increased gastrocnemius muscle mass (SIM-L-arg 6.13 ±0.12mg; SIM 5.66 ±0.17mg) were noted.
Discussion. Improved skeletal muscle function and mass of L-arg treated rats indicates its ability to reduce the impact of muscle wasting often associated with statins. Additionally, reductions in serum albumin and creatinine levels indicated less muscle damage occurring with the co-administration of L-arginine. Overall these factors demonstrate that L-arg can be utilised as a treatment to reduce the risk of developing SIM.

577 Intrinsic Dissolution Study of Aspirin

Dorothy J Saville. School of Pharmacy, University of Otago, Dunedin, New Zealand

Introduction. Dissolution is an important component of drug delivery, and thus, related lectures and laboratories are covered in Pharmacy Undergraduate education. In the laboratories, students not only begin to appreciate methods of study, together with data presentation and interpretation, but also learn to work as members of a team.
Aims. To determine the intrinsic dissolution of aspirin.
Method. Non-disintegrating disks of aspirin were prepared by compression. The disks were placed in rotating disk holders and then rotated at 50 rpm, 75 rpm or 100 rpm in two different dissolution media, acid (pH 1) and pH 6.8 phosphate buffer. Eight samples were taken at 6 min intervals. Samples were diluted with sodium hydroxide solution in order to hydrolyse aspirin to salicylic acid. A standard curve of salicylic acid was determined using UV spectroscopy, and concentrations of salicylic acid in the dissolution samples were determined. Aspirin dissolved was calculated using MW ratio.
Results. Dissolution profiles were linear and dissolution rates were calculated from gradients of dissolved aspirin v time. Dissolution was 4 to 5 times greater at pH 6.8 than in acid, reflecting the influence of solubility on dissolution rate. Dissolution rate increased with rotation speed.
Discussion. In this laboratory, the principles of an intrinsic dissolution study are explored. Surface area is maintained constant and dissolution occurs under sink conditions, thus giving a constant rate of dissolution.
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578 Effect of Storage on Release from Enteric Coated Diclofenac Tablets

Dorothy J Saville. School of Pharmacy, University of Otago, Dunedin, New Zealand.

Introduction. Enteric coating is used on diclofenac tablets to protect the stomach from the drug and then release drug rapidly once in the intestine. Ideally, the function of enteric coating remains optimal until the tablets are consumed by the patient.
Aims. To determine the release characteristics of enteric coated diclofenac tablets before and after storage under different conditions.
Methods. Three brands of EC diclofenac tablets were studied. Storage was at 25^0C and 40^0C under 75% relative humidity and non-humid conditions for approximately 2 months. Release of diclofenac was monitored in acid (acid stage) and then in pH 6.8 buffer according to USP conditions. Samples were taken at different times to obtain release profiles, rather than just single point analyses. After storage, any weight gain/loss or change in appearance was recorded. Observations of tablets occurred throughout the release experiment. SEM was carried out on controls and some of the stored tablets.
Results. Storage changed the release characteristics of all brands of EC diclofenac tablets.
Discussion. As it is desirable for EC to protect the stomach and then give fast release upon gastric emptying, storage should not change release characteristics. ¶

579 Drug content and *in vitro* dissolution of ciprofloxacin tablets: Comparison and Evaluation

Deepali Sharma, Long C. Ming, Rahul P. Patel, Syed Tabish R. Zaidi. Pharmacy, School of Medicine, University of Tasmania, Hobart, TAS, Australia.

Introduction. Counterfeit and falsified drugs are easily available worldwide and the use of these medicines could lead to treatment failure and antibiotic resistance. Quality evaluation of drug products in the market could minimize the unwanted healthcare risk and adverse effect.
Aims. To evaluate the *in vitro* dissolution and quality of different brands of ciprofloxacin tablets that are available in the local market of India, Iran and Pakistan.
Methods. Innovator and generic brands of immediate release ciprofloxacin 500mg tablets were purchased from the authorized medicine suppliers located at India, Iran and Pakistan as well as from a local pharmacy in Hobart, Australia (reference product). A total of 15 brands were tested for content uniformity and dissolution. For content uniformity analysis, ciprofloxacin tablets were dissolved in sufficient amount of 10% acetic acid which later was diluted prior to HPLC analysis. For dissolution, the tablets were added to Simulated Gastric Fluid prepared according to United State Pharmacopeia (USP) and sample was taken at 5,10,15,20,30,45 and 60 minutes. Triplicate were used and each sample was tested twice. Dissolution profile comparison was performed using similarity factor (f_2) with $f_2 \geq 50$ indicate similarity.
Results. Content uniformity analysis indicated that all the tablets were within the limits of USP (within the range of 90-110%). Dissolution testing demonstrated that all tested brands, except one brand from Iran, followed the USP requirement of not less than 80% dissolved in 30 minutes. Out of the 14 brands, four have similar dissolution profile in comparison to the reference brand.
Discussion. Drug products purchased from authorized drug suppliers tend to have lower risk of counterfeiting. Complied drug content in 14 out of 15 brands tested, however, are not in congruent with the results of drug dissolution. Different dissolution profile could affect the *in vivo* ciprofloxacin absorption because physiological-based pharmacokinetics modeling confirmed that ciprofloxacin exhibited apparent “absorption window” in gastrointestinal tract. The inadvertent failure in drug release or dissolution compared to the reference product would yield lower bioavailability that eventually affect the desired minimum inhibitory concentration.
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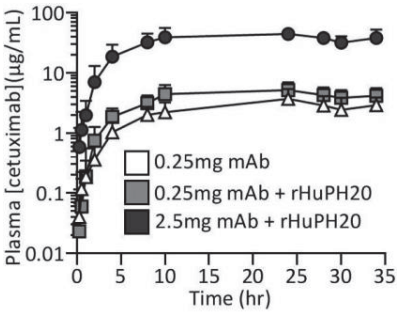
580 Removal of interstitial hyaluronan with recombinant human hyaluronidase (rHuPH20) influences the systemic and lymphatic uptake of a monoclonal antibody in rats

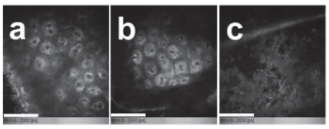
Ian K. Styles[1,2], Orlagh M. Feeney[1,2], Tri-Hung Nguyen[1], David W. Kang[3], Marie A. Printz[3], Michelle P. McIntosh[1], Christopher J.H. Porter[1,2]. Monash Institute of Pharmaceutical Sciences[1], Monash Univ, Melbourne, VIC, Australia; ARC Centre for Excellence in Convergent Bio-Nano Science and Technology[2]; Halozyme Therapeutics[3], San Diego, CA, U.S.A.



Introduction: Interstitial (e.g., intradermal (ID) or subcutaneous (SC)) administration of monoclonal antibodies (mAb) is less invasive than intravenous administration and leads to mAb uptake into both lymphatic and blood capillaries draining the injection site. Interstitial administration, however, is hindered by barriers to fluid transport that limit injection volumes. This study investigates the effect of transient removal of interstitial hyaluronan (HA), a major fluid barrier in the human interstitial space, via co-administration of recombinant human hyaluronidase PH20 (rHuPH20) on the lymphatic and systemic PK of the mAb, cetuximab, following ID or SC injection.
Methods: Male Sprague Dawley rats had cannulas inserted into the carotid artery (lymph 'intact' rats) and also into the thoracic lymph duct in lymph duct cannulated ('LDC') animals. Cetuximab (5 mg/mL) was dosed either ID or SC at volumes of 50 and 100 µL, respectively, and in the absence or presence of rHuPH20. Cetuximab was also administered at a 10-fold higher injection volume and dose in the presence of rHuPH20 (high dose). Lymph was collected for 30-34 hr and plasma sampled for 34 h.
Results: Cetuximab plasma exposure increased 1.8-fold in the presence of rHuPH20 after ID and SC administration. Cetuximab recovery in lymph was similarly increased. When the ID and SC injection volume/dose increased 10-fold, plasma AUCs increased 9.8 and 11.1-fold, respectively, consistent with approximately linear increases in absorption, although the proportional contribution of lymphatic transport appeared to reduce slightly.
Conclusion: rHuPH20 enhanced systemic and lymphatic absorption of cetuximab and enabled increases of injectable volumes up to 10-fold. At high injection volumes and doses, the relative role of lymphatic transport appeared to reduce slightly, however total cetuximab plasma exposure increased approximately linearly with dose.

581 Preparation of Viable and Metabolically Active Epidermal Membrane

Krishna Chaitanya. Telaprolu[1], Yousuf Mohammed[1], Xin Liu[1], Jeffrey Grice[1], and Michael S. Roberts[1,2], Therapeutics Research Centre, UQ Diamantina Institute[1], Translational Research Institute, Brisbane, QLD, Australia; School of Pharmacy and Medical Sciences, University of South Australia[2], Adelaide, SA, Australia



Autofluorescence of Stratum Granulosum imaged at an excitation wavelength of 760 nm (a) Dispase Separated Epidermis (DSE); (b) Dermatomed Skin (DTM); (c) Heat Separated Epidermis (HSE)*. Scale bar is 40 µm. *Specific layers not identifiable in Heat Separated Epidermis

Introduction: The skin acts as a limited route of entry for therapeutic substances and other xenobiotics and provides a metabolic defensive barrier. The current reconstructed human epidermis (RHEs) models for skin irritancy differ from the human skin in stratum corneum (SC) thickness and the permeation profile. A suitable skin model to be used for *in vitro* permeation testing (IVPT), evaluation of skin irritancy of topical formulations, and metabolic imaging studies should retain the viability and enzymatic activity of *in vivo* skin.
Aims: To separate a viable and metabolically active epidermal membrane from the excised human skin.
Methods: Epidermal membranes were separated from the excised human skin by enzymatic treatment. The viability evaluation of the separated epidermis was carried out by i) Multiphoton Microscopy-Fluorescence Lifetime imaging (MPM-FLIM) to measure intensities and lifetimes of endogenous fluorophores such as NAD(P)H, ii) MTT assay and iii) Hematoxylin and Eosin staining. The mapping of esterase enzyme distribution was carried out by staining with α-Napthyl acetate. The skin irritancy testing of known positive irritant 5% Sodium Dodecyl Sulphate (SDS) and TritonX 100 were performed according to Organisation for Economic Co-operation and Development (OECD) guidelines for new skin model development for skin irritancy testing.
Results and Discussion: The viability of the enzymatically separated epidermal membranes was confirmed by all three methods used. α- naphthyl acetate staining shows the retention of esterase activity and their distribution in the epidermis. The dose and incubation period for the positive irritants were optimised. The future studies will characterise the activity of the other main skin enzyme systems.

1. Kligman, A. M. Arch. Dermatol. 88, 702-705, (1963).
2. Sanchez et al. J Biomed Opt. 15(4):046008 (2010).
3. Manevski, N. et al. Drug Metabolism and Disposition 43, 126-139, (2015).
4. OECD. Test No. 439: *In Vitro* Skin Irritation: Reconstructed Human Epidermis Test Method. (OECD Publishing).¶

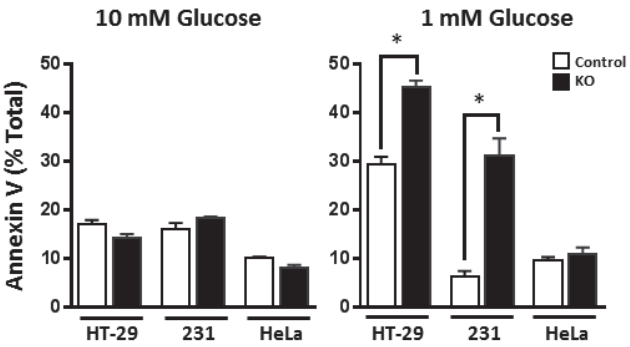
582 Arylamine N-acetyltransferase 1 regulates cancer cell survival via modulation of pyruvate dehydrogenase

LiLi Wang, Rodney F Minchin, Neville J Butcher. School of Biomed Sci, Uni of Queensland, Brisbane, QLD, Australia

Introduction. A growing body of evidence suggests that the phase II drug metabolising enzyme, arylamine N-acetyltransferase 1 (NAT1), plays a role in cancer cell biology. NAT1 has been closely associated with cancer cell growth and survival, as well as metastasis. It also has been associated with the methionine salvage pathway and palmitoleic acid homeostasis.

Aim. To determine the effect of NAT1 KO on cancer cell metabolism under normal and stressed conditions.

Methods. Cell proliferation assays used the CyQuant NF kit. Mitochondrial function was assessed using an XFe96 Analyser and Mito stress kit. CRISPR technology was used to generate NAT1 KO cell lines. Annexin V and caspase 3/7 assays were performed using a Muse analyser.



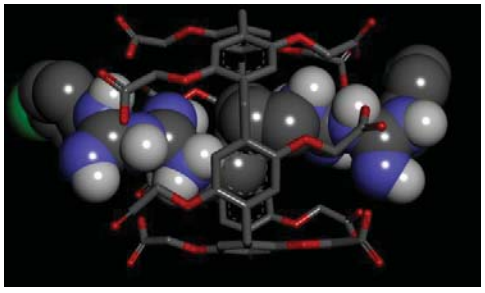
Results. Loss of NAT1 reduced cancer cell proliferation and increased apoptosis under nutrient deprivation. NAT1 KO led to decreased mitochondrial respiration via inactivation of pyruvate dehydrogenase, with concomitant increased levels of extracellular pyruvate and increased generation of reactive oxygen species. This may be via inhibition of the PI3K/AKT pathway as NAT1 KO caused a decrease in AKT phosphorylation. The above changes were observed for HT-29 and MDA-MB-231 cells, but not HeLa cells. One major difference between these cell lines is that the former have gain-of-function mutant p53 whereas the latter has wild-type p53.

Discussion. These results indicate that NAT1 is involved in the regulation of cancer cell metabolism and survival under stress, which may have implications for cancer treatment in the future. The exact molecular mechanism linking NAT1 to the observed effects is currently under investigation.

583 Biomedical applications of water-soluble pillar[*n*]arenes

Nial J. Wheate. Faculty of Pharmacy, The University of Sydney, NSW, 2006, Australia

Introduction. Pillar[*n*]arenes are a new family of macrocycles that have shown potential in a range of different applications (Ogoshi 2016). Unfortunately, native pillar[*n*]arenes are not water soluble and therefore have few biomedical applications; but the development of water-soluble carboxylated-pillar[*n*]arenes has now opened up their potential applications (Wheate 2016).



Aims. To study host-guest complex formation between water soluble pillar[*n*]arenes and a range of drug and excipient molecules.

Methods. Host-guest complex formation was analysed by ^{1}H NMR, fluorescence spectroscopy, and molecular modelling. Toxicity to human cells was analysed using in vitro growth assays with the OVCR-3 and HEK293 cell lines.

Results. Both carboxylated-pillar[6]arene (WP[6]) and carboxylated-pillar[7]arene (WP[7]) form host-guest complexes with memantine, chlorhexidine hydrochloride, and proflavine by ^{1}H NMR and modelling. Binding is stabilised by hydrophobic effects within the cavities, and hydrogen bonding and electrostatic interactions at the portals. Encapsulation within WP[6] results in the complete and efficient quenching of proflavine fluorescence, giving rise to “on” and “off” states that have potential in biodiagnostics. The toxicity testing of the pillar[*n*]arenes to the OVCAR-3 and HEK293 cell lines showed that they are relatively non-toxic to the cells except at high doses and after prolonged continuous exposure.

Discussion. The pillar[*n*]arenes form a range of host-guest complexes depend on the size of the pillar[*n*]arene and the structure of the guest. Overall, the results show that there could be a potentially large range of medical applications for carboxylated-pillar[*n*]arenes.

Ogoshi T et al (2016) Chem Rev.. 116: 7937-8002
Wheate N et al (2016) J Pharm Sci 105: 3615-3625¶

584 Distribution of therapeutic proteins into thoracic lymph after intravenous administration is protein size-dependent and primarily occurs within the liver and mesentery

Preeti Yadav[1], Victoria M. McLeod [1, 2], Angus P.R. Johnston[1, 3], Lisa M. Kaminskas[1, 4] Natalie L. Trevaskis[1]. Drug Deliv, Dispos and Dynamics[1], Monash Univ, Parkville, VIC, Australia; Florey Institute of Neuroscience and Mental Health, Univ of Melbourne, Parkville, VIC, Australia[2], ARC Centre of Excellence in Bioconvergent Nanosciences and Technology, Monash Univ, Parkville, VIC, Australia [3], School of Biomedical Sciences, Univ of Queensland, Brisbane, Australia [4].

Introduction. The lymphatic system is a primary site for cancer metastases, proliferation of infectious diseases and the immune response to inflammatory diseases and organ transplantation.
Aims. This study aimed to determine, for the first time, the major sites of thoracic lymph access of therapeutic proteins, and the protein properties that enhance lymph access, after intravenous (IV) administration.
Methods. In order to achieve this, novel methods were developed or optimised to collect hepatic, mesenteric or thoracic lymph from male SD rats. Four different sized PEGylated or non-PEGylated therapeutic proteins (native interferon α2b (IFN, 19kDa), PEGylated interferon α2b (IFN-PEG12, 31kDa), PEGylated interferon α2a (IFN-PEG40, 60 kDa) or trastuzumab (150 kDa) were then administered *via* short IV infusion, and plasma and lymph concentrations of the proteins determined *via* ELISA.
Results. The recovery of the therapeutic proteins in the thoracic lymph duct, which collects lymph from most of the body, was significantly greater for trastuzumab, IFN-PEG40 and IFN-PEG12 (all >3% dose over 8 h) when compared to native IFN (0.9% dose). Conversely, the thoracic lymph/plasma (L/P) concentration ratio and thus efficiency of extravasation and transport through the interstitium to lymph was highest for the smaller proteins IFN and IFN-PEG12 (at 90-100% vs 15-30%). The lower total recovery of IFN and IFN-PEG12 in thoracic lymph reflected more rapid systemic clearance and shorter plasma circulation half-life. For all therapeutic proteins, the majority (>80%) of lymph access occurred *via* the hepatic and mesenteric lymphatics
Discussion. Optimising the properties of IV administered therapeutic proteins represents a viable approach to better target and treat pathological states involving the lymphatics, particularly in the liver and mesentery. This includes cancer metastases, infectious and inflammatory diseases. Successful development of the novel technique to collect hepatic lymph will also enable future work to evaluate tissue-specific lymph transport in health and disease.

585 Drug Use Evaluation of Levetiracetam at a Tertiary Teaching Hospital

Oksana Burford[1], Josephine Love[1], Joshua Cathcart[1], Petra Czarniak[1].
School of Pharmacy, Faculty of Health Sciences, Curtin University[1], Bentley, WA[1]

Introduction. The management of seizures in a hospital setting is conventionally governed by site guidelines and the Australian Therapeutic Guidelines. Although guidelines provide a gold standard of evidence based therapy, they are not always adhered to. In Australia, the use of levetiracetam is restricted at multiple points, in hospital guidelines, therapeutic guidelines and by Pharmaceutical Benefits Scheme (PBS) subsidisation, despite its favourable pharmacokinetic and pharmacodynamic characteristics. Aims. To evaluate the use of antiepileptic drugs (AED's) in the treatment of acute seizures and in seizure prophylaxis at a tertiary teaching hospital, with a focus on the use of levetiracetam and its prescribing habits. Methods. In this retrospectives study, 1133 patients were identified as having seizure codes during admission in 2016. Patients with a history of seizures prior to 2016 for which they were receiving drug therapy, were excluded. For patients included in the study, medical records were reviewed to identify new antiepileptic drug therapy during acute treatment, in-hospital prophylaxis and discharge therapy. Results. 153 patients met inclusion criteria and were reviewed with regards to antiepileptic therapy focusing on valproate, phenytoin and levetiracetam, of which 132 patients received AED therapy on discharge. Of these, 59 (44.7%) patients were discharged on levetiracetam but only 11 (8.3%) were diagnosed with partial seizures and 44 (33.3%) had no previous AED therapy. Of those discharged on levetiracetam, 48 (81.6%) were provided with a PBS supply of levetiracetam but only 10 (17.5%) were appropriate. Use of Levetiracetam was higher in undiagnosed and generalised seizures rather than partial seizures (p=0.033). Compliance with site specific seizure guidelines was 53.6±10.7% and compliance with Australian Therapeutic Guidelines was 55.6±7.9%. Discussion. There was a lack of compliance with guidelines for the use of levetiracetam in acute seizure management. The high use of levetiracetam in generalised and undiagnosed seizures as a first line therapy may warrant re-evaluation of the eTG treatment pathway for epilepsy to determine if levetiracetam is an appropriate first line option due to it favourable side effect and interaction profile when compared against other AED's.
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586 Hospital pharmacists' and patients' views about what constitutes effective pharmacist-patient communication

Bernadette AM Chevalier,[1] Bernadette M Watson,[2] Michael A Barras,[1,3] W Neil Cottrell[1]
School of Pharmacy, The University of Queensland,[1]Brisbane, QLD; Department of English, The Hong Kong Polytechnic University,[2] Hong Kong; Pharmacy Department, Princess Alexandra Hospital,[3]Brisbane, QLD

Introduction. Effective conversations between patients and healthcare professionals are necessary for patients to understand and manage their medications. Knowing what patients need from a conversation with a pharmacist about their medications may assist hospital pharmacists in preparing patients for discharge and supporting patients' medication management. There are no published studies investigating hospital pharmacists' and patients' opinions about what constitutes an effective pharmacist-patient conversation.
Aims. To explore hospital pharmacists' and patients' views about what constitutes effective communication exchanges between pharmacists and patients.
Methods. Audio recorded, semi-structured interviews were held separately with pharmacists and patients following their shared medication counselling sessions. Twelve pharmacists engaged four patients each (48 interactions in total) within a large quaternary hospital. Participants were asked questions about what made pharmacist-patient conversations effective. Transcribed recordings were analysed using a process of inductive thematic analysis and then mapped to Communication Accommodation Theory (CAT) strategies.
Results. Ensuring patients were confident in managing their medications was the overall shared goal for participants. Shared themes for effective communication exchanges (*mapped to CAT strategies*) included, *well-explained information (interpretability)*, *engagement* (discourse management), *established rapport* (emotional expression) and *empowerment (interpersonal control)*. Participants offered rich exemplars for these themes.
Discussion. Pharmacists and patients provided valuable insights about what makes pharmacist-patient interactions effective. Patient identified preferences may help guide practitioners to engage patients in effective conversations and assist in the training of pharmacy students.

587 Improving community pharmacy management of non-prescription medicine requests with mystery shopping and feedback

Jack C Collins[1], Carl R Schneider[1], Clare L Naughtin[1], Frances Wilson[1], Abilio C de Almeida Neto[1], Rebekah J Moles[1]. Faculty of Pharmacy, University of Sydney[1], Sydney, NSW, Australia.

Introduction. Medicines are a common form of intervention worldwide. In recent years a large number of medicines have moved from prescription-only to non-prescription status. As pharmacies are key locations for the supply of medicines it is important to ensure that pharmacists and their staff are adherent to guidelines and provide optimal care to their patients. Mystery shopping with feedback is a form of audit and coaching that can be employed to improve pharmacy practice.
Aims. To determine if repeated mystery shopping visits with feedback improve pharmacy performance over the course of nine visits, and to determine what factors predict the occurrence of an appropriate outcome.
Methods. Sixty-one Bachelor of Pharmacy students from the University of Sydney acted as mystery shoppers to visit 36 community pharmacies in metropolitan Sydney, Australia. Students underwent theoretical and practical training then presented to an allocated pharmacy each week for nine weeks with a prescribed scenario. Standardised scoresheets were used to score each interaction. Students re-entered the pharmacy within five minutes to provide the staff member involved with feedback and coaching. Data were collated and statistically analysed.
Results. 521 visits were eligible for analysis, 54% of these resulted in an appropriate outcome. Questioning scores and the proportion of interactions resulting in an appropriate outcome significantly improved over time ($P<0.05$). Involvement of a pharmacist, the visit number, increased questioning score, and the prescribed scenario were significant predictors of an appropriate outcome ($P<0.05$).
Discussion. This is the first study to use mystery shopping with feedback across a large number of minor ailment scenarios with multiple repeated visits. The intervention improved pharmacy performance over time across all scenarios, however when examining individual scenarios this was not always the case. This inconsistency may be attributed to the varying difficulty of the scenarios. Consistent with previous work, increased information gathering and involvement of a pharmacist were positive predictors of appropriate outcome. Future work should target scenarios where staff performed poorly and explore means to strengthen the intervention. ¶

588 Surgical antibiotic prophylaxis use and infection prevalence in breast surgery procedures in a major teaching hospital in Western Australia.

Ainslie K Lavers[1], Wai Siong Yip[1], Bruce Sunderland[1], Richard Parsons[1], Jason Seet[2], Sarah Mackenzie[2] Petra Czarniak[1]. School of Pharmacy, Faculty of Health Sciences, Curtin University[1], Bentley, WA; Sir Charles Gairdner Hospital[2], Perth, WA

Introduction. Surgical site infections (SSI's) are a common complication following breast surgery procedures, despite being considered a clean surgery. The prevalence of SSI's can be minimised with the appropriate use of antibiotic prophylaxis such as outlined in the Australian Therapeutic Guidelines (eTG). Aims. The primary objective of this study was to evaluate the level of adherence to the eTG for antibiotic prophylaxis in breast surgery procedures at a Western Australian teaching hospital since the eTG 2014 update. Other aims were examining the impact of prophylactic and post-operative antibiotics on the incidence of SSI's and length of hospital stay. Methods. A retrospective cross-sectional study reviewed medical records from a randomised sample of 250 patients from 973 who underwent a breast surgical procedure between February 2015 and March 2017. Results. Overall adherence to current eTG occurred in 54.4% (123/226) of operations. Pre-operative antibiotics were prescribed in 98.4% (246 of 250) operations. Adherence rates to three specific elements of eTG (drug prescribed, drug dosage and timing of administration) were 91.6% (226/250), 52.8% (132/250) and 96.4% (216/224) respectively. For the 36 of 250 (14.4%) patients with relevant drug allergies, there was a total lack of adherence to the eTG. Post-operative antibiotics were prescribed in 11.2% (28/250) operations. Overall SSI prevalence was low at 5.2% (13/250). No statistical significance was found between SSI's and adherence to eTG. A statistically significant relationship was found between certain procedures, including soft tissue biopsy and hematoma drainage and developing SSI's ($p=0.027$, $p=0.000$ respectively). The mean length of stay in patients was 2.3±1.7 days, with no statistical relationship found between overall level of eTG adherence ($p=0.131$) or SSI's ($p=0.306$). Discussion. Although there has been some improvement in overall appropriateness of surgical antibiotic prophylaxis from 13.3% to 54.4%, further improvement is necessary especially with respect to timing of antibiotic administration and when allergy to the primary recommended antibiotic occurs, that the recommended alternative antibiotic is selected.

589 Psychometric testing of scales measuring perinatal depression literacy and comfort with providing perinatal depression care

Sarira El-Den[1], Claire L. O'Reilly[1], Timothy F. Chen[1] Faculty of Pharmacy, The University of Sydney[1], Camperdown, Australia

Introduction. Pharmacists' increased involvement in mental health care, including perinatal depression (PND), warrants research exploring their mental health literacy and comfort with providing care. Despite widespread use in the literature, mental health literacy scales lack psychometric testing.
Aims. To assess the psychometric properties of two scales measuring PND literacy and comfort with providing PND care.
Methods. Bachelor of Pharmacy students completed three PND literacy scales (34 items) at two time points, approximately one month apart. They also completed a 7-item scale measuring their comfort with providing PND care. Test re-test reliability analyses of the literacy scales were conducted using Wilcoxon Signed Rank Test ($p<0.05$). Exploratory factor analysis and Cronbach alpha calculations were conducted to explore the construct validity and internal consistency reliability, respectively, of the comfort scale.
Results. A matched sample of 47 pharmacy students was obtained. Test re-test analyses indicated that 31/34 items were reliable, as demonstrated by non-significant p-values. Principal axis factoring (n=106) with direct oblimin rotation of the comfort scale resulted in a two-factor solution with 64.5% variance explained. Factor One contained four items (0.599-0.910) and pertained to comfort with referring PND patients to external healthcare services. Factor Two contained three items (0.492-0.698) and pertained to comfort with providing care by a pharmacist. One item cross-loaded (<0.2 difference) on both factors. It is recommended that this item is modified prior to the distribution of the scale.
Discussion. There is a lack of psychometrically tested measurement tools when measuring constructs pertaining to PND[1]. By exploring the psychometric properties of the scales, the subsequent reliable and valid measurement of these constructs can be conducted in a standardised and uniform manner across studies and population groups.
El-Den S, O'Reilly CL, & Chen TF. (2015). A systematic review on the acceptability of perinatal depression screening. *Journal of Affective Disorders, 188*, 284-303.¶

590 Communication between community pharmacies and prescribers in New Zealand

Nastassja Trausch[1], James A Green[1]. School of Pharmacy, University of Otago[1], Dunedin, New Zealand

Introduction. Phone calls between pharmacists and prescribers play an important role in resolving potential errors and other issues. Despite their importance in patient care, and at times being a source of frustration for pharmacists, there is very little research on these calls.
Aims. To quantify how often phone calls occur between pharmacists and prescribers, how much time is spent on these calls, who is called, and what are the reasons for these calls.
Methods. An observational study was conducted in 11 pharmacies over 8 weeks in Dunedin, New Zealand. Data captured included information on date, time, length, pharmacy staff involved, health professionals involved, the place being called and the purpose of the call. We also surveyed pharmacists' perceptions of this communication.
Results. Data on 95 phone calls and 63 faxes were captured. The mean length was 110 seconds (95% CI 88-133), at an average of 0.7 calls per hour. Incoming calls were shorter than outgoing calls, at least in part because of delays in getting hold of the prescriber. The most frequent reasons for calling were clarifications and dose inquiries. Pharmacy staff underestimated by half the number of incoming calls, relative to the observed data.
Discussion. Calling prescribers was perceived as a frustrating. The observed frequency of calls was low but some calls were long. Time for single pharmacist interventions may be reduced using alternative communication methods but these need further study.¶

591 Medicine use in early childhood: Which vaccines, branded or generic medicines do parents of children five and under choose?

Andy Lim[1], Chixin Zhang[1], Erin Goh[1], Chelsea Smith[1], Laura Holland[1], James A Green[1]. School of Pharmacy, University of Otago[1], Dunedin, New Zealand

Introduction. Despite generic medicines being bioequivalent and cheaper, many people prefer branded medicines to generic medicines. We are not aware of any research that looks at parents' use of branded and generic medicines for their children. We were also interested in linking this vaccination behaviour, as choosing branded medicines for children may be seen as a protective behaviour. In contrast, both generics and vaccines are evidence based, so these could be associated.
Aims. This study aimed to determine the understandings and perceptions of parents of children aged five and under about generic and branded medicines, alongside their medicine preferences for their children and themselves. It also looked at parents' opinions surrounding vaccinations, whether they vaccinated themselves and their children, and whether there was a link between vaccination behaviour and preference for branded/generic medicines.
Methods. Parents of children under five were recruited through an online panel to match the New Zealand demographic profile for parents (by age, gender, ethnicity and region). They completed an online survey about the medicines they use for themselves and their children, the vaccines they and their children have received, and a variety of questions about their perceptions of vaccines, and branded and generic medicines. We also tested their ability to identify branded from generic medicines.
Results. 196 participants met the eligibility criteria and completed the survey. Parents preferred generic medicines (43%) over branded (25%) for themselves but mostly had no preference for their children. Participants more able to identify branded from generics were more likely to choose generics for themselves and their children, $ps < .001$. Parents who got more vaccines for their children were weakly less likely to report having no preference between branded and generics for their children, $p = .02$, but overall there was little link between these choices.
Discussion. Parents' vaccine choices for their young children were not linked to their preferences for branded/generic medicines for their children. Further analyses looking at how demographic variables and perceptions of these products may determine strategies that can be used to improve child health. ¶

592 What is the attitude of Australian pharmacists to the use of medicines for assisted dying at end-of life?

Tony Hall[1], Esther Lau[1], Lisa Nissen[1], David Herron[2], Andrew McGee[3], [1)]School of Clinical Science QUT, Brisbane, Qld. [2)] School of Pharmacy, James Cook University, Townsville, Qld. [3)] Australian Health Law Research Centre, QUT Brisbane, Qld.

Introduction. Many Australian State Governments have initiated debate into legalising physician-assisted dying and euthanasia for patients enduring intolerable suffering in end-of-life care. Since it is likely that medications will be utilised to facilitate the patient's death the views of the pharmaceutical profession have not currently been sought. There has been little research undertaken in this area by pharmacists
Aims. The aim of this research was to collect information to obtain the views of pharmacists to physician-assisted dying, euthanasia and palliative care.
Methods. Australian pharmacists were invited to complete an online survey to obtain their views on these topics.
Results. 93 pharmacists from a mixed background completed the survey over the period June - July 2017. 69% identified themselves as community-based; 18% as hospital-based and 3% as academic. Age groups matched Australian pharmacist demographics; 18% < 30 years, 30% 30-39 years, 15% 40-49 years, 25% 50-59 years and 12% >60 years: 63.4% females and 35.5% males. The majority claimed some religious identify (57%) and 34.4% as without. 69.9% of responders supported this legislation, 20.4% did not, 8.6% were unsure and 1.1% were unwilling to answer. 55.9% were concerned that this was a 'slippery slope where vulnerable patients might be put at risk'. 62.4% of respondents would be willing to assist supplying medication on prescription. Many respondents considered that physician-assisted dying already occurred in Australia, with 20.4% believing it to be common practice.
Discussion. Further data evaluation will be presented evaluating respondents confidence in symptom management in palliative care; whereas confidence in the management of pain, constipation, nausea and vomiting were high there was less confidence in the management of delirium and dyspnoea and in the use of non-opioid analgesics such as ketamine. Most respondents thought that palliative interventions were inadequate in the management of intolerable pain and suffering (59% vs 41%) suggesting a lack of confidence in palliative intervention.¶

593 Health professionals' opinion of a brief email format for answering medicine information enquiries.

Ann Roslyn Hutton, Bruce Hastie, Tracey Borrie, Julie Knight, Marie-Claire Morahan. Medicines Information Service, Dept of Clin Pharmacol, Christchurch Hospital, New Zealand.

Introduction. The quality and timing of responses to medicines information (MI) enquiries can affect their usefulness to the recipient for optimising medicines and improving patient outcomes. At our MI service, an increasing demand for an emailed written answer, prompted us to design a brief email format.
Aims. To assess healthcare professionals' opinion of a brief email format for answering MI enquiries.
Methods. The brief email format was used to answer MI enquiries requiring a written response, for 6 months. Enquiries relating to pregnancy or lactation and those requiring long answers were excluded. An electronic survey was sent to all enquirers receiving a brief email and could be completed anonymously. The survey used a 5-point Likert scale (strongly agree, agree, uncertain, disagree, strongly disagree) to assess the recipient's opinion of the brief email format. Their opinion was sought in five domains: overall satisfaction with the answer to the MI enquiry, whether they thought the answer was too brief, were they happy to contact the service if they needed more detail or further information about their enquiry, whether they would prefer a fully-referenced answer, and if they would like to have copies of key references attached to the email. Primary outcomes were enquirer satisfaction with the quality and length of the answer to their MI enquiry. Secondary outcomes were enquirer preferences with respect to references.
Results. For the first two months of the 6 month period, we have used the brief email format 25 times to answer MI enquiries requiring a written response. To date, we have have received 10 completed surveys (40% response rate). These showed: almost all recipients (9/10) agreed or strongly agreed that they were satisfied with the answer to their MI enquiry, most (8/10) disagreed or strongly disagreed the answer was too brief, 5/10 recipients were uncertain about whether they wanted a fully-referenced answer or whether they wanted copies of key references attached to the email. To follow are the results from the completed surveys received over the next 4 months.
Discussion. The results from the surveys received to date indicate our enquirers consider the brief email format acceptable for answering MI enquiries requiring a written response. There appears to be uncertainty regarding inclusion of references. The results from surveys received over the next 4 months will show whether these trends continue.¶

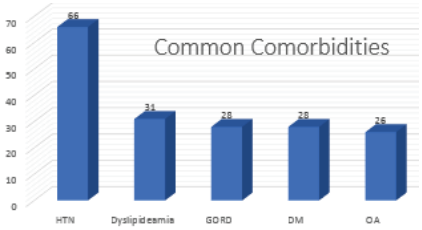
594 Pharmacy & The Ethical Dilemma of Physician Assisted Suicide (PAS): A Systematic Review

Sami Isaac[1], Prof. Andrew McLachlan[1], Dr Betty Chaar[1], Faculty of Pharmacy University of Sydney[1], Camperdown, NSW, Australia.

Introduction. The right to die with dignity has been legalised in certain countries, but to date, not in Australia where it remains illegal. However, this remains an active issue in the community and legislature. Pharmacists need to be prepared and use international experiences to help establish boundaries that protect all those who are involved. While there have been several studies on physicians, nurses and the public's views on PAS little research has been conducted on pharmacists and none on Australian pharmacists. The aim of this study was to systemically review the literature related to PAS and the role of pharmacists.
Methods. A systematic review of articles collected from 6 databases, MEDLINE, PubMed, EMBASE, CINAHL, SciFinder and International Pharmaceutical Abstracts (IPA). Inclusion criteria were limited to articles published in English from January 1987 to June 2017 clinical data on pharmacists' views on PAS and euthanasia. References of the included articles were also reviewed for any additional trials that may have met inclusion criteria.
Results. Eight qualitative studies met our inclusion criteria. The reviewed studies were of registered pharmacists across four countries: Netherlands, Belgium, UK and US, which have legislation enabling euthanasia or physician assisted suicide in some parts of, if not the entire country. The majority of pharmacists within these studies accepted the right of a patient to choose their own death at the end of life. Reports indicate that 45% of those surveyed were unsure of, or against a physicians' assistance in a patient's death. This review identified a willingness from pharmacists to partake in the dispensing of drugs for PAS if legal with the appropriate conditions and protocols for support were made available.
Discussion. This is the first systematic review of the literature pertaining to pharmacists' views on PAS and euthanasia. This systematic review sheds light on the significance of pharmacists' views, in what needs to be an interdisciplinary discussion on the legislative and ethical challenges associated with PAS and euthanasia This systematic review identifies the need for further research and greater pharmacist-based studies in this topical debate. Australian based qualitative studies on pharmacists' attitudes are especially important, in order to help shape new legislative protocols in the dawn of PAS legalisation in Australia.¶

595 Common co-morbidities and polypharmacy in elderly patients in a South Australian tertiary healthcare hospital

MS Khan[1,4], L Gebremichael[1], A Qurain[1], MD Wiese[1], DB Williams[1], L Mackenzie[1], C Phillips[2], P Russell[3], MS Roberts[1,4]. School of Pharmacy and Medical Sciences, University of South Australia, and Basil Hetzel Institute for Translational Research, The Queen Elizabeth Hospital[1]; School of Nursing and Midwifery, University of South Australia[2]; Royal Adelaide Hospital, Adelaide SA[3]; Therapeutics Research Centre, Diamantina Institute, The University of Queensland, Translational Research Institute, Brisbane, Qld, Australia.[4]



Introduction. The delivery of safe, effective and optimal treatment in an increasingly aged population is a global issue as the older patients have multiple morbidities and are the largest consumer of medicines.
Aims. The aim of this study was to characterise elderly patients who were ≥ 75 years on admission to a tertiary health care hospital in terms of co-morbidities, prescribed medications and related adverse effects.
Methods. The inclusion criteria were patients who received ≥ 5 medications and were aged ≥ 75 years on admission to Royal Adelaide Hospital, Adelaide, SA between September 2015 to September 2016. Each patient's case notes were examined for co-morbidities, prescribed medications and adverse effects as at a recorded date. Medications were classified using ATC (anatomical therapeutic classification) codes and analysed using SPSS software.
Results. A total of 474 patients (42% males) have been identified to date, with a mean age of 84 ± 6 years. Fig. 1 shows the top co-morbidities found. The top five classes of medication taken by these patients were: anti-inflammatory and anti-rheumatic medication (80%), anti-thrombotic (69%), drugs for acid related disorders (53%), agents acting on renin-angiotensin system (50%) and lipid modifying agents (48%). The top five common diseases were; hypertension (65%), dyslipidaemia (31%), GORD (28%), diabetes (28%) and osteoarthritis (26%). Polypharmacy was found to be associated with a higher incidence of adverse drug reactions, drug-drug interactions, inappropriate drug use and non-adherence.
Discussion. Our pilot data on prescribed medications and co-morbidities in elderly patients at South Australia's largest tertiary health care hospital suggests that polypharmacy and its sequelae is an ongoing issue for them.¶

596 Weight loss product usage and advice in community pharmacies in North Queensland

Gillian J Knott[1], Swapna V Chaudhary[1], Pharmacy, James Cook University[1], Townsville, QLD, Australia

Introduction. Obesity is currently one of the greatest health challenges in Australia, particularly in North Queensland, where in 2011-12, 75% of people living in the Townsville Mackay Region were either overweight or obese.[1] Community Pharmacies play a significant role in the management of obesity through the provision of weight management programs and products as well as by providing weight loss advice to consumers. However, there is limited information available regarding the weight loss products that are recommended by pharmacies, whether they are providing evidenced based advice and whether consumers are making appropriate weight loss product choices.
Aims. To identify trends in weight loss product recommendations and advice provided by pharmacies to consumers, to ascertain consumer usage patterns and to investigate the reasons for consumer choices of weight loss products.
Methods. This project involved the distribution of a questionnaire to North Queensland Pharmacies. Responding pharmacies were then asked to distribute a brief survey to their consumers on the purchase of a weight loss product.
Results. 78 different products were listed among the top 10 weight loss products sold by the respondent pharmacies. Both the pharmacist and consumer surveys indicated that the most popular weight loss products were meal replacements, with complementary medicines also being used by a significant number of consumers. Consumers were found to be predominantly female between the age of 26 and 45 years. Information sources used by community pharmacies for the provision of weight loss advice showed potential for bias as they were mainly from company weight loss product or program resources.
Discussion. There is a need for more evidence based weight management training resources for community pharmacies. There is also a need for increased consumer awareness of the available evidence or lack of evidence for many weight loss products. Meal replacement products are a popular choice of product with some evidence of short-term benefits, however further studies to determine the long term efficacy of these products may be warranted. Given the higher obesity levels of males compared to females,[1] consideration should also be given to increasing the promotion of weight loss services to the male population.

1. Queensland Health. The health of Queenslanders 2014. Fifth report of the Chief Health Officer Queensland. Queensland Government website. https://www.health.qld.gov.au/publications/research-reports/reports/cho-report/cho-full-report.pdf. Published 2014. Accessed May 16, 2016. ¶

597 Factors associated with pharmacists' perceptions of working conditions in Canada

Carlo A. Marra[1], School of Pharmacy, University of Otago, Dunedin, NZ;
Nicole Tsao[2], Shahrzad Salmsi[2], Huiquing Li[2], Larry D. Lynd,[2] Faculty of Pharmaceutical Sciences, UBC, Vancouver, BC, Canada.

Introduction: Previous evidence suggests that pharmacists often experience unsafe working conditions in the provision of patient care in the community pharmacy setting.
Aims: To determine the factors associated with perceived working conditions in five Canadian provinces.
Methods: A survey was administered with questions about demographics, practice, advanced clinical services offered to patients (prescription adaptations, immunizations, and medication reviews), and whether their practice site imposed monthly quotas for each of the advanced practice services. Respondents' satisfaction of their working conditions was assessed using six statements rated with a five point Likert scale. Associations were made using ordinal logistic regression.
Results: Of 11767 registered pharmacists who received an invitation to participate in this study, 2464 (21%) responded, 34% of whom were male. In general, pharmacists were not satisfied with their working conditions. Lack of time to do their jobs, inadequate time to have lunch, as well as inadequate number of staff were commonly reported. Overall, 20% of the pharmacists reported that they need to meet quotas for clinical services. Lack of satisfaction with working conditions was associated with quotas, filling >100 prescriptions per pharmacist per day, >20 minutes prescription wait time and working at chain pharmacy.
Discussion: Pharmacists rate their working conditions to be unsafe. Having corporate enforced quotas for reimbursed clinical services and working in chain pharmacies were associated with lower safety.
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598 What Is Polypharmacy Exactly (WIPE)

Nashwa Masnoon[1,2], Sepehr Shakib[3,4], Lisa Kalisch-Ellett[1], Gillian Caughey[1,3,4]. School of Pharmacy and Medical Sciences, Univ of South Australia, Adelaide, SA[1]; Dept of Pharmacy, Royal Adelaide Hosp, Adelaide, SA[2]; Dept of Clinical Pharmacol, Royal Adelaide Hosp, Adelaide, SA[3]; Dept of Clinical Pharmacol, Univ of Adelaide, Adelaide, SA[4].

Introduction. There are various definitions of polypharmacy and it is unclear how different clinicians define and assess polypharmacy in practice, which can provide important insight into medication review and rationalisation.
Aims. To develop a website which allows evaluation of different clinicians' assessment of polypharmacy and identification of medication related factors which are considered during medication review and rationalisation.
Methods. A website called What Is Polypharmacy Exactly (WIPE) was developed which presents de-identified patient cases from clinical practice at wipe.logicsquad.net/signup. For each case, the website presents the patient's age and setting, list of comorbidities and medications and asks users to i. rate the degree of polypharmacy ii. rate the potential for harm from medications iii. rate the potential to deprescribe medications and iv. nominate medication classes for deprescribing. WIPE provides users with feedback by expert clinicians after case completion as well as the ability to post comments and engage in clinical discussion regarding each case with other users on the website.
Results. There have been 212 responses on WIPE from 61 users comprising of hospital and community pharmacists, consultant physicians, resident medical officers and medical students. Initial data analysis shows that medication classes such as benzodiazepines, opioids, sedating antihistamines and antipsychotics obtained higher ratings regarding the degree of polypharmacy and the potential for harm compared to statins, inhaled medications and paracetamol. Clinicians were more likely to nominate the medication classes which were associated with higher degree of polypharmacy and potential to cause harm for deprescribing.
Discussion. Clinician ratings reflect important aspects of medication review and rationalisation where medications which are identified as having the potential to cause harm are assessed for the possibility of deprescribing in order to optimise patient outcomes. WIPE can be used as an educational tool and allows a novel platform for users at the national and international level to work together to collectively define polypharmacy, in order to develop clear prescribing guidelines and improve patient outcomes. ¶

599 Do Australian Pharmacists feel prepared to respond to local disasters and emergencies?

Elizabeth McCourt[1], Judith Singleton[1], Prof. Vivienne Tippett[1] & Prof. Lisa Nissen[1]. School of Clinical Sciences, Queensland University of Technology[1], Brisbane, QLD, Australia.

Introduction. During disasters local communities are the first to respond, often working for days before reinforcements from outside agencies can arrive. Health professionals provide essential roles and services during these events. For many health professionals a plethora of literature, competencies, and training support their roles within the disaster space. Despite the important role pharmacists play within the healthcare team, their preparedness to respond to disasters is unknown. Additionally, little is known about what supports pharmacists need to feel more prepared to respond to a disaster.
Aims. To determine how prepared Australian pharmacists feel to fulfil roles in local disasters and what supports they require to become more prepared.
Methods. A collection of semi-structured interviews led to the development of a mixed-methods survey. This survey will be launched at APSA-ASCEPT 2017 with registered pharmacists invited to participate. Contributors will be asked to self-assess their preparedness for playing a variety of roles that may affect their local community in a disaster. Additionally, this project will explore how pharmacists believe they could improve their preparedness, or how they could be supported in disasters.
Results. Results from this survey will feed into a larger research project examining disaster preparedness for pharmacists. The main objective of this research project is to determine how pharmacists can be better prepared to fulfil roles in disasters in Australia. Potential outcomes include competency development, legislative change, and/or short training courses for pharmacists.
Discussion. Pharmacists are essential health professionals during disasters. Unfortunately, little is known about how prepared pharmacists feel to assist in disasters and how they can be supported to play a role. The ultimate goal of this research is to improve local preparedness and professional resilience in Australian disasters and emergencies.
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600 Over-the-counter medicines: the complexity of decision-making for pharmacy students

Sara S McMillan[1], Thachaayini Thangarajah[2], Claire Anderson[2], Fiona Kelly[1]. School of Pharmacy and Pharmacology, Griffith University[1], Gold Coast, QLD, Australia; School of Pharmacy, University of Nottingham[2], Nottingham, United Kingdom.

Introduction. Community pharmacies are frequently accessed by consumers for minor ailment advice and over-the-counter (OTC) medicines. Various factors influence pharmacist and support staff decision-making in OTC consultations, yet, limited attention has been placed on pharmacy students as pharmacists-in-training.
Aims. To identify how factors affect OTC decision-making by pharmacy students, and to explore the factors influencing OTC medicine choice.
Methods. In-depth data were collected by semi-structured interviews with Queensland pharmacy students and analysed using the Critical Incident Technique. Student stories of OTC experiences were identified as critical incidents if they contained: (i) a description of the situation or trigger which led to the incident; (ii) information about student action/s or behaviours; (iii) an outcome, e.g. referral, medicine supply or refusal. Interview transcripts were coded for incidents, and using thematic analysis, factors were identified within incidents that influenced OTC decision-making.
Results. Ten pharmacy students identified 131 critical incidents, which were mostly pain, dermatology and cold related enquiries. Nine overarching themes influenced student decision-making, with a particular emphasis on customer response, confidence and scope of practice. Product requests were reported as more challenging than symptom requests; this was due to consumer expectations. Negative consumer responses prompted medicine supply against evidence-based guidelines, but only when this was assessed as safe. Real-life practice was suggested to be more effective than university learnings in developing decision-making skills.
Discussion. It became clear that OTC decision-making is a complex process for students. Pharmacy educators should consider learning activities that support students to assertively interact with consumers, and additional opportunities for experiential learning, such as work-based placements and role-plays with simulated patients.

Flanagan JC (1954). Psychol Bull. 51:327-358.¶

601 Insights into consumer use, storage and disposal of unwanted and expired medicines

Fiona Kelly, Sara McMillan, Jean Spinks, Emilie Bettington, Amanda Wheeler. Griffith University, Gold Coast, QLD

Introduction. Consumers can hoard medicines for 'just in case' use.(1) Unwanted medicines are commonly discarded in the rubbish or drain,(2) with health and environmental implications. We have limited insight into these practices.
Aims. To qualitatively explore the quantity and nature of unwanted or when required medicines in the home and self-reported practices related to medicine storage, accumulation, use and disposal.
Methods. Structured telephone interviews were conducted with people who used five or more medicines including prescribed, non-prescription medicines and/or complementary and alternative medicines such as vitamins. Interviews were transcribed verbatim, and integrity of data analysis was assured through research debriefs, quality checking of transcripts and thematic coding by two experienced researchers.
Results. Participating consumers reported 1424 unwanted medicines stored in various locations in 166 households. Although participants did not intentionally stockpile medicines by seeking out early dispensing of repeat prescriptions, a number did keep medicines 'just in case' they were needed in the future, including antibiotics. Some participants reported using expired medicines guided by individual risk assessment strategies. When asked about the risks of storing unwanted medicines, ingestion by children and pets and decreased efficacy of expired medicines were described. However, this knowledge did not always translate to appropriate storage, use or disposal of medicines.
Discussion. Knowledge of the risks of inappropriate medicine storage, use and/or disposal did not guarantee appropriate management of unwanted medicines. Application of variable individualised risk-benefit assessments emerged, with implications for health professionals and the environment. Greater exploration of the underlying basis and significance of these is needed to enable us to identify and address misconceptions.

1.Vellinga A, Cormican S, Driscoll J, Furey M, al e. Public Practice Regarding Disposal of Unused Medicines in Ireland. *Science of the Total Environment*. 2014;478:98-102.
2.Bettington E, Spinks J, Kelly F, Gallardo-Godoy A, Nghiem S, Wheeler AJ. When Is a Medicine Unwanted, How Is It Disposed, and How Might Safe Disposal Be Promoted? Insights from the Australian Population. *Australian Health Review*. 2017;in-press, accepted June 2017.¶

602 Non-prescription sales of antimicrobials in developing countries: a systematic review

Fatima Sakeena[1, 2], Alexandra Bennett[3], Andrew J McLachlan[1, 4]. Faculty of Pharmacy, University of Sydney[1], Sydney, NSW, Australia; Department of Pharmacy, Faculty of Allied Health Sciences, University of Peradeniya[2], Peradeniya, Sri Lanka; NSW Therapeutic Advisory Group[3], Sydney, NSW, Australia; Centre for Education and Research on Ageing, Concord Repatriation General Hospital[4], NSW, Australia

Introduction. Antimicrobial resistance (AMR) is a critical global challenge. Developing countries are more vulnerable to AMR than developed nations due to many complex issues pertaining in the health care system. One contributing factor to inappropriate antimicrobial use is the non-prescription availability of antimicrobials at community pharmacies.
Aims. The aim of this systematic review is to investigate non-prescription sales of antimicrobials in developing countries and assess the contributing factors to non-prescription sales in these countries.
Methods. EMBASE, MEDLINE, SCOPUS, International Pharmaceutical Abstracts and Web of Sciences were searched for articles, published between 1980 and the end of April 2017, that involved studies using simulated patient study designs that evaluated the availability of antimicrobials in community pharmacies in developing countries.
Results. 37 studies from 22 developing countries across Asia, Africa, South America, South-Eastern Europe and the Middle-Eastern regions reported antimicrobial sales without a prescription. The percentage of antimicrobials dispensed without prescription in these countries ranged from 15% to 90%. Poor medicines regulations, lack of available suitably-qualified pharmacy staff, commercial pressure on pharmacy staff, consumer demand, inappropriate prescribing practices and lack of AMR awareness were reported as contributing factors that facilitated non-prescription sales of antimicrobials in developing countries.
Discussion. Non-prescription sales of antimicrobials are substantial in developing countries and a significant contributing reason for overuse and misuse of antimicrobials in the community. Non-prescription sales of antimicrobial agents are associated with inappropriate drug choice, short duration of therapies and wrong dose. Inappropriate prescribing and supply practices contribute to the development of AMR. A multi-faceted approach is required to address the contributing factors facilitating non-prescription sales in order to reduce AMR. ¶

603 Principlism: An approach for determining ethical responsibilities of pharmacists when selling complementary medicines

Amber Salman Popattia[1], Adam La Caze[1]. School of Pharmacy, The University of Queensland[1], Brisbane, QLD, Australia

Introduction. Principlism is an ethical framework that consists in the application of the four bioethical principles to make decisions in healthcare: respect autonomy, beneficence, non-maleficence and justice. No explicit ethical framework is employed in the pharmacy literature describing the responsibilities of pharmacists when selling complementary medicines. Research regarding the responsibilities of pharmacists when selling complementary medicines consists predominantly of empirical studies. This research tends to focus on the perceptions of pharmacists, pharmacy support staff and consumers regarding pharmacist responsibilities. A number of ethical conflicts for pharmacists are identified in this literature, but little attempt is made to resolve these conflicts.
Aim. To assess principlism as an explicit ethical framework for determining ethical responsibilities of pharmacists when selling complementary medicines.
Methods. The theoretical literature describing principlism and the arguments regarding merits and otherwise of principlism are analysed to explore this approach and its key components.
Discussion. Principlism is typically criticized on the basis of its theoretical foundations and its ability to provide practical guidance when ethical conflicts are identified. It is common in healthcare to accept these criticisms and employ principlism as a form of 'ethics first-aid': a way to identify conflicts without any attempt to resolve them. We argue against this approach. We identify key developments within principlism that clarify its theoretical foundations and provide resources for resolving ethical conflict. We show how developments such as basing the principles in common morality, employing reflective equilibrium and specified principlism provide the necessary theoretical resources for determining pharmacist responsibilities when selling complementary medicines. This work provides the basis for a more informed discussion of pharmacist responsibilities when selling complementary medicines.¶

604 Implementation of the Goal-directed Medication review Electronic Decision Support System (G-MEDSS)

Dr Lisa Kouladjian O'Donnell[1], Dr Emily Reeve[1], Dr Danijela Gnjidic [1,2], Ms Mouna Sawan[1], A/Prof Timothy Chen[2], A/Prof Patrick Kelly[3], A/Prof J Simon Bell[1,4] and Prof Sarah Hilmer[1]. NHMRC Cognitive Decline Partnership Centre, Sydney Univ, Kolling Institute, St Leonards, NSW[1]; Fac Pharmacy, Sydney Univ, Camperdown, NSW[2]; Sydney School of Public Health, Sydney Uni, Camperdown, NSW[3]; Fac Pharmacy and Pharm Sci, Monash University, Melbourne, VIC[4].

Introduction. People with dementia in the community setting are prescribed more medications compared to people without dementia, and are particularly vulnerable to the adverse effects of high-risk medications (e.g. anticholinergics, antipsychotics and benzodiazepines). Implementation studies of Computerised Clinical Decision Support systems (CCDSS) interventions have demonstrated effective improvement in appropriate prescribing in older adults. We have developed the Goal-directed Medication review Electronic Decision Support System (G-MEDSS), a CCDSS that incorporates validated deprescribing tools and guides (e.g. the Drug Burden Index (DBI), Patient Attitudes Towards Desprescribing questionnaire and Goals of Care) into pharmacist Home Medicines Review (HMR).
Aims. (1) To test the efficacy and safety of the addition of the GMEDSS in HMR to reduce anticholinergic and sedative medication use in patients with/out dementia; (2) To measure the impact of the medication changes on clinical and functional outcomes.
Methods. This study is a two-arm, parallel group, cluster-randomised trial (ACTRN12617000895381). Accredited Pharmacists (AP) who meet the inclusion criteria will be randomised into the intervention (usual care + CCDSS + G-MEDSS report provided to the patient and patient's referring GP) or control (usual care HMR) group. All AP will undergo training and will be required to pass an online competency MCQ questionnaire. Accredited Pharmacists will collect data (e.g. medication profile, cognitive and physical function) from patients at baseline (during HMR interview) and at 3-months follow up. The primary outcome will be proportion of patients with a reduced DBI. The required total sample size is 500, with 50 pharmacists in each arm of the study to recruit 5 to 10 patients. This will allow us to detect a 10% difference between arms α=0.05 2-sided, 1-β=0.8, intra-cluster correlation = 0.07.
Discussion. We anticipate that the G-MEDSS will reduce anticholinergic and sedative medications, incorporate patient's attitudes towards describing and patients goals in the HMR. This may reduce the proportion of older adults using inappropriate medications and improve clinical outcomes in older adults.¶

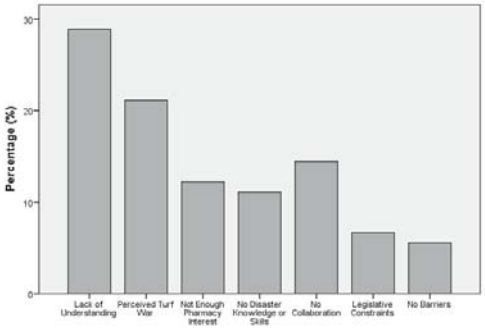
605 Pharmacist perceptions of psychotropic monitoring in australian aged care facilities

Aili V. Langford[1], Associate Professor Timothy F. Chen[1], Associate Professor Christopher Roberts[2], & Dr Carl R. Schneider[1]. Faculty of Pharmacy, The University of Sydney[1], Sydney, NSW, Australia; Sydney Medical School (Northern), The University of Sydney[2], Sydney, NSW, Australia.

Introduction. Current Australian guidelines suggest that the modest benefit of psychotropic medicine use in the geriatric population may be outweighed by associated morbidity and mortality. Psychotropic medication monitoring by Health Care Professionals (HCPs) may be valuable in reducing adverse effects resulting from this class of medicines. The extent to which psychotropic medication monitoring occurs in Aged Care Facilities (ACFs) and the factors which influence monitoring are not well established.
Aim. This qualitative study aimed to explore psychotropic medication monitoring from the perspective of pharmacists and ascertain perceived barriers and enablers to psychotropic monitoring in ACFs.
Methods. A convenience sample of 10 accredited clinical pharmacists who work in ACFs were selected for inclusion. Semi-structured face-to-face interviews were conducted and a range of questions assessing perceptions of monitoring, facilitators, barriers and proposed solutions were included. Interviews were transcribed verbatim and analysed using Nvivo software.
Results. Monitoring is a multi-faceted concept which is influenced by factors at the individual, group, organisation and system level. Thematic analysis revealed 8 primary themes: (i) patient autonomy and characteristics such as medical diagnosis and ability to consent, (ii) education of nurses and general practitioners, (iii) communication channels, (iv) ACF culture, (v) roles and responsibilities (vi) resource allocation such as staffing levels and time constraints (vii) guidelines and protocols and (viii) lack of remuneration.
Discussion. Pharmacist's felt that psychotropic medication monitoring in ACFs is largely suboptimal and recognised a need for significant improvements in practices. Pharmacists saw themselves as enablers to improving psychotropic monitoring and expressed that improved remuneration and resourcing as well as optimised communication channels and education for other HCPs would facilitate this.

606 Do Pharmacists Fit in the Disaster Health Management Team Puzzle?

Kaitlyn Porter[1,2], Judith Singleton[1,2], Vivienne Tippett[1,2,] & Lisa Nissen[1,2], &. School of Clinical Sciences, Queensland University of Technology[1], Brisbane, QLD, Australia; Institute of Health and Biomedical Innovation, Queensland University of Technology[2], Brisbane, QLD, Australia.



Introduction. Pharmacists have previously been involved in coordinating the logistics and ensuring the supply of medications in the event of a disaster. Over the last two decades, there has appeared in the literature 'poorly documented' new roles that pharmacists have undertaken in disasters. (Ford et al. 2013; Young 2005). However, the acceptance of these roles for pharmacists by the disaster health community is not known.

Aims. To determine the global opinion of the disaster health community as to the roles pharmacists could be undertaking in disasters in addition to logistics and supply chain management.

Methods. Quantitative survey released at the World Association for Disaster and Emergency Medicine (WADEM) 20th Congress from 25th – 28th April 2017, in Toronto, Canada. Data analysed using SPSS software.

Results. 126 surveys were completed out of 222 handed out (56.8%). The majority of respondents (96.7%) believed pharmacists had a role in disasters additional to the logistics and supply chain management. Out of 11 roles provided in a 5-point Likert scale, eight roles received 72.4% or higher 'agree or strongly agree' rating. The other three roles received equal neutral to 'agree or strongly agree' ratings. Lack of understanding of a pharmacist's roles and capabilities was the highest described barrier (28.9%), preventing pharmacists from being included in disaster health teams.

Discussion. The disaster health community agreed pharmacists have roles in disasters in addition to the all-important logistics and supply chain management. When provided with different roles pharmacists have performed in the literature, the disaster health community agreed pharmacists could undertake most of the roles listed. However, also named were several barriers that could be the reason pharmacists aren't currently included in disaster health teams.

607 How do health professionals perceive medicinal cannabis? Results of a systematic review

Kyle M Gardiner[1], Janie Sheridan[1,2], Judith Singleton[1], Gregory Kyle[1] Lisa Nissen[1]. Queensland University of Technology[1], Brisbane, QLD, Australia; University of Auckland[2], Auckland, New Zealand.

Introduction. The number of jurisdictions allowing access to medicinal cannabis has been steadily increasing since the US state of California introduced legislation in 1996. As of 2017, Australian citizens can legally access medicinal cannabis. Unlike jurisdictions such as California, the authorisation and supply medicinal cannabis in Australia is tightly controlled. This uniquely places Australian health professionals at the forefront of therapy.

Aims. To conduct a systematic review exploring the existing primary literature focusing on the perceptions, concerns and knowledge of health professionals regarding medicinal cannabis.

Methods. PubMed, EMBASE and Scopus were searched for articles indexed up to the 31st March 2017 (English language and studies involving humans only). Inclusion criteria were (a) primary research findings; (b) participants were health professionals (c) the study considered 'medicinal' cannabis. Exclusion criteria were: (a) study indexed as an abstract, editorial, commentary or review; (b) the study considered 'recreational' cannabis; (c) participants were students or non-health professionals. Duplicate entries were removed and remaining articles were screened against title, abstract and keywords, followed by full text review of eligible articles.

Results. Of the 2751 articles originally retrieved, 57 underwent full-text review and 18 of these were included. A major similarity among these studies was a high degree of support for medicinal cannabis by health professionals. Irrespective of these attitudes, significant concerns and barriers towards uptake existed. Six subthemes describing barriers and concerns were identified: 1) knowledge, 2) education, 3) availability of information, 4) public health, 5) safety and 6) current legislation. A lack of knowledge was reported by most irrespective of profession or expertise.

Discussion. The literature suggests that although there is a high degree of support for medicinal cannabis, considerable barriers and concerns have the potential to influence health professional decisions, potentially reducing access to treatment for those in need. These results demonstrate that barriers and concerns need to be addressed, in particular, a lack of knowledge, a desire for more education and the availability of knowledge. Subthemes allow us to focus on developing interventions to mitigate these concerns and barriers.¶

608 Community pharmacists' perception of their role in primary mental health care

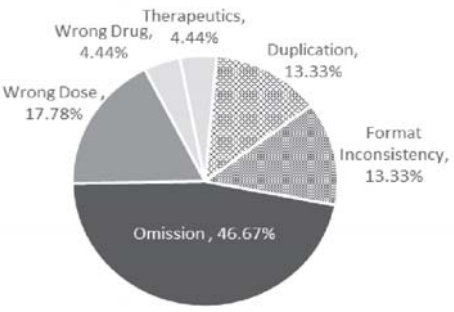
Mary A Wong, Caroline J Morris, Eileen M McKinlay, Dept Primary Health Care and General Practice, Univ of Otago, Wellington, New Zealand.

Introduction. Rates of mental health-related issues continue to rise in New Zealand, particularly for Maori and Pacific peoples. In recent years there has been an increased focus on primary mental health care to improve access and outcomes for those with mild to moderate conditions. As part of primary health care, community pharmacists can contribute towards this goal. The role of the community pharmacist has evolved over several decades from primarily a supply function to providing clinical pharmacy services including drug information and assisting in medicines optimisation to improve patient outcomes.
Aims. To explore community pharmacists' perception of their role in primary mental health care. Specifically, to identify the services that community pharmacists provide for those with mental health issues and the barriers and facilitators to providing mental health care.
Methods. A qualitative study that involved semi-structured, face-to-face, audio-recorded interviews with 15 practising community pharmacists throughout New Zealand including a broad demographic mix was undertaken. Interviews were transcribed verbatim, coded and analysed using a thematic approach.
Results. Community pharmacists believe that they have an important role to play in primary mental health care. There is, however, a wide range and variation in services provided. These spanned from simply dispensing prescriptions with no patient interaction to all-encompassing patient centred care. Barriers to service provision included lack of time, funding and training; difficulties with privacy and confidentiality in the pharmacy setting; stigma related to mental health.
Discussion. Community pharmacists hold diverse views about their role in primary mental health care. Some describe patient centred care while others describe a limited role and the significant challenges they face. They all endorsed the importance of the long-term relationships community pharmacists hold with patients and other health professionals in delivering effective care to this patient group.

609 Electronic prescribing of insulin with Medications Management, Anaesthetics & Research Support (MARS)

Hua Bing Yong. Pharmacy, Princess Alexandra Hospital, Brisbane, QLD, Australia.

Aim. To identify challenges of insulin prescribing in a new electronic medicines management system at hospital.
Methods. A retrospective analysis of insulin errors during the first 2 months of MARS implementation in March 2017 was conducted. The reported errors were sourced from the hospital incident reporting system and pharmacist interventions. The apparent effectiveness of prescribing support tools such as the 'insulin charting reminder' and 'pharmacist admission note' were evaluated.
Results. The type of insulin charting errors (n=45) were identified. Omission errors (n=21) were largely due to insulin not being prescribed (90%) rather than missed administration (10%). 98% of the not prescribed insulin was due to failure to re-chart after the insulin order expired. New digital specific errors included duplication, format inconsistency, drug selection errors from the drop-down menu and dose typing errors. Duplication arose when more than one prescriber ordered the same dose whereas format inconsistency was reported as a lack of knowledge of how to prescribe insulin in MARS, resulting in suboptimal orders. Anecdotally, difficulties accessing BGL results while prescribing precipitated the failure to intensifying therapy for patients with high blood glucose levels.



The use of the 'insulin charting reminder' and 'pharmacist admission note' was evident in 98% of reported incidents. 54% of cases reviewed had more than one 'insulin charting reminder'. Multiple reminders increased the risk of error due to chart cluttering and reminder fatigue. 83% of 'pharmacist admission notes' recorded precise dosages, however, 17% of dosages lacked accessibility by clinicians as doses were recorded elsewhere.
Discussion. Electronic insulin prescribing can lead to medication errors despite decision support tools. Errors identified are being used to inform clinician education and system re-development to improve patient safety. Safer systems will aid digital conversions at other hospitals.¶

610 Prevalence of potentially inappropriate medicine use in older Australians living in residential aged care facilities. Hosam Bony[1], Renae Lloyd[1], Brianna Kinnear[1], Emilio Petito[1], Vijayaprakash Suppiah[1], Elizabeth Hotham[1] School of Pharmacy and Medical Sciences, University of South Australia[1], Adelaide, SA, Australia.

Introduction. Older Australians living in residential aged care facilities (RACF) may present with coexistence of multiple illnesses leading to complex medical issues. Additionally, physiological changes in the elderly can impact on the homeostasis, pharmacokinetics, pharmacodynamics and the handling of drugs, making this group more vulnerable to harmful effects, especially if polypharmacy is present. Potentially inappropriate medicines (PIMs) are medicines that can cause more harm than benefit. The use of PIMs in this growing population may contribute to further illness or exacerbations of existing medical conditions. Currently, various tools have been developed to aid healthcare professionals to screen for PIMs.
Aim. To assess and characterize the prevalence of potentially inappropriate medications (PIMs) according to the American Geriatric Society (AGS) 2015 updated Beers Criteria in a population of RACF residents.
Methods. Ethics approval was granted to recruit participants from three RACFs in Adelaide, South Australia between June 2015 and February 2016. The study involved the review of charts and documentation of prescribing/medical histories of those 65 years and over. Data analysis was conducted using descriptive statistics.
Results. Three hundred and fifteen charts were reviewed. Participants were taking 9.5 medicines on average with a total of 2946 regular medications for the cohort, 94.5% of them being taken daily. Upon analysing the medication data against the AGS 2015 Beers Criteria, it was determined that there was on average 1.9 PIMs per person, that 52% of the cohort had 2 or more PIMs and that 81% had at least 1 PIM.
Discussion. The AGS 2015 Beers Criteria identified a high frequency of PIMs in our study. The fact that 81% of the cohort had at least 1 PIM suggests that the majority in the cohort are potentially at serious risk of harm and that measures such as routine drug audits should put in place to detect PIMs before they become the source of illness or injury in these patient groups.¶

611 Comparison of the management of medicines in the older-aged living in different leasehold retirement villages Sheila A Doggrell, Faculty of Health, Queensland University of Technology, Brisbane, QLD

Introduction. We have previously shown that the older-aged living in a leasehold retirement village have a low adherence to medicines but a reasonable understanding of their medicines/illnesses (Doggrell 2013).
Aims. The aim was to determine whether this was a common finding among leasehold villages by assessing the management of medicines in another leasehold village, and comparing this with our findings in the original village.
Methods. We delivered flyers to individual homes, presented an introduction to the research at a morning tea for the residents. Subsequently, we door knocked at the homes in the new village. This contrasts with the previous study where management would only allow us to interview those who volunteered at the morning tea, not door knock. After we assessed the management of medicines by the older-aged living in the new leasehold village, using semi-structured interviews, we compared the findings with the original leasehold village.
Results. The 68 participants in the new leasehold retirement village were significantly younger than the 22 participants from the original village; 78 vs 82 years old, respectively. Using the Doggrell-Kairuz measurement of adherence, it was shown that more participants were adherent and unlikely to have problems with adherence in the next 6-12 months in the new (75%) than in the original leasehold retirement village (55%). Many other aspects of the management of medicines was similar between the two villages including numbers of prescription or OTC drugs used by individuals, percentage using blister packs, the commonest medicines used by individuals, and the percentage having a good understanding of their medicines/illnesses; with 64% having a good understanding in the new, compared to 59% in the original leasehold village.
Discussion. This comparison shows that the adherence to medicines by the older-aged can vary considerable between leasehold retirement villages. Age may be a factor in this, with the need for assistance in the management of medicines being greater for those with a mean age of 82, compared to 78 years old.

Doggrell SA (2013) Int J Clin Pharmac 35:546-9.
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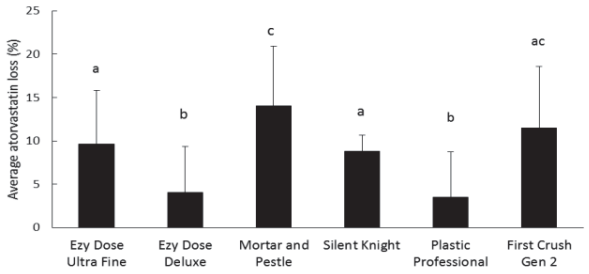
612 Tablet crushers: The investigation of powder loss using different sizes and brands of atorvastatin tablets

Mitchell Everlyn, Nahid Moghbel, Kathryn J Steadman. School of Pharmacy, The University of Queensland, Brisbane, QLD, Australia.

Introduction. Few comparisons have previously been made of tablet crushers in terms of efficacy of dose delivery.
Aims. To compare crusher efficiency in terms of loss of tablet weight and active drug concentration using atorvastatin tablets that vary in strength, size and brand.
Methods. Six tablet crushers were compared: two hand twisting crushers (Ezy Dose Ultra Fine and Ezy Dose Deluxe), one mortar and pestle (porcelain) and three crushers with disposable vessels (Silent Knight, Plastic Professional, and First Crush Generation 2). These were used to crush one tablet of each strength of Lipitor and 20 mg tablets of 5 other brands, and the quantity of atorvastatin recovered from the crusher was quantified using a validated UV-spectroscopy method. The experiment was replicated four times.
Results. Across all 9 tablet brand-strength combinations, the crushers that were consistently better than the others were the EasyDose Deluxe (3.5% loss), which is a hand-held twist-action crusher, and the Plastic Professional (4% loss), which involves pressing the tablet within two paper cups. The mortar and pestle was the worst option, with an average of 14% loss (range 5-28%). Across the four different strengths of Lipitor, losses were significantly higher for lower strength tablets, which were also smaller, with a lower proportion of excipients and lower hardness values than the higher dose tablets.



Discussion. The best crushing devices for atorvastatin tablets were not the same as those for paracetamol tablets determined in a previous study. Losses of atorvastatin ranged from essentially zero to a worrying 28%, and this was dependent on both crusher and tablet characteristics. ¶

613 Study of the 'Hospital Formularies' of different level hospitals based on the 'WHO - Essential Medicines List'

Bharat Gajjar, Barna Ganguly, Nilam Jani, Preyal Panchal. Dept of Pharmacol, Pramukhswami Medical College, Karamsad, Gujarat, India.

Aim: To compare hospital formularies of primary, secondary and tertiary level hospitals based on the 'WHO Essential Medicines List'.
Methods: A cross sectional observational study was conducted in the hospitals from primary, secondary and tertiary health care set ups. In each health care level, one hospital from Government, charitable (except primary) and private sectors was selected. From each of the eight hospitals, the hospital formulary was collected, after the permission of the hospital authority. Formularies were compared within the groups and with 'WHO Essential Medicines List'.
Results: Primary Health Care: Total number of drugs in the formulary of Government sector was 108 and the same of Private sector was 171.
Out of these, 74 (68.52%) drugs are from WHO EML in Government sector, while 81 (47.37%) drugs in Private sector.
Secondary Health Care: Total number of drugs in the formulary of Government sector was 147 and the same of Charitable and Private sectors were 314 and 1160 respectively. Out of these, 103 (70.07%) drugs are from WHO EML in Government sector, 113 (35.99%) drugs in Charitable sector, while 387 (33.36%) drugs in Private sector.
Tertiary Health Care: Total number of drugs in the formulary of Government sector was 209 and the same of Charitable and Private sectors were 944 and 730 respectively.
Out of these, 115 (55.02%) drugs are from WHO EML in Government sector, 287 (30.40%) drugs in Charitable sector, while 157 (21.51%) drugs in Private sector.
Conclusion: Effective management of 'Hospital Formularies' by the means of structuring 'Drugs and Therapeutic Committees', selection of drugs to be included in the formulary on the basis of WHO EML and adherence of clinicians' to the formularies are the mainstays for the rational, effective, safe and affordable health services to the patients.
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614 How does perceived cost influence pharmacy patronage? A scoping review.

Bethany Grew[1], Carl R Schneider[1] & Stephen R Carter[1]. Faculty of Pharmacy, Univ of Syd, Sydney, NSW, Australia

Introduction. Retail business research has identified how customer perceptions of cost, quality and value drive purchase behaviour. In contrast, community pharmacy research lacks insight into how customers perceive cost and value and if this may influence pharmacy choice. An understanding of this relationship can benefit pharmacy owners by helping retain their client base, improving patient health outcomes and ensuring the financial viability of their enterprise in an increasingly competitive marketplace. An investigation into the literature's conceptualisation of this relationship is warranted.
Aim. The aim of this review was to explore what is known about pharmacy customers' perceptions of cost and value, and how these influence patronage patterns.
Methods. A systematic search of 4 databases was conducted with the addition of articles sourced from reference lists using a scoping review framework. The database search was reported in accordance with the PRISMA-P protocol. Thematic analysis was used to identify themes and subthemes relating to cost and value. The results were reported in terms of author name, date of publication, study location, study population, methods and key findings.
Results. Twenty-four studies were yielded which were qualitative and quantitative in nature. Cost and value were found to be key elements influencing pharmacy choice, reasons for switching pharmacies and loyalty intentions. Pharmacy customers perceived costs in terms of monetary, psychological, emotional and convenience-related sacrifices. Value was perceived in two ways. Relating to the perceived worth or utility of a product or service, or in terms of a trade-off between what the consumer receives and what they give up.
Discussion. As a range of perceived costs influence customer behavioural intentions, this literature review helps to inform pharmacies on how they might increase loyalty to their stores. Despite the finding that locational convenience is the greatest cost driver of pharmacy patronage, pharmacies may attempt to influence customer behaviour by minimising unfixed costs to the consumer such as price and time costs, as well as improving patient care.

615 Improving Outcomes in Type 2 Diabetes Patients Using a Pharmacist Diabetes Intervention Tool

Shamala Ayadurai[1], V. Bruce Sunderland[1], Lisa B.G.Tee[1], Siti Norlina Md.Said[3], H. Laetitia Hattingh[1, 2] Curtin University, Perth[1]; Griffith University, Queensland[2], Hospital Sultanah Aminah, Johor, Malaysia[3].

Introduction. Pharmacists' contributions to the improvement of diabetes patients are well documented. However, there is little on pharmacists following a structured approach in the management of diabetes patients.
Aims. The aim of this study was to determine the effectiveness of a multifactorial evidence-based diabetes intervention tool in the delivery of quality diabetes care.
Methods. A tool to facilitate structured diabetes care, the Simpler™ tool, was validated for content, format and design by diabetes experts from Australia and Malaysia through the Delphi method. A two-hour training package to compliment the tool was developed and piloted among 12 pharmacists from Australia and Malaysia. The tool's effectiveness in supporting pharmacists to make interventions was subsequently evaluated during a 6 month, parallel, multi-centre randomized controlled trial among patients in Malaysia comparing those who received Simpler™ interventions with usual care. Pharmacists without formal diabetes qualifications were recruited and upskilled through online training modules on the application of the Simpler™ tool. Patients attending primary care clinics were then randomised to 1) receiving care from the pharmacists who applied the tool (n=55) and 2) patients receiving usual care and dispensing services (n=69).
Results. The Simpler™ intervention arm reduced HbA1c significantly by 1.59% (95%CI: -2.2, -0.9) compared with 0.25% (95%CI: -0.62, 0.11) in the usual care arm, (P=<0.001). In addition, there were significant improvements in systolic blood pressure: (-6.28; 95%CI: -10.5, 2.0; p=0.005) and health related quality of life (-1.75; 95%CI: -2.52, -0.97; p<0.001). The most common medication related problems were patients' *non-adherence* (n=135, 45%) followed by *sub therapeutic dose* (n=65, 22%) and *needs additional therapy* (n=52, 17%). Pharmacists worked in collaboration with doctors to add medications (n=23, 46%) and implement dosage changes (n=17, 34%).
Discussion. The Simpler™ intervention tool facilitated delivery of evidence-based structured diabetes management and improved clinical and quality of life outcomes. This study demonstrates the benefits of the Simpler™ tool to support primary healthcare pharmacists in identifying and conducting evidence based diabetes interventions.
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616 Complementary and alternative medicine (CAM) use in cancer patients commencing new chemotherapy

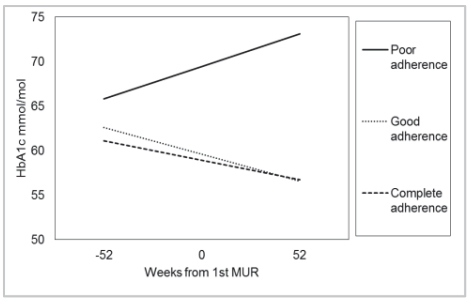
Karly M Huber[1,2,3]. Pharm Dept, Gold Coast Hosp and Health Service[1], Southport, QLD, Australia; School of Pharm and Pharmacol, Griffith Univ[2], Southport, QLD, Australia; Quality Use of Medicines Network[3], Southport, QLD, Australia.

Introduction. CAM-chemotherapy drug interactions may result in significantly harmful consequences by, either reducing efficacy or increasing toxicity of the intended chemotherapy regimen.
Aims. To determine CAM use in cancer patients commencing new chemotherapy regimens and whether CAM(s) reported could interact with the prescribed treatment.
Methods. Forty-five patients with a diagnosis of cancer and commencing a new chemotherapy treatment in a large teaching hospital day therapy unit were interviewed regarding current CAM usage. The Natural Medicines Comprehensive Database was utilised to perform an interaction check for each patient reporting CAM use. Study participants were provided with recommendations regarding the safe use of reported CAMs during chemotherapy treatment.
Results. Thirty-six percent of study participants were taking CAMs at the time of commencing chemotherapy, consuming between 1 to 14 products. Furthermore, CAMs that have the potential to interact with chemotherapy treatments were being consumed by 50% of CAM using patients. The majority of this group (69%) were taking CAMs known to have antioxidant properties, which have the potential to oppose the anticancer effect of some chemotherapy agents, such as anthracyclines. Thirty-eight percent of patients reporting CAM use were taking CAMs that could affect CYP450 enzymes that metabolise medications in their treatment protocol. Seventy percent of these CAMs had the potential to either inhibit or induce CYP3A4.
Discussion. Cancer patients being treated with new chemotherapy regimens use CAMs, some of which may interact with chemotherapy regimens and potentially compromise treatment outcomes. It is imperative these patients receive information regarding safe CAM use in chemotherapy. The development of standardised patient education would be beneficial to enable patients to make more informed decisions when deciding to use CAMs during chemotherapy treatment.

617 Are pharmacists' estimates of medication adherence related to HbA1c levels in people with type 2 diabetes?

Mangesh D. Kharjul[1], James A.Green[1], Rhiannon Braund[1]. School of Pharmacy, University of Otago, Dunedin, New Zealand.

Introduction: Providing individualized adherence support to people receiving oral hypoglycemic medications is expected to enhance clinical outcomes for people with diabetes [Sabate E, 2003]. However, there have been limited studies in real world settings to measure this. This study uses data collected in a natural setting.
Aim: To determine if medication adherence scores (1&2=poor, 3=good & 4=complete adherence) determined during a Pharmacist-led adherence support consultations (Medication Use Review and Adherence Support Service (MUR), New Zealand) are related to measured HbA1c levels over time.



Methods: Adherence support records were obtained from the providers of this service. Patient information was extracted to compile their visit dates, adherence scores, pathology testing date and biomarker (i.e. HbA1c) levels. Data was available for 86 people receiving oral hypoglycemic medications. Data were analyzed descriptively with Microsoft Excel and inferentially using IBM SPSS. Generalized estimating equations were used to explore the change in HbA1c over time, and its relationship to the adherence scores.
Results: People with poor adherence had average HbA1c levels over ~ 1% (11 mmol/mol) higher than those with complete adherence (the reference category), B =11, p = 0.014, but there was no difference between people with good & complete adherence, B = 0.7, p = 0.8. There was a marginal trend for a slight decrease with time of HbA1c levels, B = -0.04, p = 0.08, but this was qualified by an interaction between adherence level and time B= 0.11, p = 0.009 (Figure). Discussion: People who were assessed as having low adherence by pharmacists had significantly higher HbA1c levels, which continued to increase over time. Inadequate monitoring of HbA1c was also observed.

Reference: Sabate E (2003) ed. Pp 71-81, World Health Organization, Geneva, Switzerland¶

618 Developing a screening tool to identify people with swallowing difficulties of solid oral medicines

Simon YM Wong[1], Kathryn J Steadman[1,2], Lisa M Nissen[1], Julie AY Cichero[1,2], Jose Manuel Serrano Santos[1], Esther TL Lau[1]. School of Clinical Sciences, Queensland University of Technology[1], Brisbane, QLD, Australia; School of Pharmacy, University of Queensland[2], Brisbane, QLD, Australia.

Introduction. Swallowing solid oral medicines (e.g. tablets and capsules) is opposing the natural instinct of chewing food before swallowing. People who find it difficult to swallow tablets or capsules may not necessarily have an issue with swallowing food and drink. Existing screening tools for swallowing difficulties do not contain components that are important for identifying people who only have trouble with swallowing tablets and capsules.
Aims. To develop a screening tool for identifying people who require further investigations into their swallowing difficulties (true dysphagia), or those who may only need brief training on how to swallow tablets or capsules safely and effectively.
Methods. A three round modified Delphi with healthcare professionals involved with medicines and/or phobias was used to generate the screening components. Participants then ranked questions that best addressed each screening component. Group consensus for each component and question was analysed quantitatively by percentage of agreement. The importance of question rankings was compared by measuring Kappa values to observe trends in how the Delphi process impacted on the participants' views.
Results. A total of 13 healthcare professionals (pharmacists, general practitioners, speech pathologists, nurses, psychologists, radiographer) participated in the rounds. A screening tool in the form of an 8-item questionnaire was generated. Group consensus was shown by increasing agreement percentages, and stability was demonstrated by a trend of increasing Kappa values.
Discussion. This newly developed screening tool may be useful for identifying people who only have difficulties with swallowing tablets and capsules. Further research is needed to study the feasibility and validity of the screening tool.

619 Dose Administration Aids - How Useful do Patients Think They Are?

Esther TL Lau[1], J Manuel Serrano Santos[1]. Discipline of Pharmacy, School of Clinical Sciences, Queensland University of Technology (QUT)[1], Brisbane, QLD, Australia.

Introduction. Dose administration aids (DAAs) such as a Webster-pak or pill organiser, are frequently recommended to help patients manage their medication regimens, and to improve their medication adherence. Many community pharmacies also provide a DAA packaging service. However, research has suggested that use of DAAs do not encourage health literacy, nor patient self-efficacy in managing their own medicines and medical conditions.
Aims. The aim of this project is to investigate the perspectives and experiences of users of DAAs (i.e. either patients and/or carers), on how useful they find the DAAs to be for managing medicines.
Methods. Participants were recruited from a convenience sample of purposively chosen community pharmacies to achieve variation in pharmacy and consumer demographics, and to ensure that the pharmacies provided a DAA service. The perceptions and experiences of consumers using DAAs were investigated via a questionnaire which consisted of 11 questions, using a 5-point Likert scale with the anchors "Strongly Agree" to "Strongly Disagree". The questions investigated the respondents' opinions on DAAs, the amount and frequency of their medication usage and basic demographic data.
Results. A total of 124 patients or carers from 8 different pharmacies in Brisbane, Australia completed the questionnaire. Approximately 50% of the respondents were over 65 years of age. Almost all respondents found it took little effort to get used to the DAA, and agreed the DAA was helping them to manage their medication. Most participants were also confident in identifying the correct compartment from which to take their medicine and also agreed that the naming, labelling and packaging of the DAA helped them identify each of their medications. However, only two-thirds of the respondents were confident in being able to identify the exact medication in their DAA if a change were to occur.
Discussion. DAAs are useful for helping many patients with managing their medications. However, pharmacists have an important role to play in providing information to patients about the use of DAAs, particularly when any changes occur to any of the medicines being packed. This is important to help improve patient health literacy, and patient self-efficacy in managing their medicines and medical conditions.¶

620 Factors influencing non-adherence among people living with chronic health conditions in Australia

Amary Mey[1], Robbie Devlin[2], Shai Dukie[1], Sohil Khan[1], Andrew K Davey[1], David Plummer[3]. School of Pharmacy and Pharmacology, and Quality Use of Medicines Network, Griffith University[1], Gold Coast, QLD, Australia; Gold Coast Psychiatry[2], Gold Coast, QLD, Australia; College of Public Health, Medical & Veterinary Sciences, James Cook University[3], Townsville, QLD, Australia.

Introduction. Non-adherence to prescribed medications among people living with chronic health conditions is linked to adverse outcomes at both the individual and societal levels.[1, 2] However, knowledge about who is most at risk of non-adherence is lacking.
Aims. To explore relationships between participants' demographics, health status, prescription and non-prescription medication use and non-adherence to prescribed medications.
Methods. The study utilised data from the 2016 National Survey. Descriptive statistics were used to report on frequencies, generalised linear models used to examine relationships between patient variables and their non-adherence to prescribed medications.
Results. Of the 1217 respondents, the majority (58.7%) reported living with at least one chronic health condition, with88.4% of whom reported using at least one prescribed medications and 82.9% reported using at least one non-prescription medications. People with co-existing chronic health conditions are significantly less adherent to prescribed medication if they were over the age of 45, the likelihood increasing with increasing numbers of non-prescribed medications used, both were significant at the $p<0.001$ level.
Discussion. Initiatives aiming to optimise outcomes for people living with chronic conditions should target those in older age groups and living with co-existing chronic health conditions, and take into consideration their prescription and non-prescription medication use.

[1] Iuga AO, McGuire MJ. Adherence and health care costs. 2014;7:35-44.
[2] Australian Government. Australian Institute of Health and Welfare. Australia's health 2016. Canberra2016. Available from: http://www.aihw.gov.au/publication-detail/?id=60129555544&tab=2.

621 Medication information and supply behaviours in elite athletes.

Lily Ngu[1], Bronte Librizzi[1], Michael Ricciardello[1], Amy Street[1], Rhonda Clifford[1], Carmel Goodman[2], Peter Peeling[2,3], Sandra Salter[1]. [1]Pharmacy Division, School of Allied Health, The University of Western Australia, Perth, WA, Australia. [2]Western Australian Institute of Sport, Perth, WA, Australia. [3]School of Human Sciences, The University of Western Australia, Perth, WA, Australia.

Introduction. Sports pharmacy is an emerging area of pharmacy practice. Elite athletes use over-the counter (OTC) medications more often than the general population of the same age. Elite athletes are bound by strict rules around medication and supplement use, with doping and performance issues of equal importance.
Aims. To identify athlete behaviours in obtaining prescription and non-prescription medications, and their use of, and trust in, pharmacists in such processes.
Methods. This was a cross-sectional study of athletes affiliated with a state-based sporting institute. A 39-item electronic survey was developed, validated and disseminated in person at the institute during August-September 2017. The survey examined broad demographics, how athletes obtain prescription and non-prescription medications and information, and the involvement pharmacists may play in their care. Data was analysed descriptively.
Results. Overall 99 athletes aged 18 years and over completed the survey. In the past 6 months, n=91 (91.9%) athletes obtained medications (n=55 (55.6%) obtained both prescription and non-prescription medications; n=15 (16.5%) and n=21 (23.1%) obtained only prescription or non-prescription medications respectively). Of medications obtained, most were sourced from a pharmacy (97.1% of athletes obtained prescription medications and 85.5% non-prescription medications; 31.2% obtained non-prescription medications from a supermarket). Considering medication information, n=12 (12.1%) and n=63 (63.6%) would always or sometimes ask the pharmacist for information. Level of trust in the information provided by the pharmacist was predominately high or moderate (n=33 (33.3%) and n=56 (56.6%) respectively). Forty-one athletes (41.4%) thought that pharmacists could play a role in their medication management.
Discussion. Most athletes obtained prescription or non-prescription medications in the last 6 months, with pharmacy the most common source of supply. Athletes identify and trust pharmacists as sources of information with the potential for them to play a role in their medication management. The suitability of pharmacists for this role must be examined.¶

622 Healthcare and pharmacy service provision for Pakistani migrants residing in developed countries: A systematic review

Ahsan Saleem, Jasmina Fejzic, Kathryn J Steadman. School of Pharmacy, The University of Queensland, Woolloongabba, QLD, Australia.

Introduction. There has been a growing body of evidence acknowledging that healthcare and pharmacy services provision for migrants, as well as their access of these services, may be influenced by various factors. Understanding the existing dynamics around migrant service access and decision-making may assist health professionals in optimising their service provision in an informed, efficient, and culturally sensitive manner.
Aims. A systematic review of literature to explore the factors influencing healthcare and pharmacy services provision for Pakistani migrants residing in developed countries.
Methods. A comprehensive literature search was conducted using PubMed/Medline, Scopus, EMBASE, Web of Science and CINAHL from the date of inception of databases to search date (15th August 2017), using selective keywords. The initially searched citations were screened to remove duplications. After duplication removal, titles and abstracts of articles were screened to exclude irrelevant articles. The full-texts of remaining articles were retrieved and assessed against the eligibility criteria for inclusion into the review. Two reviewers (AS & JF) independently applied the eligibility criteria and discrepancies were resolved by discussion and consensus of all authors.
Results. The search strategy yielded 2424 articles, of which, 34 studies met the inclusion criteria. The thorough assessment of selected studies revealed that the healthcare and pharmacy services utilisation by Pakistani migrants were influenced by their language proficiency, access and affordability of healthcare, preference for traditional and alternative medicines, cultural and religious beliefs, and support from family and friends.
Discussion. This review highlighted that the healthcare and pharmacy services used by Pakistani migrants tend to be influenced by individual, cultural, as well as health system factors. It is important that healthcare professionals are aware of these characteristics when designing and providing care for migrant populations.¶

623 Piloting a novel observational technique for the administration of medicines to children in paediatric wards

Jose Manuel Serrano Santos[1], Suzanne Williams[2], David Kavanagh[3], Steven James Watson[4], Adrienne Hudson[2,5]. School of Clin Sciences, Queensland Univ of Technology[1], Brisbane, QLD, Australia; School of Nurs, Queensland Univ of Technology [2], Brisbane, QLD, Australia; School of Psychol & Counselling, Queensland Univ of Technology[3], Brisbane, QLD, Australia; Dept of Psychol, Lancaster Univ[4] Lancaster, UK; Children's Health Queensland Hospital and Health Service, Brisbane, QLD, Australia[5].

Introduction: The administration of oral medication to ill children in hospital is well recognised as a challenging process for both nurses and parents. The child is often unaware of the purpose of the medication and may be reluctant to take unpleasant-tasting tablets and syrups, compounding the problem of lack of adherence to treatment in addition to all the well-recognised challenges faced by nurses when administering medication. This puts nurses at the front-line of the medicines management chain when children are admitted to hospital. The aim of this study is to pilot a novel observational technique to identify errors and patient challenges in the administration of oral medication to paediatric patients by nurses.
Methods: This cross-sectional descriptive study applied a novel structured observational technique in which nurses' practices and patients' reactions were explored. The novelty of the tool is supported by the addition of three variables and a scale of acceptability of the medication to a design previously tested in other studies. The single-centre study was conducted in wards of a children's hospital in Brisbane, Australia. The participants were registered and enrolled nurses that administer medication to ill children in the hospital. The number of medicines administered to patients will be recorded along with the number of times that the administration process could be improved. Any deviations from recommended practice will be classified as Medication Administration Errors (MAEs)
Results: The preliminary data collected about the social interaction with the patient will be analysed descriptively and will incorporate new variables to the acceptability of medication. The likely link between MAEs and acceptability of the medication will also be explored.
Discussion: The findings from this study will provide an opportunity to identify acceptability variables that can impact the way that children receive medication in the clinical environment and in their own homes, and to inform the design of educational interventions customised to those practices in a paediatric care.¶

624 Evaluation of antimicrobial use in a tertiary care hospital by using specific indicators: A prospective, observational study

Siavash Shahbazi Nia[1], Shobha R. H. Hiremath[1,2]. Pharmacy Practice, Al-Ameen college of pharmacy[1], Bangalore, KA, India; Pharmacy Practice, Al-Ameen college of pharmacy[12], Bangalore, KA, India.

Introduction. The discovery and usage of antimicrobial drugs is one of the most important and significant contributions to therapeutics in the 20th century. Apart from being very frequently used, they are often misused. The use and misuse of antimicrobial agents needs to be evaluated since misuse of antimicrobials increases the risk of antimicrobial resistance while management and use of antimicrobials have clinical, economic, and environmental implications.
Aims. This study was designed to assess the pattern of antimicrobial prescriptions, to identify the most common problems with antimicrobials prescription and to apply the various antimicrobial use indicators to check the appropriateness of antimicrobial prescribing pattern.
Methods. A hospital-based study was carried out at St. Philomena's hospital located in Bangalore. Ethical committee clearance was obtained from the hospital before starting the study. The research student attended ward rounds on a daily basis and collected the cases, which have been prescribed with antimicrobial agents. Both empirically prescribed antimicrobials as well as the antimicrobials prescribed after culture sensitivity test were included. Specified indicators were applied and the collected data was analyzed
Results. The results of this study indicate that women were slightly more vulnerable than men in developing infectious diseases who were majorly above 60 years of age. In this study, it was found that antibiotics were the most common type of antimicrobials prescribed among which cephalosporins and fluoroquinolones were the most common class of antibiotics used. Antifungals (azoles) and antivirals (anti-influenza) were the next most common type of antimicrobials prescribed. It was also observed that LRTI was the most common infectious disease diagnosed in these patients. In this study, various indicators were also applied to evaluate the use of antimicrobial agents and it was found that the use of antimicrobials was not appropriate.
Discussion. The use of antimicrobials was evaluated and it was found that there is a need to promote rational use of antimicrobials, as irrational use would lead to antimicrobial resistance.¶

625 Does medication increase the risk of infection burden in residential aged care?

Mohammad Shohel, Jeffery Hughes, Lynne Emmerton. School of Pharmacy, Curtin University, Western Australia.

Introduction. Rational use of antibiotics ("antibiotic stewardship") is required to reduce the development of antibiotic resistance. One less-studied focus of antibiotic stewardship is the use of medications that reduce a person's immunity, thus increasing infection risk and antibiotic prescribing. Aged care residents are vulnerable to infection due to their multiple medications, comorbidities, and numerous environmental and physiological factors.
Aims. To determine the association between medication use and infection risk in the elderly.
Methods. A retrospective case-control study was conducted to evaluate medication-related factors associated with antibiotic use by aged care residents. Online records of 726 (375 Case and 351 Control) residents of The Bethanie Group Inc. aged care facilities were evaluated from 1st January 2015 to 31st December 2015. The Case group comprised residents who had at least one incident of infection, as indicated by a documented diagnosis and/or short-term use of antibiotics. Logistic regression determined factors associated with the incidence of at least one infection during 2015; independent variables included medication groups, medical conditions and gender.
Results. The most common infections were urinary tract infection (45.9%) and respiratory tract infection (38.9%). The most commonly prescribed antimicrobials were cephalosporins (33.9%) and penicillins (25.4%). Benzodiazepines (OR:1.78, 95%CI:1.1-2.7), antiepileptics[a] (OR:1.62, 95%CI:1.0-2.5), antidepressants[b] (OR:2.21, 95%CI:1.3-3.5) and tricyclic antidepressants (OR:2.98, 95%CI:1.6-5.5) showed statistically significant association in the increased risk of infections in multivariate analysis.
Discussion. Benzodiazepines and certain classes of antiepileptics and antidepressants were associated with increased risk of infections in aged care residents. This study demonstrated the need for rational prescribing of medications that contribute to increased infection risk, and informs an educational intervention focusing on medication review for at-risk elderly.
[a] Antiepileptics: pregabalin, valproate, carbamazepine, lamotrigine, gabapentin, phenytoin, levetiracetam, lacosamide, levetiracetam
[b] Antidepressants: mirtazapine, moclobemide, agomelatine
OR, Odds Ratio; 95%CI, 95% Confidence Interval ¶

626 Measuring menopause symptoms: a scoping review of existing tools.

Anna J Kaluzny[1], Christina M Dennis[1], M Joy Spark[2]. Department of Pharmacy, LaTrobe University[1], Bendigo, VIC, Australia; School of Science and Technology, University of New England[2], Armidale, NSW, Australia.

Introduction. Menopause symptoms have a significant impact on women's well-being and quality of life. A variety of menopause symptom tools have been used to investigate the effect of interventions on menopause symptoms limiting the ability to combine results in meta-analyses.
Aims. To identify the tools currently being used to measure menopause symptoms.
Methods. A scoping review was performed to identify tools used to assess menopause symptoms over the last five years. Four databases (EMBASE, Medline, PubMed and Scopus) were searched using the terms (menopause symptoms OR menopause women OR menopausal symptoms OR menopausal women) AND (scale OR questionnaire). All identified studies that used a tool to assess menopause symptoms and assessed more than one menopause symptom were included. The most common tools are discussed and reasons for tool selection explored.

Tool	No. of items	No times used in last 5 years	No of languages
Menopause Rating Scale	11	96	19
Kupperman Menopause Index	11	54	6
Menopause-Specific Quality of Life Questionnaire	29	54	10
Greene Climacteric Scale	21	37	7

Results. Use of a tool to assess menopause symptoms was identified in 295 studies from 43 countries. These studies used 22 named tools and 16 unnamed tools. The 4 most common tools (Table) were used in 81% of studies. Researchers reported modifying the tool prior to use in 18 studies. Validation studies to prove validity and reliability in the language they are administered in was available for 81% of the named tools. Use of invalidated tools was justified because they were considered more suited to the specific population sample due to cultural and language reasons.
Discussion. The majority of studies (⅘) used one of 4 tools because they had been validated in the population and language of administration yet other authors (⅕) considered they needed to create their own tool. It appears that no one tool is adapted to suit all study samples and contexts, consequently there is a need to modify existing tools to improve suitability for specific cultures and languages and to adapt to cultural norms and understanding of symptoms.

627 Completeness of Controlled Drug prescribing in regional NSW

Karlyn Wehlow [1], Anna Barwick[1], M Joy Spark[1]. School of Science and Technology, University of New England[1], Armidale, NSW, Australia.

Introduction. In Australia there are strict requirements for the prescribing of Controlled Drugs. Many of the requirements are consistent from state to state but there are some differences between jurisdictions.
Aims. To assess the level of completeness of prescriptions for controlled drugs in regional NSW.
Methods. Managing pharmacists in pharmacies in the Mid North Coast region of NSW were invited to participate in a prescription audit. All controlled drug duplicate prescriptions that were dispensed from the 1st January to the 30th April 2017 were assessed for completeness in accordance with NSW legislation requirements.
Results. Overall 511 prescriptions for controlled drugs from 3 pharmacies were included in the audit. Only 3% (16) of reviewed prescriptions were found to be complete. Of the Controlled Drug prescriptions requirements in NSW all 5 prescriber elements were included on 80%(411), the 2 patient elements on 93%(476), all 6 medication elements on 7%(38) and all 3 general elements on 89%(454) of the reviewed prescriptions. Only 51 prescriptions (10%) had repeats prescribed and of these only 30% (15) included the repeat interval. There were 24 prescriptions for psychostimulants and 80% (19) of these were endorsed with the appropriate code obtained from NSW Health. There were between 0 and 8 errors (*Md*=2, *IQR*=2-4) on the audited prescriptions. The errors were divided into two groups: omissions (range 0 to 8, *Md*=0, *IQR*=0-1) and medication requirements not handwritten (range 0 to 7, *Md*=2, *IQR*=1-3). Information was missing on 34%(172) prescriptions and medication information was not hand written on 83%(424) of prescriptions.
Discussion. Most audited prescriptions did not contain all elements required by NSW legislation. The most common reason for lack of completeness was that medication requirements were not handwritten on computer-generated scripts. The drug name, strength, form, quantity, directions and repeats (including none) are required to be handwritten to reduce the likelihood of forgery. Handwriting what has been printed on the prescription also provides the prescriber with an opportunity to review the prescription before giving it to the patient. Perhaps it is time to review Controlled Drug prescription requirements as very few prescriptions for Controlled Drugs were complete according to NSW legislation requirements.¶

628 Tablet crusher comparisons: usability testing by people with and without limited hand function

Su Vin Lee[1], Tammy Aplin[2], Kathryn J Steadman[1]. School of Pharmacy[1], and School of Rehabilitation Sciences[2], The University of Queensland, Brisbane, QLD, Australia.

Introduction. Tablets are crushed using a variety of devices: manual and electronic, exerting a flat press or rotating grinding motion, with or without disposable bags or cups.
Aim. To compare a range of tablet crushers for usability by people with and without limitations in their hand function and hand strength.
Methods. Approval was granted by the UQ Human Research Ethics Committee. 60 people without and 40 people with self-reported limited hand function were recruited. Hand function was assessed using the Arthritis Impact Measurement Scale (AIMS2) and hand strength by dynamometer. For each of 9 different crushers, participants attempted to crush a paracetamol tablet and then completed a Rapid Assessment of Product Usability and Universal Design (RAPUUD) validated questionnaire.
Results. Hand strength was not correlated with hand function, and the AIMS2 score was found to best distinguish participants with and without limited hand function. Two crushers failed during testing – the Minitwist with bags broke after 19 participants, and the electronic grinder stopped working after 58 participants had used it. Consequently 7 crushers were tested by all participants. The hand-held twist-action crushers with ergonomic grip scored highest in terms of usability. The lack of an ergonomic or triangular grip on the twist-action crushers reduced usability to a greater extent for participants with limited hand function. Crushers with cups and bags scored well for usability, and better if they were automatic, but once participants became aware of their high cost they were less likely to score them in their top 3 choices.
Discussion. The usability of different crushers was assessed from the point of view of personal use by people with and without limited hand function, and results may be expected to differ if tested by nurses involved in hospital or aged care medication delivery. The economical twist action crushers without separate bags or cups were generally found to have greater usability and were preferred by these participants. ¶

629 Management of non-healing mouth ulcer presentations in community pharmacies

Brigitte Janse van Rensburg[1], Katelyn Steele[1], Pauline J. Ford[2], Christopher R. Freeman[1], Meng-Wong Taing[1], [1]School of Pharmacy, University of Queensland, QLD, Australia; [2]School of Dentistry, University of Queensland, QLD, Australia.

Introduction. Oral cancer commonly presents as non-healing lesions/ulcers. Practice guidelines recommend referral to a general/dental practitioner for mouth ulcers persisting longer than 2-3 weeks. This project evaluated management and referral of non-healing mouth ulcer presentations by community pharmacy staff in the Greater Brisbane region.
Methods. Trained simulated patients visited 220 randomly selected community pharmacies within the Greater Brisbane region between March and May 2016. Mystery shoppers presented pharmacy staff with two standardised over-the-counter (OTC) non-healing (> 1 month) mouth ulcer scenarios: A direct product request (DPR) (n=110) or a symptom based request (SBR) (n=110). Results were documented and evaluated against Australian national pharmacy professional practice standards. Referral rates for pharmacy staff (pharmacist, pharmacy assistant or mixed – pharmacist and assistant) handling the interactions were also assessed.
Results. Australian pharmacy practice standards recommend pharmacy staff ask patients six key questions to enable informed decision making regarding appropriate treatment/advice. In the majority of interactions, pharmacy staff identified the patient and their symptoms (76.4%; 168/220 and 68.6%; 151/220 respectively). The remaining four questions relating to symptom duration, treatments tried, other medications and medical conditions were enquired in 32.3%, 52.7%, 30.5% and 27.3% of interactions respectively. Simulated patients were referred to the doctor/dentist in 11.8% (26/220) of all interactions.
Conclusions. Community pharmacy staff handling of non-healing mouth ulcer consultations was suboptimal compared to national professional standards. In particular, infrequent questioning regarding the duration of the non-healing mouth ulcer was likely to have resulted in low referral rates by staff. This study identifies the need for increased oral cancer awareness and education for community pharmacy staff in addition to re-enforcing the importance of practising according to professional standards to effectively screen for potentially neoplastic mouth ulcers/lesions.
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630 Chronic disease, medications & lifestyle: perceptions from a regional Victorian Indigenous Community.

Melissa Deacon-Crouch[1], Isabelle Skinner[2] and Joseph Tucci[1 1] Pharmacy & Applied Sciences, LIMS, La Trobe University Vic Australia [2] Psychological and Clinical Sciences, Charles Darwin University NT Australia.

Introduction. Poor medication management may contribute to the increased morbidity and mortality of Indigenous people in Australia. Yet while there is extensive literature about the perceptions of healthcare providers on this issue, there is limited information on the perceptions of Indigenous people themselves.
Aims. To investigate the perceptions of a group of Indigenous people attending a Victorian regional Aboriginal Health Service (AHS) with diagnosed medical conditions requiring medications, of their lifestyle, disease management and medication usage.
Methods. We used a co-research methodology in which Aboriginal Health Professionals (AHP) who worked at the Health Service were co-researchers with a team from La Trobe University, Victoria. The AHPs conducted individual interviews with a purposive sample of clients participating in chronic disease management programs in a culturally appropriate and competent manner using a semi structured *yarning* process. De-identified verbatim transcripts were coded for thematic analysis and for descriptive statistical analysis by SPSS. Themes were validated by cross check between members of the research group including the AHP research partners.
Results. Our results showed that the majority of participants perceived that changes in lifestyle factors such as diet, exercise, and smoking cessation would help improve their health. Most patients reported having been counselled on their medicines, and while the majority reported adherence and acknowledgement of the efficacy of their medicines, there was a lack of clarity regarding long term maintenance on regimens. Finally, while the majority reported taking OTC products, some did not see the need to inform their doctor about this, or chose not to.
Discussion. Chronic illness was perceived as common in families and community. Patients relied mostly on their health care professionals as sources for their drug information. Patients may have benefited from further counselling in the area of complementary and other OTC medicines, as well as on the necessity of maintenance of regimes for chronic disease management. Finally, lifestyle changes such as dietary improvements and smoking cessation were identified as areas that may assist in improving health.

631 Perceptions of credible drug information sources for Indigenous people attending a regional Aboriginal Health Service

Melissa Deacon-Crouch[1], Isabelle Skinner[2] and Joseph Tucci[1 1] Pharmacy & Applied Sciences, LIMS, La Trobe University Vic Australia [2] Psychological and Clinical Sciences, Charles Darwin University NT Australia.

Introduction. In Australia, there has been scant research into how Indigenous people source information on medications they are taking[1]
Aims. To investigate perceptions of Indigenous patients regarding sources of credible information on the medications they were prescribed.
Methods. Aboriginal Health Professionals (AHP) were co-researchers with the La Trobe University team. The AHPs conducted interviews with patients with chronic diseases in a culturally appropriate and competent manner using a semi structured *yarning* process. De-identified verbatim transcripts were coded for thematic analysis and descriptive statistical analysis by SPSS. Themes were validated by cross check between members of the research group including the AHP research partners.
Results. See table
Discussion. Further research is required to explore (i) whether such perceptions are widespread amongst Indigenous people in other metropolitan, regional and remote communities (ii) whether such perceptions are related to perceived level of expertise of the information provider (iii) whether such perceptions relate to the cultural competence with which counselling was undertaken.

Perceived credible sources of information about medications	% participants
Medical practitioners	65
Pharmacists	60
Aboriginal Health Professionals	35
Internet sites	35
Pharmaceutical Company Product Information Leaflets	20
Nurses	15

1.Tan A, Emmerton L & Hattingh H (2012) A review of the medication pathway in rural Queensland, Australia. *International Journal of Pharmacy Practice* 20:324–339