Annual Scientific Meeting
30th August – 1st September 2023

ASCEPT

Abstract and Programme Booklet

Contents

Sponsors

General Information

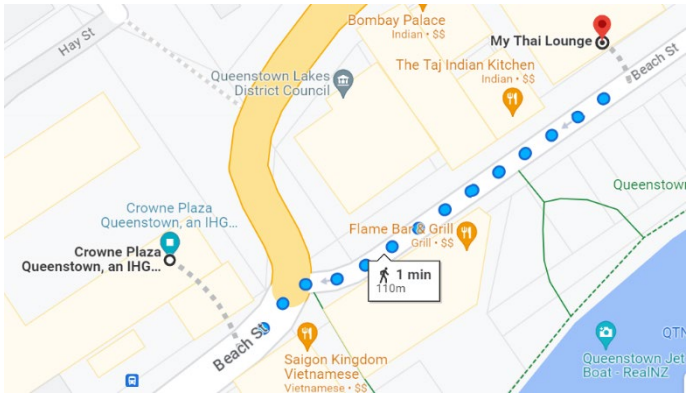
Welcome to the 2023 ASCEPT-NZ meeting, part of Queenstown Research Week. On behalf of the organising committee we hope that you have an enjoyable, informative and educational meeting.

Organising Committee Members:

Katie Burns (Chair) – University of Auckland
Matt Doogue (Secretary) – University of Otago, Christchurch
Jacqui Hannam (Treasurer) – University of Auckland
Hesh Al-Sallami – University of Otago, Dunedin
Jack Flanagan – University of Auckland
Michelle Glass – University of Otago, Dunedin

Conference Venue:

Crowne Plaza Hotel
93 Beach Street
Queenstown



Dinner Venue:

My Thai Lounge
69 Beach Street
Queenstown 9300

Invited Speakers

Associate Professor Nicola J Smith

Nicola leads the Orphan Receptor Laboratory at UNSW Sydney, where her team takes a multidisciplinary approach to orphan G protein-coupled receptors as potential cardiovascular drug targets. She prides herself on mentoring the future generation of scientists, with many receiving accolades during their time in her laboratory. Nicola is internationally recognised as a champion for research integrity, advocating for reproducibility and rigour in scientific research, and has been recognised for her research and outreach with numerous awards and fellowships. She currently holds leadership positions as ASCEPT Scientific Advisory Committee Chair and is a member of the Australian Cardiovascular Alliance Disease Mechanisms Flagship.

Professor Mike Dragunow

Mike is an internationally recognised neuropharmacologist, with research focuses on CNS drug discovery and development utilising human brain tissue microarray, human brain cell culture, high throughput devices and high-content analysis combined with molecular pharmacology methods. He was part of the team that first invented trofinetide for brain injuries (now FDA-approved for Rett's syndrome), and co-founded Neurovalida - a human brain-based drug target validation service.

Professor Arduino Mangoni

Arduino trained in Clinical Pharmacology, Cardiology and Internal Medicine in Milan, Boston and London. In 2003 he was awarded a PhD at King's College London and was appointed as Senior Lecturer in the Department of Clinical Pharmacology at Flinders University. He was promoted to Associate Professor in 2007 before taking up the Chair of Medicine of Old Age at the University of Aberdeen in 2010. In 2013 he returned to Flinders University as Professor of Clinical Pharmacology and Senior Consultant in Clinical Pharmacology and Internal Medicine. His research interests include repurposing of anti-inflammatory drugs for cardiovascular risk management and pharmacoepidemiology and drug safety in old age.

Dr Rachael Sumner

Rachael is a Research Fellow in the School of Pharmacy with a research focus on mechanism-informed rational drug selection and measuring brain-based pharmacodynamics in human clinical trials. Her current work includes a Phase 1 trial of microdosing LSD, and the follow-on Phase 2 trial determining if it is an effective treatment for depression. She has a particular passion for women's health and leads research on menstrual cycle related disorders. Her work primarily involves using electroencephalography (EEG) with computational modelling, and blood analyte measurements.

Conference Programme

DAY 1 – Wednesday 30th August 2023 – WELCOME FUNCTION	
18.30 – 18.35	**Welcome** Katie Burns *Chair of ASCEPT NZ*
18.35 – 19.30	**Registration opens.** Drinks, nibbles, and networking function

DAY 2 – Thursday 31st August 2023 – ANNUAL SCIENTIFIC MEETING	
08.30 – 09.00	**Registration opens. Tea and coffee available**
Welcome / Housekeeping	
09.00 – 09.10	**Katie Burns**
Oral Communications Session 1 – Chair: Jacqui Hannam	
09.10 – 09.30	The impact of allopurinol adherence patterns on outcomes in people with gout **Daniel Wright (A1)** University Of Otago
09.30 – 09.50	The Na+ K+ ATPase as a potential target for modulating neuroinflammation **Caitlin Oyagawa (A2)** University Of Auckland
09.50 – 10.10	Investigation of the interaction of proton-pump inhibitor drugs with capecitabine chemotherapy **Nuala Ann Helsby (A3)** University Of Auckland
10.10 – 10.40	Morning Tea
Student Presentations 1 – Chair: Katie Burns	
10.40 – 11.00	Activated yet in-active; the paradoxical effect of dasatinib on Lymphocyte Specific Kinase **Samantha Rickard (A4)** University Of Auckland
11.00 – 11.20	oCOm-21 Improves Haemodynamic Function and Enhances Ca2+ Sensitivity by a Heme-Dependent Mechanism **Fergus Payne (A5)** University Of Otago
11.20 – 11.40	Structure guided poly-pharmacology targeting the bacterial GHKL proteins to overcome antibiotic resistance **Te Xiao (A6)** University Of Auckland
11.40 – 12.00	The effect of alcohol consumption on blood glucose in young adults with type 1 diabetes mellitus **Amy (Yoonseo) Chung (A7)** University of Otago
12.00 – 12.20	The effect of compulsory indications in electronic prescriptions for cardiovascular medicines **Lorna Pairman (A8)** University Of Otago

12.20 – 13.20	Lunch
Symposium – Chair: Jack Flanagan	
13.20 – 13.50	Human brain neuropharmacology **Mike Dragunow (A9)** University of Auckland
13.50 – 14.20	The critical role of dimethylarginine dimethylaminohydrolase-1 (DDAH1) in modulating vasculogenic mimicry in cancer: current evidence and therapeutic opportunities **Arduino Mangoni (A10)** Flinders University
14.20 – 14.50	More than a Class A placebo? A randomised controlled trial of microdosed lysergic-acid diethylamide **Rachael Sumner (A11)** University of Auckland
14.50 – 15.10	**Discussion/Question Time**
15.10 – 15.40	Afternoon Tea
Oral Communications Session 2 – Chair: Ivan Sammut	
15.40 – 16.00	Investigating clozapine transport kinetics using radiolabelled drug; a lot of work to prove we picked the wrong assay **Katie Burns (A12)** University Of Auckland
16.00 – 16.20	A systems overview of the clinical data environment for evaluating medicines use in NZ Hospitals **Matt Doogue and Lorna Pairman (A13)** University of Otago
16.20 – 16.40	Use of R-Shiny Apps to Enhance Learning of Core Concepts in Pharmacology **David Reith (A14)** University Of Otago
16.40 – 16.50	Comfort Break
ASCEPT-NZ AGM	
16.50 – 17.50	**AGM**
	Break
Conference Dinner	
18.30 onwards	**My Thai Lounge**

DAY 3 – Friday 1st September 2023 – ANNUAL SCIENTIFIC MEETING

Student Presentations 2 – Chair: Hesh Al-Sallami	
09.00 – 09.20	Interruptive clinical decision support (CDS) alerts for improved prescribing: implications of prescriber overrides. **Milan Sundermann (A15)** University Of Otago
09.20 – 09.40	Prescribing Systems Alerts to Support Change in Funded ACE Inhibitors at Canterbury Hospitals **Kelvin Gong (A16)** Te Whatu Ora Waitaha Canterbury

09.40 – 10.00	Untangling the paradoxical dose-exposure-response relationship for allopurinol **Hailemichael Hishe (A17)** University Of Otago
10.00 – 10.20	Characterising the inotropic mechanism of action of oCOm-21 in isolated cardiomyocytes **Sam Nie (A18)** University Of Otago
10.20 – 10.40	Chemical proteomics approaches to elucidate the cytoprotective mechanism of compounds in human-brain derived pericyte oxidative stress models **Raahul Sharma (A19)** University Of Auckland
10.40 – 11.10	Morning Tea
ASCEPT Guest Speaker – Chair: Matt Doogue	
11.10 – 11.40	Orphan G protein-coupled receptors: pain points and opportunities **Nicola Smith (A20)** UNSW Sydney
Oral Communications 3 – Chair: Matt Doogue	
11.40 – 12.00	One inhibitor, two mechanisms? evidence for allosteric regulation of the lipid kinase PI3Kα **Jack Flanagan (A21)** University Of Auckland
12.00 – 12.20	The good and not so good of dose banding for dose individualisation **Stephen Duffull (A22)** Certara
12.20 – 12.30	Conference Close and Prizegiving
12.30 – 13.30	Lunch

Abstracts

A1: The impact of allopurinol adherence patterns on outcomes in people with gout

Daniel F.B. Wright[1], Toni J.F. Michael[2], Jian S. Chan[3], Matthew J. Coleshill[4], Parisa Aslani[2], Dyfrig A. Hughes[5], Richard O. Day[3],Sophie L Stocker[2]. Uni of Otago[1], Dunedin; Uni of Sydney[2], NSW; St. Vincent's Clinical School[3], Uni of NSW, Sydney; Black Dog Institute[4], Uni of NSW, Sydney' School of Medical and Health Sciences[5], Bangor Uni, Wales.

Aims. To determine the impact of allopurinol adherence patterns on target urate concentration achievement (<0.36 mmol/L), gout flares, and health-related quality of life (HRQoL) in people with gout.
Methods. Allopurinol adherence data from 31 gout patients were collected using electronic monitoring (MEMS®) for 1 year. Urate concentrations were self-monitored using a point of care device. Gout flares were self-reported. HRQoL was collected every 3 months using the EQ-5D-5L survey. Urate target achievement was defined as the proportion of days at the urate target. Pre-defined adherence patterns included: occasional or repeated sequential missed doses (≤2 followed by ≥30 or <30 doses taken) and occasional or repeated drug holidays (≥3 missed doses followed by ≥30 or <30 doses); OMD, RMD, ODH and RDH respectively. Participants were categorized based on the most common pattern(s) observed. The proportion of days at the target urate, overall adherence rate, and HRQoL scores were compared between adherence categories and the odds of gout flares determined.
Results. The median adherence was 91%. Fifteen people experienced ≥1 gout flare. Participants were assigned to five adherence categories: no missed doses (n=2), OMD (n=4), RMD (n=8,), OMD & RMD (n=10), and, RMD & RDH (n=7). People in the latter group recorded nearly half of the gout flares, spent less time at the urate target (28% vs 99%, p<0.0001) and had lower adherence (64% vs 96%, p<0.0001) compared to the other groups. HRQoL scores were not predicted by adherence patterns (p=0.9001), nor the odds of experiencing a gout flare (odds ratio 1.8, 95%CI 0.4-8.8).
Discussion. Individuals who took repeated allopurinol drug holidays only spent ~25% of the time at the urate target and had more gout flares. An understanding of common adherence patterns in people with gout will aid the development of interventions to medicine-taking behaviours most likely to impact outcomes.

A2: The Na^+ K^+ ATPase as a potential target for modulating neuroinflammation

Caitlin R M Oyagawa[1], Karren C Wood[1], Kevin Lee[1], Taylor J Stevenson[1], Woo Lee[1], Rebecca Johnson[1], Michael Dragunow[1]. Department of Pharmacology & Clinical Pharmacology, University of Auckland[1], Auckland, NZ.

Introduction. Neuroinflammation plays a considerable role in the pathology of numerous neurodegenerative diseases. Recent work has indicated that cardiac glycosides, selective inhibitors of the Na^+/K^+-ATPase, act as inflammatory-modulating drugs in human-derived brain cells of the blood-brain barrier (BBB) (1). However, the mechanism of action of these compounds is not yet known.
Aims. This study aimed to investigate the involvement of the Na^+/K^+-ATPase in the inflammatory-mediated effects of cardiac glycosides on human brain-derived cells.
Methods. Primary human brain-derived pericytes were treated with cardiac glycosides (Oleandrin and/or Digitoxin) and ATPase activity assays, or whole cell patch-clamp recordings were conducted. qRT-PCR was carried out to determine expression levels of Na^+/K^+-ATPase subunits in these cells. Individual α-subunit isoforms of Na^+/K^+-ATPase were knocked down with siRNA, and inflammatory paradigms, i.e. cardiac glycoside treatment followed by inflammatory stimulators such as TNFα & IL-1β, were explored.
Results. The anti-inflammatory activity of Digitoxin and Oleandrin occurred at concentrations that also inhibited Na^+/K^+-ATPase pump function. Pericytes express α1-3 isoforms of the Na^+/K^+-ATPase, and knockdown data indicated that α1 and/or α2, but not α3 are important for the immunomodulatory effects of cardiac glycosides.
Discussion. The anti-inflammatory effects of cardiac glycosides on human brain-derived pericytes are likely dependent on the inhibition of Na^+/K^+-ATPase pump function, and further understanding of the mechanisms underlying this phenotype may provide novel avenues for targeting neuroinflammation at the BBB.

A3: Investigation of the interaction of proton-pump inhibitor drugs with capecitabine chemotherapy.

Nuala Helsby[1], Soo-Hee Jeong[1], Edmond Ang[2], Sanjeev Deva[3]. School Medical Sciences, University of Auckland[1]. Whangaeri Hospital[2], Auckland City Hospital[3].

Introduction. Proton-pump inhibitor (PPI) drugs are widely prescribed to cancer patients to minimize chemotherapy-induced gastritis. There is increasing concern that PPI use leads to poorer outcomes for gastro-intestinal cancer patients treated with capecitabine. We are currently undertaking a randomized cross-over study to assess whether this is due to a pharmacokinetic interaction (ACTRN1260001317987). Capecitabine is a prodrug and conversion of the metabolite doxifluridine (DFUR) by thymidylate phosphorylase (which is present in tumours, macrophages and the liver) into 5-fluorouracil is key for its activity. Our aim was to also investigate whether PPI influence this activation step in colorectal cancer cells *in vitro* to ascertain if this is an additional possibility for this suspected drug-drug interaction.

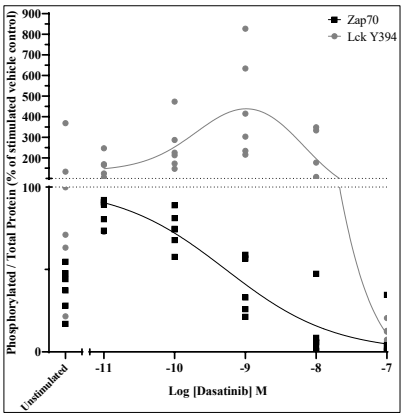
Methods Human colorectal adenocarcinoma (HCT116) cells were cultured for up to 72 hours with increasing concentrations of doxifluridine (DFUR, 0.005 µM - 5 mM) and increasing concentrations of pantoprazole, omeprazole or lansoprazole (60-260 µM). The effect of PPI on the cytotoxicity of DFUR was determined, concentration-dependent effect curves were generated, C_{50} calculated and isobologram analysis undertaken. Cell lysates were used to determine the kinetics of metabolic conversion of DFUR to 5-fluorouracil and the inhibitory effect of increasing concentrations of pantoprazole determined. Pharmacokinetics of capecitabine and its metabolites the first three patients in the interaction study were determined by ES-LCMS.

Results The PPI drugs decreased the viability of HCT116 cells (C_{50} 238, 234 and 91 µM, respectively). When combined with doxifluridine, all three PPI drugs resulted in an antagonistic effect on the viability observed in isobologram analysis since the combined effects were above the line of additivity. DFUR conversion into 5-FU was inhibited by pantoprazole in a concentration dependent manner. Initial pharmacokinetic analysis suggests a minor change in the renal clearance of DFUR in patients co-medicated with pantoprazole.

Conclusions The effect of PPI on the key precursor metabolite of capecitabine appears to be complex. Our pharmacokinetic study is ongoing and we continue to assess the metabolic effects of PPI on this pathway. Further work is needed to determine if these *in vitro* effects and small pharmacokinetic changes truly influence patient outcomes.

A4: Activated yet in-active; the paradoxical effect of dasatinib on Lymphocyte Specific Kinase

Samantha Rickard[1,2], Claire Wang[2,3], Chris Squire[2,4], Julie Spicer[2,3], Peter Shepherd[2,3,5], Jack Flanagan[1,2,3]. 1Department of Pharmacology and Clinical Pharmacology, 2Maurice Wilkins Centre, 3Auckland Cancer Society Research Centre, 4School of Biological Sciences, 5Department of Molecular Medicine and Pathology



Introduction. Lymphocyte specific kinase (Lck) plays a crucial role in T-cell mediated immune responses and is an important drug target for controlling T-cell based autoimmunity. Lck is recruited to the T-cell receptor (TCR) where it performs early phosphorylation events in the TCR signalling pathway. The multi-target kinase inhibitor dasatinib is a potent Lck inhibitor and blocker of T-cell function. While studying dasatinib, we discovered unexpectedly a bimodal effect on Lck phosphorylation at sites important to its catalytic activity.

Aims. To study the molecular pharmacology of dasatinib by investigating Lck phosphorylation status and TCR signalling in cells.

Methods: Jurkat and CCRF-CEM T-cells were treated with dasatinib at concentrations of 0.01 to 100nM with Lck phosphorylation at the activating (Y394) and inhibitory (Y505) sites and markers of TCR signalling monitored by western blot analysis. Molecular modelling was used to study drug-protein interactions.

Results. In both Jurkat and CCRF-CEM cells, 1nM dasatinib consistently caused hyperphosphorylation of Lck Y394 but not Y505 yet signalling downstream of Lck was inhibited at this concentration. At 100nM, dasatinib decreases Lck phosphorylation at both sites and completely blocks TCR signalling. An Lck-dasatinib binding model was created and used to identify other compounds that bind Lck in the same way and potentially also hyperphosphorylated Lck Y394.

Discussion. This study has identified paradoxical activation of Lck as a novel mechanism of action of an Lck inhibitor occurring at ultra-low concentrations. The paradoxical increase in activated Lck is not unique to Jurkat T-cells and does not rely on TCR stimulation indicating dependency on drug binding. Understanding how dasatinib promotes the phosphorylation state change and what binding mode is involved has important implications for the design of new compounds as well as providing insight into drug induced changes in the TCR signalosome.

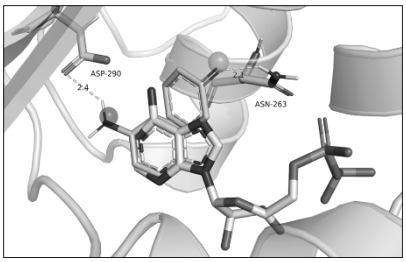
A5: oCOm-21 Improves Haemodynamic Function and Enhances Ca^{2+} Sensitivity by a Heme-Dependent Mechanism.

Fergus M Payne[1,2,3], Sam Nie[1,3], Gary M Diffee[4], Joanne C Harrison[1,3], James C Baldi[2,3], Ivan A Sammut[1,3]. Department of Pharmacology and Toxicology, University of Otago[1], Dunedin, New Zealand; Department of Medicine, University of Otago[2], Dunedin, New Zealand; HeartOtago, University of Otago[3], Dunedin, New Zealand; Department of Kinesiology, University of Wisconsin-Madison[4], WI USA

Introduction. Acute heart failure patients require inotropes for haemodynamic support. Inotropes increase contractile force by enhancing cytosolic Ca^{2+}, which can promote arrhythmias, prompting a demand for inotropes with little effect on Ca^{2+} flux. We identified that our CO-releasing prodrug oCOm-21, has a Ca^{2+} sensitising effect on skinned rat cardiomyocytes. Although this mechanism is unclear, CO can interact with myofilament proteins via a cytosolic heme interaction. We hypothesised that oCOm-21 requires free heme to induce an increase in myofilament Ca^{2+} sensitivity. Additionally, we examined whether this increased Ca^{2+} sensitivity occurred in intact oCOm-21 pre-treated hearts.
Aims. To identify whether CO release by oCOm-21 increases Ca^{2+} sensitivity via a heme-dependent mechanism and whether this increased Ca^{2+} sensitivity is conserved in cardiomyocytes isolated from oCOm-21 pre-treated hearts.
Methods. Left ventricular cardiomyocytes from male Sprague Dawley rats (320 – 360 g) were skinned in Triton X-100 and attached to a force transducer to allow myofilament contractile force to be measured as a function of pCa (-log [Ca^{2+}]). Cardiomyocytes were pre-treated with the heme scavenger hemopexin before treatment with oCOm-21 (10 μM) (9 cells/group). The Ca^{2+} concentration at which 50% of maximal force is produced (pCa_{50}), was derived and used to measure a change in Ca^{2+} sensitivity. Additionally, haemodynamic function was examined in Langendorff-perfused rat hearts treated with either vehicle or 10 μM oCOm-21 and subsequently cardiomyocytes were isolated and skinned to measure changes in Ca^{2+} sensitivity (n=5 hearts/treatment).
Results. Hemopexin reduced the Ca^{2+} sensitising effect of oCOm-21 (pCa_{50} 5.52 *vs.* 5.44 respectively). Langendorff-perfused hearts treated with oCOm-21 significantly increased both left ventricular developed pressure and Ca^{2+} sensitivity compared to vehicle, respectively (103 mmHg *vs.* 72 mmHg; $P < 0.01$; pCa_{50} 5.50 *vs.* 5.47; $P < 0.05$).
Discussion. These results indicate that CO-derived from oCOm-21 directly increases myofilament Ca^{2+} sensitivity by a heme-dependent mechanism. Importantly, the increased myofilament Ca^{2+} sensitivity was conserved in a pre-treated heart. Further analyses will examine if CO also impacts cytosolic Ca^{2+} cycling.

A6: Structure guided poly-pharmacology targeting the bacterial GHKL proteins to overcome antibiotic resistance

Te Xiao[1,2], Christopher Squire[2,3], Jane Allison[2,3], Julie Spicer[2,4], Francesca Todd-Rose[2,5], Rachel Darnell[2,5], Greg Cook[2,5], Jack Flanagan[1,2,4]. Department of Pharmacology and Clinical Pharmacology, School of Medical Sciences, University of Auckland[1]; Maurice Wilkins Centre[2]; School of Biological Science, University of Auckland[3]; Auckland Cancer Society Research Centre, University of Auckland[4]; Department of Microbiology and Immunology, University of Otago[5],



Introduction. Bacterial two-component systems (TCS) are signalling proteins involved in the development of antibiotic tolerance. Recent studies using *E. faecalis* showed that deleting the CroRS TCS histidine kinase gene can overcome antibiotic tolerance.
Aims. To discover small molecule blockers of the *E. faecalis* CroS HK ATP-binding site.
Methods. Molecular docking based virtual screening against available HK structures using known HK inhibitors was undertaken. A new virtual fragment hot-spot method was developed to improve the predictive power of HK structures generated by AlfaFold2.
Results. A molecular modelling workflow was developed that included fragment hotspot mapping and capacity for processing hundreds of protein conformations. Enrichment calculations showed that the workflow could generate HK structures capable of identifying HK inhibitors, where fragment hotspot constraints improved the predictive power for some HK structures. Only traditional comparative modelling produced a binding model for the CroS HK ATP cavity that could explain substrate binding and the model also exhibit predictive ability for known HK inhibitors. The inclusion of water molecules to account for solvation in the binding site did not increase in the ranking of the control compound.
Discussion. In the absence of crystal structures for many TCS HK proteins, methods based on AlfaFold2 predictions of protein structure can be used to develop molecular models relevant for ligand discovery, although functional models may not be possible for all HKs. Models of the CroS protein with a substrate analogue bound showed similar interactions to other HK enzymes crystallised with the substrate.

Darnell R et al (2019) mSphere vol. 4,3 e00228-19.

A7: The effect of alcohol consumption on blood glucose in young adults with type 1 diabetes mellitus

Amy (Yoonseo) Chung[1], Benjamin J Wheeler[2], Hesham S Al-Sallami[1]. Otago Pharmacometrics Group, University of Otago[1], Dunedin, Otago, New Zealand; Women's and Children's Health, Dunedin School of Medicine[2], Dunedin, Otago, New Zealand.

Introduction. Precise glycaemic control is required to prevent debilitating short and long-term complications in Type 1 diabetes (T1DM). Ethanol complicates glycaemic control by inhibiting gluconeogenesis and glycogenolysis. The extent and time-course of this inhibition varies and can result in potentially life-threatening hypoglycaemia several hours after alcohol consumption.
Aims. To determine how alcohol affects blood glucose in patients with T1DM, and how other variables such as physical activity and bolus insulin dosing influence glycaemic control in these patients.
Methods. This was a prospective, observational study of young adults with T1DM. Participants provided 10-day worth of data of blood glucose, insulin dose and dosing time, food intake, physical activity, alcohol intake, and blood alcohol. Data were summarised and used to identify glycaemic control, incidences of hypoglycaemia, and variables associated with hypoglycaemia.
Results. Preliminary results show between-subject variability in glycaemic control. One participant had a spike in their blood glucose (18.9 mmol/L) at the same time as a blood alcohol concentration of 0.054% w/v. Low blood glucose was reported but no incidences of moderate or severe hypoglycaemia. Another participant measured 9.2mmol/L in BG at 0.022% blood alcohol concentration and quickly peaked at 22.1mmol/L a couple of hours later. Hypoglycaemia also did not occur for this participant after this particular drinking occasion, with blood glucose reaching no lower than 6 mmol/L.
Discussion. Data showed suboptimal glycaemic control associated with events when alcohol is consumed. A likely reason for this is the consumption of high-sugar pre-mixed drinks and eating sugary and carbohydrate-rich snacks. It is also possible that participants would reduce or omit their insulin treatment in order to avoid severe hypoglycaemia later on. Further analysis of the data currently being collected will help confirm these correlations.

A8: The effect of compulsory indications in electronic prescriptions for cardiovascular medicines.

Lorna Pairman[1], Paul Chin[1,2], Richard McNeill[2], Matthew Doogue[1,2]. Department of Medicine, University of Otago[1], Christchurch, New Zealand; Department of Clinical Pharmacology, Te Whatu Ora Health New Zealand – Waitaha Canterbury[2], Christchurch, New Zealand.

Introduction. Recording the indication, the reason for use of a medicine, in the prescription supports communication and prevents errors. To improve recording, the indication field can be made compulsory in electronic prescriptions. However, compulsory fields risk inaccurate information being recorded. On 15/05/2023 our local health region made indications compulsory for a selection of cardiovascular medicines, providing an opportunity to evaluate this routine change in the electronic prescribing system. The text 'to be determined' was provided as a drop-down box for use when the indication is unknown.
Aims. To evaluate making indications for cardiovascular medicines compulsory in an electronic prescribing system.
Methods. The change in the proportion of prescriptions with an indication for the selected cardiovascular medicines was compared for four weeks before and after introduction of a compulsory indication field on 15/05/2023. Documented text in the indication field was manually classified as an indication ('indication present'), 'other text' (meaningful text that is not an indication), 'rubbish text' (text without meaning), 'to be determined', and blank. For prescriptions with 'to be determined' initially documented in the indication field, the proportion with the indication changed prior to discharge was measured.
Results. We analysed 6070 cardiovascular prescriptions before and 6309 after indications were made compulsory. The proportion of prescriptions with an indication increased from 5.0% to 71.6% ($p<0.01$). 'Other text' increased from 1.1% to 14.5% ($p<0.01$), 'rubbish text' from 0.0% to 2.8% ($p<0.01$) and 'to be determined' from 0.0% to 10.7% ($p<0.01$). Of 610 cardiovascular prescriptions with the indication 'to be determined' in the initial prescription, 15/610 (2.5%) were changed by discharge, of which 11/15 (73.3%) were assigned an indication.
Discussion. Introduction of compulsory indications for cardiovascular medicines increased recording indications in prescriptions significantly, with small increases in other text and rubbish text. Use of the 'to be determined' drop-down selection box increased after indications were made compulsory for cardiovascular medicines, but few of these prescriptions had the text 'to be determined' changed to an indication prior to discharge.

A9: Human brain neuropharmacology

Michael Dragunow[1]. Department of Pharmacology & Clinical Pharmacology, University of Auckland[1], Auckland, NZ.

Despite intense efforts in both academia and industry there are very few disease-modifying treatments for brain disorders. To help address this problem we have incorporated human brain-based methods into early drug discovery pipelines. We have developed human brain tissue microarray methods for drug target identification and validation, and human brain cell culture methods for drug testing, screening and mode of action studies. I will describe these methods in this talk and given examples of their use in identifying candidate molecules for treating brain disorders.

A10: The critical role of dimethylarginine dimethylaminohydrolase-1 (DDAH1) in modulating vasculogenic mimicry in cancer: current evidence and therapeutic opportunities

Arduino A Mangoni[1,2]. Discipline of Clinical Pharmacology, College of Medicine and Public Health, Flinders University[1], Adelaide, Australia; Department of Clinical Pharmacology, Flinders Medical Centre[2], Southern Adelaide Local Health Network, Adelaide, Australia.

Nitric oxide (NO) plays a critical pathophysiological role in cancer by modulating several processes such as angiogenesis, tumour growth, and metastatic potential. However, the role of NO in vasculogenic mimicry, an alternative neovascularization process involving the formation of vessel-like networks directly by the tumour cells themselves and predicting high metastatic burden and poor survival, is less clear. The pathophysiological and clinical significance of vasculogenic mimicry have been particularly well studied in triple-negative breast cancer (TNBC), a type of breast cancer characterized by aggressive behaviour, high relapse rate, poor prognosis, and lack of effective targeted treatments. Recent studies have reported that isoform 1 of the enzyme dimethylarginine dimethylaminohydrolase (DDAH1), responsible for the metabolism of the endogenous NO synthase inhibitors, the methylated arginines asymmetric NG,NG-dimethyl-L-arginine and NG-monomethylL-arginine, is essential for TNBC cells to undertake vasculogenic mimicry. Furthermore, treatment with small-molecule arginine analogues with inhibitory activity toward DDAH1 has been shown to significantly reduce vasculogenic mimicry by TNBC cells. This presentation describes the current knowledge regarding the pathophysiological and clinical significance of vasculogenic mimicry, the biology of DDAH1 and methylated arginines, and the role of DDAH1 as a promising “druggable” target to suppress vasculogenic mimicry in cancer, with a focus on TNBC.

A11: More than a Class A placebo? A randomised controlled trial of microdosed lysergic-acid diethylamide

Rachael Sumner[1]. School of Pharmacy, University of Auckland[1], Auckland, NZ.

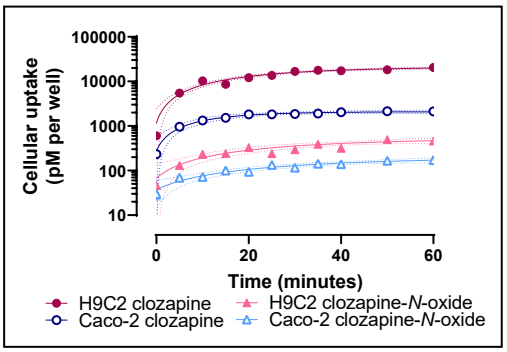
Microdosing psychedelic drugs is a widespread social phenomenon with diverse benefits claimed for mood and cognition. Randomised controlled trials have failed to support these claims, but the laboratory-based dosing in trials conducted to date may have limited ecological validity.

Healthy male volunteers were randomized into lysergic acid diethylamide (LSD) (n = 40) and placebo (n = 40) groups and received 14 doses of either 10 µg LSD or an inactive placebo every 3 days for 6 weeks. First doses were given in a supervised laboratory setting, with other doses self-administered in a naturalistic setting.

I will present the safety, pharmacokinetic, and psychometric data as well as describe our search for markers of individual variability in response and pharmacokinetics. I will also introduce where we plan to take this research next.

A12: Investigating clozapine transport kinetics using radiolabelled drug; a lot of work to prove we picked the wrong assay

Kathryn Burns[1], Philippa Campbell[1], Ellen Kingston[1], Malcolm Tingle[1]. Dept of Pharmacology and Clinical Pharmacology[1], University of Auckland, NZ.



Introduction. Clozapine is an atypical antipsychotic indicated for treatment-refractory schizophrenia and schizoaffective disorder. Although effective, it's use is associated with a range of life-threatening adverse effects including myocarditis and cardiomyopathy.

Aims. To investigate the uptake kinetics of radiolabelled (^{3}H) clozapine and its major plasma metabolites (*N*-desmethylclozapine, clozapine-*N*-oxide) into cardiac (H9C2) and control (CaCo2) cells *in vitro*.

Methods. Cells were seeded in 24 well plates and left to adhere for 24 hours (37°C, 5% CO_2) prior to incubation with ^{3}H-radiolabelled drug (0.3 – 15 µM) for up to 60 minutes. Cells were then washed with ice-cold buffer, lysed, and analysed by scintillation counting (^{3}H DPM). The effect of clozapine, *N*-desmethylclozapine, and clozapine-*N*-oxide on cell viability was also assessed by WST-8 reduction (0-72 h incubations), and intracellular concentrations were quantified by liquid chromatography-mass spectrometry (LC/MS).

Results. While uptake kinetics were successfully determined for clozapine (CaCo2: V_{MAX} 1684 pmol/min; K_M 3.52 nM) and clozapine-*N*-oxide (CaCo2: V_{MAX} 0.9319 pmol/min; K_M 4.02 pM. H9C2: V_{MAX} 138.2 pmol/min; K_M 8.71 pM), *N*-desmethylclozapine uptake could not be investigated using this assay due to an absence of commercially available radiolabelled drug. Clozapine uptake was transporter-dependent and significantly higher than uptake of clozapine-*N*-oxide. Notably, the extent of *N*-desmethylclozapine uptake was comparable to that of clozapine when assessed by LC/MS, and high concentrations were more toxic to cells than either clozapine or clozapine-*N*-oxide over 24-72 h.

Discussion. The radioactivity assay initially selected for this analysis was inappropriate for the drug investigated, as it could not explore the role of *N*-desmethylclozapine in cellular toxicity. Where sufficient cell numbers were available the LC/MS assay had adequate sensitivity and specificity for the analysis of clozapine, *N*-desmethylclozapine, and clozapine-*N*-oxide uptake into cultured cells *in vitro*.

A13: A systems overview of the clinical data environment for evaluating medicines use in NZ Hospitals

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Introduction. The rapid digitalisation of our health system has generated large quantities of clinical data. This can be used to inform clinical care and for research. Medicines are the most common mode of clinical treatment. In Christchurch hospital there are approximately 1 million prescriptions created annually in our electronic prescribing software. Prescribing data from the electronic prescribing software are uploaded daily to the regional data warehouse from which data can be extracted in different ways depending on use. Extracted data tables are linked to interactive reports to visualise aggregate data at large scale. We provide a case example of the development of an interactive report to visualise prescribing data in Canterbury hospitals.
Aims. To develop an interactive report accessible to clinicians using prescribing data from an electronic prescribing and administration system to support clinical governance.
Methods. Prescribing data are extracted in two ways: 1) using Microsoft Excel® pivot tables to extract user specified data for specific queries, or 2) using Structured Query Language (SQL) code to link prescribing data to other datasets based on unique identifiers, such as NHI, for more complex extracts. Static (method 1) or live (method 2) data extracts are linked to Microsoft PowerBI® to develop interactive web-based reports. Following validation, reports are published to the hospital intranet. The 'Indications Dashboard' is one such interactive web-based report.
Results. The 'Indications Dashboard' was developed to evaluate indications in hospital prescriptions. Text data were manually coded, and the dashboard was piloted on antimicrobial prescribing data and validated with manual review and sequential clinical evaluation. The report was used to inform clinical policy changes and to study the effect of making the indication field compulsory in the prescribing system.
Discussion. Interactive reports with live data support near real time monitoring. The case example shows how data can be used to develop a report to inform both local practice (clinical governance) and wider practice (research).

A14: Use of R-Shiny Apps to Enhance Learning of Core Concepts in Pharmacology.

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The curriculum for medical students includes core concepts in pharmacology that include pharmacokinetics and pharmacodynamics. These core concepts involve an understanding of drug absorption, distribution, metabolism and elimination, but also how individual patient characteristics impact upon exposure to a drug and its actions. Medical students and practitioners have difficulty interpreting the results of population pharmacokinetic analyses and applying these results to learning and also to clinical practice. R-Shiny apps provide an opportunity to describe relationships between patient characteristics and exposure to a drug, and its actions, and also to describe interpatient variability[1].
A series of R-shiny apps were constructed and integrated into tutorials and lectures, with cases that required use of the apps for problem solving. Apps were constructed using R version 4.3.1, R-Studio 2023.06.0 and Shiny for R. The ordinary differential equation solver was deSolver and ggplot2 was performed for plotting of the results. The data for the equations were obtained from published reports. The apps were interactive, and allowed the user to vary patient characteristics, and then view how these impacted upon the plasma concentration-time plot. Drug-, food- and herbal-drug interactions were displayed. Dose changes and drug interaction effects on steady state concentrations were displayed. Exposure effect relationships were displayed using plots of Emax relationships for efficacy and toxicity, where the curve could be altered by changing EC50, Emax and the Hill constant. Finally, a population PK model for neonatal gentamicin was translated into a R-Shiny app to display the effects of weight, gestational age, sepsis, dosing and administration upon exposure with interindividual and residual variability. Feedback from students and clinicians was that the apps enhanced their understanding of the concepts.

1. Wojciechowski, J. Hopkins, AM. Upton, RN (2015). *Interactive Pharmacometric Applications Using R and the Shiny Package* CPT Pharmacometrics Systems Pharmacology. 4, 146–159

A15: Interruptive clinical decision support (CDS) alerts for improved prescribing: implications of prescriber overrides.

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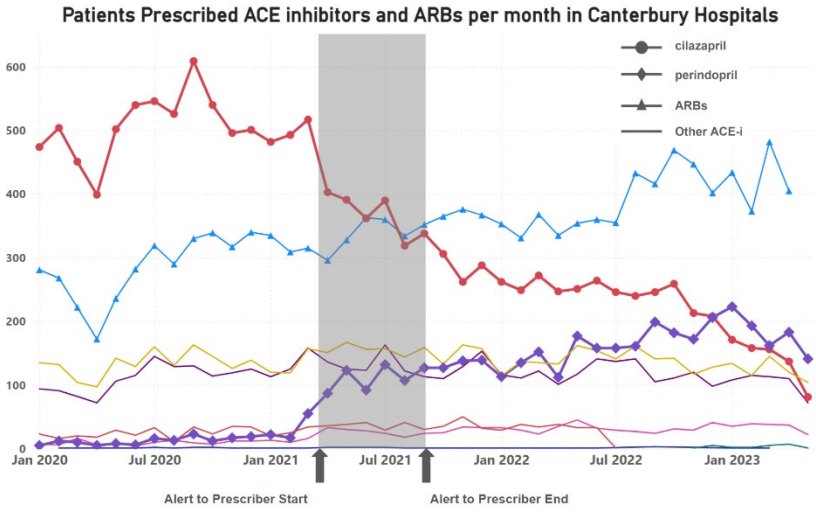
Introduction. CDS alerts are often implemented to prevent potentially harmful prescribing errors such as inadvertent duplicate prescribing (DP) of antithrombotic medicines. The majority of CDS alerts for inpatient DP are interruptive, irrelevant, and overridden by prescribers, contributing to alert fatigue. Cases where alerts are overridden appropriately can present opportunities for reconfiguration to reduce alert burden and improve prescriber adherence.
Aims. 1) To review antithrombotic DP alerts at our institution for attributes which appropriately led to the alerts being overridden. 2) To reconfigure alerts to assess alert burden and prescriber alert adherence changes.
Methods. We reviewed antithrombotic DP alert logs triggered from 01/01/2017 to 31/08/2022 by joining alert logs to relevant prescribing data. After identifying that stat prescriptions were predicates for many overridden alerts, we reconfigured alerts on 04/10/2022 to prevent triggering if the existing or added prescription was a stat. Equivalent data 7-months after reconfiguration was collected to facilitate a before-after comparison of alert burden and prescriber adherence. Alert burden was measured as alerts per 100 prescriptions able to cause alert triggering. Prescriber adherence was measured proximally as either the prescriber 'cancelling' or 'overriding' the alert when triggered and distally as overridden alerts with an alert-causing prescription ceased within an hour.
Results. A total of 17,518 and 1,283 alerts were included for analysis before and after reconfiguration. 95.2% of alerts were overridden by prescribers prior to reconfiguration, 29.1% of which involved a stat prescription. Reconfiguration resulted in a significant reduction in alert burden from 5.26 to 3.79 alerts per 100 prescriptions ($P < 0.001$). Override rates did not notably change, but overridden alerts which had an antithrombotic prescription changed within an hour of override significantly increased from 29.7% to 41.8% ($P < 0.001$) after reconfiguration.
Discussion. Initially, stat prescriptions triggered close to a third of appropriately overridden antithrombotic DP alerts at our institution. Reconfiguration of our alerts reduced alert burden but did not change prescriber adherence at the point of the alert. Reconfiguration resulted in a significantly larger proportion of overridden alerts having an associated antithrombotic prescription ceased within an hour of override.

A16: Prescribing Systems Alerts to Support Change in Funded ACE Inhibitors at Canterbury Hospitals

Kelvin Gong, Richard McNeill, Paul Chin, Matthew Doogue. Department of Medicine, University of Otago, Christchurch, New Zealand.



Introduction: Cilazapril, the most used ACE inhibitor in New Zealand, is being phased out. Canterbury selected perindopril as the 'preferred' replacement. Alerts in the prescribing system are being used to inform prescribers. The alert started on 18th March 2021 and ended on 2nd September 2021.
Aim: To examine the effect of alerts in the prescribing system alerts on ACE inhibitor prescribing in Canterbury Hospitals between when the alert began and ended.
Method: Inpatient prescribing data for 1 January 2020, to 30 April 2023 were extracted from the regional hospital prescribing system (MedChart v8.1). Number of admissions prescribed ACE inhibitors and angiotensin II receptor blockers (ARBs) per month were assessed.
Results: With the introduction of a prescribing alert cilazapril prescribing decreased 34.6% (517 to 338), perindopril increased 230.9% (55 to 127) over the same time and the others in the class did not noticeably change (figure). After removing the alert the rate of change decreased (figure).
Discussion: The alert had a significant effect on transitioning patients from cilazapril to perindopril. To support further transition from cilazapril prior to delisting in late 2023 an alert recommending switching will be added to the hospital prescribing system.

A17: Untangling the paradoxical dose-exposure-response relationship for allopurinol

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Introduction. The active metabolite of allopurinol, oxypurinol, is almost entirely renally cleared. Paradoxically, allopurinol dose reduction proportional to creatinine clearance (CLcr) results in suboptimal urate-lowering in gout patients [1]. Equally unexpected, diuretic therapy has been found to reduce oxypurinol clearance [2] but is associated with the need for higher allopurinol doses to achieve the serum urate target (<0.36 mmol/L) [3].
Aims. To explore the relationship between allopurinol dose, oxypurinol exposure and urate-lowering response in gout patients with different stages of CKD and in those taking diuretics.
Methods. Oxypurinol and urate data from five clinical studies were available. Model-derived steady-state oxypurinol area-under the concentration-time curve ($AUCss_{0\text{-}tau}$) were estimated using a Bayesian methodology. Response was the percent reduction in serum urate from baseline. Dose- and exposure-response were explored graphically. The allopurinol dose, oxypurinol exposure and urate-lowering response required to achieve the target urate were compared across CKD bands and by diuretic status.
Results. Data from 90 gout patients representing 388 paired steady-state oxypurinol and serum urate measurements were analysed. To achieve the urate target, patients with CLcr 15-30mL/min required a lower daily dose than those with CLcr≥ 90mL/min (250 vrs 475mg, $p<0.0001$) while oxypurinol exposure was significantly higher (7486 vrs 2275 µmol*h/L, respectively, $p<0.0001$). Oxypurinol exposure was also higher in those taking diuretics (4860 vrs 2664 µmol*h/L, $p<0.0001$). There was no difference in urate-lowering response related to CLcr or diuretic use.
Discussion. The lower allopurinol doses observed with reduced renal function are not proportional to CLcr. Therefore the higher oxypurinol exposure and normalised response across CKD bands and for those taking diuretics is not actually paradoxical but a function of dose individualisation to a urate target.

1. Dalbeth N *et al* (2006) J Rheumatol 33:1646–50
2. Hishe HZ *et al* (2023) Clin Transl Sci 16:422–28
3. Stamp LK *et al* (2011) Clin Pharmacol Ther 90:392–98

A18: Characterising the inotropic mechanism of action of oCOm-21 in isolated cardiomyocytes

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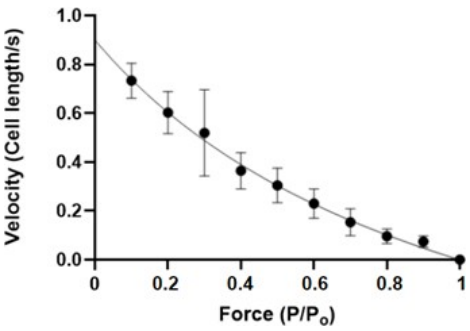
Introduction. Previous data has shown an inotropic response with our novel carbon monoxide-releasing drug, oCOm-21. Therefore, it was necessary to establish a protocol to determine the inotropy of isolated rat cardiomyocytes. This protocol was first established in vehicle-treated hearts to generate a power-curve from force-velocity tracings (right). Then it was investigated whether phosphorylation of key myofilament proteins, such as cardiac troponin I and cardiac myosin binding protein c, were related to this inotropic response.



Aims. To determine whether key myofilament protein phosphorylation contributes to the inotropic response observed with oCOm-21 in isolated rat cardiomyocytes.
Methods. Force-velocity tracings were conducted using a micro-physiology system to generate a power curve. Gel staining with Pro-Q Diamond and SYPRO Ruby, coupled with western blotting, were utilised to determine any phosphorylation changes.
Results. Gel staining confirmed noradrenaline-treated hearts had increased protein phosphorylation, however, oCOm-21-treated isolated rat cardiomyocytes exhibited no change in protein phosphorylation.
Discussion. Noradrenaline-treated hearts showed an increase in protein phosphorylation as expected. However, there were no phosphorylation changes at the myofilament level with oCOm-21. Therefore, there must be another underlying mechanism behind the inotropic effect of oCOm-21 that merits further investigation.

A19: Chemical proteomics approaches to elucidate the cytoprotective mechanism of compounds in human-brain derived pericyte oxidative stress models

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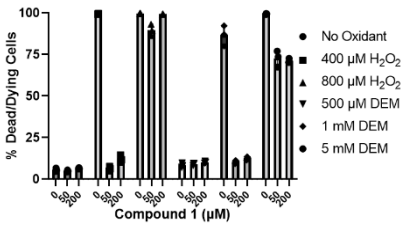

Oxidative stress is a key cellular phenomenon towards necrotic and apoptotic cell death. In neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease, oxidative stress has been linked to pathological hallmarks and deteriorating health. To address this, a 1520 member FDA approved drug library was screened against oxidative stress in human-brain derived pericytes, which identified a compound which we have called compound 1, that enabled substantial cytoprotective effects through an unknown mechanism. Aim: Characterise compound 1's efficacy in a range of oxidative stress inducers and cellular readouts, then deconvolute its molecular mechanism using label-free chemical proteomics. Methods: Compound 2, a structurally similar FDA approved drug that lacks antioxidant effects, is used as a negative control. In addition to H_2O_2, other oxidants such as DEM are used as oxidative stress models. In addition to live/dead cell staining, levels of ROS and glutathione are used as cellular readouts. Thermal proteome profiling (TPP) is used for target identification; live human-brain derived pericytes will be treated with DMSO, compound 1 or compound 2, split into various tubes and melted at different temperatures along a gradient. Unfolded proteins from each condition will be separated from intact, soluble proteins (i.e., those thermally stabilised through compound 1 binding) by centrifugation, then processed for proteomic analysis. Stability of proteins from rates of oxidation (SPROX) is used as a parallel approach to confirm targets. CRISPR-mediated genetic knockout is used to confirm therapeutic versus off-target effects. Results: Compound 1 protects against H_2O_2- and DEM-mediated cell death. Compound 1 offers protection up to 30 minutes post H_2O_2 addition, does not sequester H_2O_2, and also protects in a human mixed glial cell line. Discussion: TPP may identify proteins involved in compound 1's cell protective mechanism in a target agonistic manner. This approach circumvents the issues associated with label-based chemical proteomics as no prerequisite modification of compound 1's complex structure will be required.

A20: Orphan G protein-coupled receptors: pain points and opportunities

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G protein-coupled receptors (GPCRs) are cell surface receptors that constitute the most successful drug targets on the market. Orphan GPCRs are receptors that are yet to be paired with their endogenous ligand, with many lacking pharmacological tools altogether. Nevertheless, they hold great potential given their often restricted tissue expression patterns and numerous disease links. Our laboratory studies orphan GPCRs related to cardiovascular disease, focussing on orphans GPR37L1, GPR146 and GPR161 because of their associations with hypertension, atherosclerosis and cardiac development, respectively. In this presentation, I will describe our efforts to understand the pharmacology of these receptors, with a particular focus on our efforts to reproduce reported ligand:receptor pairings in accordance with IUPHAR-NC deorphanisation recommendations. Only a handful of orphan receptor pairings have been ratified by IUPHAR-NC in recent years, despite sundry reports of putative pairings. Our studies reflect this low conversion rate, failing to confirm proposed endogenous ligands for GPR146, GPR161, or GPR37L1. These studies were exhaustive, reflecting the burden of proof placed on researchers who wish to refute or correct the scientific record. Such research is vital, however, so that efforts and resources can be redirected to future discoveries.

A21: One inhibitor, two mechanisms ? evidence for allosteric regulation of the lipid kinase PI3K

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When activated by growth factor receptor mimicking peptides, PI3Ka undergoes conformational changes that promote its membrane interaction and catalytic activity. Some of these changes occur around the kinase domain and ATP binding site, yet the effects of ATP-site directed inhibitors on the PI3Ka membrane interactions are unknown. Using FRET and Biolayer Interferometry assays, we show that a class of ATP-site directed inhibitors represented by GSK2126458 block the growth factor activated wild type PI3Ka membrane interaction. A structure activity relationship analysis showed that the effect is dependent on the ligand forming specific ATP-site interactions. The membrane interaction for E545K and H1047R hot spot oncogenic mutations that bypass normal regulatory mechanisms in PI3Ka were insensitive to GSK2126458. GSK2126458 did regulate the membrane interaction for oncogenic mutations found in the same or in different domains. Strikingly, an ATP analogue had the opposite effect to GSK2126458, increasing the PI3Ka membrane interaction. Our data point to GSK2126458 causing the enzyme to revert from its growth factor mimic activated state to a basal state. Our findings illustrate that PI3Ka inhibitors affect not only catalysis through blocking ATP substrate binding, but also lipid substrate binding by regulating the membrane interaction, giving them a dual mechanism of action.

A22: The good and not so good of dose banding for dose individualisation

Stephen Duffull. Certara, NJ, USA

Introduction. Dose banding is the allocation of patients into a pre-specified dose group based on each patients' characteristics. This method is commonly recommended in drug labels (e.g. metformin adjusted based on renal function) in order to optimise beneficence (doing good) and minimise maleficence (doing harm). The alternative approaches are: one-dose-fits-all (e.g. 1g q6h paracetamol in adults) or each patient gets an individualised dose (e.g. 1 mg/kg for enoxaparin). The benefit of dose banding is the simplicity of application clinically. An un-explored issue with dose banding is the chance of not doing good (non-beneficence) due to assigning the patient to a lower dose group, i.e. the patient falls on the "wrong" side of a dose adjustment.
Aims. To determine the influence of dose banding vs one-dose-fits-all vs fully individualised dosing on the probability of target attainment (i.e. success) and the potential to cause harm via non-beneficence.
Methods. The aims were addressed by a simulation study. The model was a 1-parameter steady-state model defined by the parameter CL (mean=1 L/h, CV%=30) and dose (1 mg) and each virtual patient's value of CL depended on an observable characteristic (WT). Success (probability of target attainment [PTA]) was determined as a steady-state concentration of between 1 and 2 mg/L. The following dosing scenarios were considered (i) one-dose-fits-all, (ii) fully dose individualised based on WT and (iii) dose banding based on bands of WT. In addition, dose banding was evaluated when the goal was to both maximise success and minimise non-beneficence.
Results. The lowest PTA was seen with one-dose-fits-all (PTA = 0.59). In contrast, a dose based continuously on WT yielded the highest PTA (PTA=0.72). Optimising PTA with two dose levels yielded a dose band cut-off at the 52nd percentile of WT and dose levels of 1.1 and 1.8 mg. One-dose-fits-all avoided non-beneficence (as no patient was required to receive a lower dose). A balance between risk:benefit and non-beneficence yielded a dose band cut off at the 36th percentile of WT and the dose values were 1.1 and 1.3 mg.
Discussion. Exploring dose banding, using a simple model, showed a clear benefit of fully individualised dosing (based on WT) for achieving success. Dose banding is associated with harm due to non-beneficence but can be optimised to minimise this risk.