UNIVERSITY
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SAPERE – AUDE

Te Whare Wānanga o Otāgo

The 5th Annual Carney Pharmacogenomics Symposium

Christchurch
10th November, 2009

Programme

University of Otago - Christchurch,
Beaven Lecture Theatre, 7th Floor,
Riccarton Road, Christchurch

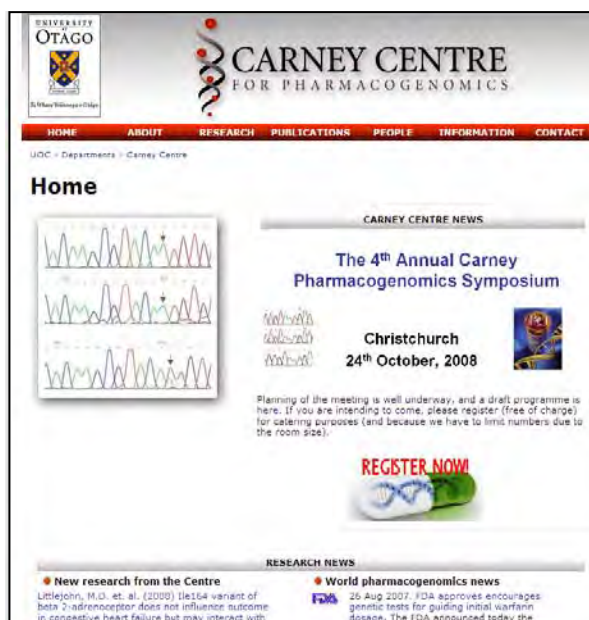CARNEY CENTRE
FOR PHARMACOGENOMICS

Origins of the Centre

The Carney Centre for Phamacogenomics was established with a generous gift from the Jim and Mary Carney Charitable Trust, which was matched by the Government under the Partnerships for Excellent scheme. The Centre was opened in May 2005, and brings together several groups throughout the University of Otago and elsewhere. Together these groups span a wide range of clinical, pharmacological and generic expertise, and they are applying genetic and genomic techniques to the understanding of drug action and drug responses.

Objectives of the Centre:

- To carry out excellent research into pharmacogenomics, from molecule to bedside
- To provide high quality postgraduate and medical training in pharmacogenomic areas
- To disseminate pharmacogenomics information in ways that inform and improve clinical practice

Contact for further information: martin.kennedy@otago.ac.nz

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CARNEY CENTRE
FOR PHARMACOGENOMICS

08:30am   Meet over coffee

8:55am   Welcome - Martin Kennedy

Chair: Martin Kennedy
9:00am   **Dr James Sikela**, *Pharmacology, University of Colorado, School of Medicine (USA).*
           "Duplication-rich, complex genomic regions: challenges for pharmacogenomics and personalized medicine"

9:15am   **A/Prof Martin Kennedy**, *Pathology, University of Otago, Christchurch*
           "Gene Regulation By Drugs Used To Treat Mood Disorders"

9:30am   **Dr Janet Coller,** *Adelaide (Aust)*
           "Genetics Of Drug Dependence"

9:45am   **Dr Rod Lea**, *Environmental and Scientific Research (NZ)/Griffith University (Aust)*
           "Identifying Genomic Signatures for Predicting Disease Risk and Drug Response"

10:00am   **Dr Amy Fletcher**, *Political Science Programme, University of Canterbury*
           "From Bench To Market: Emerging Issues In U.S. Regulation Of Pharmacogenomics"

10:15am   Morning Tea

Chair: Evan Begg
11:00am   **Dr Berit Jensen**, *Medicine, University of Otago, Christchurch*
           "The Influence of P-Glycoprotein Polymorphisms on Nortriptyline-Induced Postural Hypotension"

11:15am   **Alice Johnstone,** *Environmental and Scientific Research, (Wellington) and University of Otago.*
           "The Effect of Exposure to Benzylpiperazine or Methamphetamine on Gene Expression"

11:30am   **Dr Kit Doudney**, *University of Otago, Christchurch*
           "Upstream genetic variant near *INSIG2* is associated with adipose metabolism in bipolar patients with valproate induced weight gain."

11:45pm   **Tony Harley**, *Psychological Medicine, University of Otago, "Christchurch*
           "Blood mRNA changes induced by antidepressants"

12:00pm   **Dr Rebecca Roberts**, *Biochemistry, University of Otago, Dunedin*
           "Genetic Polymorphisms In The Folate Pathway Predict Red Blood Cell Folate Concentrations But Not Methotrexate Response In Rheumatoid Arthritis"

12:15pm   Lunch

Chair: Rebecca Roberts

1:15pm   **A/Prof Murray Barclay**, *Medicine, University of Otago, Christchurch*
"Using Genetics of Inflammatory Bowel Disease to Develop New Treatments – A Different Slant on Pharmacogenetics"

1:30pm   **Dr David Gibbs**, *Oncology Department, Christchurch Hospital, Christchurch*
"Practical Pharmacogenetics in the Oncology Clinic."

1:45pm   **Annica Svensson,** *Medicine, University of Otago, Christchurch*
"Associations Between Carboxylesterase 1 (Ces1) and Cardiovascular Outcomes"

2:00pm   **Prof Evan Begg,** *Medicine, University of Otago, Christchurch*
"From Pharmacogenetics to Drug Interactions"

2:15pm   Closing remarks

2:15pm   Afternoon Tea

DUPLICATION-RICH, COMPLEX GENOMIC REGIONS: CHALLENGES FOR PHARMACOGENOMICS AND PERSONALIZED MEDICINE

James M. Sikela

University of Colorado Denver School of Medicine

Regions of the human genome have been identified that have a disproportionately high level of duplicated sequences, sequence gaps and intraspecies variation. These regions have also been implicated in a number of human diseases and evolutionarily are highly dynamic, containing an enrichment of genes that show human lineage-specific increases in copy number. One such region, 1q21.1, has all of these qualities and has also been implicated in almost a dozen different human diseases. In addition, 1q21.1 contains a rapidly evolving duplicated sequence, the DUF1220 protein domain, that has 160 highly similar copies encoded at several locations interspersed over an 8Mb genomic region. Such a genome feature is largely refractory to conventional genotyping and, as a result, provides difficult challenges for incorporation into medical applications that rely on assessments of human genome variation such as pharmacogenomics and personalized medicine. The importance of these challenges is further magnified by the striking number of disease-associated copy number variations that are being discovered within such complex regions.

GENE REGULATION BY DRUGS USED TO TREAT MOOD DISORDERS

Sarah Deng[1], Patrick C. McHugh[1], Kit Doudney[1], Peter R. Joyce[2], <u>Martin A. Kennedy</u>[1.]

Departments of Pathology and [2]Psychological Medicine, University of Otago, Christchurch, New Zealand

Antidepressant and mood stabilizer drugs are the main treatments for mood disorders including major depressive disorder (MDD) and bipolar disorder (BD). Although widely used, the mechanisms of action of these drugs are not well understood and we are attempting to develop a simple, easily manipulated model system with a relevant cellular context.

Our work was carried out in a neuronal cell line called RN46A, which is derived from an immortalized rat serotonergic precursor cell. The serotonergic system is strongly implicated in mood disorders and their treatment, so this represents a relevant cell type in which to explore these questions. We exposed RN46A cultures to various drugs for 72 hours, and then performed quantitative PCR (Q-PCR) analysis of candidate genes. For these experiments we used the antidepressant drugs paroxetine, citalopram and nortriptyline; the antipsychotic haloperidol; and the mood stabilizer sodium valproate.

Our most striking results to date are: (1) a gene called sepiapterin reductase (*SPR*), a key enzyme in production of an essential cofactor for neurotransmitter synthesis, is massively and specifically up-regulated by sodium valproate; (2) another gene in the same pathway (*QDPR*) is also up-regulated but to a lesser extent; (3) the serotonin receptor 2A (*HTR2A*) is significantly down-regulated by paroxetine and citalopram, the two selective serotonin reuptake inhibitor antidepressants ($p = .001$ to $.003$); and (4) the histone deacetylase *HDAC2* gene is reduced significantly by all of the drug treatments except sodium valproate. We are endeavoring to assess more genes in this system, and to begin dissecting the molecular events underlying the changes in gene expression we observed

GENETICS OF DRUG DEPENDENCE

Janet K Coller, Liang Liu, Mark R Hutchinson, Jason White and Andrew A Somogyi

Discipline of Pharmacology, School of Medical Sciences, University of Adelaide, Adelaide, Australia

Alcohol and opioid abuse are a significant public problem worldwide, with reports attributing between 40 and 60% to heritable factors (Lachman 2006, Dick & Bierut 2006). Previous studies have focused on analysing candidate genes based on classical opioid / alcohol pharmacology, including metabolism, transporter and receptor pathways. However, these have failed to identify any common genes to explain the large degree of heritability. More recent evidence has highlighted the role of proinflammatory activation of immune signalling in the CNS in alcohol- and opioid-induced reward and dependence (Hutchinson *et al.* 2007, Blanco & Guerri 2006). Hence, this study investigated the association between genetic variability of the proinflammatory cytokine gene *IL-1B* and the risk of dependence. Genotyping of the -511C/T and -31T/C promoter and +3954C/T SNPs of *IL-1B* was performed with PCR-RFLP in 60 opioid and 99 alcohol dependent, and 60 healthy non-dependent controls (Liu *et al.* 2009). Nearly complete linkage disequilibrium was observed between the -511 and -31 SNPs (D'= 0.99, P < 0.0001). There was a higher frequency of -511C and -31T alleles in the alcohol and opioid dependent populations compared with healthy controls: -511 Odds ratio (OR, 95% CI) = 1.89 (1.19-2.99), P = 0.01 and 1.91 (1.14-3.2), P = 0.04, respectively; -31 OR (95% CI) = 1.8 (1.13-2.88), P = 0.01 and 1.74 (1.02-2.97), P = 0.06, respectively. There was no difference in the allele frequencies of the +3954 SNP between the populations.
In conclusion, *IL-1B* -511 and -31 promoter SNPs, which increase the proinflammatory cytokine IL-1b expression, are associated with an altered risk of alcohol and opioid dependence. We are currently exploring the association between other genetic variants of this signalling pathway and alcohol and opioid dependence.

References: Lachman (2006) An overview of the genetics of substance use disorders. Curr Psychiatry Rep. 8, 133-143; Dick & Bierut (2006) The genetics of alcohol dependence. Curr Psychiatry Rep. 8, 151-157; Hutchinson *et al.* (2007) Opioid-induced glial activation: mechanisms of activation and implications for opioid analgesia, dependence, and reward. ScientificWorldJournal. 7, 98-111; Blanco & Guerri (2007). Ethanol intake enhances inflammatory mediators in brain: role of glial cells and TLR4/IL-1RI receptors. Front Biosci. 12, 2616-2630; Liu *et al.* (2009) Association of IL-1B genetic polymorphisms with an increased risk of opioid and alcohol dependence: proinflammatory cytokine linkage to drug dependence. Pharmacogenet Genomics. Epub Oct 1.

Identifying Genomic Signatures for Predicting Disease Risk and Drug Response

Rod Lea[1,3], **Donia Macartney-Coxson**[1], **David Hall**[1,2], **Bushra Nasir**[3] **and Lyn Griffiths**[3]

[1]Environmental Science and Research Ltd, Porirua, NZ, [2]Victoria University of Wellington, NZ. [3]Griffith University, Queensland, Australia

Being able to accurately predict an individual's disease risk and/or drug response is a major goal of clinical medicine in the 21st century. For many common conditions a patient's health outcome is influenced by the complex interplay of both genetic and environmental factors. The advent of high-throughput SNP-typing technologies has created great potential to identify risk factors of heritable traits by scanning many 1000s of polymorphisms spanning the entire genome. To date there have been many so called "Genome-Wide Association Scans (GWAS)" conducted and susceptibility markers have been identified for a variety of serious disease traits. Unfortunately, the conventional study design for GWAS is limited to identification of single genetic markers, which considered alone explain very little of the overall disease risk. Moreover, findings from GWAS are based on populations and not usually presented as a simple test result that can be used clinically for predicting disease in individuals.

We have developed a novel bioinformatic method for analysing large GWAS data to identify multi-marker genomic signatures for predicting disease risk in individuals. Our method involves a multi-factor data reduction approach and is genetic model-free and utilises intelligent software and high-performance computers to discover and validate multiple markers associated with disease risk. Despite the complexity of the data set the final output from our bioinformatics pipeline is in the form of a simple risk score which can be interpreted by clinicians and patients as a diagnostic test result. This paper will provide a general overview of the bioinformatics pipeline and show how we have used our method to identify novel genomic signatures for predicting risk of bipolar disorder and Crohn's disease.

FROM BENCH TO MARKET: EMERGING ISSUES IN U.S. REGULATION OF PHARMACOGENOMICS

Amy L. Fletcher, PhD[1] and **Jonathan S. Kruger, PhD, JD**[2]

[1]Department of Political Science, University of Canterbury, Christchurch, New Zealand and [2]Panovel Technology Corporation, Shanghai, China

As pharmacogenomics enters the crucial transition period from the lab to the market in the United States, interest in 'personalized medicine' dominates media and public attention. Regulation of this nascent industry also occurs at the intersection of several policy issues, including:

- President Obama's controversial health care reform initiatives;
- Organized interest in the persistence of the 'blockbuster' drug model;
- Social concerns about using 'racial differences' to promote personalized medicine;
- The appropriate intellectual property rights model to stimulate innovation in both biotechnology and public health;
- The emergence of well-funded non-profit organizations, such as the Personalized Medicine Coalition and the Genetic Alliance, which seek to influence research and policy priorities.

This presentation on the American regulatory environment for pharmacogenomics draws upon empirical data from an ongoing, cross-national research project, and focuses primarily on the issue of intellectual property rights and innovation. Preliminary evidence (drawn from expert interviews, media analysis, policy document analysis, and analysis of relevant patents and lawsuits) suggests that pharmacogenomics fits the model of a disruptive technology, with the potential to transform health care provision, practice and costs. However, we argue that this transformation will require both legislative changes to the patent system and more active and effective scientific/expert engagement with the public and regulators.

THE INFLUENCE OF P-GLYCOPROTEIN POLYMORPHISMS ON NORTRIPTYLINE-INDUCED POSTURAL HYPOTENSION

Berit P Jensen[1], **Ritva Vyas**[2], **Rebecca L Roberts**[1,3], **Gitte Bonke**[1], **David Jardine**[1,4] **and Evan J Begg**[1,2]

Departments of [1]Medicine and [3]Biochemistry, University of Otago, Christchurch, New Zealand; Departments of [2]Clinical Pharmacology and [4]General Medicine, Christchurch Hospital, New Zealand

P-glycoprotein (P-gp) is a transporter protein encoded by the gene *ABCB1*. In a previous study (Roberts et al 2002), a single nucleotide polymorphism in *ABCB1* (3435C>T) was associated with symptomatic nortriptyline-induced postural hypotension in depressed patients. To further investigate this finding, a prospective study was undertaken. Following genetic screening of 67 healthy volunteers, eight CGC homozygotes and nine TTT homozygotes of *ABCB1*(1236-2677-3435) were identified. All had at least one functional allele of *CYP2D6*, which is involved in nortriptyline metabolism. A single oral dose of 25 mg nortriptyline was administered. Blood pressure and heart rate was monitored at 0, 2, 4, 6 and 8h post-dose while the subject changed from supine to the upright position by active standing and by using a tilt table. Multiple blood samples were taken over 72h to determine the exposure of nortriptyline and its active metabolites. No difference was seen in pharmacokinetic variables between haplotype groups. Both groups showed normal blood pressure and heart rate response to standing. Following nortriptyline treatment, heart rate increased on changing to upright position in both haplotype groups with a maximum at 6h post-dose (p=0.0001), but no difference was seen between groups. No changes in systolic blood pressure were observed with nortriptyline and there was no evidence of a difference between haplotype groups. The association between P-gp polymorphism and nortriptyline-induced postural hypotension found in the previous patient study could thus not be confirmed in this study in healthy volunteers following a single oral dose of nortriptyline.

Reference: Roberts et al (2002) A common P-glycoprotein polymorphism is associated with nortriptyline-induced postural hypotension in patients treated for major depression. Pharmacogenomics J, 2, 191-196.

THE EFFECT OF EXPOSURE TO BENZYLPIPERAZINE OR METHAMPHETAMINE ON GENE EXPRESSION

Alice C. Johnstone[1,2,3]**, Martin A. Kennedy**[1,2]**, Rod A. Lea**[3] **and Paul S. Fitzmaurice**[3]

[1]Departments of Pathology and [2]Carney Centre for Pharmacogenomics, University of Otago, Christchurch, New Zealand, [3]Institute of Environmental and Scientific Research, Porirua, New Zealand

Benzylpiperazine (BZP) has previously shown similar stimulant behavioural effects to methamphetamine (MA) at a ten-fold dose (Brennan *et al.* 2007). It was theorised that a similar effect on mRNA expression would be observed within the striatum of rodents exposed to the behaviourally active dose of BZP or MA. Three exposure experiments were performed, two acute and one chronic exposure. Microarray and QPCR analyses of RNA isolated from the striatal region were used to interogate the transcriptome. This was subsequently followed by Western blot analyses of five target proteins, from whole protein concurrently isolated with the RNA, from the striatum. Results indicate a down-regulation of developmental pathways after chronic exposure to MA. Changes are also observed in cell adhesion and SNARE related genes in both MA and BZP treated animals. This indicates exposure to abused stimulant drugs suppresses neuronal development and affects regulation of snaptic transmission and plasticity.

Reference: Brennan *et al.* (2007) Chronic benzylpiperazine (BZP) exposure produces behavioral sensitization and cross-sensitization to methamphetamine (MA) Drug and Alcohol Dependence (88) 204-213

UPSTREAM GENETIC VARIANT NEAR INSIG2 IS ASSOCIATED WITH ADIPOSE METABOLISM IN BIPOLAR PATIENTS WITH VALPROATE INDUCED WEIGHT GAIN

K Doudney[1], **JA Harley**[2], **JF Pearson**[3], **A Miller**[1], **A Aitchison**[1], **MA Kennedy**[1], **RJ Porter**[2], **JL Elmslie**[2] **and PR Joyce**[2]

Departments of Pathology[1] Psychological Medicine[2] and Public Health and General Practice[3] University of Otago Christchurch, New Zealand

The protein INSIG2 is involved in cholesterol and triglyceride metabolism and homeostasis. Variation at rs7566605 near the gene *INSIG2* has been associated with increased BMI. We aimed to evaluate the effect of rs7566605/*INSIG2* genotype on the ability of valproate-treated bipolar patients (BMI≥25kg/m^2) to lose weight using carnitine supplementation during a 26 week lifestyle intervention study. Forty-eight bipolar patients with clinically significant treatment emergent weight gain were genotyped at the rs7566605 SNP. Participants were randomised to L-carnitine (15mg/kg/day) or placebo for 26 weeks in conjunction with a moderately energy restricted, low-fat diet. Weight, body fat percent, waist circumference and dual-energy x-ray absorptiometry were measured to assess changes in body composition. Obesity related biomarkers were measured at baseline and 26 weeks.

We found a significant interaction between rs7566605/*INSIG2* genetic status and treatment with carnitine or placebo. Carnitine had no significant effect on body composition measures in G allele homozygous patients who lost between 0.97kg and 2.23kg of fat. However C allele carriers on average gained 2.28kg when given a placebo. Carnitine supplementation in this group enabled average weight loss of 2.22g of fat (P=0.01). Approximately half this mass was in the vital truncal compartment (P=0.002). Bioinformatic analysis detected that the SNP lies in a highly conserved 336bp sequence which we speculate affects *INSIG2* gene expression.

These results are consistent with previous studies that associate rs7566605INSIG2 with adipose tissue metabolism, and may indicate that carnitine is a useful supplement for patients with treatment emergent weight gain.

Reference: Doudney K. et al. (2009). Upstream genetic variant near *INSIG2*, influences response to carnitine supplementation in bipolar patients with valproate induced weight gain. *Acta Neuropsychiatrica* 2009 **3**:133-40.

BLOOD mRNA CHANGES INDUCED BY ANTIDEPRESSANTS

Harley, J. A[1,2]**., Doudney, K.**[1]**, Allington, M.**[1]**, Pearson J.**[1]**, Black, M.**[3]**, Joyce, P. R.**[2]**, and Kennedy, M. A.**[1]**.**

[1]University of Otago, Christchurch. Department of Pathology; [2]University of Otago, Christchurch. Department of Psychiological Medicine; [3]University of Otago, Otago School of Medical Sciences. Department of Biochemistry.

The actions of antidepressants are closely linked to the promotion of neurogenesis and the modulation of synaptic plasticity, events that require modification of gene expression in the brain. Changes induced in the brain by these drugs may be reflected by expression differences in a more readily sampled tissue, the blood.

To identify blood gene expression changes produced by antidepressants, we have used a rat model and delivered citalopram, paroxetine, haloperidol or vehicle via sub-cutaneous osmotic minipumps for 12 days. RNA was isolated using PAXgene blood RNA collection tubes, quantified, labelled and hybridised to rat whole genome expression arrays (Affymetrix Rat gene 1.0-ST). Analysis was carried out using the R-based package aroma.affymetrix. Significant transcript expression differences have been detected between paroxetine treated and vehicle only treated samples which include genes involved in neuronal signalling and development. Once we have generated a full set of data, we aim to validate our most promising results by real time PCR and immunohistochemistry of brain tissue.

Our ultimate aim is to take this work into the human setting, and measure a selection of rat-verified genes' expression levels in patients beginning antidepressant therapy. Identification of a biomarker in the form of human blood transcripts affected by antidepressants has great potential clinical utility in predicting treatment outcome, and consequently reduce serious suffering in depressed patients and their families.

GENETIC POLYMORPHISMS IN THE FOLATE PATHWAY PREDICT RED BLOOD CELL FOLATE CONCENTRATIONS BUT NOT METHOTREXATE RESPONSE IN RHEUMATOID ARTHRITIS

RL Roberts[1], JL O'Donnell[2], PT Chapman[2], M Zhang[3], J James[2], C Frampton[1], MA Kennedy[4], ML Barclay[1,3], LK Stamp[1,2]

Departments of [1]Medicine, [2]Rheumatology, [3]Clinical Pharmacology, and [4]Pathology, University of Otago, Christchurch, New Zealand

Aim: Methotrexate (MTX) is the gold standard disease modifying anti-rheumatic drug in the management of rheumatoid arthritis (RA). However, as yet it is not possible to predict which RA patients will achieve disease remission on MTX and which will develop adverse effects. The aim of this study was to determine whether genetic polymorphisms within the folate pathway influence MTX response and red blood cell (RBC) folate concentrations. Methods: 200 RA patients on long-term oral MTX were enrolled. Data on MTX adverse effects (AEs) was obtained through a standardised questionnaire and synovial disease activity was assessed by the 28-joint disease activity score. Allele-specific PCR was used to screen for known polymorphisms in the folate pathway which had a frequency of >10% in Caucasians and showed prior association with MTX response. Results: We found no association of any polymorphism with MTX response. Only weak associations were observed between the single nucleotide polymorphism (SNP) *AMPD1 34C>T* and CNS AEs (p=0.04), and between *MTHFD1 1958G>A* and occurrence of gastro-intestinal AEs (p=0.03). In contrast, RBC folate concentration was significantly higher in patients with high disease activity compared to low disease activity (p=0.002). Furthermore, lower RBC folate concentration was significantly associated with *MTHFR677C>T* (p=0.002), *MTRR66A>G* (p=<0.0001), *MTHFD1958G>A* (p=0.001) and *SHMT1420C>T* (p=0.01). However, allowing for RBC folate concentrations, no association of these SNPs with disease activity was detected. Conclusion: Our data suggests that whilst specific SNPs within the folate pathway are predictive of RBC folate concentration no direct relationship exists between these SNPs and response to MTX.

USING GENETICS OF INFLAMMATORY BOWEL DISEASE TO DEVELOP NEW TREATMENTS – A DIFFERENT SLANT ON PHARMACOGENETICS

Murray L. Barclay,[1-4] **Rebecca L. Roberts**,[3,4] **and Richard B. Gearry**[1,3,4]

Departments of [1]Gastroenterology, and [2]Clinical Pharmacology, Christchurch Hospital; [3]Department of Medicine, University of Otago, Christchurch; [4]Carney Centre for Pharmacogenomics, University of Otago, Christchurch, New Zealand

Pharmacogenetics is traditionally based on the study of how the pharmacokinetics or actions of drugs are influenced by variation in genes amongst and between populations. In this respect, for a number of years we have investigated the pharmacogenetics of the thiopurine drugs and methotrexate in the treatment of inflammatory bowel disease (IBD). Another arm of the group's research has been the genetics of susceptibility to IBD. DNA samples from 1420 patients with IBD in Canterbury have been analysed, along with control samples, to examine for genetic variation that is associated with either Crohn's disease, ulcerative colitis or both. Many other groups internationally have done similar research and the combined data now shows that there are over 30 distinct susceptibility loci associated with Crohn's disease and 10-15 for ulcerative colitis. Many of these genetic variants are in genes that encode for proteins that are involved in immune mechanisms, gut wall integrity, inflammation, and bacterial recognition and handling, providing useful information on the pathogenesis of IBD. In addition, knowledge of these gene variants provides potential therapeutic targets. Pharmacogenetics may therefore be evolving to include drug development based on the genetics of disease susceptibility. It is also possible that new drug therapies might be targeted to patients with specific gene variants, to overcome specific defects.

Dr David Gibbs, *Medical Oncologist, Oncology Department, Christchurch Hospital , Christchurch*
"Practical Pharmacogenetics in the Oncology Clinic."

ASSOCIATIONS BETWEEN CARBOXYLESTERASE 1 (CES1) AND CARDIOVASCULAR OUTCOMES

Annica Svensson[1], Evan Begg[1,3], Rebecca Roberts[3], Nick Davis[2], Vicki Cameron[2], Katrina Ellis[2].

Department of Clinical Pharmacology[1], Cardioendocrine Research Group[2], University of Otago, Christchurch, New Zealand; Carney Centre for Pharmacogenomics[3], University of Otago, Christchurch, New Zealand.

Carboxylesterase 1 (CES1) is a broad substrate specificity enzyme that hydrolyzes endogenous and exogenous ester-containing compounds to the corresponding alcohol and carboxylic acid. CES1 metabolizes the anti-thrombogenic agent clopidogrel and it is also responsible for the activation of a number of ester prodrugs such as angiotensin-converting enzyme (ACE) inhibitors. In addition CES1 is involved in lipid homeostasis, including cholesterol metabolism and transport, with a proposed role in the development of atherosclerosis. Polymorphisms of the CES1 gene have been associated with alterations in pharmacokinetics and drug response of CES1 substrates. In this study, collection of a large database of acute coronary syndrome (ACS) patients with extensive demographic and clinical data enabled comparisons between pharmacogenetic groups to be made. Patients were genotyped for the CES1 mutation, p.Gly143Glu, to investigate associations with cardiovascular outcomes. Genotype frequencies for p.Gly143Glu were wild-type 96.8% and heterozygote 3.2%. None of the subjects carried two variant alleles. The heterozygous p.Gly143Glu genotype was not associated with greater mortality (p=0.140) in the overall cohort nor in patients on ACE-inhibitor treatment (p=0.371). Further survival analysis was done to compare mortality of subjects on or off clopidogrel treatment and to see if there were any associations between genotype and clopidogrel treatment. Mortality among patients not on clopidogrel was significantly greater (p= 0.0001), but the p.Gly143Glu genotype was not associated with greater mortality in patients on clopidogrel treatment (p=0.230). These findings show that CES1 does not appear to have a major effect on cardiovascular outcomes.

FROM PHARMACOGENETICS TO DRUG INTERACTIONS

Evan Begg[1], Paul Chin[1], Annica Svensson[1], Nick Davis[2].

Department of Clinical Pharmacology[1], Cardioendocrine Research Group[2], Christchurch Hospital, and University of Otago, Christchurch.

In 2008 at this meeting we proposed 'the prodrug hypothesis'. This stated that drug/metabolising enzyme pairings were more likely to have clinical relevance to pharmacogenetics for relevant enzymes if the drug involved was a prodrug. Of 8 drug/metabolising enzyme pairings that have clinical relevance, 4 are prodrugs – azathioprine, tamoxifen, codeine and clopidogrel. Interestingly, in a recent survey of clinical pharmacologists in Australasia (n=22), regarding clinically important drug interactions, these same drugs featured at the top of the list. The specific interactions involved allopurinol (azathioprine), tamoxifen (paroxetine/fluoxetine), codeine (paroxetine/fluoxetine) and clopidogrel (omeprazole). There is clear evidence of clinical effect in relation to the first 3 of these. With regard to the clopidogrel/omeprazole interaction, evidence is conflicting, with 2 large studies providing contrary findings. We believe that the differences are likely to relate to study design, and that the results from the study arguing FOR a clinically significant interaction are more compelling. We present evidence from the local Acute Coronary Syndrome study which supports the clinical significance of the clopidogrel/omeprazole interaction.