

**LIPID & DIABETES  
RESEARCH GROUP  
Christchurch Hospital**

**ANNUAL REPORT 2009**

**30 June 2008 – 30 June 2009**

**Website:** [www.cdhb.govt.nz/diabetes/research.htm](http://www.cdhb.govt.nz/diabetes/research.htm)

**Telephone (64 3) 364 0449**

**Facsimile (64 3) 364 0457**

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# 1

## Research Staff 2008/2009

Rob Williams		Medical Secretary
Chris Florkowski	MD, MRCP (UK), FRACP, FRCPA	Physician
Nikki Reid	RGON, BN	Clinical Nurse Specialist
Alison Luckey	BM, MFPM	Physician
Roberta McEwan	RGON	Research Nurse
Patrice McGregor	RGON	Research Nurse
Zarnia Morrison	BN, RCPN	Research Nurse
Sarah Plot	BN	Research Nurse
Annette Reinheimer	RGON, B.Sc (Hons)	Research Nurse
Russell Scott	MB, ChB, BMedSci, PhD (Monash), FRACP	Physician
Brett Shand	PhD	Senior Research Scientist
Peta Taylor	RGON, B.Sc (Hons), PGDip (Teach)	Post-graduate Student
Jinny Willis	B.Sc (Hons), PhD	Senior Research Scientist
Jo Young	B.Sc, M.Sc	Research Scientist

## STAFF DEPARTURES DURING THE YEAR

Jeremy McRae	B.Sc (Hons), PhD	Postgraduate Student
Maree Piebenga	B Cap Sci, PGDip Diet	Research Dietician
Meghan Shannon	B.Sc, PG Dip Diet (Dist), NZRD	Research Dietitian

## DIRECTOR

- Russell Scott

## 2 Collaborative Associations

- **Department of Paediatrics CDHB (Diabetes Projects)**  
Professor B A Darlow  
Dr Karen Mackenzie
- **Crop and Food**  
Dr Alison Wallace  
Sarah Eady
- **Clinical Biochemistry and molecular pathology CDHB**  
Dr Peter George, Dr A Fellowes
- **NHMRC Clinical Trials Unit**  
Professor A Keech  
Sydney, Australia
- **Type 1 Diabetes Genetic Consortium – Asia Pacific Network**  
Professor Peter Colman, Professor Grant Morahan  
Royal Melbourne Hospital and Walter & Eliza Hall Institute
- **Type 1 Diabetes TrialNet – Australasian Network**  
Professor Len Harrison, Professor Peter Colman  
Royal Melbourne Hospital and Walter & Eliza Hall Institute
- **Geohealth Laboratory, University of Canterbury**  
Dr Laura Miller, Dr Jamie Pearce, Professor Ross Barnett
- **Steroid and Immunobiochemistry Laboratory, CDHB**  
Dr John Lewis and Dr Peter Elder.
- **Westland Milk**
- **Duke University and Diabetes Trial Unit Oxford**  
The TECOS study (CVD and diabetes)

### **3 Main Scientific Research activities for 2008/2009**

- 1. Vascular function in diabetes and insulin resistance**
- 2. The Metabolic Syndrome and Cardiovascular Disease**
- 3. The Diabetes Registry: Health outcomes and implications of Diabetes**
- 4. Morbidity and Mortality in Diabetes Mellitus**
- 5. Familial Hypercholesterolaemia**
- 6. HDL and atherosclerosis**
- 7. Immunogenetic aspects of Type 1 Diabetes (TrialNet and the Diabetes Genetic Consortium)**
- 8. Lipid Clinic database: Plasma lipid fractions, cardiovascular risk factors and health outcomes.**
- 9. Type 1 Diabetes Prevention and Intervention Studies**
- 10. Effects of thiazolidinediones on glomerular function.**

## **4 Attendances at Scientific Meetings & Educational Courses**

National Diabetes Nurse Symposium, Wellington July 2008.  
Attendee: Z Morrison, S Plot, A Renheimer

INITII Investigators Meeting, Melbourne, August 2008  
Attendees: J A Willis

Symposium: Obesity & Diabetes: Are we doing enough?  
Edgar National Centre for Diabetes Research, Dunedin, October, 2008  
Attendees: J A Willis, BI Shand

Bayhill Investigator Meeting, Melbourne, February, 2009  
Attendees: J A Willis

Investigators meeting for BI Renal Study, Sydney, Australia, January 2009  
Attendee: Z Morrison

Investigators meeting for MERCK Protocol MK-0941-018, Copenhagen, Denmark, January 2009.  
Attendees: S Plot, R Scott

INITII Study Co-ordinators Meeting, Sydney, March, 2009  
Attendees: J A Willis

Steering Committee Meeting TrialNet, Bethesda, USA; April, 2009.  
Attendees: J A Willis

New Zealand Society for the Study of Diabetes, Annual Scientific Meeting, Dunedin, 2009.  
Attendees: J A Willis, BI Shand

Merck Investigator meetings, Auckland NZ, April and June 2009.  
Attendee: P. McGregor, R McEwen.

Investigators meeting for Takeda Alogliptin Study, Kuala Lumpur, Malaysia, May 2009.  
Attendee: Z Morrison, R Scott

ASEANZ Cardiovascular Forum, June 2009, Melbourne.  
Attendees: N Reid

Investigator meeting for Merck (MK-0941) New York, June 2008  
Attendees: A Renheimer, R Scott

XV International Symposium on Atherosclerosis, Boston, US; June 2009.  
And Post-Satellite Symposium: Atherosclerosis and Pharmacology, New York, June 2009.  
Attendee: J Young

ADA meeting New Orleans, June 2009

Attendee: R Scott.

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## Publications

(Collective within group; see individual reports for other publications)

Chan JC, Scott R, Arjona Ferreira JC, Sheng D, Gonzalez E, Davies MJ, Stein PP, Kaufman KD, Amatruda JM, Williams-Herman D. Safety and efficacy of sitagliptin in patients with type 2 diabetes and chronic renal insufficiency. *Diabetes Obes Metab.* 10: 546-555, (2008).

Lewis JG, Shand BI, Elder PA, Scott RS. Plasma retinol-binding protein is not a marker of insulin resistance in overweight subjects: a three year longitudinal study. *Clinical Biochemistry* 41:1034-1038 (2008)

Torn C, Mueller PW, Schlosser, Bonifacio E, Bingley PJ and Participating Laboratories (Willis JA – Participant). Diabetes Antibody Standardisation Program: evaluation of assays for autoantibodies to glutamic acid decarboxylase and islet antigen-2. *Diabetologia* 51: 846-852 (2008)

Lewis JG, Shand BI, Frampton CM, Elder PA, Scott RS. Plasma levels of sex hormone-binding globulin, corticosteroid-binding globulin and cortisol in overweight subjects who develop impaired fasting glucose: a 3 year prospective study. *Hormone Metabolic Research* 41:255-259 (2008)

Wallace AJ, Eady SL, Scott RS, Willis JA, Frampton CM. Considerable temporal variability in glucose reference curves in humans for a year period. *Nutr Res.* 8:495-500 (2008)

SL Molyneux, JM Young, CM Florkowski, M Lever, PM George. Coenzyme Q<sub>10</sub>; Is There a Clinical Role and a Case for Measurement? *Clin Biochem Rev* 29: 71-82 (2008)

Young JM, Strey CH, George PM, Florkowski CM, Sies CW, Frampton CM, Scott RS. Effect of atorvastatin on plasma levels of asymmetric dimethylarginine in patients with non-ischaemic heart failure. *Eur J Heart Fail* 10: 463-466 (2008)

Barrett JC, Clayton DG, Concannon P, Akolkar B, Cooper JD, Erlich HA, Julier C, Morahan G, Nerup J, Nierras C, Plagnol V, Pociot F, Schuilenburg H, Smyth DJ, Stevens H, Todd JA, Walker NM, Rich SS and the Type 1 Diabetes Genetics Consortium (Willis JA – Member). Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. *Nature Genetics* 41: 703-707 (2009)

Scott R, O'Brien R, Fulcher G, Pardy C, d'Emden M, Tse D, Taskinen MR, Ehnholm, C, Keech A. on behalf of the Fenofibrate Intervention and Event Lowering In Diabetes (FIELD) Study Investigators. *Diabetes Care* 32: 493-98 (2009)

Miller LJ, Pearce J, Barnett R, Willis JA, Darlow BA, Scott RS. Is population mixing associated with childhood type 1 diabetes in Canterbury, New Zealand? *Social Science and Medicine* 68: 625-630 (2009)

Wallace AJ, Eady SL, Willis JA, Scott RS, Monroe JA, Frampton CM. Variation in measurements of blood glucose response to foods in human subjects is not reduced after a standard breakfast. *Nutrition Research* 20: 238-243 (2009)

Elmslie JL, Porter RJ, Joyce PR, Hunt PJ, Shand BI, Scott RS. Insulin resistance, the metabolic syndrome and adiponectin in overweight bipolar patients taking sodium valproate. *Australian & New Zealand Journal of Psychiatry* 43: 53-60 (2009)

Shand BI, Scott RS, Elder PA, Frampton CM, Lewis JG. Comparison of insulin resistance indices and metabolic syndrome classifications to predict the development of impaired fasting glucose in overweight and obese subjects. A 3 year prospective study [Accepted for publication: *International Journal of Obesity*, July 2009].

SL Molyneux, CM Florkowski, AM Richards, M Lever, JM Young, PM George. Coenzyme Q<sub>10</sub>; an adjunctive therapy for congestive heart failure? *NZMJ* (In press, July 2009)

Lever M, George PM, Slow S, Elmslie JL, Scott RS, Richards AM, Fink JN, Chambers ST. Fibrates may Cause an Abnormal Urinary Betaine Loss which is Associated with Elevations in Plasma Homocysteine. *Cardiovasc Drugs Ther* published online 14 August 2009.

Lewis JG, Shand BI, Elder PA, Scott RS. Plasma retinol-binding protein is likely not a useful marker of insulin resistance. [In Press: *Diabetes Research and Clinical Practice*, July 2009].

## 6 Other Activities – National and International

### **Professor Russell Scott**

Regional Editor: Diabetes Research and Clinical Practice, Western Pacific Region

Editorial Board

- ◆ Diabetes Obesity and Metabolism

Medical Consulting Group

- ◆ MSD (New Zealand)
- ◆ Jansen Cilag (Australia)

Referee of Publications

- ◆ Diabetes Care (American Diabetes Association)
- ◆ Royal Australasian College of Physicians
- ◆ New Zealand Medical Journal
- ◆ Diabetes Research and Clinical Practice
- ◆ Diabetes Obesity and Metabolism

Referee of Research Applications

- ◆ Heart Foundation of New Zealand
- ◆ Health Research Council

New Zealand Principal Investigator and member of Management Committee for the FIELD Study – a 3 country study on heart disease prevention in diabetes mellitus through lipid-modification.

Operations Committee (TECOS) with Univ Oxford DTU

Supervision of PHD Fellows

P Taylor

J Young

Invited Speaker:

Advances in Medicine 2008, Chinese University of Hong Kong, June 2008. 'What after metformin: Incretin Enhancers and DPP-4 Inhibition'

Advances in Medicine 2008, Chinese University of Hong Kong, June 2008. 'Achieving glycemic control without therapeutic compromise with Sitagliptin'

### **Dr Chris Florkowski**

New Zealand Branch Chairman of the Australasian Association of Clinical Biochemists

Member, Committee of Evidence Based Laboratory Medicine (EBLM) of the International Federation of Clinical Chemistry (IFCC).

Member, Organising Committee, 2009 Programme for Annual Royal College of Pathologists of Australasia (RCPA) Update Meeting.

Examiner, Royal College of Pathologists of Australasia.

Member, Editorial Board of Clinical Biochemist Reviews.

Member, Expert Panel for Clinical Commenting of the Quality Assurance Programme of the Royal College of Pathologists of Australasia (QAP-RCPA).

Member, AACB Porphyria Working Party.

Referee of Publications

- Diabetes Research and Clinical Practice
- Clinical Endocrinology
- Clinical Biochemist Reviews.
- Mayo Clinic Proceedings
- Annals of Clinical Biochemistry.
- New Zealand Medical Journal.

Invited Speaker:

International Federation of Clinical Chemistry (IFCC) Worldlab Meeting, Fortaleza, Brazil. September 2008. Two invited talks on "Evidence Based Laboratory Medicine".

Malaysian Medical Association 2008: Coenzyme Q10 and cardiovascular disease outcomes. Invited speaker (talks in Melacca, Ipoh, Penang and Kuala Lumpur).

## **Dr Brett Shand**

Referee of Publications –

- Diabetes Research and Clinical Practice
- Diabetes Obesity and metabolism
- Clinical Biochemistry
- Gender medicine
- Arch Gynecology and Obstetrics
- African Health Sciences

Coordination of the Diabetes Skin auto-fluorescence project.

Coordination of milk whey protein project

Collaboration with Betaine and Homocysteine Research Group, Christchurch Hospital on betaine metabolism in metabolic disorders and patients with type 2 diabetes.

Presentation of talk titled "New non-invasive skin test for screening and assessment of diabetes" at Annual General Meeting of Diabetes NZ Christchurch Inc. June 28, 2009.

## **Dr Jinny Willis**

National Co-ordinator (New Zealand Data Centre), TrialNet  
NZSSD Treasurer and Executive Member

### Referee of Publications

New Zealand Medical Journal  
Diabetes Research & Clinical Practice

### Invited Speaker:

Pharmacy Department, Christchurch Hospital, September, 2008  
Paediatric Department, Christchurch Hospital, November 2008

### Referee of Grant Applications

Eli Lilly Specialist Diabetes Research Award  
Novo Nordisk Specialist Diabetes Research Award

### Supervision of PhD Fellows

P Taylor  
K Volkova

### Presentations/Publications for Lay Groups

Diabetes diagnosis for family, DNZ Magazine, Winter 2009  
Diabetes, a common Disease, The Press, Nov 2008  
Interview, The Body, CTV, July 2008

## 7 Research Grants and other Funding Support

### **New Zealand Heart Foundation :**

Cardiovascular Disease and HDL-Cholesterol Function \$ 14,770

### **Health Research Council (continuing grant):**

Does Ezetimibe correct vascular dysfunction? \$ 102,122

### **NZSSD Eli Lilly award:**

HDL cholesterol function and CVD in Diabetes \$ 30,000

### **National Heart Foundation:**

Coenzyme Q<sub>10</sub> supplementation in high-risk patients with inadequate blood pressure control \$ 179,580

### **Canterbury Community Trust Grant:**

J Young research funding \$ 10,760

### **Special Grants:**

Diabetes and Heart Research Trust (Salary) \$ 50,000

**Montgomery Trust** support for Type 1 Diabetes Research Projects  
2 years \$ 80,000

### **Awards to Skin Fluorescence project, Dr B Shand**

Pub Charity, Wellington \$ 5,000

Novo Nordisk Diabetes Grant \$ 10,000

Southern Trust, Dunedin \$ 29,500

Maurice & Phyllis Paykel Trust \$ 15,000

Diabetes Research and Training Trust \$ 4,000

### **Travel Grants:**

Dr B Shand to attend the 3<sup>rd</sup> International Congress on Prediabetes and the Metabolic Syndrome, Nice, France.

Canterbury Medical Research Foundation \$ 500

New Zealand Diabetes Foundation \$ 2,500

National Heart Foundation of New Zealand \$ 2,000

Dr B Shand to attend 33<sup>rd</sup> New Zealand Society for the Study of Diabetes Conference, Dunedin.

\$ 300

Dr J Young to attend the International Atherosclerosis Society

National Heart Foundation of New Zealand Travel Grant \$ 3,500

Royal Society of NZ Canterbury Branch Travel Grant \$ 1,000

## **Other RESEARCH Funding and EDUCATION Support**

The George Institute (University of Sydney)  
Merck and Co (USA and NZ)  
Novartis (Australia)  
Boehringer Ingelheim (Australia)  
Juvenile Diabetes Research Foundation (USA)  
Parexel (Australia)  
Sanofi Aventis  
MedPace (USA)  
Trilogie Phytotherapy (Australia)  
Takeda (International)  
GlaxoSmithKline (International)  
Jansen Cilag (Australia and International)  
Schering Plough  
Diabetes and Heart Research Trust  
Lipid and Diabetes research Trust  
Gilead (USA)

## 8 Reports by Research Staff

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### **CHRISTOPHER FLORKOWSKI** **Clinical Research Physician**

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#### **Present Positions**

Consultant in Chemical Pathology to Canterbury Health Laboratories

Clinical Research Physician, Lipid and Diabetes Research Group

Physician to Diabetes and Lipid Disorders Clinics, Canterbury Health Board

Clinical Associate Professor in (Chemical) Pathology,  
Christchurch School of Medicine and Health Sciences, University of Otago

#### **Research Projects**

**Co-Investigator to Clinical Trials programme** undertaken by Lipid and Diabetes Research Group (see reports by other staff).

#### **Co-enzyme Q10 studies.**

1. Further Bio-availability studies undertaken using commercial preparations.
2. Studies ongoing of CoQ10 in subjects with Familial Hypercholesterolaemia.
3. Studies have been initiated of the effects of co-enzyme Q10 supplementation in patients with metabolic syndrome.
4. Publication on outcomes in heart failure in relation to CoQ10 levels.
5. Intervention study ongoing in Hypertension.

**Glucose Meter evaluation studies** undertaken in Diabetes Services.

**Fluorescence of skin collagen in diabetes:** protocols developed for studies.

#### **Meetings Attended**

**Royal College of Pathologists of Australasia, Update Meeting;** Sydney, Australia; March 2009.

**Chemical Pathology Course (CPC) for Australasian Association of Clinical Biochemists / Royal College of Pathologists,** Melbourne; February 2009.

**International Federation of Clinical Chemistry (IFCC) Worldlab Meeting,** Fortaleza, Brazil. September 2008. Two invited talks on "Evidence Based Laboratory Medicine".

**Malaysian Medical Association 2008:** Coenzyme Q10 and cardiovascular disease outcomes. Invited speaker (talks in Melacca, Ipoh, Penang and Kuala Lumpur).

**Porphyryns and Porphyrins Conference.** Stockholm, Sweden. June 2009. Invited Round Table Discussant. Oral Presentation.

## **Publications**

1. **Florkowski C**, Budgen C, Kendall D, Lunt H, Moore M. A comparison of blood glucose meters in a New Zealand Diabetes Centre. *Ann Clin Biochem* 2009 (In Press).
2. **Florkowski CM**, Molyneux SL, George PM, Lever M, Richards M. Omega 3 polyunsaturated fatty acids and statins in heart failure. *Lancet* 2009 Jan 31; 373(9661):379-80.
3. Molyneux SL, **Florkowski CM**, George PM, Pilbrow AP, Frampton CM, Lever M, Richards AM. Coenzyme Q10: an independent predictor of total mortality in chronic heart failure. *J Am Coll Cardiol*. 2008 Oct 28; 52(18):1435-41.
4. Ganly P, Saleem M, Marr H, Burt M, **Florkowski C**, Williamson A. Not walking or communicating. Is all well? *Lancet* 2008; Dec 13; 372(9655):2086.
5. Walmsley TA, Potter HC, George PM, **Florkowski CM**. Pseudo-hypertriglyceridaemia: a measurement artefact due to glycerol kinase deficiency. *Postgrad Med J*. 2008 Oct; 84(996):552-4.
6. **Florkowski CM**. Sensitivity, specificity, Receiver-Operator Characteristic (ROC) curves and likelihood ratios: communicating the performance of diagnostic tests. *Clin Biochem Rev*. 2008 Aug; 29 Suppl 1:S83-7.
7. Mackay RJ, **Florkowski CM**, George PM, Sies CW, Woods S. Uncertainty of sweat chloride measurement. Does the right hand know what the left hand is doing? *Ann Clin Biochem*. 2008 Nov; 45(Pt 6):535-8.

## **Other Activities**

Chair, New Zealand Branch of the Australasian Association of Clinical Biochemists (AACB).

Member, Committee of Evidence Based Laboratory Medicine (EBLM) of the International Federation of Clinical Chemistry (IFCC).

Member, Organising Committee, 2009 Programme for Annual Royal College of Pathologists of Australasia (RCPA) Update Meeting

Examiner, Royal College of Pathologists of Australasia.

Member, Editorial Board of Clinical Biochemist Reviews.

Member, Expert Panel for Clinical Commenting of the Quality Assurance Programme of the Royal College of Pathologists of Australasia (QAP-RCPA).

Journal Referee: Diabetes Research and Clinical Practice, Clinical Endocrinology, Clinical Biochemist Reviews, Pathology, Annals of Clinical Biochemistry.

Member, Australasian Creatinine Consensus Working Group (2007-).

Member, AACB Working Party on Porphyria (2007-). Organiser of Porphyria Expert Comments Programme, with global membership.

### **Invited talks:**

**International Federation of Clinical Chemistry (IFCC) Worldlab Meeting,** Fortaleza, Brazil. September 2008. Two invited talks on "Evidence Based Laboratory Medicine".

**Malaysian Medical Association 2008:** Coenzyme Q10 and cardiovascular disease outcomes. Invited speaker (talks in Melacca, Ipoh, Penang and Kuala Lumpur).

## **NIKKI REID**

### **Clinical Nurse Specialist: Lipid Disorders and CVD Prevention**

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#### **Current Responsibilities**

- Co-ordination of Lipid Disorders and CVD Prevention Clinics for the CDHB
- Lipid disorders and cardiovascular risk identification, assessment, diagnosis, treatment and education for cardiovascular prevention of patients and families referred to the Clinics
- Familial Hypercholesterolemia Program in Canterbury
- Education of other health professionals in lipid disorders and cardiovascular prevention
- Liaison with staff of the Lipid and Diabetes Research Group

#### **Databases**

- Maintain databases of special risk groups
- Maintain records and organise genetic screening for relatives of clients with identified familial cholesterol disorders

#### **Attendances at Scientific meetings:**

### **Other Activities**

Family Screening Programme for identification of Familial Hypercholesterolemia

Lectures to Practice Nurses, Cardiology nursing staff, Post Graduate nursing students, pharmacists and general public on Cardiovascular Risk Assessment, Lipid Lowering Therapies and Familial Hypercholesterolemia.

## **ROBERTA "BOBBY" McEWAN** **Research Nurse**

### **Current Research Projects**

- (1) **RECORD study – A long term, open label, randomised study in patients with type 2 diabetes, comparing the combination of Rosiglitazone and either Metformin or Sulphonylurea with Metformin plus Sulphonylurea on cardiovascular endpoints and glycaemia.**  
A worldwide study in > 20 countries. 4466 participants were randomised with an average 6-year follow-up. Christchurch has recruited 7 participants. Completed December 2008.
- (2) **CRESCENDO study – Randomized, multinational, multicenter, double-blind, placebo-controlled, two-arm parallel group trial of Rimonabant (SR141716) 20 mg OD for reducing the risk of major cardiovascular events in abdominally obese patients with clustering risk factors.**  
**Lead site** – A worldwide study to recruit 17,000 participants. Early termination February 2009.
- (3) **DORADO study – DORADO-AC – Optimized Doses of Darusentan as Compared to an Active Control in Resistant Hypertension**  
**A Phase 3 Randomized, Double-Blind, Placebo- and Active-Controlled, Multi-centre, Parallel Group Study to Evaluate the Safety and Efficacy of Darusentan in Subjects with Resistant Hypertension Receiving Combination Therapy with Three or More Antihypertensive Drugs, Including a Diuretic, as Compared to Guanfacine or Placebo (Protocol DAR-312)**  
**Lead site** – Being conducted worldwide, 18 week intensive Blood Pressure study commenced August 2007, concluded 2009.
- (4) **DORADO-AC-EX – A Double-Blind, Active-Controlled, Long-Term Safety Extension Study to the Phase 3 DORADO-AC Study (Protocol DAR-312) of Darusentan in Resistant Hypertension**  
**A Double-Blind, Active-Controlled, Long-Term Safety Extension Study of Optimized Doses of Darusentan in Subjects with Resistant Hypertension Despite Receiving Combination Therapy with Three or More**

## **Antihypertensive Drugs, Including a Diuretic, as Compared to Guanfacine (Protocol DAR-312-E)**

**Lead site** – A long term extension to DORAD-AC study. Duration is until termination/completion of study or drug comes to market.

- (5) **MK024-04. A Multicenter, Randomized, Double-Blind, Parallel Group, 12 Week Study to Evaluate the Efficacy and Safety of MK-0524B (dosed as coadministered MK-0524A and Simvastatin Tablets) Versus Atorvastatin in Patients With Mixed Hyperlipidemia**

**Lead site** -2330 participants around the world. There will be about 20 people taking part in Christchurch.

- (6) **A double-blind, randomised, placebo controlled, 12-week cross-over study to assess the effect of CoenzymeQ<sub>10</sub> treatment on 24 hr mean ambulatory systolic blood pressure and diastolic blood pressure in inadequately treated hypertensive patients with the metabolic syndrome.**

Investigator led trial funded by the Heart Foundation, recruiting 30 Christchurch participants

### **Meetings Attended**

MERCK Investigator meeting, Auckland, NZ; June 2009.

## **PATRICE MCGREGOR Research Nurse Coordinator**

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### **Current Research Projects**

**1. Coordinator for MK0431 082 (TECOS) Study**

A study of adding Sitagliptin to metformin and **Coordinator for TECOS study-Trial Evaluating Cardiovascular Outcomes with Sitagliptin.**

A multinational, placebo-controlled, double-blind, randomised, parallel-group pragmatic clinical trial, to assess the impact of Sitagliptin therapy upon cardiovascular outcomes in a large population from a diverse group of countries and practice environments.

14,000 participants from 33 countries will be recruited over a two year period, with an estimated follow-up of at least four years. Approximately 250 participants will be recruited from 8 sites in New Zealand. Recruitment will begin in August 2009.

**2. Coordinator for MK0431 128 Study**

Safety and efficacy of Sitagliptin in patients with type 2 DM treated with Pioglitazone plus metformin combination therapy .

The treatment period is 26 weeks and 8 participants will be recruited from Christchurch, with two other New Zealand sites participating. Recruitment will finish in November 2009.

**3. Coordinator for SYR 322 study Open – label Extension Study**

A multi-centre, randomised, double-blind, placebo controlled study to determine the efficacy and safety of SYR-322 compared to placebo in subjects with Type 2 Diabetes. Three treatment arms, 26 week treatment duration study.

A new medication being developed to improve blood glucose levels in Type 2 diabetes.

12 participants have now completed the initial 26 week study of the Metformin arm and all 12 have entered the open label extension study which continues until the end of 2012

**5. Does ezetimibe correct vascular dysfunction?**

Hypercholesterolemia contributes to plaque formation in the arterial wall and impairs the ability of cells lining the arteries (endothelium) to govern vessel-relaxation and so regulate blood flow. Statins improve vascular function and reduce cardiovascular events through both LDL- lowering and LDL-independent effects, but the effect of ezetimibe on vascular function is unknown. Combination therapy for hypercholesterolemia with ezetimibe plus low-dose statin will achieve identical reductions in LDL-cholesterol levels as compared with high-dose statin. This 16-week study will investigate whether LDL-lowering with ezetimibe plus low-dose statin corrects vascular dysfunction to the same extent as high dose statin in subjects with the metabolic syndrome. Comparable improvements in vascular function would indicate that subjects using this safe low-dose combination therapy would receive similar benefits in reducing cardiovascular disease as more risky high-dose statin therapy. This study is funded by a grant from the Health Research Council of NZ.

**6. REASSURE STUDY**

A Randomized, multinational, multicentre, double-blind, placebo controlled, parallel group, fixed dose Rimonabant (SR141716)20mg OD study on HbA1c in overweight or obese subjects with type 2 diabetes not adequately controlled on two oral antidiabetic agents.

Christchurch recruited twenty participants. Early termination December 2008.

**7. ADVANCE-ON**

**Action in Diabetes and Vascular Disease.**

Preterax and Diamicron MR controlled evaluation post –trial observational study to determine the long term effects of the two interventions studied in the ADVANCE study completed in 2007. Follow-up will be for 5-10 years.

Meetings attended:

Merck Investigator meeting for MK 431 128 study, Auckland NZ, April 2009.

## ZARNIA MORRISON Research Nurse

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### Current Research Projects

- (1) **A multinational randomised double blind placebo controlled forced titration 2x2 factorial design study of efficacy and safety of long term administration of nateglinide and valsartan in the prevention of diabetes and cardiovascular outcomes in subjects with Impaired Glucose Tolerance (IGT). (Navigator Study)**

This 6-year study using nateglinide 60mg and valsartan 180mg daily commenced in June 2002. There are 600 participating centres in 40 countries throughout the world. There are two centres in New Zealand one in Christchurch and one in Dunedin. An amendment to the protocol increased the number of participants to be recruited from 7500 to 9150 and worldwide recruitment closed in November 2003, 9,524 patients have been recruited worldwide. Our site recruited 15 patients and the Dunedin site recruited 20. The study is due to finish in September 2009.

- (2) **A Phase III, Multicentre, randomised, Double blind clinical trial to study the safety and efficacy of the addition of sitagliptin (MK-0431) to patients with type 2 diabetes mellitus who have inadequate glycemic control on Insulin therapy (alone or in combination with metformin)**

This is a placebo controlled double blind 24 week study. Patients on insulin alone or in combination with metformin at a dose of at least 1500mg per day with inadequate glycemic control will be eligible to participate. Patients will continue on their current insulin +/- metformin regimen and be randomized to treatment with sitagliptin 100mg qd or placebo for a 24 week fixed insulin dose double blind treatment period. This study commenced in February 2007 in Christchurch, Hastings and Auckland. Christchurch enrolled 10 patients and the study was completed at the end of 2008.

- (3) **A 76-Week, Worldwide, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Assess the Tolerability and Efficacy of Anacetrapib When Added to Ongoing Therapy With a Statin in Patients With Hypercholesterolemia or Mixed Hyperlipidemia**

This is a 92 week, phase III, parallel group study to assess MK-0859 (anacetrapib) as an add on treatment to statin therapy in participants with high cholesterol or mixed hyperlipidemia. The study will assess the long-term effectiveness, safety and tolerability of anacetrapib. Approximately 1500 males and females will be enrolled world-wide. The participants will already be taking a stable dose of lipid modifying therapy (must include a statin) with less than ideal HDL cholesterol levels. Participants will remain on their current lipid modifying therapy for the study duration and if eligible, they will be randomised to either anacetrapib or placebo at a 1:1 ratio for 76 weeks. At each visit bloods will be drawn, vital signs taken, medication compliance and adverse events monitored. A physical examination and electrocardiogram will be completed before randomisation, at 24 weeks

and the end of the study. After stopping the study drug, participants will be followed up with two phone calls and will attend a visit 12 weeks post their final dose. The Christchurch site randomised 14 participants and the study is due to end in July 2010.

**(4) A multicenter, double-blind, randomized, 12-month, placebo-controlled study to evaluate the lipid-lowering effect, safety and tolerability of AVE5530 25 mg/day and 50mg/day when added to ongoing stable statin therapy (HMG-CoA reductase inhibitors) in patients with primary hypercholesterolemia.**

This study will assess the efficacy and safety of AVE5530 (25 mg and 50 mg) when added to statin treatment in (comparison with placebo) in the management of patients with primary hypercholesterolemia and LDL-C levels still equal or greater than 100 mg/dL (2.59 mmol/L). The minimum duration of treatment will be 12 months but may be extended up to approximately 18 months. We randomised 15 participants into this study, however the study was terminated early by the sponsor in March 2009 due to lack of efficacy.

**(5) A Phase III, randomised, double-blind, placebo-controlled, parallel group, safety and efficacy study of BI 1356(5mg), compared to placebo as add on to pre-existing antidiabetic therapy (insulin or any combination with insulin; sulphonylurea or glinides as monotherapy; pioglitazone or any other antidiabetics, excluding only DPP-4 inhibitors other than BI 1356) over 52 weeks in type 2 diabetic patients with severe chronic renal impairment.**

This study compares BI 1356 (5mg) to placebo as add-on therapy to pre-existing antidiabetic therapy, insulin or any combination with insulin; sulphonylurea or glinides as monotherapy. Approximately 300 patients will be enrolled in 6 countries, approx 3-4 patients should be enrolled at each site. Patients will be randomised to the 52 week period of the study in which they will receive either 5mg of BI 1356 or placebo in addition to their pre-existing therapy. Recruitment for this study commenced in April 2009 and continues until September 2009.

**(6) A Multicenter, Randomized, Double-Blind, Active-Controlled Study to Evaluate the Durability of the Efficacy and Safety of Alogliptin Compared to Glipizide When Used in Combination with Metformin in Subjects with Type 2 Diabetes.**

The purpose of the study is to evaluate the efficacy and safety of alogliptin 12.5mg or 25mg once daily compared to glipizide 5mg (all as add-on to metformin) when given to patients with T2DM for 104 weeks (approximately 2 years). Participants currently taking metformin, with inadequate blood glucose control will be enrolled. Participants enrolled in this study will undergo a screening period, a 4-week stabilization period, a 104 week treatment period and a 2-week follow up period. We are currently awaiting final ethical approval to commence this study.

### **Attendances at Meetings**

- (1) National Diabetes Nurse Symposium, Wellington July 2008.

- (2) Investigators meeting for BI Renal Study, Sydney, Australia, January 2009
- (3) Investigators meeting for Takeda Alogliptin Study, Kuala Lumpur, Malaysia, May 2009.

## **SARAH PLOT**

### **Nurse Specialist Study Co-ordinator**

#### **1. A Long-Term, Open Label Extension Study to Investigate the Long-Term Safety of SYR110322 (SYR-322) In Subjects with Type 2 Diabetes (Protocol SYR-322-OLE-012) Phase III.**

SYR-322 is a new medication being developed to improve blood glucose levels in Type 2 diabetes. This study commenced in December 2006 and has now been extended to four years in duration. Participants who had successfully completed SYR-322 Phase III, protocols SYR-322-SULF-007, SYR-322-MET-008, SYR-322-PIO-009, SYR-322-PLC-010 or SYR-322-INS-011 were able enter this study and have been assigned to open label study medication. The study is due to be completed in 2011.

#### **2. A Multi-Centre, Randomised, Double-Blind Study to Evaluate the Safety and Efficacy of the Addition of Sitagliptin Compared With the Addition of Glimepiride in Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Metformin. (Protocol 803-01) Phase III.**

This study completed recruitment in March 2009. People in the study are using high dose Metformin ( $\geq 1500$  mg/day) and have inadequate diabetes control i.e. HbA1c  $\geq 6.5$ -  $\leq 9.0$  %. This study lasts for 35 weeks. The study medication Sitagliptin has been approved for use by the FDA as a prescription medicine for Type 2 Diabetes.

#### **3. A 78 Week Open Label Extension to Trials Assessing the Safety and Efficacy of BI 1356 (5 mg) as Monotherapy or in Combination with other Antidiabetic Medications in Type 2 Diabetic Patients. (Protocol BI 1218.40) Phase III.**

BI 1356 is a new medication being developed to improve blood glucose levels in Type 2 diabetes. All study participants at the L&DRG who completed study participation in protocol BI 1218.17 had the option of enrolling into this open label extension. This extension study has treatment period of 78 week with all participants receiving study medication BI 1356, 5mg a day.

#### **4. A Phase IIa, Multicenter, Randomised, Double Blind, Placebo-Controlled Clinical Trial of MK-0941 in Patients With Type 2 Diabetes Mellitus with Inadequate Glycaemic Control on Insulin. (Protocol MK-0941-018).**

MK-0941 is a new medication being developed to improve blood glucose levels in Type 2 diabetes. People in this study are using insulin plus or minus an oral diabetes medication and have inadequate diabetes control. All participants are converted to Lantus® insulin at week -10 of the study; the Lantus® insulin remains in place for the duration of the study. People in the study are then assigned to either the study medication or placebo at day 1 for the 20 week treatment period of the study. Recruitment for this study closes on the 17<sup>th</sup> July 2009.

## **Completed Research Projects**

- 1. A Multi-Centre, Randomized, Double-Blind Study to Determine the Efficacy and Safety of the Addition of SYR-322 25 mg versus Dose Titration from 30 mg to 45 mg of ACTOS® Pioglitazone HCl in Subjects with Type 2 Diabetes Mellitus Who Have Inadequate Control on a Combination of Metformin and 30 mg of Pioglitazone HCl Therapy. (Protocol 01-06-TL-3222OPI-004) Phase III.**

SYR-322 is a new medication being developed to improve blood glucose levels in Type 2 diabetes. This study was completed in April 2009. Participants in this study were using metformin plus pioglitazone 30mg and were then assigned to receive either SYR-322 25 mg or placebo or an additional 15 mg of pioglitazone or placebo. The study lasted for a maximum of 74 weeks.

- 2. A Randomised, Double-Blind Placebo –Controlled Parallel Group Efficacy and Safety Study of BI 1356 (5mg administered orally once daily) Over 24 Weeks in Type 2 Diabetic Patients With Insufficient Glycaemic Control Despite Metformin Therapy (Protocol BI 1218.17) Phase III.**

BI 1356 is a new medication being developed to improve blood glucose levels in Type 2 diabetes. All study participants at the L&DRG completed study participation of 32 weeks by April 2009. Most study participants enrolled into the open label extension to this study (Protocol BI 1218.40) with a 78 week open label treatment period.

## **Attendances at Meetings**

National Diabetes Nurse Symposium, Wellington July 2008.

Investigators meeting for MERCK Protocol MK-0941-018, Copenhagen, Denmark, January 2009.

Investigators meeting for MERCK Protocol MK-0431-128, Auckland New Zealand, April 2009.

**ANNETTE REINHEIMER**  
**Clinical Study Co-ordinator**

## **Current Research Projects**

- 1) A Long Term, Open-Label Extension Study to Investigate the Long-Term safety of SYR110322 (Alogliptin) in Subjects with Type 2 Diabetes. Recruitment for this study began in January 2007.**
- 2) A Phase 11B, Multicenter, Double-Blind, Placebo, Dose-Ranging Finding Clinical Trial of MK-0941 in Patients with Type 2 Diabetes Mellitus with Inadequate Glycemic Control on Basal Insulin. Recruitment began in August 2008**
- 3) IMPROVE-IT: A Multicenter, Double-Blind, Randomised Study to Establish the Clinical Benefit and safety of Vytorin versus Simvastatin in patients presenting with Acute Coronary Syndrome. Recruitment is in progress (initiated by another research group)**

### **Completed Research Projects**

- 1) A Multi-Center, Randomised, Double-Blind, Placebo-Controlled 36 week- Study to Evaluate the Efficacy and Safety of extended Release (ER) Niacin/Laropiprant in Patients with Type 2 Diabetes mellitus. Recruitment closed for this study in December 2007 with the last patient completing the study July 2008.**
- 2) A Multicenter, Randomized, Double-Blind, Placebo- and Active-Controlled Study to Assess the Efficacy, and Tolerability of MK- 6213 co-administered with Atorvastatin in Patients with Primary Hypercholesterolemia. Recruitment closed for this study in December 2008.**

### **Attendances at Meetings**

Investigator meeting for Merck (MK-0941) New York June 2008

Diabetes Nurses Symposium Wellington 2008

**DR BRETT SHAND  
Scientist**

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### **Current Research Projects**

- (1) Studies comparing the role of markers of insulin resistance to predict the development of impaired glucose control and atherosclerosis in overweight subjects .**

This prospective study in 250 overweight individuals, evaluated the ability of several markers of insulin resistance to predict worsening in blood glucose control over a 3-year period. Particular emphasis was given to the insulin sensitising cytokine, adiponectin and binding proteins involved in steroid and vitamin metabolism. The study was carried out in collaboration with the Steroid and Immunobiochemistry Laboratory, Canterbury Health Laboratories. Data collection and the laboratory assays were finished in early 2008, followed by statistical analysis of the database. The study showed plasma adiponectin level and indices derived from plasma triglyceride concentration were more sensitive markers of the development of glucose intolerance than indices derived from blood glucose levels. We also showed Maori people tended to have lower levels of adiponectin in their blood than Caucasian people. It is possible these low adiponectin levels may contribute to the higher prevalence of type 2 diabetes in the Maori population. The results of the study have been published in several papers.

(2) **An investigation of the mechanism of the anti-proteinuric effects of pioglitazone.**

Pioglitazone is a drug with insulin sensitising properties used in the treatment of type 2 diabetes. In addition to its insulin sensitising effect, pioglitazone also reduces protein loss in the urine. The mechanism of this anti-proteinuric effect is not fully understood. This aim of this study, funded by the 2006 Eli Lilly Diabetes Specialist Research Grant, is to investigate the effect of pioglitazone on the filtration units in the kidney. The study involves measuring the urinary excretion levels of proteins of different size and electrostatic charge in patients with type 2 diabetes and kidney disease, before and after a 3-month course of pioglitazone. This data will be used to determine whether pioglitazone causes changes in the size of the pores in the filter or the level of electrostatic charge barriers in these filters. Seven patients have completed the study and laboratory analysis of the urine samples collected during the study is being carried out at present.

(3) **Assessment of a new, non-invasive, skin test for measuring blood glucose control.**

There is evidence that measuring the fluorescent properties of skin may provide a simple method for detecting people with diabetes from those without the disorder. The basis of this test is that increased amounts of sugar attached to a protein in the skin, called collagen, results in higher skin fluorescence and indicates that circulating blood sugar levels have been raised for a relatively long period of time. Until recently, devices used to measure skin fluorescence have not had sufficient sensitivity to be used for diabetes screening. However, development of a new measuring device by the Department of Medical Physics, Canterbury University, has led to a test with increased sensitivity. This new skin test has the advantages of being non-invasive and painless, does not require the patient to be fasting, with the results being available within 2-3 minutes. As the fluorescent measuring device is small and portable, the skin test has the potential to be used for diabetes screening of a large number of people in a community setting.

A pilot study carried out by Sally van der Hulst as a summer studentship showed skin autofluorescence discriminated between diabetes and non-diabetes. We are

shortly to start a comprehensive evaluation of a modified version of the measuring device that will involve calibration of the measurements, followed by clinical evaluation of the test in patients having an oral glucose tolerance test or attending a diabetes out-patient clinic.

(4) **Epidemiological studies using the Lipid Clinic database.**

Since 1997, a clinical database and frozen plasma sample repository have been collected from new patients attending the Lipid Outpatient Clinic at Christchurch Hospital. To date, 3186 patients are included in this database, which has been updated to include the Framingham variables and indices of insulin resistance. The data base is now used in several studies to examine relationships between lipid fractions and other cardiovascular risk factors and also acts as a patient database for enrollment in a number of clinical studies.

(5) **Dietary supplementation with whey protein in the metabolic syndrome and diabetes.**

There is increasing evidence that proteins derived from milk, specifically whey protein concentrates, have a wide range of beneficial effects on both metabolic syndrome characteristics and blood glucose control. It is therefore possible dietary supplementation with whey protein has the potential to prevent or minimise the development of type 2 diabetes in "at risk patients, or alternatively to improve blood glucose control in patients with diabetes. We are currently in the planning phase of a series of studies that will examine the effect of whey protein dietary supplementation on metabolic syndrome characteristics and glucose and insulin responses to a standard meal test. It is envisaged these studies will start in the latter part of 2009.

## Publications in referred journals

Lewis JG, **Shand BI**, Elder PA, Scott RS. Plasma retinol-binding protein is not a marker of insulin resistance in overweight subjects: a three year longitudinal study. *Clinical Biochemistry* 2008;41:1034-1038.

Lewis JG, **Shand BI**, Frampton CM, Elder PA, Scott RS. Plasma levels of sex hormone-binding globulin, corticosteroid-binding globulin and cortisol in overweight subjects who develop impaired fasting glucose: a 3 year prospective study. *Hormone Metabolic Research* Oct 2008; 41:255-259.

Elmslie JL, Porter RJ, Joyce PR, Hunt PJ, **Shand BI**, Scott RS. Insulin resistance, the metabolic syndrome and adiponectin in overweight bipolar patients taking sodium valproate. *Australian & New Zealand Journal of Psychiatry* 2009;43:53-60.

Lewis JG, **Shand BI**, Elder PA, Scott RS. Plasma retinol-binding protein is likely not a useful marker of insulin resistance. [In Press: *Diabetes Research and Clinical Practice*, July 2009].

**Shand BI**, Scott RS, Elder PA, Frampton CM, Lewis JG. Comparison of insulin resistance indices and metabolic syndrome classifications to predict the development of impaired fasting glucose in overweight and obese subjects. A 3 year prospective study [Accepted for publication: *International Journal of Obesity*, July 2009].

## Published abstracts of conference proceedings

**Shand B**, Scott R, Elder P, Lewis J, Frampton C. Comparison of commonly used markers of insulin resistance to predict the development of impaired fasting glucose in overweight subjects. Poster presentation, 3<sup>rd</sup> International Congress on Prediabetes and the Metabolic Syndrome, Nice, France, April 1-4, 2009. *Journal of Diabetes* 2009;1 (Suppl. 1):A132; 33<sup>rd</sup> New Zealand Society for the Study of Diabetes Conference, Dunedin, July 2009.

**Shand B**, Florkowski C, Scott R, van der Hulst S, Reinisch L. Assessment of a new non-invasive skin test to discriminate between people with and without diabetes. Oral presentation at 33<sup>rd</sup> New Zealand Society for the Study of Diabetes Conference, Dunedin, July 2009.

**Shand B**, Scott R, George P. Comparison of clinical and biochemical parameters in subjects with and without diabetes attending a lipid disorders outpatient clinic. Poster presentation at 33<sup>rd</sup> New Zealand Society for the Study of Diabetes Conference, Dunedin, July 2009.

## Research Grants and other Support

(1) Funding for skin autofluorescence study

Pub Charity, Wellington	\$5000
Novo Nordisk Diabetes Grant	\$10000

Southern Trust, Dunedin	\$29500
Maurice & Phyllis Paykel Trust	\$15000
Diabetes Research and Training Trust	\$4000

(2) Travel Grants to attend meetings

3<sup>rd</sup> International Congress on Prediabetes and the Metabolic Syndrome, Nice, France.

Canterbury Medical Research Foundation	\$500
New Zealand Diabetes Foundation	\$2500
National Heart Foundation of New Zealand	\$2000

33<sup>rd</sup> New Zealand Society for the Study of Diabetes Conference, Dunedin  
 NZSSD Travel grant in aid \$300

### **Attendances at Scientific Meetings**

3<sup>rd</sup> International Congress on Prediabetes and the Metabolic Syndrome, Nice, France.  
 33<sup>rd</sup> New Zealand Society for the Study of Diabetes Conference, Dunedin.

### **Other Activities**

Preparation of funding applications for clinical assessment of skin autofluorescence to 2009 Canterbury Medical Research Foundation Project Grant and 2009 Health Research Council DHB Translational Research Fund.

Collaboration in studies with Betaine and Homocysteine Research Group, Christchurch Hospital on betaine metabolism in metabolic disorders and patients with type 2 diabetes.

Review of papers for Diabetes Research and Clinical Research, Diabetes Obesity and Metabolism, Clinical Biochemistry, Gender Medicine, Archives of Gynecology and Obstetrics and African Health Sciences.

Presentation of talk titled "New non-invasive skin test for screening and assessment of diabetes" at Annual General Meeting of Diabetes NZ Christchurch Inc. June 28, 2009.

## **PETA TAYLOR**

### **Post-graduate Student**

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### **Current Research Activities**

Peta joined the Lipid and Diabetes Research Group as a PhD student in 2007 after completing an honours degree at the University of Canterbury. Peta is investigating HDL function in participants with very high levels of HDL in the presence and absence of cardiovascular disease.

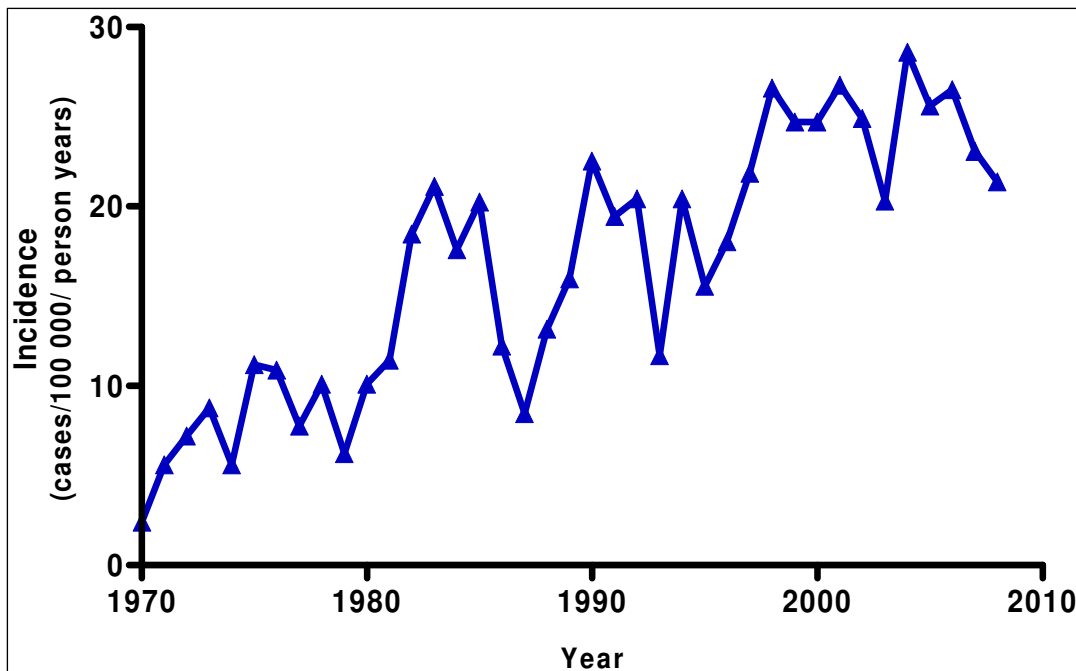
**DR JINNY WILLIS**  
**Scientist**

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**Current Research Projects**

**1. Epidemiology of Diabetes in Canterbury Children and Adolescents**

Type 1 diabetes is an autoimmune disorder thought to be precipitated by environmental factors in individuals with permissive genotypes. Around one in every 500 New Zealand school children are affected by the disorder. Prospective ascertainment of all incident cases commenced in this region in 1982. Prior to 1982 incident cases were ascertained retrospectively from hospital records. Accordingly, 2009 completes a 40-year record of all incident cases of type 1 diabetes presenting before than 20 years of age in the Canterbury geographical area. *This register represents the only longitudinal prospective register for type 1 diabetes in New Zealand, and is unique resource by international standards.* Very few countries have type 1 diabetes registries of such duration. Clinical and demographic data, including address, are collected at diagnosis. Age and sex specific annual incidence rates are determined from five-yearly census population denominators. The incidence of type 1 diabetes in Canterbury children and adolescents from 1970 – 2009 is illustrated below.



For the years 1970-2008, there were 664 new type 1 diabetes cases (346 males, 318 females) aged 0-19 years diagnosed in the Canterbury geographical region. The incidence ranged from 2.40 cases to 28.60 cases/100 000 person years. The mean (SEM) age at diagnosis of diabetes was 10.74 (0.20) years. There was a trend for a decrease in the age at presentation of diabetes over the study period ( $p=0.08$ ). Mean (SEM) incidence rates for the age groups 0-4 years, 5-9 years, 10-14 years, 15-19 years were 11.74 (1.42), 14.69 (1.59), 21.37 (2.14) and 10.27 (1.38) cases/100 000 person years respectively. The increase in incidence rate over 39 years was 0.55 cases/100 000 per year ( $P<0.0001$ ), with a three-fold increase in the mean incidence rate per

decade over the study period. Of note, there has been a marked increase in cases identifying with Maori ethnicity in the last decade.

The rate of presentation of type 1 diabetes in Canterbury children and adolescents is high and continues to increase. Increasing rates of presentation with type 1 diabetes have been reported in many populations. The prevalence of high-risk HLA genotypes has decreased over time in type 1 diabetes cases, suggesting that environmental factors are contributing to increasing disease penetrance. This may account for the increase in the disease in Maori and Pacific Island children, who have traditionally been over-represented in type 2 diabetes cases and under-represented among type 1 diabetes cases. The highest risk is still associated with European ethnicity, though there is an increase in individuals identifying with ethnicities traditionally associated with lower risk.

## **2. WHO DiaMond Study**

The WHO DiaMond Study is a multinational project determining the incidence of type 1 diabetes in children under 15 years of age. Canterbury incidence data has been contributed to the study since commencement of the study in 1990. Data is available from 106 centres in 55 countries, representing about 4% of the world's children. Data collected in the first 10 years of the study, 1990-1999, revealed a total of 36,316 cases were diagnosed in the study population of 78 million children. The age-adjusted incidence of type 1 diabetes among 106 centres (108 populations) varied from 0.1/100,000/year in China and Venezuela to 40.9 per 100,000/year in Finland. The average annual increase in incidence calculated over 96 centres was 2.8 % (95% CI 2.4-3.2%). During 1990-1994, the increase was 2.4% (95% CI 1.3-3.4%) and during the second study period 1995-1999 it was slightly higher 3.0% (95% CI 1.9-4.2%). Canterbury is ranked internationally in the highest 10% of the incidence distribution for risk of childhood diabetes, defining a high-risk population with respect to type 1 diabetes.

## **3. TrialNet ANZ**

TrialNet is an international network of clinical centres, experts in diabetes and immunology and specialized laboratories dedicated to testing new approaches to understanding and preventing type 1 diabetes. The network has developed from the infrastructure of the Diabetes Prevention Trial (DPT-1) conducted in the United States. The network is sponsored by a number of groups within the NIH (eg. NIDDK, NIAID, NHCHD), the American Diabetes Association and the Juvenile Diabetes Research Foundation. The Australasian TrialNet group is co-ordinated from the Royal Melbourne Hospital and the Walter & Eliza Hall Institute of Medical Research, and is one of four international TrialNet Centres. There are five New Zealand centres co-ordinated by the New Zealand Data Centre in Christchurch (Dr Jinny Willis). Recruitment of first degree relatives in New Zealand commenced in January 2006. To date there are 1370 individuals who are enrolled in the study in New Zealand. Of these, 68 individuals are positive for autoantibodies against beta cell antigens and are participate in phase 2 and 3 of the study in which  $\beta$ -cell function is assessed at six-monthly intervals. Individuals meeting the inclusion criteria will soon be invited to participate in a trial of Oral Insulin, the first TrialNet intervention study being undertaken in New Zealand. 4.

## **4. Intranasal Insulin Study (INITII)**

Research on mice developing type 1 diabetes has shown that exposure of the mucous membranes to insulin acts like a vaccine. Protective ("good") immune cells are stimulated and these then counteract the "bad" immune cells that damage the beta cells. A trial in children and young adults at risk for type 1 diabetes (Intranasal Insulin Trial I – INIT I), in which insulin was given via a nasal spray found that the treatment stimulated immune changes similar to those observed in mice that were protected from getting diabetes by this treatment. The INIT I trial also showed that the insulin spray was safe. The Intranasal Insulin Trial II (INIT II) is designed to determine if, along with the immune changes, intranasal insulin can protect beta cells and stop progression to diabetes. This study co-ordinated by the Diabetes Vaccine Development Centre (DVDC), is a randomised – placebo controlled trial of intranasal insulin in antibody-positive first degree relatives of individuals with type 1 diabetes.

A screening phase measures type 1 diabetes associated autoantibodies in relatives of individuals aged 4-30 years. Individuals who are positive for two autoantibodies and have normal glucose tolerance are eligible to participate. These individuals have a 26-50% 5-year risk of developing type 1 diabetes. Participants will be entered into a randomised, double-blind, trial of intranasal insulin versus insulin carrier (placebo) for 12 months, with three monthly follow-up in the first year and 6 monthly follow-up for 4 subsequent years. The monitoring phase will determine if intranasal insulin: 1) prevents loss of  $\beta$ -cell function, 2) improves insulin action, 3) causes changes in immunity to insulin consistent with induction of mucosal tolerance, and 4) reduces development of diabetes.

The study is underway in Christchurch and Auckland and two New Zealand children have been randomised to receive intranasal insulin or insulin carrier. Recruitment continues. The study is open to participants living anywhere in New Zealand. Travel costs of participants living outside Christchurch and Auckland will be met by the DVDC.

### **5. Type 1 Diabetes Genetic Consortium (Asia and Pacific Network)**

The consortium is funded by the Juvenile Diabetes Research Foundation (USA). The aim of this international consortium is to establish a combined resource of 4300 affected sib-pair families to identify novel genes for type 1 diabetes susceptibility genes. When recruitment concluded in 2007 the New Zealand arm of the study had recruited 43 multiplex families (174 individuals). This year saw the first published report from the consortium which revealed that over 40 loci affect risk of type 1 diabetes (*Nature Genetics* 41: 703-707, 2009).

### **6. The safety and efficacy of BHT-3021, a plasmid vector containing the human proinsulin gene, in subjects with type 1 diabetes.**

A plasmid vector, BHT-3021, produced by Bayhill Therapeutics, containing the genetic material which codes for human pro-insulin is being investigated in individuals with type 1 diabetes. The research aims to assess the safety of BHT-3021 and to determine if therapy with BHT-3021 affects the immune cells that may be responsible for causing damage to the insulin-producing cells in people with type 1 diabetes. The company have successfully completed a study using a similar agent, BHT-3009, in individuals with relapsing remitting multiple sclerosis (n=289). BHT-3021 is designed to decrease this abnormal immunity to insulin and decrease damage to the insulin-producing cells in the pancreas. The protocol involves weekly intramuscular injections of BHT-3021 or placebo for 12 weeks and blinded follow-up until 12 months from first injection. Placebo-treated individuals may cross-over to active therapy after unblinding.

Preliminary data presented at the American Diabetes Association Annual Scientific Meeting in June revealed preservation of stimulated C-Peptide and stable HbA1c in treated individuals over 12 months, compared with declining stimulated C-Peptide and deteriorating HbA1c in placebo-treated individuals. The research is underway in Auckland, Hamilton, Wellington and Christchurch, as well as study sites in Australia and the USA. In Christchurch, one subject has completed eight weekly injections and several individuals are commencing screening for the study. Studies of this type have not been undertaken in New Zealand to date. There is a real need for these studies in new onset type 1 diabetes, where there is still some remaining beta-cell function to be preserved. Further, individuals newly-diagnosed with type 1 diabetes are very keen to participate in studies that could potentially improve the outcome of their disease process.

### **7. Genetic Aspects of Type 2 Diabetes**

*This research was the basis for the PhD research of Jeremy McRae. The degree was conferred in December 2008.*

Type 2 diabetes represents approximately 90% of all diabetes presentations. While more likely to present in adulthood, the disorder is becoming increasingly prevalent in children and adolescents. In New Zealand, the prevalence of known diabetes is 1.9% in Europeans, 5.2% among Maori, and around 4% in Pacific Island peoples and other ethnic groups. A novel adipose-specific protein, adiponectin, has been implicated in the pathogenesis of obesity and type 2 diabetes. Our research

investigated polymorphisms or variations in the genes for the adiponectin receptors, AdipoR1 and AdipoR2, to determine whether any of these variations were associated with obesity and type 2 diabetes. Nucleotide variants in the gene for adiponectin have been reported to affect susceptibility to type 2 diabetes. This project investigated whether nucleotide variants in the genes for the cellular receptors of adiponectin affect susceptibility to type 2 diabetes and obesity in a New Zealand population. Healthy controls, obese non-diabetic individuals and diabetic individuals were studied (n=932 individuals). The exons of *ADIPOR1* and *ADIPOR2* were sequenced in forty individuals, twenty of whom were Maori, in order to define nucleotide variation in the New Zealand cohorts. Subjects were genotyped for multiple variants within *ADIPOR1* and *ADIPOR2*. Alleles of SNP 9881 and SNP 4644 in *ADIPOR1* were significantly associated with obesity, but not type 2 diabetes. Further SNPs were observed to affect quantitative traits such as HbA1c and cholesterol:HDL ratios. Collectively these findings suggest that variants within the adiponectin receptors are more important in determining susceptibility to obesity than type 2 diabetes. New Zealand Maori are at greater risk of developing obesity and type 2 diabetes. This research demonstrated significant differences in genotype frequencies between Maori and non-Maori, which may be a contributing factor in the increased prevalence of obesity and type 2 diabetes in Maori. This project also investigated the regulation of the gene expression of *ADIPOR1* and *ADIPOR2*. The promoter regions of the adiponectin receptor genes were isolated and a series of segments were sequentially deleted from each promoter region. The deletion constructs were used to drive expression of chloramphenicol acetyltransferase in tissue culture models of human skeletal muscle and human liver, where the adiponectin receptors are known to operate, and the level of expression was determined. Multiple regions within the promoters of the adiponectin receptor genes were found to regulate expression. These regions differed between the two cell types as well as between the two promoter regions. Candidate binding sites were identified within the regulatory regions. This project has determined, to a 200 bp resolution, the regulatory regions of over 2.3 kb of promoter sequence of *ADIPOR1* and *ADIPOR2*.

Deciphering the role of these genetic loci should contribute to the extent to which the natural history of type 2 diabetes may be manipulated and, through this process lead to recommendations for preventing or minimising the effect of the disease. The research may lead to the development of new therapies, such as variant adiponectin molecules capable of binding to the different receptor isoforms, or receptor agonists.

## **8. Glycaemic Glucose Equivalents**

The Glycaemic Glucose Equivalents (GGEs) system measures how blood glucose changes after consumption of a serving of a food. This system classifies whether a food has a high GGE, that is, it causes a large increase in blood glucose after it is eaten or a low GGE; that is, the response of blood glucose is lower and more sustained. Low GGE foods will produce a smaller, more sustained increase in blood glucose and will improve blood glucose control in people with diabetes. In addition, low GGE foods will help increase satiety. This research is being undertaken in collaboration with Dr Alison Wallace, Sarah Eady and Dr John Munro of the NZ Crop and Food Research Institute.

## **9. Functional Studies in HDL**

High density lipoprotein cholesterol (HDL) is thought to protect against CVD by promoting cholesterol efflux from macrophages. There is a well established inverse relationship between the concentration of high density lipoprotein cholesterol (HDL) and cardiovascular disease. Increasing plasma levels of HDL is a major goal of treating dyslipidaemia, in addition to lowering levels of LDL. Individuals with very high HDL levels do present with cardiovascular disease, suggesting that in some individuals the high HDL does not afford protection. It is possible that while the amount of HDL is substantial, the composition or functional behaviour of the HDL is different in these individuals. This research which forms the basis for PhD research being undertaken by Peta Taylor will investigate the functional and biochemical characteristics of HDL isolated from individuals with high HDL without cardiovascular disease and individuals with high HDL who have manifest cardiovascular disease.

## Attendances at Scientific Meetings & Educational Courses

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INITII Investigators Meeting, Melbourne, August 2008

Attendees: J A Willis

Symposium: Obesity & Diabetes: Are we doing enough?

Edgar National Centre for Diabetes Research, Dunedin, October, 2008

Attendees: J A Willis, BI Shand

INITII Study Co-ordinators Meeting, Sydney, March, 2009

Attendees: J A Willis

Bayhill Investigator Meeting, Melbourne, February, 2009

Attendees: J A Willis

Steering Committee Meeting TrialNet, Bethesda, USA; April, 2009.

Attendees: J A Willis

New Zealand Society for the Study of Diabetes, Annual Scientific Meeting, Dunedin, 2009.

Attendees: J A Willis, BI Shand

## Publications

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TORN C, MUELLER PW, SCHLOSSER, BONIFACIO E, BINGLEY PJ and Participating Laboratories (**WILLIS JA** – Participant). Diabetes Antibody Standardisation Program: evaluation of assays for autoantibodies to glutamic acid decarboxylase and islet antigen-2. *Diabetologia* 51: 846-852, 2008

BARRETT JC, CLAYTON DG, CONCANNON P, AKOLKAR B, COOPER JD, ERLICH HA, JULIER C, MORAHAN G, NERUP J, NIERRAS C, PLAGNOL V, POCIOT F, SCHUILENBURG H, SMYTH DJ, STEVENS H, TODD JA, WALKER NM, RICH SS and the Type 1 Diabetes Genetics Consortium (**WILLIS JA** – Member). Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. *Nature Genetics* 41: 703-707, 2009

MILLER LJ, PEARCE J, BARNETT R, **WILLIS JA**, DARLOW BA, SCOTT RS. Is population mixing associated with childhood type 1 diabetes in Canterbury, New Zealand? *Social Science and Medicine* 68: 625-630, 2009.

WALLACE AJ, EADY SL, **WILLIS JA**, SCOTT RS, MONRO JA, FRAMPTON CM.

Variation in measurements of blood glucose response to foods in human subjects is not reduced after a standard breakfast. *Nutrition Research* 20: 238-243, 2009

## Research Presented at National and International Meetings

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JA WILLIS, RS SCOTT, B A DARLOW on behalf of Paediatric and Adult Diabetes Services, CDHB. Four decades of type 1 diabetes in Canterbury children and adolescents. New Zealand Society for the Study of Diabetes Annual Scientific Meeting, Dunedin, 2009.

## Research Presented at Local Meetings

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JA WILLIS Type 1 Diabetes in Canterbury Children and Adolescents: Incidence and Geography. Continuing Education Programme, Pharmacy Department, Christchurch Hospital, September, 2008

JA WILLIS Type 1 Diabetes in Canterbury Children and Adolescents: Incidence, Geography, Clinical Trials. Paediatric Department, Christchurch Hospital, November 2008

Presentations/Publications for Lay Groups

Diabetes diagnosis for family, DNZ Magazine, Winter 2009

Diabetes, a Common Disorder, The Press, Nov 2008

Interview, The Body, CTV, July 2008

## **Research Grants and Other Funding Support**

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### **National Heart Foundation of New Zealand**

Cardiovascular Disease and HDL-Cholesterol Function

2 years, \$14,770

### **Diabetes & Heart Research Trust:**

Montgomery Trust support for Type 1 Diabetes Research Projects

2 years, \$80,000

### **New Zealand Society for the Study of Diabetes, Travel Award**

Travel grant, \$300

## **Other Activities – National and International**

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National Co-ordinator (New Zealand Data Centre), TrialNet

NZSSD Treasurer and Executive Member

Referee of Publications

New Zealand Medical Journal

Diabetes Research & Clinical Practice

Referee of Grant Applications

EliLilly Specialist Diabetes Research Award

Novo Nordisk Specialist Diabetes Research Award

Supervision of PhD Fellows

P Taylor

K Volkova

## **JO YOUNG**

### **Research Scientist**

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#### **Current Research Projects**

(1) **Coenzyme Q<sub>10</sub> supplementation to improve cardiovascular risk in statin-treated patients with the metabolic syndrome.**

Coenzyme Q<sub>10</sub> is an increasingly used complementary medicine for prevention of cardiovascular disease. Although simultaneous coenzyme Q<sub>10</sub> therapy in patients receiving statin therapy can prevent plasma coenzyme Q<sub>10</sub> depletion, it remains unknown if prophylactic coenzyme Q<sub>10</sub> replacement in statin treated patients would translate into clinical benefits. We have previously shown that reductions in coenzyme Q<sub>10</sub> levels due to statin therapy were associated with improvements in vascular function. It is possible that these reductions in coenzyme Q<sub>10</sub> levels may be limiting the maximum beneficial effect of statin therapy. There is preliminary evidence that coenzyme Q<sub>10</sub> supplementation with and without fibrates can improve endothelial function. This study is designed to investigate whether supplementing with coenzyme Q<sub>10</sub> in statin-treated patients with the metabolic syndrome further improves vascular function, thereby giving additional benefit to cardiovascular disease reduction. To date, 22 patients have been recruited for this study. This study is funded by a grant from the National Heart Foundation of New Zealand.

(2) **Does ezetimibe correct vascular dysfunction?**

Hypercholesterolemia contributes to plaque formation in the arterial wall and impairs the ability of cells lining the arteries (endothelium) to govern vessel-relaxation and so regulate blood flow. Statins improve vascular function and reduce cardiovascular events through both LDL- lowering and LDL-independent effects, but the effect of ezetimibe on vascular function is unknown. Combination therapy for hypercholesterolemia with ezetimibe plus low-dose statin will achieve identical reductions in LDL-cholesterol levels as compared with high-dose statin. This 16-week study will investigate whether LDL-lowering with ezetimibe plus low-dose statin corrects vascular dysfunction to the same extent as high dose statin in subjects with the metabolic syndrome. Comparable improvements in vascular function would indicate that subjects using this safe low-dose combination therapy would receive similar benefits in reducing cardiovascular disease as more risky high-dose statin therapy. This study is funded by a grant from the Health Research Council of NZ.

(3) **Coenzyme Q<sub>10</sub> supplementation in high-risk patients with inadequate blood pressure control**

Coenzyme Q<sub>10</sub> (CoQ) is an important antioxidant. High blood pressure is an important risk factor for heart disease and is a leading cause of kidney failure. It is therefore important to have good blood pressure control in order to reduce the risk of heart and kidney disease. However, some people still do not have adequate blood pressure control, despite taking medications for lowering blood pressure. This study aims to determine whether co-supplementation with coenzyme Q<sub>10</sub> can

lower blood pressure measurements in patients with high blood pressure that is not adequately controlled with their current medication. These measurements will be taken throughout the day and night (ambulatory) when a patient is both moving around and resting for a total of 24 hrs. As part of this study, we will also investigate the mechanisms, by which coenzyme Q<sub>10</sub> may reduce blood pressure. If it is found that co-supplementation with coenzyme Q<sub>10</sub> does reduce blood pressure, this therapy will be able to be offered to people in New Zealand with inadequate blood pressure control as an addition to their regular blood pressure lowering medications. This study is funded by a grant from the National Heart Foundation of New Zealand.

(4) **Mechanisms of susceptibility to statin-induced muscle aches.**

People with high cholesterol levels are often prescribed drugs called statins, which lower cholesterol levels by stopping their body making cholesterol. Some people cannot take statins to lower their cholesterol levels, because they experience severe muscle pain (myalgia) and fatigue as side effects. Approximately 140,000 New Zealanders currently taking this medicine are affected by these side effects of statins. This study is designed to explore potential mechanisms for increased susceptibility to statin-induced myalgia (muscle aches). It is possible inherited (genetic) variation associated with muscle aches may increase a person's susceptibility to statin induced muscle aches. Therefore we compared mutations associated with three inherited metabolic myopathies in patients who have previously stopped taking statin medication due to this side effect with patients who do not experience myalgia with statin therapy. For one of the mutations, Q12X in the *AMPD1* gene, we found 37% of statin intolerant patients with this mutation compared with 26% of statin tolerant patients,  $p=0.10$ . We are now collaborating with another research group in order to increase the number of patients in this study. If it is found that these genetic variations increase susceptibility to statin-induced myalgia, this may help us to predict those people who are more likely to develop muscle aches when given statin medication. This study is funded by a grant from the National Heart Foundation of New Zealand.

(5) **Cardiovascular health and coenzyme Q<sub>10</sub>**

People with high cholesterol levels, either inherited (familial hypercholesterolemia) or not inherited, have an increased risk of heart disease and are often prescribed statins. Statins lower cholesterol levels by up regulating the liver receptors for cholesterol uptake. Coenzyme Q<sub>10</sub> is an essential compound for the production of energy in muscles and is also an antioxidant. Coenzyme Q<sub>10</sub> is made by the same pathway that makes cholesterol. As a result of the shared pathway, statins also lower coenzyme Q<sub>10</sub> in the body. This study examined plasma coenzyme Q<sub>10</sub> levels in patients with genetic conditions of FH (Familial Hypercholesterolemia - when cholesterol levels are very high in the untreated state) compared to patients without FH on statin therapy and healthy controls. We found that coenzyme Q<sub>10</sub> levels were similar in the statin-treated groups compared to controls, suggesting that long-term statin therapy does not lead to suboptimal coenzyme Q<sub>10</sub> levels. We also observed that statin-treated patients with more impaired vascular function had lower coenzyme Q<sub>10</sub> levels, and thus may benefit from coenzyme Q<sub>10</sub> supplementation to further reduce cardiovascular risk.

## (6) **Coenzyme Q<sub>10</sub> bioavailability study**

Coenzyme Q<sub>10</sub> is increasingly used as an adjunctive therapy for cardiovascular disease. However coenzyme Q<sub>10</sub> supplements are relatively expensive and are poorly absorbed. Recently, new formulations of CoQ<sub>10</sub> have been prepared with the aim of improving uptake of coenzyme Q<sub>10</sub> by the body. This study will compare the coenzyme Q<sub>10</sub> levels in the blood following supplementation of either a soy bean oil coenzyme Q<sub>10</sub> preparation or new formulation of coenzyme Q<sub>10</sub>. The study involved 36 male subjects taking a single dose of the two preparations two weeks apart, with blood samples being collected before and during a 10-hour period following ingestion of either supplement. Coenzyme Q<sub>10</sub> levels in the blood samples were measured to determine if there are any differences in the magnitude of the increase in coenzyme Q<sub>10</sub> levels caused by the two supplements. We found the new formulation was bioequivalent to the generic formulation following a single coenzyme Q<sub>10</sub> dose. This study was funded by Trilogie Products Pty Ltd and was completed in October 2008.

### **Abstracts of Research**

**JM Young**, SL Molyneux, CM Florkowski, AJ Reinheimer, RS Scott, PM George. Coenzyme Q<sub>10</sub> levels and vascular function in patients on long-term statin therapy for familial hypercholesterolemia. *Atherosclerosis Supplement* 10, (2), 2009 (Poster presentation).

### **Publications**

SL Molyneux, CM Florkowski, AM Richards, M Lever, **JM Young**, PM George. Coenzyme Q<sub>10</sub>; an adjunctive therapy for congestive heart failure? *NZMJ* (In press, July 2009)

SL Molyneux, **JM Young**, CM Florkowski, M Lever, PM George. Coenzyme Q<sub>10</sub>; Is There a Clinical Role and a Case for Measurement? *Clinl Biochem Rev* 29 (2): 71-82 (2008)

### **Research Grants and other Support**

National Heart Foundation Project Grant	\$179,580
Canterbury Community Trust Grant	\$10,760
National Heart Foundation of New Zealand Travel Grant	\$3,500
Royal Society of NZ Canterbury Branch Travel Grant	\$1,000

### **Attendances at Scientific Meetings**

- (1) XV International Symposium on Atherosclerosis, Boston, US; June 2009.
- (2) Post-Satellite Symposium: Atherosclerosis and Pharmacology, New York, June 2009.

### **Other Research Activities**

PhD Student – Department of Medicine, University of Otago, Christchurch

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# Directors Report

17 th July 2009, 1500 hours

The Research Group became a limited liability Company in June 2008.

All hardware and equipment becomes property of the Research Group.

The financial asset base of the Group was zero at incorporation of the company. Set up costs were met by a donation.

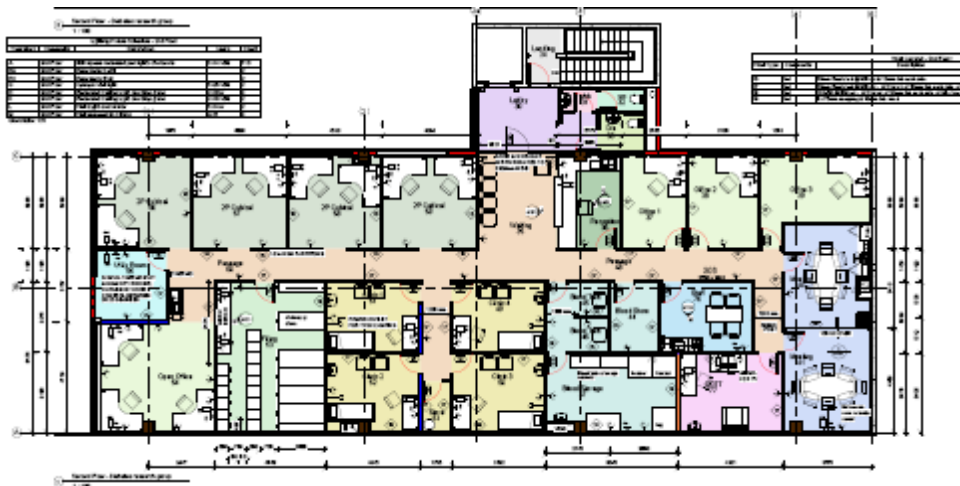
Each financial year finishes on March 31<sup>st</sup> with GST being reconciled 2 monthly.

The auditors and accountant are JL Hibbard Ltd.

The Group downsized slightly by not replacing staff in order to improve potential profitability, and the staffing position will need to be reviewed regularly.

The financial position was that a small profit was made for the year end (unaudited still), and this positive direction has been maintained into 2009 financial year.

The important event for 2009 is the move to new premises at the new Diabetes Research Institute. This will physically separate research from the hospital for most administrative aspects. The Research Group will have non owner residence in the building, once completed, and fit out will be to our design. The financial contribution of the group to the fit out costs remains uncertain but may be of the order of 150 – 180,000 dollars. These funds thus need to be costed into our likely expenditure for the 2009-2010 financial year.



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## Summary of Accounts

The audited accounts are for the period 1 July 2008 til 31 March 2009

Provided by JL Hibbard Accounting Ltd

Income: \$724,920.00

Expenses: \$659,415.00

Profit/Loss: \$ 65,505.00

Depreciation: \$ 681.00

2009 Residual tax:

\$ 18,819.69