Annual Scientific Meeting
3rd – 5th September 2025

ASCEPT

NZ Forum

Abstract and Programme Booklet

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Contents

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General Information

Welcome to the 2025 ASCEPT-NZ meeting. 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
- Michelle Glass – University of Otago, Dunedin
- Jack Flanagan – University of Auckland

Invited Speakers

ASCEPT Plenary Speaker

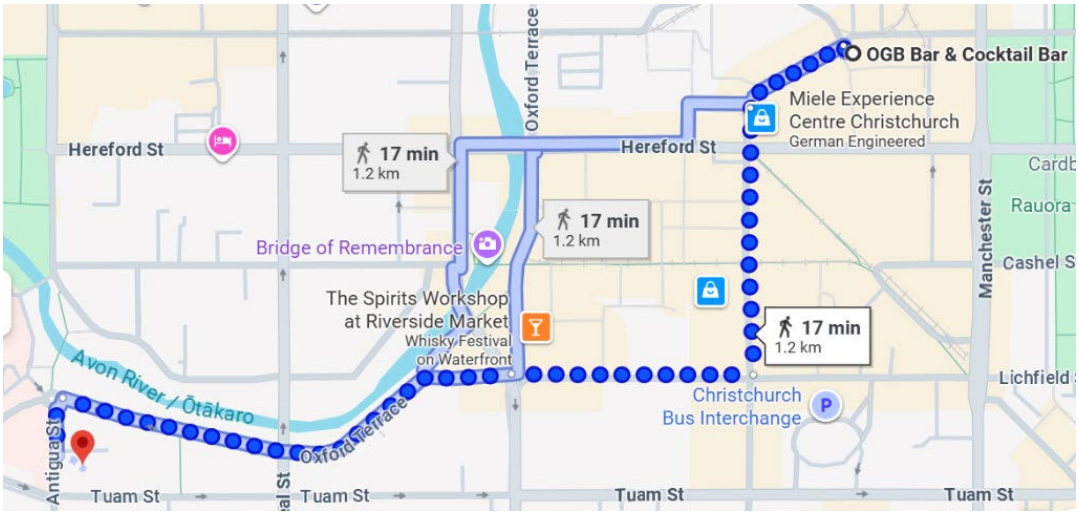
- Dan Wright. Associate Professor in Clinical Pharmacy, University of Sydney, Sydney.

Symposium speakers:

- Murray Barclay. Clinical pharmacologist & gastroenterologist, U of Otago, Christchurch
- Deanna Bell. Professional Teaching Fellow, University of Auckland, Auckland
- Paul Chin: Clinical pharmacologist, University of Otago, Christchurch
- Carl Kirkpatrick. Professor of Pharmacy Practice, Monash University, Melbourne.
- Paul Glue. Professor of Psychological Medicine, University of Otago, Dunedin

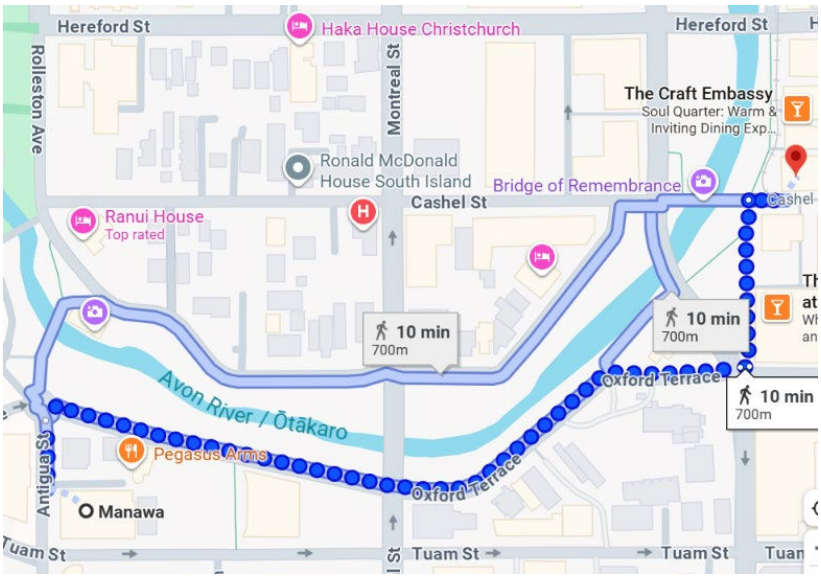
Welcome Reception Venue:

The Parlour Room
O.G.B Cocktail Bar
28 Cathedral Square
Christchurch 8011



Conference Venue:

Manawa Campus
276 Antigua Street
Christchurch Central City
Christchurch 8011



Dinner Venue:

King of Snake
Level 1/79 Cashel Street
Christchurch Central City
Christchurch 8011

Conference Programme

DAY 1 – Wednesday 3rd September 2025 – WELCOME FUNCTION	
18.00 – 18.10	Welcome **Katie Burns** *Chair of ASCEPT NZ*
18.00 – 19.30	**Registration.** Drinks, nibbles, and networking function

DAY 2 – Thursday 4th September 2025 – ANNUAL SCIENTIFIC MEETING	
08.30 – 09.00	**Registration** (Coffee can be purchased at Flora Café, ground floor)
Welcome / Housekeeping	
08.50 – 09.00	**Katie Burns** *Chair of ASCEPT NZ*
Oral Communications Session 1 – Chair: Katie Burns	
09.00 – 09.15	Chemical space travel connects patients to early stage drug discovery science **Jack Flanagan (A1)** *University of Auckland*
09.15 – 09.30	Ibogaine - can cardiac safety be improved? **Natalie Hughes (A2)** *University of Otago*
09.30 – 09.45	Real-world rivaroxaban concentration monitoring – the Christchurch experience **Paul Chin (A3)** *University of Otago*
Student Presentations	
09.45 – 10.00	Clozapine-associated perturbation of arachidonic acid metabolism: A future direction for clozapine-induced cardiotoxicity **Ellen Kingston (A4)** *University of Auckland*
10.00-10.15	Antibiotic prescribing for inpatients with cellulitis who have labelled adverse drug reactions to penicillins and/or cephalosporins: a retrospective cohort study **Milan Sundermann (A5)** *University of Otago*
10.15 – 10.30	Regional variability in dabigatran dosing within New Zealand **Liam Berryman (A6)** *University of Otago, Christchurch*

10.30 – 11.00	Morning Tea
Student Presentations – Chair: Dan Wright	
11.00 – 11.15	Antimicrobial tolerance will no longer be tolerated **Te Xiao (A7)** *University of Auckland*
11.15 – 11.30	Investigation of AGXT2 deficiency as a potential mechanistic risk factor for 5-fluorouracil-induced cardiotoxicity **Sihan Wang (A8)** *University of Auckland*
11.30 – 11.45	CRISPR/Cas9-Mediated ABCC2 Knockout Enhances Intracellular Platinum Accumulation in Caco-2 Cells **Stella Park (A9)** *Auckland University of Technology*
11.45 – 12.00	Evaluating a pharmacometrics model of procalcitonin in an adult ICU population **Isabella Cleland (A10)** *University of Auckland*
12.00 – 12.15	Insights into clozapine-CYP2J2 binding and membrane partitioning **Bailee Lough (A11)** *University of Auckland*
12.15 – 12.30	PBPK modelling of clozapine and its metabolites to explore cardiac tissue exposure during titration **Sophia Kahn (A12)** *University of Auckland*
12.30 – 13.30	Lunch
Symposium: Drug Repurposing – making better use of existing medicines – Chair: Matt Doogue	
13.30 – 13.40	*Introduction by Chair (Matt Doogue)*
13.40 – 14.05	The repurposing of thioguanine for use in inflammatory bowel disease – a very long, winding road **Murray Barclay (A13)** *University of Otago*
14.05 – 14.30	Repurposing anakinra for Inflammation of prematurity – defining dose regimens using mechanistic population pharmacokinetics. **Carl Kirkpatrick (A14)** *Monash University*
14.30 – 14.55	Ketamine as a fast-acting antidepressant - expanding access through reformulation **Paul Glue (A15)** *University of Otago*
14.55 – 15.15	**Discussion/Question Time**

15.15 – 15.45	Afternoon Tea
Oral Communications Session 2 – Chair: Carl Kirkpatrick	
15.45 – 16.00	Does *COMT* genotype influence DNA methylation and mRNA expression in breast cancer patients? **Katie Burns (A16)**
16.00 – 16.15	Safety of a computerised physician order entry system assessed using simulation scenarios **Milan Sundermann (A17)** *University of Otago*
16.15 – 16.30	Empiricism vs Mechanism – does it matter? **Steve Duffull (A18)** *Certara*
16.30 – 17.00	Using Our Data to Improve Our Health – using medicines in NZ **Richard McNeill & Matt Doogue (A19)** *University of Otago*
17.00 – 17.10	Comfort Break
ASCEPT-NZ AGM	
17.10– 18.10	**AGM**
	Break
Conference Dinner	
20.15 onwards	**King of Snake**

DAY 3 – Friday 5th September 2025 – ANNUAL SCIENTIFIC MEETING	
Symposium: Current Research in Pharmacology Education – Chair: Jacqui Hannam	
09.00 – 09.10	*Introduction by Chair (Jacqui Hannam)*
09.10 – 09.35	Teaching and Assessment – a Tale of Two Prescribing Projects **Paul Chin (A20)** *University of Otago*
09.35 – 10.00	Embedding authentic research into undergraduate pharmacology education: An integrated lab and lecture model using a kinase exemplar **Deanna Bell (A21)** *University of Auckland*
10.00 – 10.15	**Discussion/Question Time**
10.15 – 10.30	Application of Virtual Reality to Pharmacology Learning **David Reith (A22)** *University of Otago*
10.30 – 10.45	Is it time to replace the 'prescription' with the medication management plan? **Matt Doogue (A23)** *University of Otago*

10.45 – 11.15	Morning Tea
Oral Communications Session 3 – Chair: Jack Flanagan	
11.15 – 11.30	Can a population model describing procalcitonin from neonates to adults predict infection status in ICU adults at admission? **Jacqui Hannam (A24)** *University of Auckland*
11.30 – 11.45	Computational Approaches for Small Molecule Drug Discovery **Lauren May (A25)** *Monash University*
11.45 – 12.00	Pharmacokinetics, and efficacy/safety signals, of thioguanine administered by suppository in patients with refractory ulcerative proctitis **Murray Barclay (A26)** *University of Otago*
ASCEPT Guest Speaker	
12.00 – 12.40	Potion, Poison, or Panacea? Getting the dose right for the 'new' wonder drug colchicine **Dan Wright (A27)** *Institution*
Conference Close and Prizegiving	
12.40 – 13.00	**Katie Burns** *Chair of ASCEPT NZ*

Abstracts

A1: Chemical space travel connects patients to early stage drug discovery science.

Flanagan J. U.[1,2], Copping J.M.[1], Chand S.[3], Senanayake D.[4], Abbasi H.[3], Lee W-J.[1,2], Dragunow M.[1,2]
[1]Dept of Pharmacology and Clinical Pharmacology, University of Auckland, Auckland, New Zealand. [2]Centre for Brain Research, University of Auckland, Auckland, New Zealand. [3]Auckland Bioengineering Institute, University of Auckland, New Zealand. [1]National eScience Infrastructure, New Zealand.

The chemical space available to support drug discovery is exploding, reaching almost 100 billion readily obtainable compounds. These ultra-large compound libraries go far beyond the scale accessible to traditional wet-lab based high throughput screening. The existence of massive chemical spaces also creates the tantalizing prospect that the specific molecules destined to be our future medicines already exist, all we need to do is find them. Since these ultra-large chemical spaces exist primarily in a digital format, it is only possible to screen them with methods supported by super-computing environments. Inclusion of drug target 3-dimensional atomic structure data means that it is possible to pin-point specific molecules that bind a drug target. Molecular docking is an established virtual screening method, it performs embarrassingly parallel brute-force calculations that create 3D-structures for every compound on the surface of a drug target. Some of largest molecular docking screens are now covering at least a billion molecules. To keep pace with chemical space expansion, AI applications capable of predicting molecular docking outcomes based only on the compound chemistry are being developed, a needed booster for space travel.
So how do we derive benefit in New Zealand from these global advances ? our national high performance computing infrastructure creates opportunity to link our drug discovery sciences directly to patient samples giving New Zealand patients opportunity to participate in early drug discovery and potentially identify new chemistry for future medicines. Targeting the underlying neuroinflammation of many brain diseases, we created a precision drug discovery pipeline that seeks to screen ultra-large chemical spaces against new drug targets identifying new chemistry relevant for pre-clinical development. Our molecular docking platform has identified molecules able to modulate inflammation in brain cells. We are now investigating machine learning to increase the scale and speed of our screening platform.

A2: Ibogaine - can cardiac safety be improved?

Natalie J. Hughes-Medlicott, Jacob Dresser, David M. Reith and Paul Glue. School of Pharmacy, Otago School of Medicine and Department of Psychological Medicine, Otago School of Medicine, University of Otago

Introduction. Ibogaine has been used off-label for treatment of substance dependence. There are concerns about ibogaine cardiotoxicity due to QT interval prolongation, especially in people with poor CYP2D6 metaboliser status.
Aims. To create a parent-metabolite model for ibogaine and noribogaine and use this to simulate plasma concentrations corresponding to safe QTc changes from potential ibogaine dosing regimens.
Methods. Ibogaine and noribogaine plasma concentrations in twenty healthy volunteers were used (Glue et al. 2015). The dose of ibogaine was 20mg ibogaine orally. Half the volunteers were pre-treated with paroxetine (CYP2D6 inhibitor) to mimic poor metabolisers. Phoenix 64 NLME (8.3.4.295) was used to create the pharmacokinetic model. There were 160 observations available (ibogaine and noribogaine concentrations). Fitting was performed using FOCE ELS (First Order Conditional Estimation-Extended Least Squares).
Results. A two-compartment parent (ibogaine) – metabolite (noribogaine) model was created with CYP2D6 inhibition included as a categorical variable. The target plasma concentrations for combined ibogaine + noribogaine (umol/L) were consistent with those reported for noribogaine to produce QTcI change of 20 msec (Glue *et al*, 2016). Simulations were made for different dosing regimens using a loading and maintenance dose strategy over 24h with doses (maintenance and loading) lower if CYP2D6 was inhibited.
Discussion. This study suggested reduced dosing of ibogaine in people with poor CYP2D6 metaboliser to reduce the risk of cardiotoxicity due to QTcI prolongation. Future clinical PKPD studies may confirm this and assist with safer use of ibogaine in patients seeking detoxification from substances.
References: Glue et al. (2015) J ClinPharmacol., 55. 680, Glue *et al.* Clin Pharm Drug Dev, 2016, 460–468.

A3: Real-world rivaroxaban concentration monitoring – the Christchurch experience

Yassar Alamri[1], Adele O'Mahony[1], Isabel Hiskett[1], Mei Zhang[2], Milan Sundermann[1], Catherine Neal[3], Paul Chin[1,2]. Department of Clinical Pharmacology, Health NZ[1], Christchurch, CAN, NZ; Department of Medicine, University of Otago[2], Christchurch, CAN, NZ; Department of Clinical Haematology, Health NZ[3], Christchurch, CAN, NZ.

Introduction. Direct oral anticoagulants including rivaroxaban are now preferred over warfarin-based therapy. Various clinical contexts have been identified where plasma concentration monitoring may provide therapeutic benefits.
Aims. This investigation sought to characterise clinical experience with rivaroxaban treatment in adult patients and create a predictive model for rivaroxaban concentrations using standard coagulation tests.
Methods. Data collection spanned 2019-2023, capturing patient characteristics, measured rivaroxaban plasma concentrations, and available coagulation screening results. Prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin clotting time were incorporated into concentration prediction modelling.
Results. A total of 403 rivaroxaban plasma levels were analysed with a median concentration of 66 mcg/L. The predominant clinical indications for rivaroxaban concentration assessment included routine post-initiation monitoring (78/403, 19%), clinical events involving breakthrough thromboembolism or haemorrhage (98/403, 24%), and evaluation following dose modifications (42/403, 10%). Dose adjustments to rivaroxaban regimens occurred in 85 patients (85/403, 21%) following concentration determination. Statistical correlation was demonstrated between each of PT and aPTT measurements versus rivaroxaban concentrations. Nevertheless, efforts to develop a reliable predictive mathematical framework using linear regression to estimate rivaroxaban concentrations from these routine coagulation assays were unsuccessful.
Discussion. Rivaroxaban concentrations showed considerable variation, reflecting diverse clinical reasons for measurement, with many cases leading to dosing modifications. Given the common occurrence of dose changes following concentration results, future work should examine relationships between concentration measurements and clinical outcomes to establish reference ranges. A reliable predictive model for rivaroxaban concentrations using routine coagulation tests could not be established.

Alamri Y (2025) Ther Drug Monitor DOI: 10.1097/FTD.0000000000001361

A4: Clozapine-associated perturbation of arachidonic acid metabolism: A future direction for clozapine-induced cardiotoxicity

Ellen Kingston[1], Kathryn Burns[1], Malcolm Tingle[1].
Department of Pharmacology and Clinical Pharmacology[1], The University of Auckland, New Zealand.

Introduction. Clozapine is an effective antipsychotic medication utilised for treatment-resistant schizophrenia. However, clinical use of clozapine is limited due to the risk of several toxicities, including clozapine-induced myocarditis. Oxidation of clozapine and reduction of clozapine-*N*-oxide can be catalysed by the cardio-selective cytochrome P450 (CYP) isoforms CYP2J2, CYP1A1 and CYP1B1, which are also reported to metabolise arachidonic acid, a key component in the maintenance of cardiac homeostasis. Any interaction with CYP-catalysed arachidonic acid metabolism may perturb the balance of pro-inflammatory hydroxyeicosatetraenoic acids (HETEs) and anti-inflammatory epoxyeicosatrienoic acids (EETs), priming the heart to an inflammatory state. Thereby making it more susceptible to the damage that may induce clozapine-induced myocarditis.
Aims. The purpose of this preliminary study was to investigate whether an interaction between arachidonic acid and clozapine or clozapine-*N*-oxide occurs at CYP2J2, CYP1A1 and CYP1B1, in comparison to the hepatic isoform CYP2C19.
Methods: Recombinant CYP isoforms were co-incubated with 50 µM arachidonic acid and a range of therapeutic to supratherapeutic concentrations of clozapine or clozapine-*N*-oxide. Changes in both arachidonic acid and clozapine metabolite concentrations were detected with liquid-chromatography mass spectrometry.
Results. CYP1B1 catalysed arachidonic acid metabolism was altered in the presence of clozapine and clozapine-*N*-oxide, with a concentration-dependent decrease in the formation of 8(9)-EET and an additional unidentified metabolite. Each isoform also had decreased *N*-desmethylclozapine formation relative to incubations with clozapine alone and impaired clozapine and clozapine-*N*-oxide REDOX cycling capacity.
Discussion. Although limited by analytical sensitivity, these preliminary data provide evidence of a metabolic interaction between arachidonic acid and clozapine. This approach offers a novel hypothesis for patient susceptibility and a feasible mechanism behind the cardiac-selective inflammation observed in clozapine-induced myocarditis. Further investigation with improved analytical sensitivity will help to elucidate the nature of this interaction.

A5: Antibiotic prescribing for inpatients with cellulitis who have labelled adverse drug reactions to penicillins and/or cephalosporins: a retrospective cohort study.

Milan Sundermann[1], James Mehrtens[2], Nicholas M Douglas[1,2,3], Sharon Gardiner[2], Matthew Doogue[1,2], and Paul KL Chin[1,2]. Department of Medicine, University of Otago[1], Christchurch, New Zealand; Health New Zealand | Te Whatu Ora Waitaha Canterbury, New Zealand[2], Division of Global and Tropical Health, Menzies School of Health Research, Charles Darwin University, Darwin, NT, Australia[3].

Introduction. Cephalosporins are often avoided in patients with penicillin adverse drug reaction (ADR) labels. Our institution's electronic medication management system is set up not to generate cross-reactive alerts for penicillin and cephalosporin ADR labels. Penicillins and cephalosporins are preferred treatments for cellulitis.
Aims. To describe penicillin, cephalosporin, and non-penicillin, non-cephalosporin (NPNC) prescribing for inpatients with cellulitis in the presence/absence of penicillin and/or cephalosporin ADR labels.
Methods. Index cellulitis admissions were included during 2017-2024 with penicillin and/or cephalosporin ADR labels and at least one penicillin, cephalosporin, or NPNC administered. Index admissions were categorised according to presence/absence of labels to penicillins and/or cephalosporins. Penicillin, cephalosporin, and NPNC prescribing was compared between groups with and without labels using odds ratios (OR).
Results. Of 8,374 index admissions, 7,567 had no penicillin/cephalosporin labels, 729 had penicillin-only labels, 42 had cephalosporin-only labels, and 36 had both labels. Inpatients with penicillin labels were significantly more likely (OR 13.07; 95% CI, 11.05–15.45) to be prescribed cephalosporins than those without labels. There were no differences in penicillin prescribing between those with cephalosporin labels and those without labels (OR 1.04; 95% CI, 0.44–2.47). Inpatients with penicillin and/or cephalosporin labels were 6 to 52 times more likely to receive NPNC antibiotics than those without labels.
Discussion. Absence of cross-reactivity alerts was associated with increased cephalosporin use for cellulitis in inpatients with penicillin ADR labels, sparing NPNC antibiotics that may be less effective. Removal of cross-reactivity alerts may be effective for increasing cephalosporin prescribing for inpatients with penicillin ADR labels.

A6: Regional variability in dabigatran dosing within New Zealand

Liam T Berryman[1], Paul K.L Chin[1,2], Lorna J Pairman[1], Milan Sundermann[1], and Matthew Doogue[1,2]
1. Department of Medicine, University of Otago, Christchurch, New Zealand
2. Department of Clinical Pharmacology, Health New Zealand, Christchurch, New Zealand

Introduction: Dabigatran etexilate is an oral anticoagulant with increased bleeding at high drug exposure. It is available in three capsule strengths (75, 110, and 150 mg).
Aims: To compare the use of 75 mg dabigatran etexilate between New Zealand health districts.
Methods: National community dispensing data from 2019–2023 were obtained from Health New Zealand's Pharmaceutical Data Web Tool. The number of people dispensed each capsule strength in each district was linked to district population estimates to calculate dispensing rates per 10,000 people per year.
Results: Canterbury had the highest 75 mg use (22.2 vs 1.6–7.6 people per 10,000 in the other districts), with correspondingly lower use of 110 mg and 150 mg capsules. Overall dabigatran use was similar across districts. This pattern was maintained over the five years studied.
Discussion: Canterbury is unique in offering a clinical therapeutic drug monitoring service for dabigatran, along with specialist consultation and training through its clinical pharmacology department. Additionally, unlike most districts, Canterbury's local guidelines recommend 75 mg twice daily dosing in certain cases. The observed trends relate to this combination of factors. It is unknown if there are differences in patient outcomes.

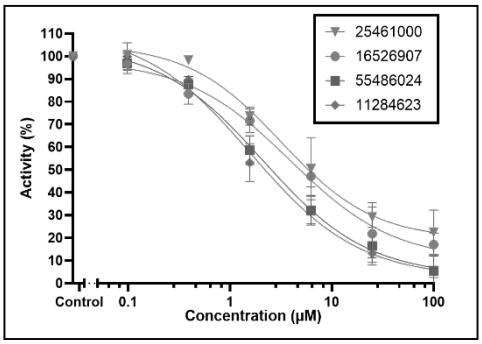
A7: Antimicrobial tolerance will no longer be tolerated.

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

Introduction. Bacterial two-component systems (TCS) are signaling proteins involved in antibiotic tolerance. Recent studies with *E. faecalis* showed that deleting the CroRS TCS histidine kinase (HK) gene overcomes tolerance.

Aims. To identify small-molecule inhibitors of the CroS kinase to test whether pharmacological inhibition of the TCS could also overcome antimicrobial tolerance.

Methods. A virtual screening campaign was performed using GOLD molecular docking and CroS homology models derived from the PhoQ HK from *T. maritima*. Multiple ATP site conformations were explored through iterative ligand-steered homology modelling. Protein structures were ranked by their predictivity, and the best model was used for virtual screening of a 6-million compound library. Top hits were tested in binding and enzyme assays, followed by bacterial cell assays for the four most active compounds.



Results. The models could predict the AMP-PNP binding mode with interaction constraints. The best model could also distinguish known HK inhibitors from property-matched decoy molecules. Over 90 compounds were purchased from Enamine and Chembridge and tested in binding and enzyme assay, with 9 showing inhibitory activity. In bacterial assays, 4 active compounds reduced the minimum bactericidal concentration of *E. faecalis* when combined with vancomycin.

Discussion. In the absence of CroS crystal structures, iterative ligand-steered homology modelling proved effective in identifying protein structures capable of explaining ATP-substrate analogue binding and facilitated prospective HK inhibitor discovery. Selected compounds demonstrated synergistic effects with antibiotics that reduced bacterial tolerance to vancomycin.

A8: Investigation of AGXT2 deficiency as a potential mechanistic risk factor for 5-fluorouracil-induced cardiotoxicity

Sihan Wang[1], Soo-Hee Jeong[2], Adrian Blaser[3], Shreeya Bhardwaj[1], Katie E Burns[2], Nicky Lawrence[4], Malcolm Tingle[2], Nuala A Helsby[1]. Molecular Medicine & Pathology[1]; Pharmacology & Clinical Pharmacology[2]; Auckland Cancer Society Research Centre[3]; Oncology[4], University of Auckland, Auckland, New Zealand.

Introduction. Cardiotoxicity is a common but underappreciated adverse effect of the anticancer drug 5-fluorouracil (5-FU). This toxicity is associated with fluoro-β-alanine (FBAL), the primary metabolite of 5-FU catabolism. This FBAL is further metabolised via alanine–glyoxylate aminotransferase 2 (AGXT2) and can generate potential cardio-toxicants. There is inherited variation in AGXT2 and the endogenous substrate, β-aminoisobutyric acid (BAIB) is a biomarker of AGXT2 activity. We hypothesise that individuals with low AGXT2 function will be protected from production of FBAL-related cardio-toxicants.

Aims. To establish the AGXT2 phenotype assay and investigate the FBAL catabolic pathway and formation of putative cardio-toxicants in patients receiving 5-FU.

Methods. Baseline urine samples were available from 39 cancer patients, with an additional 6 urine samples from these patients after administration of 5-FU (14/NTA/186 and 2024 FULL 20472). The baseline samples were analysed for BAIB concentrations using a validated HPLC-FLD assay. This same assay was used to quantify excretion of FBAL. Excretion of the putative cardiotoxic metabolite(s) was detected using ^{19}F-NMR. Defluorination of FBAL following *in vitro* metabolism of FBAL (rat and human liver homogenates) was quantified by fluoride ion-specific potentiometry.

Results. BAIB concentrations ranged 1.98–238.6 µmol/mmol Cr and published cutpoints identified 24% of patients as AGXT2 poor metabolisers. These had higher BAIB than normal metabolisers (mean 113.3 vs 4.896 µmol/mmol Cr, $P < 0.0001$). Urinary FBAL concentrations were 324.5–868.2 (IV bolus 5-FU) and 946.6–1971 µmol/mmol Cr (continuous infusion 5-FU). Preliminary data suggests a relationship between AGXT2 phenotype and the FBAL concentration. The AGXT2 metabolites, 2-fluoro-3-hydroxypropanoic acid (FHPA) and fluoride ion, were detected in patients. The *in vitro* data (rat and human liver) also detected formation of these metabolites in FBAL incubations. Notably one patient produced substantial amounts of an unidentified product that has not previously been reported in the literature.

Discussion. Urinary BAIB is potentially a useful tool to assess AGXT2 activity and future work will continue to assess the relationship between AGXT2 and 5-FU-induced cardiotoxicity.

A9: CRISPR/Cas9-Mediated ABCC2 Knockout Enhances Intracellular Platinum Accumulation in Caco-2 Cells

Seohyun Park[1], Riya Biswas[1], Yan Li[1]. School of Science, Auckland University of Technology[1], Auckland, New Zealand.

Multidrug Resistance-Associated Protein 2 (MRP2/ *ABCC2*) has been identified as a targetable factor limiting oxaliplatin accumulation and response in gastrointestinal (GI) cancers [1]. Previous experimental work attempted to define the roles of MRP2 using siRNA gene knockdown, but those were confounded by the incomplete disruption of MRP2. To establish a robust cellular platform for probing MRP2's role in drug efflux – and to set the stage for rational inhibitor choice – *ABCC2*-knockout Caco-2 cell lines were generated via CRISPR/Cas9. Genomic cleavage assays and Western blotting confirmed complete disruption of *ABCC2* and absence of MRP2 expression in subclones. Functional evaluation using a model MRP2 substrate CDCF revealed a marked increase in intracellular fluorescence in knockout cell lines relative to wild-type controls, and similarly, oxaliplatin-derived platinum measurements demonstrated significantly enhanced drug accumulation in the absence of MRP2. Building on these findings, our group next sought to identify small-molecule ligands capable of modulating MRP2 activity. Using AutoDock Vina, a panel of putative MRP2 inhibitors was docked, including myricetin, against MRP2. The *in silico* screen suggested that naringin (-9.2 kcal/mol), chrysin (-8.7 kcal/mol), and genistein (-8.7 kcal/mol) potentially outperforms a model ABCC2 inhibitor, myricetin (-7.9 kcal/mol), based on both binding energy and the density of hydrogen bonding and π-stacking interactions within the substrate-binding cavity. Together, this integrated experimental and computational workflow not only underscores MRP2's critical role in ABC transporter-mediated resistance but also delivers a ranked shortlist of candidate inhibitors for future biochemical and cellular validation. This approach could help us design MRP2-targeted drugs that can overcome resistance in colorectal and other GI tumours.

1.Myint K, Biswas R, Li Y, Jong N, Jamieson S, Liu J, Han C, Squire C, Merien F, Lu J, Nakanishi T, Tamai I, and McKeage M.: Identification of MRP2 as a targetable factor limiting oxaliplatin accumulation and response in gastrointestinal cancer. Sci Rep 2019, 9(1):2245

A10: Evaluating a pharmacometrics model of procalcitonin in an adult ICU population

Isabella M Cleland[1], Jacqueline A Hannam[1], Eamon Duffy[2], Steven Ritchie[2,3], Colin McArthur[4]. [1]Pharmacology and Clinical Pharmacology, University of Auckland, Auckland, New Zealand; [2] Department of Infectious Diseases, Auckland City Hospital, Auckland, NZ; [3]Department Molecular Medicine and Pathology, University of Auckland, Auckland, NZ; [4]Department of Critical Care Medicine, Auckland City Hospital, Auckland, NZ

Introduction. Procalcitonin (PCT) increases during infection. It may support bacterial infection diagnosis and early stopping of antibiotics in some settings but performs poorly in adult ICU patients. A population PCT model was previously developed from data arising from six published studies, including ICU adults with infection +/-sepsis. The predictive performance of this model in a NZ population is unknown.

Aims. To determine whether the model captures observed PCT concentrations in our local population.

Methods. Data were from 100 adults admitted to ICU. PCT sampling was based on leftover clinical blood draws. Model evaluation was performed in two subgroups: admitted with sepsis (n=21), and not-infected (n=26). Error metrics were median prediction error (MPE), median absolute prediction error (MAPE), and root mean square error (RMSE). Visual predictive checks (VPCs) were used to assess model misspecification. Maximum a posteriori (MAP) estimates were compared to Empirical Bayesian Estimates (EBEs).

Results. The sepsis group MPE was -12.6% (95% CI -18.9, -8.4), MAPE 20.13% (17.3, 26.0) and RMSE 22.5 ng/mL (17.4, 27.6). The not-infected group MPE was -7.4% (-13.4, -0.2), MAPE 34.0% (30.2, 36.9) and RMSE 8.1 ng/mL (5.7, 10.1). VPCs revealed underprediction during sepsis. In not-infected patients, PCT was underpredicted at the first two days of ICU admission. All MAP estimates and EBEs were within 30% for the sepsis group but differed by 45% for clearance in the not infected.

Discussion. Error metrics were moderate. VPCs indicate model misspecification, particularly in days 0-2 and for sepsis patients. The model captures non-infected patients but fails to capture sepsis in our local population.

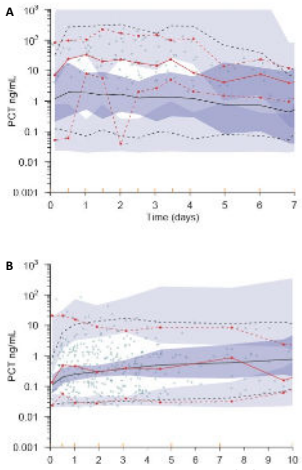
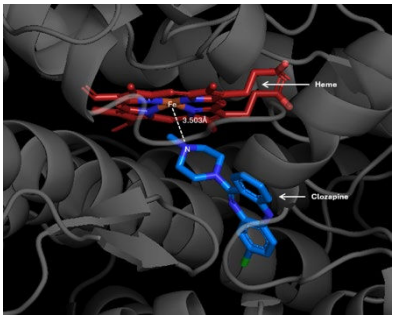


Figure 1. VPCs for sepsis (A) and not-infected (B) patients. Red are observations; black are predictions. Solid lines indicate median, dashed lines indicate 5th and 95th percentiles. Shaded regions indicate 95% prediction intervals. Blue dots indicate individual observations.

A11: Insights into clozapine-CYP2J2 binding and membrane partitioning

Bailee Lough[1], Malcolm Tingle[1], Jack Flanagan[1]. Department of Pharmacology and Clinical Pharmacology, The University of Auckland[1], Auckland, New Zealand.



Introduction. Clozapine is an atypical antipsychotic effective in managing treatment-resistant schizophrenia. However, up to 3% of patients may suffer life-threatening cardiotoxicity. Its metabolism involves various cytochrome P450 (CYP) enzymes, including extrahepatic isoform CYP2J2. Clozapine's interaction with CYP2J2 remains unknown due to the lack of atomic level structure data as does the membrane partitioning ability of the drug and its metabolites.

Aims. 1) Investigate molecular interactions supporting clozapine binding and N-oxidation by CYP2J2. 2) Explore molecular mechanisms facilitating clozapine partitioning from aqueous solvent into lipid membrane systems.

Methods. AlphaFold generated protein structures of CYP2J2, CYP1A2, CYP2D6, CYP2C19 and CYP3A4 and were evaluated for their accuracy in predicting clozapine N-oxidation. Molecular dynamics (MD) simulations were used to study clozapine's movement into different synthetic bilayers.

Results: CYP2J2 docking calculations used cavity sizes 10Å, 12Å, 15Å & 20Å to incorporate different binding site features and revealed 10.0Å was best for identifying binding modes supporting N-oxidation. Larger cavities increased ligand binding pose variability. When used for hepatic CYPs, a 10Å cavity poorly predicted N-metabolism binding compared to CYP2J2. MD simulations demonstrated membrane partitioning of clozapine within 5-10ns, recruitment of the metabolite N-desmethylclozapine was slower at 25-50ns and clozapine-N-oxide was mostly found in the aqueous phase.

Discussion: CYP2J2 AlphaFold models support favourable clozapine binding for N-metabolism, though their superiority over traditional homology modelling remains an open question. Membrane partitioning results highlight differential membrane interactions of clozapine and its metabolites. Future directions will explore physiologically relevant membranes and investigating how protein-membrane orientation dictates clozapine's entry and exit from CYP2J2.

A12: PBPK modelling of clozapine and its metabolites to explore cardiac tissue exposure during titration

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Introduction: Clozapine-induced myocarditis is a serious adverse effect associated with clozapine initiation. Plasma concentration monitoring is standard practice; however, cardiac tissue exposure remains unquantified.

Aims. To develop a PBPK model of clozapine incorporating cardiac tissue and include its two major metabolites, N-desmethylclozapine (NDMC) and clozapine N-oxide (CNO).

Methods. A validated whole-body PBPK model for amitriptyline, detailing cardiac tissues, was reproduced in R using mrgsolve and adapted with clozapine-specific parameters. The model was validated against an existing PBPK model, then extended to incorporate NDMC and CNO as distinct compounds with separate hepatic and cardiac metabolic pathways, permeability and clearances. Predicted clozapine, NDMC and CNO concentrations were compared with trough concentrations for 19 patients undergoing clozapine titration.

Results. Simulated cardiac concentrations exceeded plasma levels. NDMC exhibited higher cardiac concentrations than CNO, particularly in the endocardium, consistent with its lipophilic profile. The model reasonably reproduced observed plasma concentrations of clozapine and metabolites when applied to the clinical dataset.

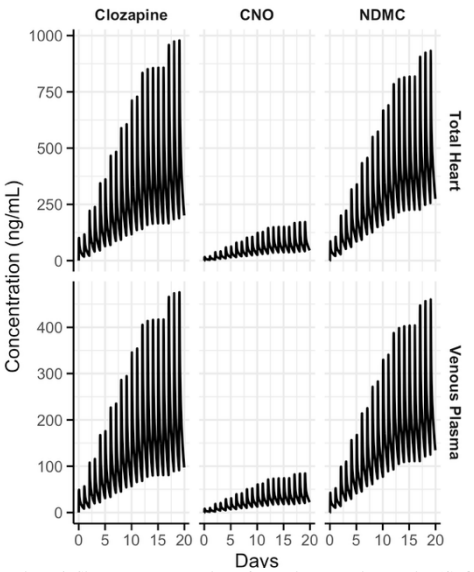

Figure 2: Simulated concentrations of clozapine, clozapine-N-oxide (CNO), and norclozapine (NDMC) in total heart tissue (top row) and venous plasma (bottom row) over a 21-day titration period. escalating from 12.5 mg to 100 mg daily. Simulations model clozapine dose escalation in patient ID 1 with a weight of 72 kg.

Discussion. This is the first PBPK model to include clozapine and its metabolites in plasma and cardiac tissues. Although preliminary, it provides insight into how cardiac drug accumulation may evolve during titration. It will be used to support ongoing research into pharmacogenetics, drug interactions and lab-based investigations aimed at mitigating cardiac risk in clozapine therapy.

A13: The repurposing of thioguanine for use in inflammatory bowel disease – a very long, winding road

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Thioguanine was first developed in 1950 by Gertrude Elion and George Hitchings in the USA, for the treatment of leukaemia. 6-mercaptopurine was developed in 1951 and azathioprine in 1960, also for cancer treatment. Ironically, although azathioprine was used for many years in IBD, and more recently 6-MP, TG has emerged as the peak thiopurine, ie. in reverse order to their development.

There are many metabolites, some toxic, in the thiopurine pathway and use of TG bypasses these. However, one rather poor study in IBD patients in the USA in 2003 suggested severe liver toxicity of TG, which almost completely stopped all use of TG in IBD. However, the Dutch had a strong belief in TG and persisted with a range of studies and a nationwide registry of TG use in IBD. They eventually showed better efficacy, tolerability and safety compared with either AZA or 6-MP.

The process for registering TG in the Netherlands, and Europe, has been very difficult due to being a generic drug, long out of patent, with little or no financial backing, and little provision or support in the regulations for re-purposing. The TG registry in the Netherlands has been critical for gaining registration of the medication, mostly to help indicate the safety of TG. TG is now the first line immunosuppressive medication for IBD in the Netherlands (over 10 years), is becoming (or has become) first-line in New Zealand (over ~4 years), and has pockets of enthusiast use in the UK and Australia. Research has shown that TG applied topically to the lining of the GI tract is particularly effective compared to usual systemic exposure and new oral and rectal formulations are now being developed and researched in New Zealand.

A14: Repurposing anakinra for Inflammation of prematurity – defining dose regimens using mechanistic population pharmacokinetics.

Cark Kirkpatrick

A15: Ketamine as a fast-acting antidepressant: expanding access through reformulation

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Introduction. The first report that low dose ketamine (K) produced fast-onset antidepressant effects in patients with treatment-resistant depression (TRD) was published in 2000. Since that time, these findings have been replicated in over 50 RCTs (Nikolin et al 2023), mainly with K given by injection or nasal spray. These routes of administration produce marked dissociation and sedation, and K has to be given in clinic with medical/nursing support. This significantly limits access to treatment for patients with TRD.

Aims. To describe the development program of an extended-release K (ERK) tablet, in collaboration with Douglas Pharmaceuticals and Otago Pharmacy School collaborators, based on a review of multiple K formulations and their tolerability (Glue et al 2021).

Results. The ERK tablet exhibited high first pass metabolism and delayed Tmax. Tolerability (dissociation) was minimal, as were blood pressure changes. A Phase 2 RCT demonstrated a statistically significant improvement in depression ratings compared with placebo after 3 months of treatment (6.1, p=0.019), with excellent tolerability and safety (Glue et al 2024). Most patient dosing occurred at home.

Discussion. The ERK tablet formulation is effective for patients with TRD, and compared with injectable/intranasal K, has much improved safety/tolerability. This or similar formulations could assist with home treatment for patients with TRD.

Glue P et al. Eur J Clin Pharmacol. 2021; 77:671-6.
Glue P et al. Nature Medicine. 2024;30:2004-9.
Nikolin S et al. EClinicalMedicine. 2023 Aug 1;62.

A16: Does *COMT* genotype influence DNA methylation and mRNA expression in breast cancer patients?

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Introduction. We have previously reported significant associations between two SNPs in the gene encoding catechol-*O*-methyltransferase (*COMT*; rs6269, rs4818) and moderate to severe persistent pain after breast cancer surgery (PPBCS) in a cohort of Aotearoa New Zealand patients (Chiang et al 2023). These SNPs form part of a functional haplotype group with strong linkage disequilibrium between the SNP pairs rs6269-rs4818 and rs4680-rs4633. Both rs4633 (C>T) and rs4680 (G>A) abolish a CpG site while rs6269 inserts one, suggesting these variants may influence epigenetic regulation of *COMT*.

Aims. To investigate the relationship between *COMT* genotype (rs6269, rs4633, rs4680, rs4818) and the extent of DNA methylation at adjacent CpG sites, as well as any temporal changes in DNA methylation or *COMT* mRNA expression.

Methods. Preoperative, 14-days postoperative, and 6-months postoperative blood samples were assayed (n=144). All genomic analyses were undertaken as a service by Grafton Clinical Genomics (Auckland, NZ). *COMT* genotype (rs6269, rs4818, rs4680, rs4633) and CpG site methylation status (n=36 sites) were assessed by Sequenom® MassARRAY. *COMT* mRNA expression was quantified by NanoString PlexSet assay.

Results. Temporal changes in DNA methylation were CpG site-specific in the region assayed and associated with genotype at several loci. mRNA expression was bimodal in the cohort and correlated with methylation at CpG site #-99 (co-located with rs6269) across all timepoints assayed, but no association with *COMT* genotype or haplotype.

Discussion. While *COMT* genotype is associated with methylation changes at some of the assayed sites, its lack of association with mRNA changes suggests additional mechanisms drive temporal changes in COMT expression.

Chiang DLC, Rice DA, Helsby NA, Somogyi AA, Kluger MT. Pain Medicine. 2023;24(9):1023-1034.

A17: Safety of a computerised physician order entry system assessed using simulation scenarios

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Introduction. Inpatient prescribing errors are common, costly, and result in preventable patient harm. Computerised physician order entry (CPOE) systems have been introduced to facilitate safer prescribing, yet often fail to protect against prescribing errors. In various countries including New Zealand, Australia, and the United Kingdom, the CPOE system MedChart™ is used for hospital-based prescribing. At our tertiary institution a mixture of standard configuration and local configuration of alerts and warnings are implemented.
Aims. This study aimed to assess the vulnerability of MedChart™ to prescribing errors.
Methods. Ten prescribers were recruited to each attempt a set of 16 erroneous test scenarios in MedChart™. The ease with which prescribers completed the test cases was recorded using a five-point Likert scale (1 = easily, 5 = impossible). For scenarios involving two prescriptions, five prescribers were instructed to sign-off prescriptions sequentially, whilst five prescribers were instructed to sign-off simultaneously. Likert scores were summarised using medians (range). Differences in median and minimum scores ≥ 1 were defined as showing clinically significant inter-prescriber variability. Likert scores were compared using Mann-Whitney U tests.
Results. The median (range) ease of completing test scenarios overall was 3.0 (1-5). The best protection (Likert 5) was against erroneously omitting a dose and erroneously specifying 'as required' dose frequency for a regularly prescribed medicine. The worst protection (Likert 1) was for six scenarios, three of which involved drug-drug interactions. Sequential prescribing was associated with greater protection than simultaneous prescribing for only one scenario involving duplicate enoxaparin prescribing (median 3.0 vs 1.0, p = 0.012). Inter-prescriber variability was clinically significant for two scenarios: prescribing insulin aspart with inappropriate units (median 4.5, minimum 2), and prescribing phenytoin chewable tablets as 'applicatorsful' (median 3, minimum 2).
Discussion. Vulnerability testing of MedChart™ identified opportunities to improve protection against common prescribing errors. System protections were bypassed due to varying prescriber workflows. These factors need to be carefully considered when designing and configuring CPOE system protections.

A18: Empiricism vs Mechanism – does it matter?

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Introduction. We are trained to rely on empirical statistical tests to determine statistical significance, and the BOT (Bloody Obvious Test) to determine whether we care about the result of the experiment. The DTMS test (Does This Make Sense) is relegated to whether the actual result agrees with prior beliefs (assuming our prior beliefs are right). Metformin-induced lactic acidosis (MALA) is a case example of ticking every box (statistical significance, BOT, DTMS), yet we are still wrong. There are three factors that govern our risk of wrongness (i) complicated biology, (ii) empiricism (letting only the data speak), recursion (nonlinear feedback).
Aims. To illustrate the influence of the three-factor problem with a toy insulin-glucose example and the more complicated MALA case.
Methods. Toy example: Historic empirical data was used to describe the influence of insulin on glucose (Ethics HD16/013). MALA case: A literature search was conducted and the proposed mechanisms of lactate associated acidosis were reviewed.
Results. Toy example: it was shown that insulin increases blood glucose concentrations. MALA case: two mechanisms were uncovered. In one case lactic acid deprotonates to cause acidaemia (lactate is the cause of acidosis), in the other case lactate is a bystander which reduces intracellular acidosis. The former agrees with 50 years of literature and clinical expectation but is mechanistically implausible. The latter is mechanistically plausible.
Discussion. We know the toy example is wrong and that analysis of this data would not cause an issue because the first-factor (the biology is complicated) is not sufficient to allow this misinterpretation to stand. The MALA case however fulfils all three factors and has caused empirical data to be misinterpreted for the last 50 years. The three-factor problem probably occurs more often than we think and may be important if your experiment yields different results from what you expect (i.e. you can't explain the results via your DTMS coffee session). A solution is to use an independent mechanistic framework for interpreting your data where the mechanism is not developed from the current data.

A19: Using Our Data to Improve Our Health

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Introduction. New Zealand is data-rich yet insight-poor for medicines optimisation. Research datasets inform generalisable knowledge, whereas routinely-collected health data describe real-world practice and outcomes for every patient. Harnessing both is essential for safe, effective and equitable use of medicines.
Aims. To describe the architecture, methods and early impact of an integrated medicines data programme, and to share practical lessons for clinicians, researchers and health system leaders.
Methods. Rich medicines data arrived at Christchurch Hospital with the introduction of electronic prescrinbing and administration in 2016. Initially hidden in complex application tables, the prescribing data were cleaned and extracted to the district data warehouse alongside other health data sets. Reporting layers of aggregated and patient level data were developed to support clinical governance and quality improvement. Data visualisation tools were used to develop and validate dashboards to examine medicines use with hierarchical variables to support a broad range of use cases.
Results. Dashboards to examine prescribing, drug-drug interactions, indications for medicines, and adverse drug reactions have been developed and deployed to support quality use of medicine. This includes continuous improvement of clinical decision support for prescribing using near real time data from the prescribing system.
Discussion. Health data enables a learning health system for medicines. Key enablers include clinical leadership and close collaboration between clinical and technical staff. Major challenges remain around consent models, indigenous data sovereignty, and sustainable resourcing for curation. We propose a vision of an open, standards-based medicines data ecosystem that supports continuous improvement of clinical systems using near clinical data. Next steps include scaling from one district to one country with many districts and to link data from multiple systems.

A20: Teaching and Assessment – a Tale of Two Prescribing Projects

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Introduction. Effective prescribing education for medical students requires both standardised assessment and authentic workplace learning experiences. Two projects addressed prescribing competency development.
Aims. Project 1 examined the educational and clinical utility of final-year medical students creating pre-prescriptions in live electronic prescribing systems (ePA) for doctor activation at Christchurch Hospital. Project 2 investigated implementation, student performance, and acceptability of the Australia and New Zealand Prescribing Skills Assessment (ANZ PSA) for final-year students across ANZ.
Methods. Project 1: interviews with students, post-graduate doctors, and supervisors were subjected to inductive thematic analysis. ePA prescribing data (2021-2024) were extracted and clinical records reviewed for potentially inappropriate prescriptions. Project 2: mixed-methods analysis of student data (n=6440, 2017-2019) including PSA scores and evaluation surveys.
Results. Project 1: Five themes emerged: 'Practice, practice, practice', 'Finding my place in work', 'Conquering time', 'Safety protected', and 'Becoming a real doctor'. Overall, 355/370 students completed 25,324 pre-prescriptions in 3,268 patients (median 63 per student), with doctors activating 58% to live prescriptions. Students mistakenly generated 296 live prescriptions; 33% had doses administered, 3% were potentially inappropriate with no documented adverse reactions. Project 2: Pass rates were 89% (2017), 85% (2018), 86% (2019) with minimal inter-school differences. Students provided positive feedback on interface clarity, but 35% cited insufficient time and 70% felt unprepared, with limited prescribing experience reported (69% completed ≤10 prescriptions during training).
Discussion. Electronic pre-prescribing enabled learning about safe prescribing and facilitated student-to-doctor transition. ANZ PSA demonstrated high pass rates, though student preparedness requires investigation. Together, these projects demonstrate complementary approaches: workplace learning for skill development and standardised assessment for competency verification.
Chin PKL et al (2023) BJCP 89: 3105-3115
Charles KA et al (2025) BJCP DOI: 10.1002/bcp.70126

A21: Embedding authentic research into undergraduate pharmacology education: An integrated lab and lecture model using a kinase exemplar

Dr Deanna Bell1, A/Prof Jack Flanagan1, Dr Leslie Schwarcz1. Department of Pharmacology and Clinical Pharmacology, Faculty of Medical and Health Sciences, University of Auckland, Auckland, NZ.

Abstract:
Over the past five years, we have developed and refined an integrated laboratory and lecture course for third-year molecular pharmacology students, designed to bridge core pharmacological principles with real-world application in drug discovery. Central to the course is an authentic research-question framework that immerses students in the process of target-based drug development, with a focus on lipid kinases.
Students apply core pharmacodynamic concepts concerning affinity, potency and efficacy, through a series of scaffolded experimental and computer-based activities. These include computational ligand screening and laboratory-based assays such as AlphaScreen and Kinase-Glo to determine IC_{50}, EC_{50} and Emax values. Emphasis is placed on experimental design, data interpretation, and numeracy, as students generate novel data addressing research questions not yet answered in the published literature.
Pedagogically, the course is underpinned by research-based teaching, assessment alignment, and relational teaching practices. We explicitly teach threshold concepts in pharmacology, supporting students' progression from knowledge acquisition to knowledge fluency. This course offers a model for embedding authentic, research-led learning into the undergraduate pharmacology curriculum, fostering both conceptual understanding and scientific identity development.

A22: Application of Virtual Reality to Pharmacology Learning

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Introduction. As greater numbers of students are being accepted into medical degree courses there is increasing pressure on scarce teaching and clinical immersion resources. In order to augment these scarce resources there is an opportunity to use emerging technologies such as virtual reality (VR) (non-immersive, semi-immersive and fully immersive) to provide some or all of the teaching and learning for selected learning objectives. Dunedin School of Medicine participated in a multicentre study of VR in pharmacology learning, and this presentation is the local results.
Aims. To assess the usability and user experience of VR animations in teaching pharmacokinetic principles.
Methods. Fourth year medical students were recruited from the Dunedin School of Medicine. The participants watched one VR animation video using a VR headset. After watching the VR animations, participants were asked to complete an online survey using SurveyXact. The primary outcome was the System Usability Scale (SUS). Statistical analysis was performed using Stata Intercooled Version 16.1. The survey was anonymous. Ethics approval was obtained via the University of Otago Human Ethics committee. Written informed consent was obtained from each participant.
Results. The VR animation was watched and the survey completed by 22 Otago medical students. For 13 (59%) students, this was their first experience of VR. For 11 (50%) students the experienced changed their understanding of drug absorption. Two students found the weight of the headset uncomfortable and two experienced some technical difficulties. The mean (SD) SUS total score was 76.8 (13.1), which indicates good usability. None of the students reported that the animation conflicted with their prior understanding of pharmacology, and 19 (86.4%) participants agree or strongly agreed that it did not in any way conflict with their prior understanding. Eighteen (81.8%) participants agreed or strongly agreed that "The use of VR technology will make it easier for me to retain pharmacological knowledge.
Discussion. VR in pharmacology learning had good acceptability and a positive user experience.

A23: Is it time to replace the 'prescription' with the medication management plan?

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Introduction. A prescription is legally defined and regulated as a single task. This was valid in the mid 20th century when a patient 'problem' was treated with a short course of a single medicine determined in a single health encounter. The plan and order were recorded in the three lines of text of a prescription. The 21st century patient has one or more chronic conditions each managed with one or more medicines.
Aims. To question the existing definition of 'prescription' and propose a set of tasks to manage medicines.
Methods. Iterative review and updating of teaching prescribing to medical students in a clinical pharmacology course over 12 years. Concurrent implementation of electronic prescribing systems and prescribing complex medication regimens to complex patients in an acute general medical service informed iterative review.
Results. The WHO guide to good prescribing was initially used. We found the six steps did not capture the clinical tasks and iteratively developed an alternative framework. Lectures, workshops and tutorials were developed and used to evolve the framework. A medication management plan spans many health encounters across a health system, needing common definitions and standards. The plan with the patient to treat a new 'problem' is an update to the plan to treat existing diseases with medicines. In addition to ordering supply of product this includes: specifying monitoring of disease response and adverse effects at specified times; and scheduling review with criteria for dose titration and/or criteria to continue, cease or change treatment. Orders to renew product supply only sometimes coincide with clinical review. Definitions and standards for the tasks of medication management are lacking.
Discussion. Regulatory reform in Australia and New Zealand is redefining scopes of practice of health professionals. The different tasks required to manage each patient's medicines safely and effectively have not had similar attention. We have developed a three-step process to managed medicines of plan, act and review each with four tasks. Access to and effective use of medicines is constrained by an outdated definition of a prescription. It is time to define and agree the elements of a medication management plan. This includes: a living plan to treat with medicines, as well as the tasks of product supply and dose administration, and the tasks of monitoring responses and reviewing and updating treatment based on agreed goals and criteria for success (benefit) and failure (harm, or lack of response).

A24: Can a population model describing procalcitonin from neonates to adults predict infection status in ICU adults at admission?

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Introduction. Serum procalcitonin (PCT) concentrations increase during illnesses caused by infection. However, use of PCT to support diagnosis of infection is limited by high variability, particularly in adults in intensive care unit (ICU).
Aims: To determine whether a population PCT model, derived from data obtained from non-infected neonates and adults in ICU with infection/sepsis, could categorise an external set of 100 adult ICU patients into infection or non-infection categories at time of ICU admission.
Methods. In the external dataset 66 patients were admitted without infection and 34 patients with infection. PCT was quantified from leftover blood samples obtained for clinical use. Categorisation of infection status at admission was explored by running the model under two hypotheses: no infection (null) and infection. NONMEM's objective function value (OFV) was outputted for each subject under both hypotheses, with a reduction of ≥3.84 ($p<0.05$) required to reject the null hypothesis of no infection (the "OFV method"). A second method was explored, in which the model was used to generate a subject- and time- specific distribution of expected concentrations for the non-infected state. Subjects were categorised as infected if their observed PCT exceeded the 92.5th percentiles of the expected concentration distribution.
Results: Using the OFV method and the first PCT observation obtained, 98.5% of non-infected subjects and 84.8% of infected subjects were correctly categorised. Categorisation did not improve with additional PCT observations. The second method correctly categorised just 38.5% non-infected and 69.2% infected patients.
Discussion. Two approaches to using the model were explored in an external dataset. The OFV method was able to reliably exclude infection with one PCT observation at admission (specificity 98.5%, sensitivity 85%) and enabled incorporating more than one observation, although this did not improve the prediction. Future work includes refinement of the model by inclusion of the new dataset, combining PCT with CRP and time to event analysis.

A25: Computational Approaches for Small Molecule Drug Discovery

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The process of small molecule drug discovery remains an expensive and time-consuming process[1]. Computational methods can predict drug-receptor interactions, accelerating the exploration of chemical space and enabling an improved rate of hit identification. These methods predict drug-target interactions using different types of input data. Sequence-based approaches rely on one-dimensional (1D) inputs, such as ligand SMILES and protein sequences, or two-dimensional (2D) representations, including molecular graphs and predicted contact maps. Structure-based approaches incorporate three-dimensional (3D) protein structures, determined experimentally or predicted *in silico* (e.g., via AlphaFold2).

We have employed both structure-based[2,3] and AI-based structure-independent[4] approaches to identify G protein-coupled receptor (GPCR) orthosteric and allosteric small molecule ligands, using the adenosine A_1 receptor (A_1R) as a model system. Structure-based virtual screening was to identify design subtype-selective A_1R antagonists[2], exploiting a non-conserved sub-pocket within the orthosteric binding site[5]. Computational screening of a 4.6 million compound library and subsequent structure-guided optimization yielded subtype-selective A_1R orthosteric antagonists with nanomolar potency. More recently, we identified A_1R positive allosteric modulators (PAMs) using structure-based virtual screening[3]. This virtual screening targeted a challenging membrane-facing extrahelical pocket revealed by a cryo-EM structure[6]. We identified a lead PAM that enhanced A_1R agonist binding and potency, and had improved physicochemical properties relative to known A_1R PAMs.

To complement structure-based efforts, we developed PSICHIC (PhySIcoCHemICal graph neural network) , an artificial intelligence framework that predicts small molecule binding affinity and functional effects directly from sequence data[4]. By learning interpretable interaction fingerprints, PSICHIC achieves state-of-the-art accuracy in virtual screening tasks, even in the absence of structural information. In a screening campaign for A_1R agonists, PSICHIC successfully ranked the sole active novel compound within the top three candidate compounds. The residue- and atom-level interpretability provided by PSICHIC provides insight into the molecular determinants of binding and selectivity.

Together, these approaches illustrate how structural biology and artificial intelligence can be integrated to advance drug development, enabling the discovery of different types of ligands, even for pharmacologically challenging targets.

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A26: Pharmacokinetics, and efficacy/safety signals, of thioguanine administered by suppository in patients with refractory ulcerative proctitis

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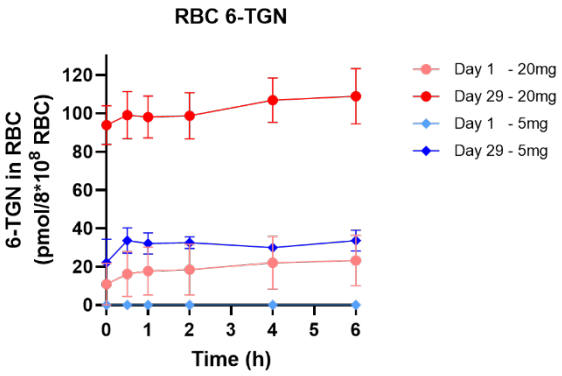
Introduction: Refractory proctitis can be difficult to manage even with newer inflammatory bowel disease treatments. A case series showed that rectal thioguanine appears to have a high rate of response. Thioguanine suppositories have been developed in NZ (Douglas Pharmaceuticals).

Aim: To assess the pharmacokinetics of thioguanine (TG) and its metabolite 6-thioguanine nucleotides (TGN), and assess for efficacy and safety signals, following rectal administration of thioguanine suppositories.



Methods: Eight patients with refractory ulcerative proctitis were prescribed either 20mg (n=6) or 5mg (n=2) thioguanine suppositories at night for 4 weeks. The pharmacokinetics of TG and TGN was assessed over 6h on days 1 and 29. Efficacy was assessed using weekly disease activity, and endoscopy scores before treatment and on day 29. Safety was assessed by weekly questionnaire and blood testing.

Results: RBC TGN concentrations on days 1 and 29 are shown in Figure 1. Clinical response at 4 weeks (SCCAI ≥3 point reduction) occurred in 8/8 patients (100%) and remission (SCCAI<3) in 3/8 (38%). Endoscopic remission (Mayo score 0 or 1) occurred in 6/8 patients (75%). UCEIS improved in 7/8 patients (88%) with remission in 4/8 (50%). No adverse effects were reported.

Discussion: In this phase IIa study, the efficacy at 4 weeks has high, without toxicity, with thioguanine 20mg or 5mg suppositories. TGN concentrations observed in RBCs were ~10-fold lower than seen with similar doses given orally.

A27: Potion, Poison, or Panacea? Getting the dose right for the 'new' wonder drug colchicine

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Potion. Colchicine is an alkaloid found in the plants *Colchicum autumnale* (autumn crocus) and *Gloriosa superba* (glory lily). Extracts from the bulbs of these plants have been harvested since antiquity for use as a potion, particularly in the treatment of gout flares.

Poison. Colchicine has long been recognised to process a narrow margin of safety. Inadvertent and intentional poisonings involving colchicine containing plants are a significant cause of morbidity and mortality [1]. As a modern therapeutic agent, colchicine is known to cause treatment-limiting gastrointestinal effects in therapeutic doses while severe myopathies, nerve damage, bone marrow suppression and death have been reported in acute overdose [2].

Panacea. The ability of colchicine to dampen the innate immune response has been exploited for the management of several inflammatory conditions including Familial Mediterranean Fever, Behcet's disease, pericarditis and others. More recently, colchicine has shown promise in the secondary prevention of cardiovascular disease. In short, colchicine appears to be a 'drug repurposing' success story.

Dosing. Colchicine dose requirements have historically been determined by trial and error. For some indications, a one-dose-fits-all approach has been employed despite a narrow margin of safety and variable pharmacokinetics. Evidence to support dose requirements in obese people, those with altered organ function, or for patients taking interacting drugs is scant. A speculative therapeutic range for steady-state colchicine plasma concentrations of 0.5-3 mcg/L has been proposed but this is not supported by clear evidence for efficacy and safety.

This talk will summarise the first steps towards a rational dosing approach for colchicine, including an exploration of the factors that predict the pharmacokinetics and exposure-response of colchicine.

1. Wijerathna,TM et al (2019) Clin Toxicol 57:1080-1086
2. Putterman et al (1991) Semin Arthritis Rheum 21: 143-155.
3. Wright DFB et al (2025) Clin Pharmacokinet https://doi.org/10.1007/s40262-025-01551-y