2013 RESEARCH REPORT

ENDOCRINOLOGY AND DIABETES

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ENDOCRINOLOGY AND DIABETES

The Endocrinology and Diabetes department consists of a clinical service working in parallel with a clinical research unit (Eastern Clinical Research Unit [ECRU]) that operates under the auspices of Monash University.

The focus of the unit's research program includes clinical research in gestational diabetes, clinical trials in diabetes management, treatment of diabetes complications, vascular effects of anti-diabetic agents, new treatment for post-menopausal osteoporosis as well as research into the genetic pathology of thyroid cancer.

Medical staff and investigators

Box Hill Hospital	Maroondah Hospital	Angliss Hospital
Dr Mathis Grossmann	Dr Murray Gerstman (ECRU)	Dr Suresh Bohra
Dr Jonathan Taft	Dr Shirley Elkassaby	
Dr Jenny Ng		
Dr George Kalogerakis		
Dr Shilpa Verma		
Dr Miram Bartlett		

Nursing and allied health personnel are an integral part of department and contribute directly to the research effort. The diabetes education team led by Jennifer Cross has an interest in research in gestational diabetes, continuous glucose monitoring in type 1 diabetes and inpatient management of diabetes secondary to cancer treatments. The ECRU (Endocrinology) clinical research program is executed by a team of research coordinators lead by Joanne Phillips and includes Adriana Chronopoulos, Caroline Harris, Gabby Phillips, Vanessa Viola, Leanne Auchterlonie, Jenny Bennett, Joan Green and Melissa Kessel.

The unit collaborates in research with the Department of Medicine AMREP Centre at The Alfred and the ECRU Translational Research Division led by Dr Anthony Dear. Professor Gilfillan co-supervises PhD student Dr Michael Mond whose research into the genetics of thyroid cancer takes place at Prince Henry's Institute of Medical Research. The unit is also collaborating with the Australian Centre for Behavioural Research in Diabetes at Deakin University, headed by Professor Jane Speight, in a study into the patient experience of acute versus community-based diabetes ambulatory services.

The unit is committed to an active and expanding research program ranging from clinical audits undertaken by registrars, clinical research with novel anti-diabetic agents to cutting-edge genetic research. Collaborative research will continue to be pursued with industry partners, community health centres, general practices, academic departments at partner universities (Monash and Deakin), research institutes (Prince Henry's Institute) and with the Victorian Government Department of Health. The Unit is further working to expand its role in medical research which provides a stimulating and purposeful environment for clinicians as well as attracting students embarking on research careers.

Program Directors	Professor Chris Gilfillan
	Associate Professor Richard Simpson

Funding/Grants

Characterisation of potential therapeutic effects of liraglutide in animal models of atherosclerosis, plaque stability and obesity. Novo Nordisk **Dear AE** and **Simpson RW**. $280,000.

The genetic pathology of thyroid cancer Victorian Cancer Agency Grant **Gilfillan Prof C**. $193,000

IDEAS evaluation study Department of Health (Victoria) **Gilfillan Prof C, Speight Prof J**. $100,000

IDEAS evaluation study Eastern Health Foundation $40,000

Projects in progress

Projects in progress by the unit during the course of the past year have included:

Characterisation of the potential therapeutic benefits of Glucagon Like Peptide-1 analogues and dipeptidyl peptidase 4 inhibitors in *in vitro* and *in vivo* models of obesity

Lead researchers: **Dear A, Simpson R,** Knudsen L (Novo Nordisk). The project aims to ascertain the potential therapeutic benefits of novel treatments for diabetes in animal models of heart disease and obesity.

AMGEN OSTEO (ARCH)

Phase III, multicenter, international, randomised, double-blind, alendronate-controlled, parallel-group study to determine the efficacy and safety of AMG 785 in the treatment of postmenopausal women with osteoporosis at high risk of fracture. The primary objective of this study is to evaluate the effect of AMG 785 treatment for 12 months compared with alendronate on the subject incidence of new vertebral fracture.

TAK 875 302 (PI-RWS & Co I CF)

A multicenter, randomised, double-blind, placebo and active controlled, phase III study to evaluate the efficacy and safety of TAK-875 25 mg and 50 mg compared to placebo and sitagliptin 100 mg when used in combination with metformin in subjects with type 2 diabetes.

Amgen Denosumab

A randomised, double-blind study to evaluate the safety and efficacy of denosumab compared with zoledronic acid in postmenopausal women with osteoporosis previously treated with oral bisphosphonates.

1276.10

Phase III randomised 'dbpcpg' Empagliflozin bd in two different doses versus Empagliflozin od in two different doses over 16 weeks as add-on to bd metformin.

DUAL III

Phase IIIb trial – comparing fixed combination of insulin degludec/ liraglutide(IDegLira) and unchanged GLP-1 therapy in T2DMs inadequately controlled on GLP-1 and metformin. In Australia this will be a trial evaluating the switch from exenatide to IDegLira.

AMGEN 145 CV Study (FOURIER)

A double-blind, randomised, placebo-controlled, multicenter study assessing the impact of additional LDL-Cholesterol reduction on major cardiovascular events when AMG 145 is used in combination with statin therapy in patients with clinically evident cardiovascular disease.

Study 1275.9

A phase III, randomised, double-blind, parallel group study to evaluate efficacy and safety of the fixed dose combinations of empagliflozin 25 mg/linagliptin 5 mg and empagliflozin 10 mg/ linagliptin 5 mg compared to linagliptin 5 mg alone, administered orally once daily for 24 weeks, in patients with type 2 diabetes mellitus and insufficient glycaemic control after 16 weeks treatment with linagliptin 5 mg once daily on metformin background therapy.

Accelerate I1V-MC-EIAN

Assessment of clinical effect of cholesteryl ester transfer protein inhibition with evacetrapib in patient at high risk for vascular outcomes.

Roche Mobile study

This project aims to test whether a new blood glucose monitoring system increases the number of tests that patients with type 1 diabetes do as compared with an existing blood glucose monitoring system.

BIAJ

Phase III, double-blind, 18-month trial comparing LY2605541 with insulin glargine using standard of care insulin algorithm. Insulin-naive subjects T2DM.

BIAO Lilly Type 1 study

The Impact of LY2605541 versus insulin glargine for patients with type 1 diabetes mellitus treated with preprandial insulin lispro: a double-blind, randomised, 52-week study (The IMAGINE 3 Study).

EX2211-3748 LEADER- Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome results

A long-term, multicentre, international, randomised, double-blind, placebo-controlled trial to determine liraglutide effects on cardiovascular events.

TECOS

A multicentre randomised, phase IV, double-blind study to evaluate cardiovascular outcomes following treatment with study drug or placebo in addition to standard of care in subjects with type 2 diabetes and CVD risk.

IDEAS evaluation study

A randomised, controlled trial comparing care in a community-based diabetes service (IDEAS) with care in an acute diabetes clinic. Study recruiting 100 patients attending four clinics and evaluated after six months. Funded by a grant from Department of Health and supported by the Eastern Health Foundation.

The molecular pathology of differentiated thyroid tumours

A major project funded by the Victorian Cancer Agency and the topic of Michael Mond's PhD thesis. This project is in collaboration with investigators at Prince Henry's Institute. Key elements include determining the clinical utility of genetic testing on FNA specimens to aid pre-surgical diagnosis and assist with planning follow-up; investigating downstream effects of BRAF mutations and pathological phenotype on expression of nuclear receptors; and investigation of known

thyroid differentiation and growth factors for potentially oncogenic mutations and characterising the frequency and functional significance of these mutations.

REGISTRAR PROJECTS

Point prevalence study of diabetes in Victorian Hospitals
Completed 2012 with data being analysed.

The glycaemic effect of hospital food in diabetic patients
Ethics approval obtained and due for completion in 2013.

An evaluation of the precision and sensitivity and applicability to clinical practice of two high sensitivity thyroglobulin assays
Ethics approval achieved. Study underway expanded to include collaboration with Canberra Hospital.

The cost benefit of thyroid function screening in medical patients
Data to be collected 2013.

The prevalence of thyroid function abnormalities in interferon-treated hepatitis patients
Analysis proceeding.

Vitamin D levels and falls prediction in hospitalised patients
Analysis proceeding.

Projects completed

Projects undertaken in the Unit and successfully completed during the course of the past year include:

Characterisation of the potential therapeutic benefits and mechanisms of action of Dipeptidyl Peptidase-4 (DPP-4) inhibitors in *in vitro* models of endothelial cell dysfunction
Lead researchers: **Dear A, Simpson R.** The project successfully identified for the first time GLP-1 independent effects of the DPP-4 inhibitor sitagliptin. These observations may herald the potential development of novel anti-atherogenic agents for the treatment of atherosclerosis in diabetic and non-diabetic patients.

Characterisation of the potential therapeutic benefits of Glucagon Like Peptide-1 analogues in *in vivo* models of atherosclerosis
Lead researchers: **Dear A, Simpson R,** Knudsen L (Novo Nordisk).The project demonstrated a first in class effect of the GLP-1R agonist liraglutide in reducing atherogenesis and enhancing plaque stability suggesting potential benefits in reduction of cardiovascular disease burden in diabetic and non-diabetic patients.

Research Training

Mond M PhD Year 3, Genetic pathology of thyroid tumours, Monash University, F/T

Publications for period 1 July 2012 – 30 June 2013

JOURNALS

Published

Liu HB, Hu Y, **Simpson RW, Dear AE.** GLP-1-Dependent and independent effects and molecular mechanisms of dipeptidyl peptidase IV inhibitors in vascular endothelial cells. *Mol Biol Rep.* 2013; 40:2273-2279.

Gaspari T, Welungoda I, Widdop RE, **Simpson RW, Dear AE.** The GLP-1 receptor agonist liraglutide inhibits progression of vascular disease via effects on atherogenesis, plaque stability and endothelial function in an apoE-/- mouse model. *Diab Vasc Dis Res.* 2013; 10:353-60.

Dear AE. Incretin-based therapeutics: Connections to vascular biology and implications for potential cardiovascular disease prevention. Invited Editorial, *Cardiovasc Drugs and Therapy.* May, 2013; DOI:10.1007/s10557-013-6465-x.

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Thuy V, Varadarajan S, Seeman E, Jerums G, MacIsaac R. Hypocalcaemia induced by raloxifene. *Current Drug Safety.* 2012; vol 7(2): 176-8.

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In press

Ng Tang Fui M, Dupuis P, **Grossmann M.** Lowered testosterone in male obesity: mechanisms, morbidity and management. *Asian Journal of Andrology.* 2013 (in press) (Impact Factor: 2.14).

Grossmann M, Cheung AS, Zajac JD. Androgens and prostate cancer; pathogenesis and deprivation therapy. *Best Practice & Research Clinical Endocrinology & Metabolism.* 2013 (in press) (Impact Factor: 4.59).

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Ng Tang Fui M, Hoermann R, Gianatti EJ, Zajac JD, **Grossmann M.** Obesity and age as dominant correlates of testosterone in men irrespective of diabetes status. *Andrology.* 2013. (in press) (Impact Factor: 3.29).

Cheung AS, Pattison D, Bretherton I, Hoermann R, Lim Joon D, Ho E, Jenkins T, Hamilton EJ, Bate K, Chan I, Zajac JD, **Grossmann M.** Cardiovascular risk and bone loss in men undergoing androgen deprivation therapy for prostate cancer: implementation of standardised management guidelines. *Andrology,* 2013, (in press) (Impact Factor: 3.29, Citations: 2).

ABSTRACTS

Gaspari T, Welungoda I, Widdop RE, Knudsen LB, **Simpson RW**, **Dear AE**. The GLP-1 receptor agonist liraglutide attenuates atherosclerotic lesion development and potentially enhances plaque stability in an ApoE-/- mouse model. In proceedings ADS-ADEA Annual Scientific Meeting, Gold Coast, August 2012.

Gaspari T, Welungoda I, Widdop RE, Knudsen LB, **Simpson RW**, **Dear AE**. The GLP-1 receptor agonist liraglutide attenuates atherosclerotic lesion development and enhances plaque stability in an ApoE-/- mouse model. In proceedings of the 48th EASD Annual Meeting, Berlin, October 2012.

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Urban E, Raval M, Miller R, **Elkassaby S**, Martinelli D. Type 2 diabetes management with GLP-1 Exanatide (Byetta) in morbid obesity. Australian Diabetes Society ASM. Sydney, August 2013.

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Readers note: Where projects are collaborative with our respective research partners, Eastern Health staff names are in bold.

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