

**Australasian Society of Clinical and
Experimental Pharmacologists
and Toxicologists
and
Carney Symposium**

New Zealand Annual Scientific Meeting



**Beaven Lecture Theatre
University of Otago, Christchurch
29 – 31 August 2010**



SCIENTIFIC AND SOCIAL PROGRAMME

SUNDAY, 29 AUGUST 2010

6.00 – 7.30 pm **REGISTRATION AND OPENING RECEPTION - CAFÉ MEDICI**

MONDAY, 30 AUGUST

8:00 - 9:00 am **REGISTRATION**

Posters to be placed

Tea/Coffee/Danish pastry

9:00 am Welcome and Announcements

1. ASCEPT LECTURE

CHAIR: EVAN BEGG

9:05 am 1.1 **PLENARY SPEAKER**

Peter Molenaar, University of Queensland and Institute of Health and Biomedical Innovation, QUT, Queensland, Australia

The highs (β_{1H}) and lows (β_{1L}) of human heart β_1 -adrenoceptors (AR)

10:00 am 1.2 *Richard Robson, CCST Ltd, Christchurch*

Early phase Clinical Trials in New Zealand

10.30 am *Break*

Morning Tea available

2. CLINICAL

CHAIR: MURRAY BARCLAY

11:00 am 2.1* *Daniel Wright, University of Otago, Dunedin*

Is simvastatin really more effective when taken in the evening?

* For consideration for student prize

11:15 am	2.2	<i>Andrew McKean, Hillmorton Hospital, Christchurch</i>	Drug usage to alleviate the adverse effects of clozapine is common
11:30 am	2.3	<i>Mark McKeage, University of Auckland, Auckland</i>	Detecting acute neurotoxicity during platinum chemotherapy by neurophysiological assessment of motor nerve hyperexcitability
11:45 am	2.4*	<i>Abhishek Gulati, University of Otago, Dunedin</i>	Development and evaluation of a clotting time test for monitoring enoxaparin therapy
12:00 noon	2.5	<i>Chris Cameron, Wellington Hospital, Wellington</i>	Blood, sweat and tears - the downside of enoxaparin therapy. How can we make it safer?
12:15 pm	2.6	<i>Alasdair Millar, Southland Hospital, Invercargill</i>	Guidelines for medical thromboprophylaxis based on risk factor weights: pilot study
12:30 pm	<i>Break</i>		
	<i>Lunch available</i>		

3. PHARMACOKINETICS

CHAIR: BERIT JENSEN

1:30 pm	3.1	<i>Paul Chin, Christchurch Hospital, Christchurch</i>	An empirical equation for maintenance dose rate adjustment in adults based on pharmacokinetics
1:45 pm	3.2*	<i>Lee-Kien Foo, University of Otago, Dunedin</i>	Designs for bridging studies in pharmacokinetics
2:00 pm	3.3	<i>Lisa Stamp, University of Otago, Christchurch</i>	Using allopurinol above the dose based on creatinine clearance is effective and safe in chronic gout, including in those with renal impairment
2:15 pm	3.4	<i>Murray Barclay, University of Otago, Christchurch</i>	Effects of changing from oral to subcutaneous administration of methotrexate on RBC MTX polyglutamate concentrations and disease activity in patients with rheumatoid arthritis

2.30 pm	3.5*	<i>Finna Shen, University of Otago, Dunedin</i>	A dosing regimen for immediate N-acetyl cysteine treatment of paracetamol overdose	* For consideration for student prize
2:45 pm	3.6	<i>Evan Begg, University of Otago, Christchurch</i>	Intratympanic versus intravenous delivery of dexamethasone into cochlear perilymph compared with plasma	
3.00 pm	<i>Break</i> <i>Afternoon Tea available</i>			

4. EXPERIMENTAL SCIENCE

CHAIR: JANE VELLA-BRINCAT

3.30 pm	4.1*	<i>Virginia Ip, University of Auckland, Auckland</i>	Differential expression of ATP7A, ATP7B and CTR1 in adult rat dorsal root ganglion tissue	* For consideration for student prize
3:45 pm	4.2*	<i>Pradeep Lukka, University of Auckland, Auckland</i>	Tumour pharmacokinetics and lipophilicity of benzonaphthyridine derivatives in mice	* For consideration for student prize
4:00 pm	4.3*	<i>Helle Larsen, University of Otago, Christchurch</i>	LC-MS/MS assay for the determination of total and free concentrations of lorazepam, oxazepam and temazepam in human plasma	* For consideration for student prize
4:15 pm	4.4	<i>Paul Fawcett, University of Otago, Dunedin</i>	The effect of monoketocholate on the pharmacodynamics and pharmacokinetics of morphine 6-glucuronide in rat	
4.30 pm	4.5	<i>David Joyce, University of Western Australia, Australia</i>	Methotrexate-induced apoptosis in macrophages requires extracellular adenosine accumulation but is not mediated through nf-kb suppression	

4:45 pm **ASCEPT AGM**

POSTER

- Poster 1 *Hesham Al-Sallami, University of Otago, Dunedin*
A rationale for the routine monitoring of anti-activated Factor X (Anti-Xa) during enoxaparin treatment
- Poster 2 *Carolyn Coulter, University of Otago, Dunedin*
Prediction of Torsades De Pointes – amisulpride case series
- Poster 3 *Yan Li, University of Auckland, Auckland*
The effect of curcumin on multi-drug resistance protein 5 (MRP5) – mediated resistance in pancreatic cancer
- Poster 4* *Julia Korell, University of Otago, Dunedin*
Design of survival studies for red blood cells
* For consideration for student prize
- Poster 5 *Johnson Liu, University of Auckland, Auckland*
Studies of copper and platinum uptake and toxicity in cultured primary sensory neurons
- Poster 6* *Simran Maggo, University of Otago, Dunedin*
Statin induced anxiety: What happens when you make guinea pigs swim
* For consideration for student prize

7.00 pm

CONFERENCE DINNER AT OCTAGON LIVE

TUESDAY, 31 AUGUST



6TH ANNUAL CARNEY PHARMACOGENOMICS SYMPOSIUM

8:00 – 9:00 am **CARNEY REGISTRATION**

Tea/Coffee/Danish pastry

9:00 am Welcome and Announcements

5. PLENARY

CHAIR: MARTIN KENNEDY

9.05 am 5.1 **PLENARY SPEAKER**

David Joyce, University of Western Australia

Drugs metabolised by Cytochrome P450 2D6: Drug assay and pharmacogenomics in clinical decision making

10.00 am 5.2 *Andrew Lea, Genetic Test Evaluation Program, Hayes Inc*

Pharmacogenomic Tests: The Good, the Bad and the Unknown

10:30 am *Break*

Morning Tea available

6. PHARMACOGENETICS

CHAIR: EVAN BEGG

11.00 am 6.1 *Chris Frampton, University of Otago, Christchurch*

Understanding statistical analyses as a process of extracting 'signal' and 'noise'

11.25 am 6.2 *Barry Palmer, University of Otago, Christchurch*

Cardiovascular pharmacogenetics – gems or junk

11.50 am	6.3	<i>Berit Jensen, University of Otago, Christchurch</i>
		Total and free clearance of R- and S-warfarin in elderly people
12.05 pm	6.4	<i>Dhairesh Patel, Christchurch Hospital, Christchurch</i>
		Is frailty associated with impaired drug clearance in the elderly?
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12.20 pm	<i>Break</i>	
	<i>Lunch available</i>	
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7. CARNEY SESSION 1

CHAIR: REBECCA ROBERTS

1:30 pm	7.1	<i>Janet Coller, University of Adelaide, Australia</i>
		Impact of Donor and Recipient ABCB1, CYP3A5 and immune genetics on kidney transplant outcome
1.50 pm	7.2	<i>Mik Black, University of Otago, Dunedin</i>
		Pharmacogenomics of breast cancer treatment
2.10 pm	7.3*	<i>Wing-Yee Lo, University of Auckland, Auckland</i>
		Effect of tumour burden on CYP2C19 drug metabolising activity in patients
		* For consideration for student prize
2.25 pm	7.4	<i>Tony Harley, University of Otago, Christchurch</i>
		Antidepressant specific changes in rat whole blood gene expression identified by Gene-Chip Analysis
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2.40 pm	<i>Break</i>	
	<i>Afternoon Tea available</i>	
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8. CARNEY SESSION 2

CHAIR: PAUL CHIN

3:15 pm	8.1	<i>Rebecca Roberts, University of Otago, Dunedin</i>
		Are there pharmacogenetic indicators for allopurinol combination therapy in inflammatory bowel disease?

- 3:30 pm 8.2 *Les Sheffield, Murdoch Childrens Research Institute, Australia*
Comparison of predicted dose versus actual dose using pharmacogenomic algorithms in 483 patients on long term warfarin therapy
- 3:45 pm 8.3 *Richman Wee, University of Otago, Dunedin*
Tailor-making pharmacogenetic research for the New Zealand context: ethical, legal & policy issues
- 4:00 pm 8.4 *EM Peñas-LLedó, University of Extremadura, Spain*
CYP2D6 and psychological functioning
- 4:15 pm 8.5 *A LLerena, Extremadura University Hospital and Medical School, Spain*
Pharmacogenetics in Hispanics and Latinamericans: implication for psychiatry
- 4:30 pm **CLOSING STATEMENT AND SESSION CLOSED**

REGISTRANTS 2010

SURNAME	FIRST NAME	DEPARTMENT	INSTITUTE/ORGANISATION
Aitchison	Alan		University of Otago, Christchurch
Al-Sallami	Hesham	School of Pharmacy	University of Otago, Dunedin
Bagshaw	Andrew		University of Otago, Christchurch
Barclay	Murray	Clinical Pharmacology	University of Otago, Christchurch
Beckman-Persson	Cecilia		University of Otago, Christchurch
Begg	Evan	Clinical Pharmacology	University of Otago, Christchurch
Bengtsson	Karin		University of Otago, Christchurch
Berglund	Marie		University of Otago, Dunedin
Black	Mik	Biochemistry	University of Otago, Dunedin
Borrie	Tracey	Clinical Pharmacology	Christchurch Hospital
Buffery	Pam	Clinical Pharmacology	Christchurch Hospital
Cameron	Chris	Wellington Hospital	Capital & Coast DHB
Chin	Paul	Clinical Pharmacology	Christchurch Hospital
Coller	Janet	Pharmacology	University of Adelaide, Australia
Coberger	Elle	Clinical Pharmacology	Christchurch Hospital
Coulter	Carolyn	School of Pharmacy	University of Otago, Dunedin
Doudney	Kit		University of Otago, Christchurch
Doogue	Matt		Flinders University of South Australia
Duffull	Stephen	School of Pharmacy	University of Otago, Dunedin
Fawcett	Paul	School of Pharmacy	University of Otago, Dunedin
Fitches	Allison		University of Otago, Dunedin
Foo	Lee-Kien	School of Pharmacy	University of Otago, Dunedin
Frampton	Chris		University of Otago, Christchurch
Gibb	Andrew		University of Otago, Christchurch
Gulati	Abhishek	School of Pharmacy	University of Otago Dunedin
Han	Min-Hi		University of Otago, Christchurch
Harley	Tony		University of Otago, Christchurch
Hart	Joanne		Medsafe, Wellington
Helsby	Nuala	Molecular Medicine and Pathology	University of Auckland
Henshaw	Kathryn	Clinical Pharmacology	Christchurch Hospital
Ip	Virginia	Pharmacology & Clinical Pharmacology	University of Auckland
Innes	Caroline	Clinical Pharmacology	Christchurch Hospital
Jensen	Berit	Clinical Pharmacology	University of Otago, Christchurch
Jodczyk	Sarah		University of Otago, Christchurch
Joyce	David	School of Medicine & Pharmacology	University of Western Australia
Joyce	Peter		University of Otago, Christchurch
Keir	Pam		Roche Diagnostics, Christchurch
Kennedy	Martin	Gene Structure	University of Otago, Christchurch
Khwaounjoo	Prashannata	Pharmacology & Clinical Pharmacology	University of Auckland
Kidd	Alexa	Molecular Pathology	CDHB
Kim	Yaeseul	Pharmacology & Clinical Pharmacology	University of Auckland
Korell	Julia	School of Pharmacy	University of Otago Dunedin
Lagishetty	Chakradhar	School of Pharmacy	University of Otago Dunedin
Larsen	Helle	Clinical Pharmacology	University of Otago, Christchurch
Lavery	Dick		University of Otago, Dunedin
Lea	Andrew		Genetic Test Evaluation Program, Hayes Inc
Li	Yan	Pharmacology & Clinical Pharmacology	University of Auckland
Liu	Johnson	Pharmacology & Clinical Pharmacology	University of Auckland
LLerena	Adrián		Extremadura University Hospital and Medical School, Spain
Lo	Wing-Yee	Molecular Medicine and Pathology	University of Auckland
Lukka	Pradeep	Pharmacology	University of Auckland
Maggo	Simran	Pharmacology	University of Otago Dunedin
Maling	Tim		Central Coast DHB, Wellington

SURNAME	FIRST NAME	DEPARTMENT	INSTITUTE/ORGANISATION
McKeage	Mark	Pharmacology & Clinical Pharmacology	University of Auckland
McKean	Andrew	Pharmacy Department	Hillmorton Hospital, Christchurch
Millar	Alasdair	Medical Department	Southland Hospital
Miller	Allison		University of Otago, Christchurch
Molenaar	Peter	Faculty Science and Technology	Queensland University of Technology, Brisbane, Australia
Owens	Katie	School of Pharmacy	University of Otago Dunedin
Palmer	Barry	School of Medicine	University of Otago, Christchurch
Patel	Dhairesh	Pharmacy Department	Christchurch Hospital
Paxton	James	Pharmacology & Clinical Pharmacology	University of Auckland
Pearson	John		University of Otago, Christchurch
Peñas- Lledó	E M		University of Extremadura, Spain
Pilbrow	Anna		University of Otago, Christchurch
Plajer	Sabine	Clinical Pharmacology	University of Otago, Christchurch
Reith	David	Paediatric and Child Health	University of Otago, Dunedin
Revalde	Jezrael	Pharmacology & Clinical Pharmacology	University of Auckland
Roberts	Rebecca	Biochemistry	University of Otago, Dunedin
Robson	Richard		CCST Ltd
Salis	Emma	School of Pharmacy	University of Otago, Dunedin
Sheffield	Leslie		GenesFX Health, Victoria, Australia
Shen	Finna	School of Pharmacy	University of Otago, Dunedin
Smart	Roger		Douglas Pharmaceuticals
Stamp	Lisa	School of Medicine	University of Otago, Christchurch
Vella-Brincat	Jane	Clinical Pharmacology	Christchurch Hospital
Wee	Richman		University of Otago, Dunedin
Wilson	Julia		University of Otago, Dunedin
Wright	Dan		University of Otago, Dunedin
Zhang	Mei	Clinical Pharmacology	University of Otago, Christchurch

ASCEPT (NZ) AGM 2010

Agenda of the Annual General Meeting to be held in Beaven Lecture Theatre, University of Otago
on Monday, 30 August at 4.45pm

1. Apologies
2. Minutes of 2009 AGM in Dunedin and matters arising
3. President's Report – EB
4. Treasurer's Report – PC
5. Other Business

MINUTES OF ASCEPT (NZ) ANNUAL GENERAL MEETING

Friday 4th September 2009 at 5:30pm in Department of Pharmacology and Toxicology,
Room 308 Adams Building, 18 Frederick Street, Dunedin

PRESENT

John Ashton, Murray Barclay, Evan Begg, Chris Cameron, Cynthia Darlington, Steve Duffull, Fred Fastier, Paul Fawcett, Michelle Glass, Greg Giles, Berit Jensen, Steve Kerr, George Lees, Tim Maling, Ray Morris, James Paxton, Ivan Sammut, Roger Smart, Paul Smith, Daniel Wright, Jacqui Carroll (scribe)

1. APOLOGIES

David Clark

2. MINUTES OF 2009 ANNUAL GENERAL MEETING

Approved

Moved (James Paxton)

Seconded (Murray Barclay)

3. TREASURER'S REPORT – JOHN ASHTON

- Sponsorships gratefully received from Douglas Pharmaceuticals \$1,000 and ASCEPT \$4,000NZD
- 59 registrants this year with subsidised registration for ASCEPT members as well as additional subsidising of registration, conference dinner for student members of ASCEPT. There was one application for travel grant received, and accepted
- The Fred Fastier term deposit account is sitting at \$12,756, with the account earning \$449 in interest (after tax). John raised the question whether this should be registered as a non-profit account
- Outgoings on a par with income for this conference. Bank balance, once all invoices settled, will be around \$6,000

4. COUNCIL'S REPORT – GEORGE LEES

- NZ membership is doing okay, there has been a push within this department to get students on board
- Christchurch will take over from this meeting; Evan Begg has already been nominated as Chair. Usually this takes place at the AGM but as no ratification required, this handover being endorsed now
- To go forward to Council is the concept of discounted membership for those who are members of both APSA and ASCEPT
- Evan Begg advised that:
 - the Strategic Planning Group (SPG) has been formed and will hold its first formal meeting during the AGM in December
 - RACP (as was) will be delegating training to ASCEPT. To take over and move forward and to augment the clinical element of meetings
 - a SPG sub-group will look into SIGs, as deemed that they are not up to full potential, how best formed and actually work, their numbers and how meeting run
- Ray Morris spoke for the Council:
 - there is to be a 5 year plan established:
 - ❖ to keep the discipline moving forward

- ❖ SIG's – annual scientific meetings (running of – possibility of Meetings First taking over the organisation of non scientific elements from local organising committee)
 - ❖ maintain and enhance collaborations with other associations
 - ❖ continued subsidising of registrations and finances
 - if organisation continues spending at its current rate there is a possibility it will be bankrupt in 7years
 - every 2nd year the ASCEPT AGM is run within the AHMRC meeting – fewer ASCEPT members attend this joint meeting, a possibility is that the timing does not work. Next year there will be a freestanding meeting in Melbourne. In 2011 the meeting will be in Perth held jointly with High Blood Pressure Research Council (HBPRC)
 - Ray was happy that the 1st training event between Australia and New Zealand would be taking place. There would be didactic half-day training before the ASCEPT meeting which includes advance trainee presentations during the afternoon/evening
 - there is a proposal being put forward that the theme for the SAC programme would be decided first, then a speaker chosen to match the theme. A deviation from history and an evolution that would bring benefits
- The New Zealand meeting will continue as is, at a similar time of year. The timing during the mid-semester break works for all groups and it will continue be a standalone event
 - ❖ Chris Cameron, Cynthia Darlington and James Paxton to email Evan with mid-semester dates for next year's meeting
 - Professor Ann Daly (Pharmacogenetics, Institute of Cellular Medicine, Newcastle University, UK) is this year's BPS visiting speaker, Ann will be Dunedin around 14th December and will presenting to School of Pharmacy and Department of Pharmacology & Toxicology
 - the relationship between Australasia and BPS/BTS has declined over recent years, partly due to the quality of speakers lowering and consequently the decline in reception they've received – there was a time when the BPS/BTS invited speaker would be a Nobel Prize Winner

Meeting closed 18:10

ASCEPT LECTURE – CHAIR: EVAN BEGG

1.1 PLENARY SPEAKER

THE HIGHS (β_{1H}) AND LOWS (β_{1L}) OF HUMAN HEART β_1 -ADRENOCEPTORS (AR). P Molenaar (1,2), P Klenowski (2), AB Semmler (2), K Chee (2), M Iconomou (2), N Tugiono (3), H Kiriazis (3), Q Xu (3), XJ Du (3), U Ravens (4), T Christ (4) & A Kaumann (5) (1) Department of Medicine, Univ of Queensland, Qld 4032, (2) Institute of Health and Biomedical Innovation, QUT, Qld 4059, (3) BakerIDI Heart and Diabetes Institute, Vic 3004, (4) Department of Pharmacology and Toxicology, Dresden Univ of Technology, Germany & (5) Department of Physiology, Development and Neuroscience, Univ of Cambridge, Cambridge, UK

The β_1 AR has two binding sites which can be activated to cause cardiostimulation. The first, termed, β_{1H} AR (high affinity site β_1 AR) is activated by noradrenaline and adrenaline and is blocked by relatively low concentrations of β -blockers including carvedilol. The other, termed, β_{1L} AR (low affinity site β_1 AR) has lower affinity for adrenaline and noradrenaline and is activated by some β -blockers including CGP12177 and pindolol at higher concentrations than those required to block the receptor. (-)-CGP12177 is a non-conventional partial agonist that causes modest and transient increases of contractile force in human atrial trabeculae. These effects are markedly increased and maintained by inhibition of phosphodiesterase PDE3. The stimulant effects of (-)-CGP12177 at human β_1 ARs were verified with recombinant receptors (Kaumann and Molenaar, 2008). However, Skeberdis et al (2008) proposed that the positive inotropic effects of CGP12177 are mediated through β_3 ARs in human right atrium. This proposal was not consistent with the lack of blockade of (-)-CGP12177 inotropic effects or increases in L-type Ca^{2+} current (I_{Ca-L}) by the β_3 AR blocker LY748,337 (1 μ M, Christ et al, 2010). In contrast, (-)-CGP12177-evoked increases in inotropic effects and I_{Ca-L} were blocked by (-)-bupranolol 1-10 μ M (Christ et al, 2010). Chronic infusion of (-)-CGP12177 (10 mg/Kg/24 hours) for 4 weeks in a mouse model of left ventricular hypertrophy induced by aortic constriction caused increases in ventricular wall thickness, fibrosis- and inflammation-related gene expression levels. β -Blockers with cardiostimulant effects mediated through β_{1L} AR could potentially be harmful in cardiac disease.

Christ T et al (2010) Br J Pharmacol, In press
Kaumann A and Molenaar P (2008) Pharmacol Ther 118, 303-336
Skeberdis VA et al (2008) J Clin Invest, 118, 3219-3227

1.2

EARLY PHASE CLINICAL TRIALS IN NEW ZEALAND. R Robson, CCST Ltd, Christchurch,

A brief overview of the history of clinical trials in New Zealand will be presented. The Standing Committee on Therapeutic Trials (SCOTT) was established in 1969 to (a) report to the Medical Research Council “research needs in the fields of therapeutics particularly clinical trials of new drugs”; (b) advisory service to the Department of Health “therapeutic trials of new drugs”. The fundamental purpose of SCOTT was to encourage clinical trial work to be undertaken in New Zealand and particularly phase III trials. In 1981 the terms of reference of SCOTT were altered to be “specific review of the safety, efficacy and scientific validity of the trial and the competence of the investigators”. With the alteration of the Medicines Act in 1981, SCOTT took on, not only an advisory role, but a regulatory role on behalf of the Ministry of Health. Since then the number of clinical trials approved by SCOTT has slowly increased over the decades and now averages approximately 100 new clinical trials / year. The majority of these clinical trials undertaken in New Zealand were phase III studies until the late 1990s. In 1999 Christchurch Clinical Studies Trust was established as a purpose-built unit to undertake phase I studies. Although earlier phase I and phase II work had been conducted in New Zealand this was a first for New Zealand. Subsequently Auckland Clinical Studies was established in 2006 and Primorus was established in Christchurch in 2005. With the advent of purpose-built units the number of early phase clinical trials has increased significantly in New Zealand. The safety of phase I studies has been quoted to have been safer than “window-cleaning” and data will be presented on the incidence of adverse events and significant adverse events.

2. CLINICAL – CHAIR: MURRAY BARCLAY

2.1

IS SIMVASTATIN REALLY MORE EFFECTIVE WHEN TAKEN IN THE EVENING? DFB Wright, VPK Vajjah, HS Al-Sallami, SB Duffull. School of Pharmacy, University of Otago, Dunedin, NZ.

Introduction: Simvastatin reduces serum low-density-lipoprotein (LDL) concentrations by inhibiting HMG-CoA reductase, the rate limiting enzyme for cholesterol production in the liver. Cholesterol synthesis follows a diurnal pattern, with peak production occurring at night. For this reason, it is usually recommended that simvastatin be taken as a single daily dose in the evening, on the grounds that this will result in a greater effect. The implication is that this will match peak plasma drug concentrations with peak cholesterol synthesis. However, while simvastatin has a relatively short time course in the plasma (half-life about 2 hours), the time course of effect on LDL is considerably delayed. We, therefore, question whether evening dosing will result in greater reductions in steady-state LDL concentrations compared to morning or dinnertime dosing, particularly in light of the reduced compliance noted with evening dosing. *Aim:* To explore the time course of simvastatin effect on LDL after morning, dinnertime, evening and non-compliant evening dosing (10% missed doses) using simulations from published pharmacokinetic-pharmacodynamic (PKPD) models. *Methods:* The PKPD model parameters, including variability between patients and error estimates, were sourced from two published models (Idkaidek NM et al 2008, Kim et al 2010). These were coded in MATLAB (2010a). Four LDL datasets were simulated, each containing one-thousand patients taking 40mg of simvastatin daily for 30 days. Daily dosing times were 0800, 1700 and 2200 hours, with an additional „non-compliant‘ (10% missed doses) group at 2200 hours. Diurnal LDL production was also simulated. Steady state LDL concentrations were compared by an unpaired, 2 sided t-test. *Results:* Percent reductions in LDL concentrations from baseline were significantly greater after evening dosing compared to morning (36.4±15.3 vs 32.1±16.9 [mean±SD] respectively, p<0.0001), however, when non-compliance with evening dosing was accounted for, this difference disappeared (32.4±15.9, p=0.22 compared to morning). Dinnertime dosing (36.8±16.5) also resulted in greater reductions in LDL compared to morning (p<0.0001) but not evening dosing (p=0.61). Simulations suggest that the differences in LDL concentrations are within the acceptable range for two bioequivalent products and hence are negligible clinically. *Conclusions:* Our simulations suggest that taking simvastatin in the evening is not superior to the morning or dinnertime dosing.

Idkaidek NM et al (2008) Saudi Pharmaceutical Journal 2008; 16: 82-84

Kim J et al (2010) Poster presentation, PAGANZ Annual Conference, Adelaide, SA Feb 8-10 2010

2.2

DRUG USAGE TO ALLEVIATE THE ADVERSE EFFECTS OF CLOZAPINE IS COMMON. A. McKean (1). J Vella-Brincat (2). (1) Pharmacy Department, Hillmorton Hospital, Christchurch (2) Dept of Clinical Pharmacology, Christchurch Hospital, Christchurch.

The aim of this audit was to describe what medicines are prescribed to treat the adverse effects of clozapine. Inpatients at Hillmorton Hospital and the Seagar’s Clinic, who had been taking clozapine for at least one month, were included. Medicines used to treat adverse effects of clozapine were identified from a combination of drug charts and medical records. There were 46 inpatients identified who had been taking clozapine for greater than one month. They had a mean age (± s.d.) of 38.8 (±11.3) years; a mean daily clozapine dose of 471 (± 216) mg and 70% (32/46) were male. A total of 108 medicines were identified as being prescribed to treat the adverse effects of clozapine. A mean of 2.3 (± 1.54) medicines were prescribed per patient. Of these medicines, 38% (41/108) were to treat constipation; 20% (22/108) to treat raised lipids and triglycerides; 15% (16/108) to treat gastric reflux; 14% (15/108) to treat hypersalivation; 6% (7/108) to treat type two diabetes mellitus; 4% (4/108) to treat tachycardia; 1% (1/108) to treat nocturnal enuresis and 1% (1/108) each to prevent priapism and for seizure prophylaxis. Polypharmacy to treat the adverse effects of clozapine is common. As clozapine is often the most effective option to treat schizophrenia for many patients, it is important to recognise and treat the adverse effect burden of clozapine without making the medicine regime excessively complicated or leading to further iatrogenic complications.

2.3

DETECTING ACUTE NEUROTOXICITY DURING PLATINUM CHEMOTHERAPY BY NEUROPHYSIOLOGICAL ASSESSMENT OF MOTOR NERVE HYPEREXCITABILITY. Andrew Hill (1,3), Peter Bergin (2), Fritha Hanning (3), Paul Thompson (3), Michael Findlay (3), Dragan Damianovich (3) & Mark J McKeage (1,3). (1) Cancer Clinical Pharmacology Research Group, School of Medical Sciences, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand, (2) Departments of Neurophysiology and (3) Department of Medical Oncology, Auckland City Hospital, Auckland, New Zealand.

Platinum-based drugs, such as cisplatin and oxaliplatin, are well-known for inducing chronic sensory neuropathies but their acute and motor neurotoxicities are less well characterised. Use was made of nerve conduction studies and needle electromyography (EMG) to assess motor nerve excitability in cancer patients during their first treatment cycle with platinum-based chemotherapy in this study. Twenty-nine adult cancer patients had a neurophysiological assessment either before oxaliplatin plus capecitabine, on days 2 to 4 or 14 to 20 after oxaliplatin plus capecitabine, or on days 2 to 4 after carboplatin plus paclitaxel or cisplatin, undertaken by a neurophysiologist who was blinded to patient and treatment details. Patients completed a symptom questionnaire at the end of the treatment cycle. Abnormal spontaneous high frequency motor fibre action potentials were detected in 100% of patients (n=6) and 72% of muscles (n=22) on days 2 to 4 post-oxaliplatin, and in 25% of patients (n=8) and 13% of muscles (n=32) on days 14 to 20 post-oxaliplatin, but in none of the patients (n=14) or muscles (n=56) tested prior to oxaliplatin or on days 2 to 4 after carboplatin plus paclitaxel or cisplatin. Repetitive compound motor action potentials were less sensitive and less specific than spontaneous high frequency motor fibre action potentials for detection of acute oxaliplatin-induced motor nerve hyperexcitability but were present in 71% of patients (n=7) and 32% of muscles (n=32) on days 2 to 4 after oxaliplatin treatment. Acute neurotoxicity symptoms, most commonly cold-induced paraesthesiae and jaw or throat tightness, were reported by all patients treated with oxaliplatin (n=22) and none of those treated with carboplatin plus paclitaxel or cisplatin (n=6). Abnormal spontaneous high frequency motor fibre activity is a sensitive and specific endpoint of acute oxaliplatin-induced motor nerve hyperexcitability, detectable on EMG on days 2 to 4 post-treatment. Objective EMG assessment of motor nerve excitability could compliment patient-reported symptomatic endpoints of acute oxaliplatin-induced neurotoxicity in future studies. Supported by the Cancer Society of New Zealand.

2.4

DEVELOPMENT AND EVALUATION OF A CLOTTING TIME TEST FOR MONITORING ENOXAPARIN THERAPY. A Gulati (1), J Faed (2), G Isbister (3, 4) & SB Duffull (1) School of Pharmacy, University of Otago, Dunedin 9054, Department of Pathology, School of Medicine, University of Otago, Dunedin, Department of Clinical Toxicology and Pharmacology, Calvary Mater Newcastle, NSW, Menzies School of Health Research, Charles Darwin University, Darwin, Australia

Introduction: Enoxaparin is a low molecular weight heparin (LMWH) anticoagulant and is used in the treatment of pulmonary embolism, deep vein thrombosis and acute coronary syndromes. Enoxaparin has a narrow therapeutic index and is associated with thrombosis if dosing is insufficient and bleeding after excessive dosing. There is no standard measure of enoxaparin clinical effectiveness. Rarely anti-Xa activity is used to assess the dose for enoxaparin, particularly where renal impairment is present, but has poor ability to predict the risk of clotting or bleeding, and can only be measured in a few hospitals in NZ at a delay of 1-3 days. *Aim:* The aim of the study was to develop a clotting time test for monitoring enoxaparin therapy. *Methods:* Our computerized model of the coagulation network was used to identify a plausible activating agent for a clotting time test with enoxaparin. In-vitro experiments were then carried out using equal volumes (100 μ L) of pre-warmed (37°C) human plasma and activator solution (equal volumes of 0.025 M calcium chloride and factor Xa, 0.005-5 μ M). Timing of clotting was measured using a digital timer and visual inspection to identify the appearance of fibrin (apparent as a sudden increase in turbidity). The effect of enoxaparin was determined at concentrations of 0.1-1U/mL (1:10 dilutions of enoxaparin in plasma). *Results:* Assessment of our computerized model identified either tissue factor or factor Xa as plausible activating agents for a clotting time test to assess anticoagulant effects of LMWH. In-vitro experiments with human plasma showed a clotting time prolongation of 2.4-fold in the presence of enoxaparin (0.1U/mL) where 2.5 μ M factor Xa was used to activate clotting. *Conclusion:* A clotting time test was developed and supported the mechanistic components of our mathematical model. This test needs to be assessed for reliability with normal and pathological plasma samples and ultimately clinical utility. In theory, a clotting time test similar to the prototype method could be performed at any laboratory that can perform basic coagulation tests.

2.5

BLOOD, SWEAT AND TEARS-THE DOWNSIDE OF ENOXAPARIN THERAPY. HOW CAN WE MAKE IT SAFER? C R Cameron, Wellington Hospital, Wellington South 6242.

After four recent fatal adverse events resulting from enoxaparin (Clexane®) therapy, a safety campaign was run at Capital & Coast District Health Board (C&C DHB). The cornerstone of the campaign was the establishment of a policy to guide safe prescribing practice in both primary and secondary care. The policy was developed in response to an audit of prescribers which confirmed that knowledge around prescribing enoxaparin in renal impairment and obesity, and monitoring of therapy via Anti-Xa levels was inadequate. Writing the policy was made more difficult by a paucity of validated research into the safety of enoxaparin in renal impairment, appropriate dose adjustments for the various degrees of renal impairment, and specific dose adjustments to be made on the basis of Anti-Xa levels. The policy adopted at C&C DHB is different to the dosing adjustments advised by the manufacturers of Clexane®, and to those advised by Medsafe. This presentation reviews the cases, looks at similarities and differences, and discusses strategies to make prescribing and administration of enoxaparin safer.

2.6

GUIDELINES FOR MEDICAL THROMBOPROPHYLAXIS BASED ON RISK FACTOR WEIGHTS: PILOT STUDY. JA Millar & CA Wright, Medical Department, Southland Hospital, Invercargill 9840

Current guidelines published by NICS or by the Australia and New Zealand Working Party for Prevention of Venous Thromboembolism provide for “consideration” of thromboprophylaxis in all patients, and deployment under a liberal interpretation of risk. We believe this approach leads to significant overuse of low molecular weight heparin (LMWH) in patients who receive little benefit but are exposed to the risk of bleeding (Millar, 2009), and argue that there is a need for precise patient selection based on the statistical weight of risk factors present in each case. We conducted a pilot observational study (n = 52) to assess the use of LMWH in relation to the above current guidelines (CG) and a new empirical guideline that took account of risk factor weights (WG), namely prophylaxis for (I) either a malignancy or previous history of DVT, (II) any 2 of post-phlebotic syndrome, recent surgery or ICU admission, or acute multi-organ sepsis; (III) any 3 of positive blood culture, peripheral vascular disease, symptomatic COPD, Grade IV heart failure, neurological disease with immobility excluding acute stroke, or acute colitis, or (IV) 1 of group II plus any 2 of group III. Exclusion factors were age < 40 y, admission to ICU or day ward, acute stroke, use of therapeutic heparin or warfarin, NFR status or admission under the care of JAM. **RESULTS:** No patient developed a symptomatic DVT, PE or major bleed. Only five patients were given LMWH. Twenty three (all > 60 y, cancer, 8; heart failure, 2; or COPD, 13) and 11 (cancer, 10; COPD, 8; heart failure, 2; colitis, 2 and 1 each of prior DVT, recent surgery or PVD) patients were eligible under CG and WG criteria respectively. The proportion of eligible patients under CG and WG guidelines was 0.44 and 0.21 respectively. **CONCLUSIONS:** Thromboprophylaxis at Southland Hospital is well below current guidelines but this may be beneficial. Application of empirical weighted eligibility is practical but the WG used here may not be optimal. The eligibility is driven by malignancy and respiratory disease (both criteria) and age (CG), both of which are frequent co-morbidities or primary reasons for admission.

Millar JA (2009) Int Med J, 39, 606-612

3. PHARMACOKINETICS – CHAIR: BERIT JENSEN

3.1

AN EMPIRICAL EQUATION FOR MAINTENANCE DOSE RATE ADJUSTMENT IN ADULTS BASED ON PHARMACOKINETICS. PKL Chin, EJ Begg. Department of Clinical Pharmacology, Christchurch Hospital, Private Bag 4710, Christchurch.

Background Maintenance dosing of drugs should be tailored for the individual patient in relation to factors altering clearance such as renal and metabolic function. Initial maintenance dosing of renally eliminated drugs is based on the fraction excreted unchanged of the drug and an assessment of the glomerular filtration rate of the patient. It is currently less clear how to dose for drugs that have a significant component of metabolic elimination.

Aim To develop a pharmacokinetically based empirical equation for estimating the initial maintenance dose rate for both renally and metabolically eliminated drugs using readily available clinical variables. *Method* The equations developed for estimating renal function were used as the basis for exploring clinical variables for estimating maintenance dose rates of metabolically eliminated drugs. This was then combined with the equation for adjusting the maintenance dose rate for renally eliminated drugs. *Results* Initial clinical variables considered included age (reflecting the decline in hepatic intrinsic clearance as per the hypothesis of Butler and Begg), weight (using the model for scaling physiological parameters according to Anderson and Holford), gender, and hepatic function biomarkers such as albumin. An empirical equation was then derived for estimating initial maintenance dose rate for metabolised drugs in daily clinical practice based on age and weight as modifiers of metabolic function. Combining this equation with the equation for adjusting maintenance dosing of renally eliminated drugs produced an equation unifying the dose-adjustment for the two main types of drug clearance, with weighting of each type according to the fraction excreted unchanged. *Conclusion* An empirical pharmacokinetic equation using readily available clinical variables may be used to provide an initial estimate of maintenance dose rate for all drugs.

Butler JM, Begg EJ. Clin Pharmacokinet 2008; 47: 297-321.

Anderson BJ, Holford NHG. Drug Metab Pharmacokinet 2009; 24: 25-36.

3.2

DESIGNS FOR BRIDGING STUDIES IN PHARMACOKINETICS. L.-K.Foo. & S.B.Duffull. School of Pharmacy, University of Otago, Dunedin, 9054, New Zealand.

Introduction. Bridging studies are used to extrapolate information gathered from clinical studies in an original region (e.g. adult patients) to a new region (e.g. paediatric patients). Since the pharmacokinetics (PK) of original and new regions may be different then an optimally designed experiment based solely on the original region may be suboptimal and possibly fail when applied to the new region. *Aim.* To develop an adaptive design strategy that will be optimal for bridging studies. *Methods.* We propose the application of a D-optimal adaptive design, where patients are enrolled in batches and analysed cumulatively and the design optimized for the next batch based on the current best estimates of the parameters over the cumulative batches enrolled to date. We test this method with two scenarios (1) a bridging study from adults to paediatrics in which the optimal design from the adult study (original region) is close to optimal for the paediatric population (target region) – this serves as a positive control; (2) a bridging study from normal weight adults to obese adults for a large molecule in which the optimal design from the normal weight adult study is poor for the target population – this serves as a negative control since the target population is widely divergent from the original population. *Results.* (1) The optimal design from the adult study provided good parameter estimates for the paediatric study and the proposed adaptive design method was not inferior. (2) The proposed method performed significantly better than the optimal design from the normal weight adults which resulted in poor parameter estimates for the obese adults. *Conclusion.* Adaptive optimal designs are potentially useful for conducting bridging studies in pharmacokinetics since it provides reasonable parameter estimates for the new region even when the PK profile of the original and new regions are widely divergent.

3.3

USING ALLOPURINOL ABOVE THE DOSE BASED ON CREATININE CLEARANCE IS EFFECTIVE AND SAFE IN CHRONIC GOUT, INCLUDING IN THOSE WITH RENAL IMPAIRMENT. LK Stamp(2,3), JL O'Donnell (2), M Zhang (1), J James (2), C Frampton (3), ML Barclay (1,3), PT Chapman (2,3). Departments of (1) Clinical Pharmacology & (2) Rheumatology, Immunology and Allergy, Christchurch Hospital, & (3) Department of Medicine, University of Otago, Christchurch.

Aim: To determine the efficacy and safety of increasing allopurinol dose above current proposed dosing guidelines in patients with gout. *Methods:* Patients with gout on stable dose allopurinol for \geq one month were recruited. Allopurinol dose was increased to obtain the target serum urate (SUA) $<0.36\text{mmol/L}$ (6mg/dL). Patients were seen monthly until SUA was $<0.36\text{mmol/L}$ (6mg/dL) for 3 consecutive months, then 3 monthly until at least 12 months. Data were analyzed using allopurinol mg/day above recommended dose, as defined by the Hande criteria. *Results:* Ninety patients were enrolled. Mean age 58.3years (range 27-83yrs), 87.8% male, and 78% European. 45 patients had SUA $\geq 0.36\text{mmol/L}$ (6mg/dL) and had allopurinol dose increased. Three patients developed rashes and discontinued allopurinol or ceased dose escalation. Six patients were lost to follow-up. 31/35 (88%) patients who completed the study achieved a SUA $<0.36\text{mmol/L}$ (6mg/dL) at the 12 months. 2/5 patients who had SUA $\geq 0.36\text{mmol/L}$ (6mg/dL) had undetectable plasma oxypurinol indicating non-compliance. There was a significant reduction in SUA at all allopurinol doses above recommended ($p<0.001$). 18/45 patients were receiving frusemide or a thiazide diuretic. Patients on frusemide were just as likely to achieve SUA $<0.36\text{mmol/L}$ (6mg/dL) as those not on frusemide (72% vs 88.5% $p=0.24$). Patients on frusemide required a higher dose to achieve the target serum urate. There were no serious adverse events. *Conclusion:* Increasing allopurinol above the proposed CrCL based dose led to a significant reduction in serum urate. 86% of patients achieved a SUA $<0.36\text{mmol/L}$ (6mg/dL). There was no increase in toxicity with higher doses of allopurinol in this cohort, including those with renal impairment.

3.4

EFFECTS OF CHANGING FROM ORAL TO SUBCUTANEOUS ADMINISTRATION OF METHOTREXATE ON RBC MTX POLYGLUTAMATE CONCENTRATIONS AND DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS. ML Barclay (1,3), LK Stamp(2,3), JL O'Donnell (2), M Zhang (1), J Drake (2), C Frampton (3), PT Chapman (2,3). Departments of (1) Clinical Pharmacology & (2) Rheumatology, Immunology and Allergy, Christchurch Hospital, & (3) Department of Medicine, University of Otago, Christchurch.

Aim: To determine the effects of changing from oral to subcutaneous (SC) methotrexate (MTX) in patients with active rheumatoid arthritis (RA) on red blood cell MTX polyglutamate (RBC MTXGlu) concentrations, disease activity and adverse effects. *Methods:* 30 patients receiving weekly low dose MTX for RA were changed from oral to SC administration. Disease activity was assessed by DAS28 at weeks 0, 8, 16 and 24. Responders were defined as having a reduction in DAS28 >0.6 . Trough RBC MTXGlu concentrations were measured by HPLC weekly until week 8, then fortnightly until week 16, then 4-weekly until week 24. *Results:* Of the 30 patients, 76.7% were female and mean age was 51.8 years (32-70). The median dose of MTX was 20mg/week (10-20). A decrease in DAS28 was associated with an increase in RBC MTXGlu₅ ($p=0.035$) and RBC MTXGlu₃₋₅ ($p=0.032$). There was a significant reduction in the proportion of RBC MTXGlu₁ and MTXGlu₂ and an increase in proportion of RBC MTXGlu₃, MTXGlu₄, and MTXGlu₅ contributing to the total RBC MTXGlu from week 0 to week 24. MTXGlu₃, MTXGlu₄, MTXGlu₅ and MTXGlu₃₋₅ concentrations fitted a first-order exponential model well whilst MTXGlu₁ and MTXGlu₂ fitted poorly. No change in adverse effect frequency was seen between weeks 0 and 24. *Conclusion:* Changing to SC MTX results in an alteration in the ratio of long and short chain MTX polyglutamates and improved disease activity in some patients. However, it takes at least 6 months for steady state concentrations to be achieved.

3.5

A DOSING REGIMEN FOR IMMEDIATE N-ACETYL CYSTEINE TREATMENT OF PARACETAMOL OVERDOSE. F Shen (1), CV Coulter (1), GK Isbister (2) & SB Duffull (1); (1) School of Pharmacy, University of Otago, Dunedin, NZ & (2) Department of Clinical Toxicology, Calvary Mater Hospital, Newcastle, Australia/Discipline of Clinical Pharmacology, University of Newcastle, Newcastle, Australia

Paracetamol is often implicated in poisonings due to its wide accessibility. N-acetyl cysteine (NAC) is an effective antidote. The conventional dosing regimen for NAC incurs an initial delay of at least four hours post-paracetamol overdose and is started by a high rate NAC infusion often leading to adverse reactions. The aim was to develop a dosing regimen for NAC that can be administered immediately upon presentation of paracetamol overdose. Using a published population pharmacokinetic model of NAC (Brown *et al.* 2004) proposed dosing regimens were simulated in MATLAB and compared to the conventional dosing regimen. Two hypothetical scenarios were considered, the first where the patient arrives 2 hours post-overdose and there is a 4 hour delay, and the second where there is a further delay to 8 hours post-overdose (the commonly accepted maximum delay). The proposed infusions started immediately on presentation of the patient rather than waiting for the paracetamol concentration result and were chosen to give an area under the concentration-time curve (AUC) value that is the same or higher than the conventional regimen on 90% of occasions. If the paracetamol concentration is below the treatment threshold on the nomogram (BNF 2009) the treatment is discontinued. In the first scenario instead of the three-phase regimen of 150mg/kg over 1 hour, then 50mg/kg over 4 hours, then 100mg/kg over 16 hours, the proposed regimen consists of a dose of 110mg/kg to be given over 5 hours which would be followed by the infusion of 50mg/kg over 4 hours. In the second scenario the proposed regimen consists of 104mg/kg over 7 hours then the infusion of 50mg/kg over 4 hours. Both proposed NAC regimens use a lower rate infusion and avoids the high peak concentrations associated with adverse reactions while maintaining at least the same AUC over the interval of interest. The proposed regimens need to be prospectively assessed.

Brown M *et al.* (2004) *Eur J Clin Pharmacol* 60:717-23.
British National Formulary September 2009;58:29-31.

3.6

INTRATYMPANIC VERSUS INTRAVENOUS DELIVERY OF DEXAMETHASONE INTO COCHLEAR PERILYMPH COMPARED WITH PLASMA. EJ Begg (1), M Zhang (1), PA Bird (2). (1) Department of Department of Medicine, University of Otago, Christchurch. (2) Department of Otolaryngology, Christchurch

Background: Intratympanic (IT) drug administration may achieve higher concentrations in the inner ear and lower systemic concentration than intravenous (IV) administration. We have previously demonstrated this with methylprednisolone. *Objective:* To compare dexamethasone concentrations in the plasma and perilymph of the human ear after IT and IV administration. *Methods:* Dexamethasone sodium phosphate was given IT at a dose 4mg (1 mL of a 4 mg/mL solution) or IV at 0.17mg/kg, around 0.5 to 2 hours prior to cochlear implantation. The IT dose was injected into the middle ear cavity through the external auditory canal via a 27-gauge needle passed through a small anterosuperior myringotomy. The IV dose was given as a single injection over 30 secs. A single sample of around 20µl of perilymph was collected using a needle passed through the round window, and blood was sampled simultaneously. Concentrations of free dexamethasone and dexamethasone sodium phosphate were measured using a validated LC/MS-MS method. *Results:* In 22 patients studied, 22 perilymph and 19 plasma samples were measurable. The median perilymph concentration of dexamethasone after IT administration was 1.4 mg/L (n=13, range 0.1 to 16.3), and 0.016 mg/L (n=9, range 0.008 to 0.17) after IV administration, representing 88-fold difference (p=0.0004). The median plasma concentration after IT injection was 0.003 mg/L (n=12, range 0.0005 to 0.005) and 0.12 mg/L (n=7, range 0.07 to 0.14) after IV injection, representing a 40-fold difference (p=0.0005). Concentrations of dexamethasone sodium phosphate were of similar magnitude but more variable. *Conclusion:* Administration of dexamethasone IT results in much higher perilymph concentrations and much lower plasma concentrations compared with IV administration.

4. EXPERIMENTAL SCIENCE II - CHAIR: JANE VELLA-BRINCAT

4.1

DIFFERENTIAL EXPRESSION OF ATP7A, ATP7B AND CTR1 IN ADULT RAT DORSAL ROOT GANGLION TISSUE. V Ip (1), J Liu (1), J Mercer (2) & M McKeage (1), (1) Department of Pharmacology and Clinical Pharmacology, University of Auckland, Auckland, New Zealand, (2) Centre for Cellular and Molecular Biology, School of Life and Environmental Sciences, Deakin University, VIC 3125

ATP7A, ATP7B and CTR1 are metal transporting proteins that control the cellular disposition of copper and platinum drugs, but their expression in dorsal root ganglion (DRG) and their role in platinum-induced neurotoxicity are unknown. Expression of these transporters in lumbar DRG and other tissues was determined using quantitative PCR, RT-PCR, immunohistochemistry and Western blot analyses in healthy adult rats and rats treated with oxaliplatin (1.85 mg/kg, I.P.) twice weekly for 8 weeks or drug vehicle as control. In healthy animals, DRG ATP7A mRNA was clearly detectable at levels comparable to that of brain and spinal cord. Intense ATP7A immunoreactivity was localised to the cytoplasm of cell bodies of smaller DRG neurons without staining of satellite cells, nerve fibres or co-localisation with phosphorylated heavy neurofilament subunit (pNF-H). High levels of CTR1 mRNA were detected in all tissues from healthy animals, and strong CTR1 immunoreactivity was associated with plasma membranes and vesicular cytoplasmic structures of the cell bodies of larger-sized DRG neurons without co-localisation with ATP7A. Morphometric analysis revealed that ATP7A- positive and CTR1- positive DRG neurons had distinct cell body size profiles with minimal overlap between them. Oxaliplatin treatment of rats did not alter the size profile of ATP7A-positive neurons but significantly reduced the size profile of CTR1-positive neurons. ATP7B mRNA was barely detectable in DRG tissue, and no specific immunoreactivity for ATP7B was found on DRG sections of healthy animals. In conclusion, rat DRG exhibits a specific pattern of expression of copper transporters with distinct subsets of peripheral sensory neurons intensely expressing either ATP7A or CTR1, but not both or ATP7B. The DRG neuron subtype-specific and largely non-overlapping distribution of ATP7A and CTR1 may be required to support the differing cuproenzyme requirements of distinct subsets of sensory neurons, and could influence the transport and neurotoxicity of oxaliplatin. The work was supported by Cancer Society of New Zealand.

4.2

TUMOUR PHARMACOKINETICS AND LIPOPHILICITY OF BENZONAPHTHYRIDINE DERIVATIVES IN MICE. P Lukka (1,2), JW Paxton (2), P Kestell (1), & BC Baguley (1), Auckland Cancer Society Research Centre (1), Department of Pharmacology & Clinical Pharmacology (2), The University of Auckland, Auckland, NZ.

SN28049 is one of a series of benzonaphthyridine derivatives demonstrating excellent anti-tumour activity in a colon-38 murine tumour model in comparison to standard topoisomerase II poisons (Deady et al, 2003). A homologous series of benzonaphthyridine derivatives with substitutions at N-2 (SN28101, -H; SN28049, -CH₃; SN28668, -C₂H₅; SN32116, -C₃H₇; SN28048, -C₄H₉) (see figure) were used to study the effect of increasing lipophilicity on pharmacokinetics and tumour uptake in mice. Five groups (n=30 per analogue) of C57 BL/6 female mice with subcutaneous colon-38 tumours (8–10 mm in diameter) received 25 µmol/kg ip dose of each analogue. Blood and tumour were collected at various time points (0.08–72 h; n=3 mice per timepoint) and samples were analysed by LC–MS. Pharmacokinetic analysis was performed using WinNonlin®. LogD values for the analogues were determined by the octanol/phosphate-buffered saline (pH=7.4) partition method. The plasma area under the concentration-time curve (AUC) for these compounds ranged from 3.30 ± 0.01 for the least lipophilic (SN28101) to 0.90 ± 0.03 µM.h for the most lipophilic (SN28048) and showed a significant negative correlation (r = -0.95; P = 2x10⁻⁶) with their LogD values. The tumour AUCs were much greater, ranging from 26.3±3.5 for SN28101 to 2334 ± 60 µM.h for SN28049 but did not correlate with LogD. The greatest tumour/plasma AUC ratio was observed for SN28049 (825 ± 56 fold), followed by 151 ± 15 for SN28668, 13 ± 6 for SN28048, 78 ± 15 for SN32116, and 8.7 ± 1.6 for SN28101. These results indicate the importance of lipophilicity in determining plasma, but not tumour exposure of these benzonaphthyridine derivatives in this colon-38 murine tumour model.

Deady LW et al. J. Med. Chem. 2003;46(6):1049-1054.

4.3

LC-MS/MS ASSAY FOR THE DETERMINATION OF TOTAL AND FREE CONCENTRATIONS OF LORAZEPAM, OXAZEPAM AND TEMAZEPAM IN HUMAN PLASMA. H S Larsen, B P Jensen & E J Begg, Clinical Pharmacology, Department of Medicine, University of Otago-Christchurch

Drug protein binding has been shown to change with age for many, but not all, drugs. For the benzodiazepines; lorazepam, oxazepam and temazepam, the results are few and conflicting. As part of a research project to investigate changes in protein binding with age, an assay was needed to measure total and free concentrations of these three drugs in human plasma. *Aim:* To develop and validate a sensitive and specific LC-MS/MS assay for measuring the total and free concentrations of lorazepam, oxazepam and temazepam in human plasma. *Methods:* Preparation for measurements of total concentrations was accomplished using acetonitrile (ACN) for protein precipitation, while ultrafiltration was used to separate of the free concentration. A chromatographic 4.5 minute separation was performed with a 35% ACN isocratic elution containing 0.1% formic acid (v/v) at a flow rate of 0.3 ml/min on a C₁₈-column. A one minute washing step reaching 90% ACN was included after 3 minutes. Deuterated lorazepam, oxazepam, temazepam were used as internal standards (IS). Mass spectrometric detection in positive mode was used monitoring the transitions *m/z* 321/275, 287/241, 301/255 for lorazepam, oxazepam and temazepam, respectively. Retention times were 2.06, 2.23 and 3.28 min for oxazepam, lorazepam and temazepam, respectively. *Results:* Standards curves in plasma (total), were linear when weighted 1/x in the range 10-100µg/L ($r^2 > 0.98$) (lorazepam), 200-2000 µg/L ($r^2 > 0.99$) (oxazepam) and 100-1000 µg/L ($r^2 > 0.99$) (temazepam). Standard curves in ultrafiltrate (free) were linear when weighted 1/x in the range 1-10µg/L ($r^2 > 0.99$) (lorazepam), 20-200 µg/L ($r^2 > 0.99$) (oxazepam) and 10-100 µg/L ($r^2 > 0.99$) (temazepam). Intra- and interday precision (% CV) were within 15% and bias was within 15% in all cases. The recovery after protein precipitation was >80% and matrix effects were negligible. In the ultrafiltrates all drugs (and each respective IS) had a matrix factor of ~70%. Several ultrafiltration devices were evaluated (Centrifree, Ultrafree, Amicon, Vivaspin), with Ultrafree having the lowest non-specific binding (6%). The drug protein binding was found to be independent of changes in temperature (room temperature and 37 °C) and whether the plasma was concentrated 1.4 fold by ultrafiltration. *Conclusion:* A sensitive and specific assay for measuring total and free concentrations of lorazepam, oxazepam and temazepam has been developed and validated.

4.4

THE EFFECT OF MONOKETOCHOLATE ON THE PHARMACODYNAMICS AND PHARMACOKINETICS OF MORPHINE 6-GLUCURONIDE IN RAT. JP Fawcett, L Yang, H Xhang & IG Tucker, School of Pharmacy, University of Otago

Previously the semi-synthetic bile salt, monoketocholate (MKC), has been shown to enhance the brain uptake of quinine and increase the activity of morphine and pentobarbital in rats (Mikov et al 2004). In the present study, the effect of MKC on the analgesic potency and brain concentration of morphine 6-glucuronide (M6G) was studied in rats. In the pharmacodynamic study, four groups of rats (n=8) were administered 5, 10 and 20 mg/kg MKC or normal saline (control) by subcutaneous (sc) injection 30 min before an sc dose of 5 mg/kg M6G. Hot-plate testing was performed on each rat at 5, 15, 30, 45, 60, 75, 90, 120, 150 and 180 min after the M6G dose. The area under the analgesic effect versus time curve (AUAE) was calculated for each rat and the MKC effect analysed by one-way ANOVA. The AUAE was significantly ($p < 0.05$) greater in the MKC treated rats than in the control rats but only at the highest dose of MKC. After a two week washout period, the same rats (n=30) were randomized to two equal groups (control and treatment) for the study of brain penetration of M6G. Rats were administered MKC (20 mg/kg sc) or normal saline (control) 30 min before the sc dose (5 mg/kg) of M6G administered on the contralateral side. At 30, 60, 90, 120 and 180 min after M6G administration, 3 rats from each group were euthanized by decapitation and blood and brain collected. Values of M6G area under the curve (AUC) in both plasma and brain were greater in MKC treated rats than in control rats but the brain:plasma AUC ratio was lower. This suggests that concomitant administration of MKC does not enhance the brain permeability of M6G in rat.

Mikov M et al (2004) Pol. J. Pharmacol. 56, 367-71.

4.5

METHOTREXATE-INDUCED APOPTOSIS IN MACROPHAGES REQUIRES EXTRACELLULAR ADENOSINE ACCUMULATION BUT IS NOT MEDIATED THROUGH NF- κ B SUPPRESSION. DA. Joyce, SZY. Lo, JH Steer. Pharmacology Unit, School of Medicine and Pharmacology, University of Western Australia, 35 Stirling Highway, Crawley, Western Australia 6009, Australia.

The canonical NF- κ B pathway is constitutively active in inflammatory macrophages. Interrupting NF- κ B signalling leads to apoptosis. Methotrexate, which is used in the management of the inflammatory arthritis, rheumatoid arthritis, leads to macrophage apoptosis *in-vitro*. We therefore examined MTX action in macrophages, particularly interactions between MTX, NF- κ B signalling and apoptosis. Caspase-3 activity, annexin-V affinity and cell-cycle analysis were used to identify steps in apoptosis of murine macrophages that had been exposed to MTX. We were able to confirm that the potent NF- κ B activator, TNF- α , could counter MTX-induced apoptosis in primary murine macrophages. A less potent activator (RANKL) could not. Neither could the primary macrophage differentiation and survival factor, Colony Stimulating Factor-1, which we found did not activate NF- κ B signalling. However, MTX did not suppress either constitutive or induced NF- κ B signalling, ruling out a direct apoptotic action through NF- κ B inhibition. The action of MTX did require the extracellular accumulation of adenosine. This is consistent with an action of 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), which has been reported to accumulate because of MTX inhibition of AICAR transformylase. However, adenosine receptor stimulation alone was insufficient for the induction of apoptosis, implying additional intermediaries in MTX-induced macrophage apoptosis.

5. PLENARY – CHAIR: MARTIN KENNEDY

5.1 PLENARY SPEAKER

DRUGS METABOLISED BY CYTOCHROME P450 2D6: DRUG ASSAY AND PHARMACOGENOMICS IN CLINICAL DECISION MAKING. David A Joyce, University of Western Australia, PathWest Laboratory Medicine & Sir Charles Gairdner Hospital, Perth, Western Australia.

Cytochrome P450 2D6 (CYP2D6) transformations contribute importantly to the elimination of basic lipophilic drugs, including many tricyclic antidepressants, selective serotonin reuptake inhibitors and antipsychotic drugs. Additionally, CYP2D6 transformation is responsible for creating biologically active metabolites from codeine and tamoxifen. CYP2D6 polymorphism allows substantial variation in activity within a population. In practice, though, CYP2D6 genotype is only very loosely predictive of a patient's response to most CYP2D6-transformed drugs. Measuring blood concentrations of CYP2D6 drugs or active metabolites after starting therapy should supply better dosing guidance, as it integrates all determinants of pharmacokinetics, not just those genetically determined. However, therapeutic ranges are very ill-defined for these drugs. For the psychotropic medications, this reflects substantial variation in disease responsiveness and toxicity (pharmacodynamics). Consequently, neither CYP2D6 genotyping nor drug or metabolite analysis is standard in the clinical care of unselected patients taking psychotropic medications. In the practice of specialist clinical pharmacology, where the question relates to non-response or toxicity in critical therapy of an individual patient, how can we integrate knowledge of a drug's transformation pathways, clinical observation and judicious use of genotyping or drug assay to optimise individual treatment? A good knowledge of the evidence base, recognition of non-pharmacokinetic determinants of response and toxicity, focused surveillance for response and toxicity take precedence in determining drug choice and dose, with a limited role for drug assay and genotyping. We will elaborate these concepts through examples drawn from psychiatric, pain management and oncological practice, with particular reference to the unresolved issue of CYP2D6 genotyping prior to prescribing tamoxifen.

5.2

PHARMACOGENOMIC TESTS: THE GOOD, THE BAD AND THE UNKNOWN. Andrew Lea PhD; Diane J. Allingham-Hawkins PhD, FCCMG, FACMG; Lisa Spock PhD; Susan A. Levine DVM, PhD. Genetic Test Evaluation Program, Hayes, Inc., 157 S. Broad Street Suite 200, Lansdale, PA 19446, USA.

Objectives: Pharmacogenomic tests have the potential to revolutionize personalized healthcare by allowing the accurate prediction of drug efficacy and/or the risk of adverse side effects. Unfortunately, many pharmacogenomic tests in the United States are made clinically available before sufficient evidence exists to support their routine use. The Genetic Test Evaluation (GTE) Program at Hayes, Inc., a private health technology research and consulting company, has performed evidence-based reviews of 20 widely available pharmacogenomic tests. *Methods:* All reviews are based on the ACCE model for assessing genetic tests that was developed by the Centers for Disease Control and Prevention (CDC). Comprehensive literature reviews were performed for each test evaluated and the relevant gray literature (conference proceedings, websites, etc.) was reviewed. A Hayes GTE Rating that reflects the strength and direction of the evidence was assigned for each possible unique application of a test. *Results:* Some tests, such as *BCR-ABL* testing to predict response to imatinib in chronic myelogenous leukemia patients and *HLA-B*5701* testing to detect those individuals most likely to experience a potentially fatal hypersensitivity reaction to abacavir, have been sufficiently studied and clinical utility can be demonstrated. For other tests, such as *KRAS* testing to predict response to the anti-epidermal growth factor receptor antibodies cetuximab and panitumumab used to treat metastatic colorectal cancer, there is consistent evidence of potential utility, although the number of patients studied to date is relatively small. The majority of tests reviewed (16/20; 80%), however, currently have either conflicting or inconsistent evidence, or the evidence is insufficient to evaluate their clinical utility. Of the 28 applications of the 20 tests evaluated, 22 (78.6%) were not supported by current evidence. As such, the use of these tests, which include *CYP2C19* and *CYP2D6* testing to predict response to clopidogrel or tamoxifen, respectively, and *CYP2C9* and *VKORC1* testing for management of warfarin dosing, among others, appears to be premature. *Conclusions:* Although a small number of pharmacogenomic tests have demonstrated clinical utility based on published evidence, for the majority, the current evidence does not support their use in routine clinical practice.

6. PHARMACOGENETICS – CHAIR: EVAN BEGG

6.1

UNDERSTANDING STATISTICAL ANALYSES AS A PROCESS OF EXTRACTING ‘SIGNAL’ AND ‘NOISE’. C. Frampton, University of Otago, Christchurch

The process of statistical analysis can be viewed as the systematic partitioning of variability within a dependent variable into ‘Signal’ and ‘Noise’. The Signal will usually represent the variability due to hypothesised effect(s) that are to be tested with the data and the noise is the variability not explained by these effects. These two components are extracted and the strength of the signal is evaluated with reference to the noise. The magnitude of the residual noise is then placed in context by further evaluating the extent to which this residual might be further partitioned and therefore, explained by additional measured and unmeasured factors and how much of it may be due to ‘random’ variation or imprecision in the process of measurement. Standard statistical procedures such as ANOVA (Analysis Of Variance) and regression are readily understood from this perspective, as methods which attempt to discriminate signal and noise amongst the variability inherent to any dependent measure. This perspective on statistical analysis will be presented in the context of a pharmacological question whereby the progressive identification of signal from noise will identify important determinants and assist understanding and quantifying the extent of ‘unexplained’ variability.

6.2

CARDIOVASCULAR PHARMACOGENETICS – GEMS OR JUNK. Dr Barry Palmer, Christchurch Cardioendocrine Research Group, Department of Medicine, University of Otago, Christchurch

Two genetic studies on a cohort of post-acute coronary syndrome patients demonstrate the potential of genetic polymorphisms as prognostic markers and guides to drug selection. The CYP1A1 T6235C polymorphism (rs4646903) has been linked to the development of coronary heart disease and smoking-related lung cancer. Patients with ACS (n=1251) were genotyped for rs4646903. Patients had a mean age of 67.0 years, 69.8% were male and followed over a median of 1.9 years. Patients with the CC genotype had poorer survival than TT/TC patients ($p=0.014$), independent of ethnicity and established clinical risk factors. After stratification by smoking history, the T6235C genotype was particularly associated with mortality in past or current smokers (mortality CC 23.5, TT/TC 9.4%; $p=0.019$) compared with those who had never smoked (mortality CC 11.1, TT/TC 11.5%; $p=0.853$). Carboxylesterase 1 (CES1) is an enzyme with broad substrate specificity, responsible for the activation of a number of ester prodrugs. It was hypothesised that CES1 genotypes might influence survival, through altered cholesterol homeostasis, decreased inactivation of clopidogrel and/or decreased activation of ACE inhibitors. Patients (n=1597) were genotyped for the CES1 polymorphism, p.Gly143Glu. Genotype frequencies for p.Gly143Glu were 96.8% wild-type and 3.2% heterozygous. The heterozygous p.Gly143Glu genotype was significantly associated with better survival in the overall cohort when adjusted for covariates ($p=0.024$) but not when unadjusted ($p=0.140$). In patients on clopidogrel treatment there was a marked decrease in mortality ($p=0.0001$), but there was no difference in mortality between the two genotype groups ($p=0.230$), even with covariates adjustment. These examples of potential pharmacogenetic effects from our cohort studies illustrate the potential of genetic testing to aid in the optimization of drug treatment. However the polymorphisms with the strongest pharmacogenetic influence are often rare and these studies border on the limits of statistical power.

6.3

TOTAL AND FREE CLEARANCE OF R- AND S-WARFARIN IN ELDERLY PEOPLE. BP Jensen (1), P Chin (2), RL Roberts (1,3), EJ Begg (1,2). (1) Department of Medicine, University of Otago, Christchurch, (2) Clinical Pharmacology, Christchurch Hospital, (3) Department of Biochemistry, University of Otago.

Background: Metabolic drug clearance (CL) has been consistently shown to be impaired in the elderly for flow-limited (high CL) drugs and for capacity-limited (low CL) drugs with low protein binding. In contrast, there have been conflicting results for capacity-limited drugs with high protein binding (McLean & Le Couteur, 2004). We hypothesize that CL of capacity-limited drugs with high protein binding is indeed decreased in the elderly and that the discordance between studies is the result of CL being estimated using total drug concentrations, rather than free (unbound) concentrations (Butler & Begg, 2008). *Aim:* To test the hypothesis that the CL of warfarin, which is a capacity-limited and highly protein bound drug (~99%), is impaired in the elderly. *Methods:* A steady-state blood sample was taken from 72 patients (age range 18-89 y) in routine treatment with warfarin. Concentrations of R- and S-warfarin were determined in plasma (total) and ultrafiltrate (free) by an LC-MS assay developed for the study. Total and free CL were determined and regressed against age. CYP2C9 genotype was assessed. *Results:* For R-warfarin a significant decrease with age was found for both total and free CL. For S-warfarin a decrease in free CL was found with age but no change was observed for total CL. The decrease in free CL of R- and S-warfarin was found to be ~0.5% per year. The protein binding of R-/S-warfarin was not significantly changed with age. CL of S-warfarin, but not R-warfarin, was clearly dependent on CYP2C9 polymorphism. The S/R-warfarin ratio could be used as a phenotype marker to identify patients with poor CYP2C9 activity. *Conclusion:* This data supports the hypothesis that the CL of warfarin is impaired in elderly people. More precise information was gained when measuring free CL.

Butler JM & Begg EJ (2008): Clinical Pharmacokinetics; 47: 297-321.

McLean AJ & Le Couteur DG (2004): Pharmacological Reviews; 56(2):163-84.

6.4

IS FRAILTY ASSOCIATED WITH IMPAIRED DRUG CLEARANCE IN THE ELDERLY? Patel D¹, Vella-Brincat J², Chin P³, Jensen B⁴, Begg E⁵ ¹ Intern Pharmacist, Christchurch Hospital Pharmacy, ² Drug Utilisation Pharmacist, Clinical Pharmacology, Christchurch Hospital, ³ Registrar, Clinical Pharmacology, Christchurch Hospital, ⁴Research Fellow, Clinical Pharmacology, University of Otago, Christchurch, ⁵ Clinical Pharmacologist, Christchurch Hospital.

Introduction: Frailty is a term for which there is no set definition. How to measure frailty is currently a contentious issue with various scales available, with their own drawbacks. The scales come from different groups, although key variables measured in them are similar. These include cognition, activities of daily living, nutrition and mobility. Few studies have assessed frailty and the clearance of drugs. *Aim:* To develop and use a telephone frailty assessment tool. To establish a relationship between frailty and clearance of warfarin in the elderly. *Method:* All elderly patients (> 65 years old) who had taken part in a warfarin clearance study in 2008/2009 were recruited. A frailty assessment tool was developed using existing published frailty scales. Ethics permission was sought and granted. Recruits were contacted initially by letter and then telephoned. Answers were recorded and used to allocate a score of frailty using the Canadian Study of Health and Aging scale, in 3 groups: fit, almost frail and frail. Statistical analysis of warfarin clearance was performed in relation to frailty. *Results:* There were 27 participants > 65 years old in the warfarin study, of which 23 were studied (1 died, 3 declined). Ages ranged from 66 to 86, median age was 73. There were 18 males and 5 females. Frailty scores separated these into 12 fit, 4 almost fit and 7 frail. When warfarin clearance was compared between the fit and the frail groups using a student-t test there were no significant differences, nor any marked trends. *Discussion:* No correlation was evident between frailty and warfarin. The novel telephone assessment tool needs to be validated further before firm conclusions can be drawn.

7. CARNEY SESSION 1 – CHAIR: EVAN BEGG

7.1

IMPACT OF DONOR AND RECIPIENT ABCB1, CYP3A5 AND IMMUNE GENETICS ON KIDNEY TRANSPLANT OUTCOME. Janet K Coller¹, Andrew A Somogyi¹, Mark R Hutchinson¹, Benjamin D Noll², Graeme R Russ³, Toby P Coates³, Raymond G Morris^{1,2}, Benedetta C Sallustio^{1,2}, ¹Discipline of Pharmacology, University of Adelaide, ²Clinical Pharmacology, The Queen Elizabeth Hospital, and ³Central Northern Adelaide Renal and Transplantation Service, The Royal Adelaide Hospital, Adelaide, Australia.

The substantial inter-individual variability in the incidence and severity of tissue rejection and drug-induced nephrotoxicity following kidney transplant are dependent on the blood and graft tissue concentrations of immunosuppressants, such as cyclosporine and tacrolimus. Recent studies have shown that in addition to the modulators of immunosuppressant drug concentrations, CYP3A5 and P-glycoprotein, immune mediators and their receptors also impact on transplant survival. Hence variability of multiple genes in the donor organ and the recipient may impact on outcomes. This pilot retrospective study investigated the relationship between donor and recipient genotypes and kidney transplant outcome (graft function and incidence of rejection) with the following genes in patients (n=46) receiving cyclosporine or tacrolimus in an Australian setting: CYP3A5 (with respect to the *3 variant), ABCB1 haplotype (SNPs at 61, 1199, 1236, 2677 and 3435), cytokines (IL-1B, IL-6, IL-6R, IL-10, TNF- α , TGF- β), toll like receptors (TLR2, TLR4), and immune mediators (MD2, MYD88, BDNF, CRP, ICE). Individual genotype data were combined in hierarchical cluster analysis to assess differences in genes between donor and recipients, and the impact of multiple genes on outcome. 19% of recipients experienced rejection and 9% of recipients had decreased graft function (defined by a 30% increase in serum creatinine compared to baseline) in the 3 years post-transplant. Recipient SNPs (position number) in ABCB1 (1199), IL-1B (-511, -31, +3954) and TNF- α (-308) were associated with rejection. Recipient SNPs in ABCB1 (61, 1236, 2677 and 3435), TGF- β (-509), IL-6 (-6331) and CRP (4284) were associated with decreased graft function. Combining data from both the donor and recipient revealed a significant (P=0.024) contribution of SNPs in CRP (4284), BDNF (66), IL-6R (358) and MYD88 (1593) to kidney rejection episodes. Integration of these associations into a linear “rejection model” correctly classified 22% of confirmed kidney rejection episodes (with no false positives) with a significant OR (95% CI) = 0.04 (0.002 - 0.92) P=0.03. None of the SNPs identified in the cluster analysis were individually associated with rejection or decreased graft function (P>0.09). In summary, multiple genes of both donors and recipients that regulate both the concentration of immunosuppressants and immune response may be clinically important determinants of transplant outcome. A larger patient cohort is currently being studied.

7.2

PHARMACOGENOMICS OF BREAST CANCER TREATMENT. Michael A Black, Department of Biochemistry, University of Otago, Dunedin, New Zealand.

Over the past decade, advances in genomics technologies and associated analytic techniques have allowed biomedical researchers to move closer to achieving the goal of “personalized medicine”. In the treatment of cancer, this has involved the use of gene expression profiles from a patient’s tumour to select the most appropriate course of chemotherapy for that patient. Variations on this approach have made their way into a number of small clinical trials over the past few years, and some evidence of benefit has been demonstrated in early prospective studies. Concern has been expressed, however, over the bioinformatic and statistical methodology used to extrapolate from tumour expression data through to the prediction of chemosensitivity in some of these trials – these concerns have recently led to the suspension of three clinical trials that utilize this approach. In this talk I will provide an overview of the methodology driving these trials, and will use a large “meta-cohort” of publicly available gene expression data to illustrate the application of these techniques in breast cancer.

7.3

EFFECT OF TUMOUR BURDEN ON CYP2C19 DRUG METABOLISING ACTIVITY IN PATIENTS. WY Lo (1), G Laking (2), K Spells (2), M Findlay (3), NA Helsby (1). (1) Dept of Molecular Medicine and Pathology, Univ of Auckland, Auckland, New Zealand. (2) Auckland Regional Cancer and Blood Service, Auckland District Health Board, Auckland, New Zealand. (3) Cancer Trials New Zealand, Univ of Auckland, Auckland, New Zealand.

Pharmacogenetics is the study of genetic variability in how people metabolise and respond to drugs. One pharmacogene, CYP2C19, is involved in the metabolism of chemotherapeutic drugs such as cyclophosphamide, bortezomib and thalidomide. Variants of this pharmacogene exist and are associated with poor metabolism of CYP2C19 drug substrates. The relationship between CYP2C19 genotype and phenotype is well-validated in healthy populations. We have previously reported that 37% of cancer patients have an acquired CYP2C19 poor metaboliser status independent of the genetic loss of function SNPs (Helsby et al. 2008. Br J Cancer. 99; 1251-1255). However, these patients had advanced incurable disease and it is not known whether CYP2C19 activity is also compromised in other stages of cancer. The inflammatory cytokines are known to down regulate CYP2C19 expression in hepatocyte cell cultures and may be a factor in these patients. The aim of this study was to determine CYP2C19 functional activity and inflammatory status in patients with earlier stages of disease and to compare this data with the previous results in patients with advanced incurable cancer. The study population comprised patients with gastro-intestinal tumours with either (a) stage IV disease or (b) no evaluable disease (NED) post surgery. CYP2C19 genotype and functional activity were determined using previously validated methods. Inflammatory cytokines were measured using Lincoplex® multiplex immunoassay. Preliminary results indicated that 3 out of 10 stage IV patients also displayed compromised CYP2C19 activity, similar to the 37% incidence of poor metabolisers observed previously in patients with advanced incurable disease. 2 out of 11 patients with no evaluable disease post-surgery also displayed compromised CYP2C19 activity. The inflammation marker CRP, was elevated in patients with stage IV (median 4.5, IQR 2.4-12.95) and advanced incurable disease (median 8.95, IQR 2.08-23.5) compared with patients with no evaluable disease post-surgery (median 1, IQR 1-1.85). Recruitment is ongoing to further elucidate the role of cancer related factors on CYP2C19 activity.

7.4

ANTIDEPRESSANT SPECIFIC CHANGES IN RAT WHOLE BLOOD GENE EXPRESSION IDENTIFIED BY GENE-CHIP ANALYSIS. James A. Harley^{1,2,3}, Kit Doudney^{1,3}, Melanie A. Allington¹, Les McNoe⁴, John Pearson, Mik Black⁴, Peter R. Joyce^{2,3} and Martin A. Kennedy^{1,3}. ¹Departments of Pathology and ²Psychological Medicine, University of Otago, Christchurch, New Zealand; ³Carney Centre for Pharmacogenomics, University of Otago, Christchurch, New Zealand; ⁴Department of Biochemistry, University of Otago, Dunedin.

We have previously demonstrated that exposure to antidepressant medications alter the production of messenger RNA in cultured embryonic stem-cells, a rat serotonergic cell line and in rat brain tissues. Gene activation-inactivation events are likely to contribute to the mechanisms of synaptic remodelling and neurogenesis which are emerging as the likely means for the long-term brain changes required to alleviate mood disorders. As we seek to translate these results to future human studies the development of a method to measure these antidepressant-induced changes in non-brain tissues is essential. Rats were dosed with Citalopram (5mg/kg/day, n=9), Paroxetine (5mg/kg/day, n=9), Haloperidol (0.25mg/kg/day, n=9) and a vehicle control (1:1 ethanol:H₂O, n=9) via Azlet osmotic minipumps implanted subcutaneously on the back of the animals. RNA was isolated using PAXgene blood RNA collection tubes, quantified and assessed for quality. The 6 best samples from each treatment arm were labelled and hybridised to rat whole genome expression arrays (Affymetrix Rat gene 1.0-ST) at the Otago Genomics Facility, Dunedin. Analysis was carried out using the R package aroma.affymetrix (significance for differential expression was set at a false discovery rate p-value of <0.05) and tools from the Broad Institute Gene Pattern webserver. (<http://www.broadinstitute.org/cancer/software/genepattern/>) Twenty-three transcripts (including *GALNT2* and *GNAI2*) were altered by the two SSRI antidepressants and not by the antipsychotic haloperidol. These have become candidates for further investigation within our laboratory. We aim to use these data to guide analysis of blood mRNA samples from patients initiating treatment with antidepressants, and evaluate them as blood-based biomarkers for drug exposure and treatment response.

8. CARNEY SESSION 2 – CHAIR: PAUL CHIN

8.1

ARE THERE PHARMACOGENETIC INDICATORS FOR ALLOPURINOL COMBINATION THERAPY IN INFLAMMATORY BOWEL DISEASE? Rebecca L. Roberts^{1,2,3}, Richard b. Geary^{2,3,4} and Murray L. Barclay^{2,3,4} Departments of ¹Biochemistry (Dunedin) and ²Medicine (Christchurch), University of Otago, New Zealand; ³Carney Centre for Pharmacogenomics, University of Otago, Christchurch, New Zealand; ⁴Department of Gastroenterology, Christchurch Hospital, Christchurch, New Zealand.

Azathioprine and 6-mercaptopurine are first-line immunosuppressants for the management of inflammatory bowel disease (IBD). Both are pro-drugs which undergo metabolism via three competing pathways to generate the pharmacologically inactive metabolites as well as the toxic metabolite 6-methylmercaptopurine ribonucleotides (6-MMPR) and the active metabolite 6-thioguanine nucleotides (6-TGN). Around 10% of IBD patients are resistant to thiopurine therapy and are prone to developing hepatotoxicity through the generation of supra-therapeutic concentrations of 6-MMPR. Some, but not all, treatment refractory patients have by very high red blood cell activity of thiopurine s-methyltransferase (TPMT), whereas others may have reduced guanine monophosphate synthetase (GMPS) or inosine monophosphate dehydrogenase (IMPDH) activity. Recent studies have shown that a combination therapy of low-dose thiopurine with low-dose allopurinol shifts metabolism away from 6-MMPR toward 6-TGN resulting in an improved therapeutic response and reduced hepatotoxicity in these patients. On average it takes 1 month for thiopurine metabolites to reach steady state concentrations but up to 6 months for non-response to be confirmed. The ability to predict which patients will be thiopurine resistant prior to commencing therapy would enable clinicians to opt for alternative treatments thereby substantially reducing the time it takes for disease remission to be achieved in these individuals. Preliminary data suggests genetic polymorphisms within the purine biosynthesis pathway may aid in the prediction of thiopurine resistance. Here we will discuss the potential of these genetic variants, in conjunction with TPMT phenotyping, to serve as prospective pharmacogenetic indicators for allopurinol combination therapy.

8.2

COMPARISON OF PREDICTED DOSE VERSUS ACTUAL DOSE USING PHARMACOGENOMIC ALGORITHMS IN 483 PATIENTS ON LONG TERM WARFARIN THERAPY. Diug Basia¹, Sheffield Leslie^{2,3}, Dooley Michael³, Lowthian Judy¹, Evans Sue¹, Maxwell Ellen¹, Street Alison¹ Byron Keith³, McNeil John¹ ¹NHMRC Centre of Research Excellence in Patient Safety, Monash University, ²Murdoch Childrens Research Institute, ³GenesFX Health, ⁴Heathslope Advanced Pathology

Purpose: This study aims to compare the predicted dose against the actual dose using pharmacogenomics in patients on long-term warfarin therapy in the community. *Method:* A case control study was conducted with patients recruited by a metropolitan pathology provider. Warfarin predicted dose was calculated by application of two published pharmacogenomic algorithms. Actual dose was compared with mean average percentage (MAPE). Cases had an elevated INR ≥ 6.0 whilst controls were within their therapeutic range for at least 3 months. Patient interviews investigated demographic and clinical risk factors, time in range and dosage. Pharmacogenomic testing was done for CYP2C9 and VKORC1. *Results:* A total of 483 patients were recruited: 156 cases and 327 controls. Mean duration of treatment was 4 years (0.5-31) in cases and 5 years (0.6-45) in controls. Atrial fibrillation was the most common primary indication. Mean dosage for cases was 4.5 mg (1-12) whilst controls were 4.3 mg (0.75-14.5). *Conclusions:* Our findings show no difference between the results from the NEJM and Gage algorithms. However, MAPE showed significant variations between expected and predicted dosages between our cases and controls in community-based patients on long-term warfarin maintenance therapy.

	Cases n=156	Controls n=327	Total
	MAPE(95%CI)	MAPE (95%CI)	MAPE(95%CI)
GAGE (2008)	33.2(36.1-40.1)	20.4(21.9-26.5)	27.1(24.4-29.8)
NEJM (2009)	32.3(27.1-37.6)	20.9(24.4-29.0)	28.5(26.2-30.8)

8.3

TAILOR-MAKING PHARMACOGENETIC RESEARCH FOR THE NEW ZEALAND CONTEXT: ETHICAL, LEGAL & POLICY ISSUES. Richman Wee, Centre for Law and Policy in Emerging Technologies, Faculty of Law, University of Otago, Dunedin, New Zealand

The collection, use and retention of human specimens and personal information can raise challenging ethical, legal and policy issues. There are recently developed New Zealand rules, principles and guidelines that researchers should take into account when designing studies. This presentation will outline those rules, principles and guidelines relevant to pharmacogenomics research. The presentation will raise points for consideration with the aim of helping researchers think ahead and refine their study design. Issues dealing with the continuing retention, future uses, and de-identification, of specimens or information will be examined. A selection of legal material and ethical guidelines specific to conducting research in the New Zealand context will be discussed, for example, the Code of Health and Disability Services Rights, Health Information Privacy Code, and Guidelines for the Use of Human Tissue for Future Unspecified Research. Questions or comments on current ethical, legal and policy issues relating to pharmacogenomics research will be welcome from participants. Declaration: Richman Wee presently chairs the Multi-Region Ethics Committee but the presentation and comments that he will provide are based on his work with the Law Foundation-sponsored Human Genome Research Project, and the Centre for Law & Policy in Emerging Technologies, at the Faculty of Law, University of Otago.

8.4

CYP2D6 AND PSYCHOLOGICAL FUNCTIONING. E.M.Peñas-Lledó, University of Extremadura, Spain

8.5

PHARMACOGENETICS IN HISPANICS AND LATINAMERICANS: IMPLICATION FOR PSYCHIATRY. A.LLerena, Extremadura University Hospital and Medical School, Spain

POSTERS

1

A RATIONALE FOR THE ROUTINE MONITORING OF ANTI-ACTIVATED FACTOR X (ANTI-Xa) DURING ENOXAPARIN TREATMENT HS Al-Sallami (1), MA Barras (2), B GREEN (3), & SB Duffull (1), School of Pharmacy, University of Otago, Dunedin; Mater Heath Services, Brisbane, Australia; Model Answers Ltd, Brisbane, Australia

Introduction and aims: Enoxaparin is a low molecular weight heparin (LMWH) used in the treatment of thrombosis. Unlike unfractionated heparin (UFH), no routine monitoring of plasma activity is recommended for enoxaparin treatment. The activity of enoxaparin in plasma is determined by assaying anti-activated factor X (anti-Xa). The aim of this study was (1) To identify an anti-Xa treatment target for enoxaparin. (2) To determine whether routine monitoring of anti-Xa concentrations in patients receiving enoxaparin treatment is warranted. *Methods:* From a cohort study (Montalescot, 2004) and through a meta-analysis of a randomised controlled trial (Barras, 2008), a target peak and trough anti-Xa concentration was obtained. Based on this target, and using a two-compartment PK model for enoxaparin, 10000 virtual patients were simulated with a dosing regimen of 1 mg/kg total body weight twice daily. Patients with creatinine clearance < 30 mL/min were excluded. Activated partial thromboplastin times (aPTTs) were also simulated for UFH when it was given as a constant infusion at 1500 units/hour assuming a Michaelis-Menton PK model with an empirical PD model linking concentration to aPTT. *Results:* The target anti-Xa concentration of enoxaparin for effectiveness and safety was 5 mg/L. Twice daily dosing regimens that achieve this target have peak concentrations that exceed 5 mg/L and trough concentrations that fall below 5 mg/L. Based on this target, 46% of patients had peak or trough concentrations outside the proposed target. This figure was comparable to the UFH heparin model where 52% of patients had an aPTT outside the target range (1.5-2.5 x initial aPTT). *Conclusions:* Based on the current dosing practice for enoxaparin only 54% of patients are dosed optimally. This success rate is as poor as with UFH. Given that monitoring PD endpoints is strongly recommended with UFH, it follows that the same approach should also apply for enoxaparin and probably should be generalised to all LMWHs.

Montalescot et al (2004) *Circulation*, 110, 392-398; Barras et al (2008) *CPT*, 83, 882-888

2

PREDICTION OF TORSADES DE POINTES – AMISULPRIDE CASE SERIES. CV Coulter (1), JP Joy (1), SB Duffull (1) & GK Isbister (2); (1) School of Pharmacy, University of Otago, Dunedin, New Zealand & (2) Department of Clinical Toxicology, Calvary Mater Newcastle Hospital, Newcastle, Australia

Torsades de Pointes (TdP) is a potentially fatal ventricular arrhythmia that is associated with a drug-induced QT prolongation. Prior reports have looked at a wide spectrum of different drugs which has confounded the causal relationship of the magnitude of QT prolongation with the inherent cardiotoxicity of the drug. This amisulpride case series has eliminated this and allowed the magnitude of QT prolongation to be assessed. The objective of this study was to assess whether the magnitude of QT prolongation is a better predictor of TdP than dose alone in a series of amisulpride poisonings (Isbister, 2006). The study included 457 ECGs from 86 patients with amisulpride overdoses who ingested a median dose of 6 g (range: 1.2 g to 120 g). The QT interval was manually measured on each ECG using a standardised method (Isbister, 2009). For cases of TdP the longest QT interval was chosen that occurred prior to the episode of TdP, and for controls the longest QT interval was selected over the entire admission period. For each ECG the following measurements of QT were used: the absolute QT, corrected QT values using Bazett's formula [QTcB] and Fredericia's formula [QTcF], and the orthogonal QT interval defined as the shortest distance of the QT-HR [HR = heart rate] pair from the "at risk" line on the QT-nomogram, termed orthogonal distance (OD). Logistic regression using NONMEM (version 6) was performed to investigate the association between dose, RR interval, and the various measurements of the QT interval, on the probability of TdP. TdP occurred in 8 (9.3%) of the patients. The dose of amisulpride in these patients ranged from 4g to 80g. Both dose and RR interval improved the prediction of TdP over and above simply the presence of a prolonged QT interval. All four QT measures, the absolute QT, QTcB, QTcF, and OD, were superior to both dose and HR interval – but the different QT measures were indistinguishable from each other. For all QT measures, QT, QTcB, QTcF, and OD, the extent of the prolongation was a useful predictor of TdP compared to dose.

Isbister GK *et al.* (2006). *Med J Aust* 184:354-6

Isbister GK *et al.* (2009). *Clin Toxicol (Phila)* 47:884-8

3

THE EFFECT OF CURCUMIN ON MULTI-DRUG RESISTANCE PROTEIN 5 (MRP5)-MEDIATED RESISTANCE IN PANCREATIC CANCER. Y Li, JL Revalde, JW Paxton, Department of Pharmacology and Clinical Pharmacology, University of Auckland, Auckland 1142

Chemotherapy of pancreatic cancer often fails due to intrinsic and acquired resistance during drug treatment. Recent studies have suggested that MRP5 conferred resistance to first-line drugs, 5-fluorouracil and gemcitabine by active efflux from the cell (1, 2). Our aim was to evaluate whether curcumin could reverse this multi-drug resistance by inhibition of MRP5-mediated efflux. Cell proliferation and drug accumulation studies were undertaken in mock and MRP5 over-expressing HEK293 cells and two pancreatic cancer cell lines. The cellular accumulation of a specific MRP5 fluorescent substrate 2',7'-Bis(2-carboxyethyl)-5(6)-carboxyfluorescein (BCECF) was measured by flow cytometry and cell proliferation determined by a 72-h CyQuant assay. The MRP5 mRNA level was determined by real-time PCR and MRP5 protein detected by immunocytochemistry using a monoclonal antibody. In the presence of curcumin (5 and 10 μM) and a MRP5 inhibitor MK571 (25 μM), the cellular accumulation of BCECF in HEK293-MRP5 cells increased $68 \pm 9\%$ ($p < 0.01$), $215 \pm 12\%$ ($p < 0.01$) and $397 \pm 17\%$ ($p < 0.01$), respectively. Curcumin and MK571 had no effects on cellular accumulation of BCECF in mock cells. In the proliferation assays, curcumin caused a concentration-dependant increase in the sensitivity to the cytotoxic drug 5-fluorouracil in HEK-MRP5 cells, PANC-1 and MiaPaCa-2 pancreatic cancer cells, but not in HEK293 mock cells. Our results suggest that curcumin is an inhibitor of MRP5 and may be useful in the reversal of multi-drug resistance in pancreatic cancer chemotherapy.

Hagmann, W. et al. *Pancreatology*. 9:136-144 (2009).

Oguri, T. et al. *Mol Cancer Ther*. 5:1800-1806 (2006).

4

DESIGN OF SURVIVAL STUDIES FOR RED BLOOD CELLS. J Korell, CV Coulter & SB Duffull, School of Pharmacy, University of Otago, Dunedin, New Zealand

Knowledge of the lifespan of red blood cells (RBCs) is important for the treatment of diabetes, as the most commonly used marker for glycaemic control, glycated haemoglobin (HbA_{1c}), depends on the lifespan of RBCs (Goldstein et al, 2004). However, the commonly accepted lifespan of RBCs is poorly determined. This is due to the lack of accurate methods for determining RBC longevity. The most current methods involved labels for RBCs. Two types of labelling methods have been developed: cohort labelling, where cells of a certain age are labelled, and random labelling, where all cells present at one moment in time are labelled. However, both methods contain significant flaws resulting in biased estimates of the RBC lifespan (Franco, 2009). Though, mathematical models can be used to overcome these flaws. A model for the survival time of RBCs was developed that accounts for the plausible physiological processes of RBC destruction. The model was able to adequately describe the ideal behaviour of random and cohort labelling methods. Furthermore, the flaws associated with random labelling with radioactive chromium and cohort labelling with heavy nitrogen were also able to be accounted for by the model. By applying optimal design theory, the number of patients and blood sampling times were determined for RBC survival studies using random and cohort labelling, and it was determined whether the parameter values describing RBC survival in the model can be estimated from these studies. In general, between 50 and 100 patients each providing 6 blood samples is sufficient to provide precise parameter estimates for the cohort labelling method even when considering the flaws associated with this method. However it appears that random labelling with chromium, due to its short half-life of 27 days compared to the probable RBC lifespan of more than 100 days, does not allow the model to be completely characterised with 100 patients. Therefore, cohort labelling should be considered for the development of new labels for RBCs.

Franco, R (2009) *Am J Hematol* 84, 109-114

Goldstein, D et al. (2004) *Diabetes Care* 27; 1761-1773

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STUDIES OF COPPER AND PLATINUM UPTAKE AND TOXICITY IN CULTURED PRIMARY SENSORY NEURONS. JJ Liu (1), Y Kim (1), JFB Mercer (2) & MJ McKeage (1). (1) Department of Pharmacology and Clinical Pharmacology, School of Medical Sciences, Faculty of Medical and Health Sciences, The University of Auckland, New Zealand; (2) Centre for Cellular and Molecular Biology, School of Life and Environmental Sciences, Deakin University, Victoria, Australia.

Neuro-sensory toxicities are dose-limiting toxicity for platinum-based anticancer drugs and difficult-to-treat in clinics. Its mechanism remains unclear but preferential accumulation of platinum in peripheral neurons is linked to the toxicity in patients (Krarup-Hansen et al 1999) and rodent models (Screnci et al 2000). We have shown the association between platinum drug neurotoxicity in rats and the neuronal expression of the copper transporter 1 (CTR1) (Liu et al 2009), a major high-affinity Cu uptake protein involved in platinum transport (Ishida et al 2002). Here we established an *in vitro* cell system to investigate the neuronal transport of chemotherapy drugs. Primary sensory neurons were dissociated from rat dorsal root ganglion and identified by phase morphology and immunoreactivity to neuronal markers neurofilament heavy subunit and microtubule-associated protein 1. mRNA and protein expression of CTR1 in the cultured neurons was detected by RT-PCR, qPCR, immunostaining and immunoblotting. After the exposure of the neurons to extracellular CuCl₂ (3, 10, 30 and 100 µM) at 37°C for up to 2 h, the cellular content of copper increased in a time- and concentration-dependent manner. The neuronal uptake and cytotoxicity of platinum drugs were determined by ICP-MS and lactate dehydrogenase release assays. In conclusion, the cultured sensory neurons showing specific Cu/platinum kinetics are suitable for studies on CTR1-dependent mechanisms of platinum neurotoxicity. The work was supported by Cancer Society of New Zealand and University of Auckland Faculty Research Development Fund.

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STATIN INDUCED ANXIETY: WHAT HAPPENS WHEN YOU MAKE GUINEA PIGS SWIM. S Maggo, DWJ Clark & J Ashton. Department of Pharmacology & Toxicology, University of Otago, Dunedin, New Zealand.

New Zealand's national Pharmacovigilance centre (NZPhvC) has identified an increase in the proportion of psychiatric adverse drug reactions reported for the cholesterol lowering group of drugs, primarily the statins but also ezetimibe and the fibrates [1]. Previously (ASCEPT 2009), we presented results from an experimental study focussed on investigating the effect of high dose simvastatin and atorvastatin treatment on memory in an animal model of spatial memory and learning. The hypothesis that there will be a decrease in total cholesterol (TC) and LDL-C which will correspond with behavioural impairment was assessed through the Morris water maze task. Results of the investigation showed that high dose atorvastatin and simvastatin treatment for 6 weeks significantly (P<0.01) reduced TC and LDL-C and increased the time animals took to find the platform over 5 days, though this result was not significant when compared with control animals. Further analysis using TOPscan[®] maze software has revealed that thigmotaxis (measure of anxiety), the time spent by the animal on the periphery of the maze was significantly (P<0.05) elevated in the drug treated groups compared with control animals. Furthermore, when animals were de-challenged for two weeks, thigmotaxis (anxiety) levels were comparable with control animals. The mechanism(s) of statin-induced psychiatric ADRs are hypothesised to be associated with cholesterol lowering within the CNS. The hippocampus is a major area of the brain involved in memory, learning and anxiety-related processes [2]. To investigate the mechanism of statin-induced psychiatric events we are currently conducting electrophysiological studies within the hippocampus which will provide further insight into a possible mechanism.

Tatley M and Savage R. Drug Safety. 30(3), 195-201 (2007).

Bertoglio LJ, Joca SRL, and Guimaraes FS. Behavioural Brain Research. 175(1), 183-188 (2006).

GENERAL INFORMATION

HOSTS	Clinical Pharmacology, Christchurch Hospital, 2 Riccarton Road, Christchurch Department of Medicine, University of Otago, 2 Riccarton Road, Christchurch <i>T: +64 3 364 1055</i> <i>F: +64 3 364 1003</i>		
VENUE	Beaven Lecture Theatre , <i>University of Otago</i> <i>7th Floor, 2 Riccarton Road, Christchurch</i> <i>University Reception: +64 3 364 0530</i> <i>Map of location on following page</i>		
REGISTRATIONS	Sunday, 29 August	6.00 - 7.30pm	Café Medici
SOCIAL FUNCTIONS	Monday, 30 August	Conference Dinner 7.00pm	Octagon Live 124 Worcester Street
REFRESHMENTS	Breaks & Lunch		Beaven Lecture Theatre foyer
AGM	Monday, 30 August	4.45pm	Beaven Lecture Theatre

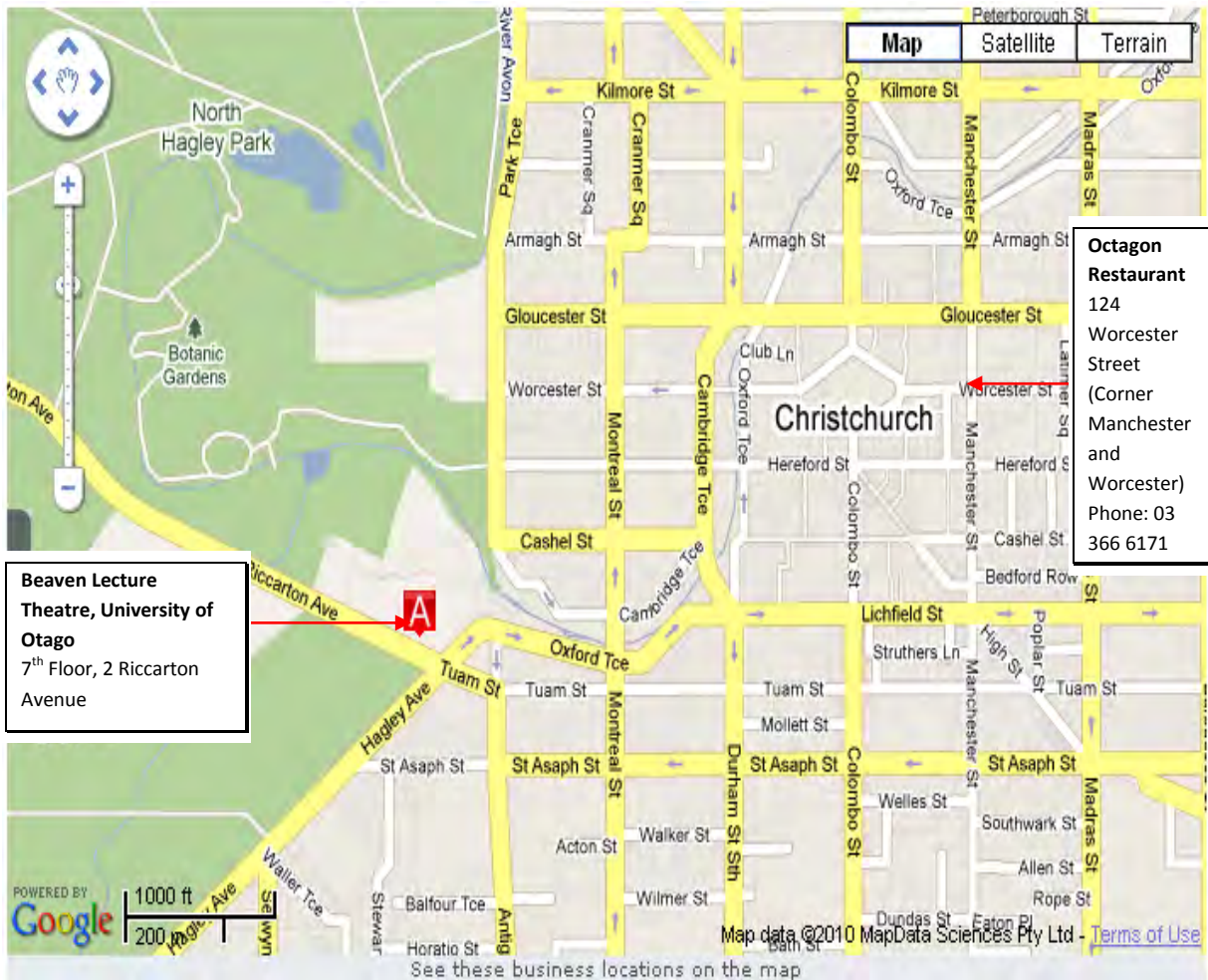
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Map adapted from <http://www.wises.co.nz/>

