ABOUT US

Vision
To provide Leadership and excellence in health and medical research activities throughout Australia, with a focus on aging, to improve the future health and medical care for the Australasian community. In so doing, the Foundation will provide a lasting legacy to the veterans and their families who have created the society we have today.

Mission

• To establish and operate a state-of-the-art biomedical research institute on the campus of Concord Hospital that is affiliated with the University of Sydney.

• To encourage, collaborate in and undertake basic, clinical and epidemiological research, with a particular focus on ageing, that aims to improve health and medical care and is dedicated to the memory of our war veterans and their families.

• To gain and optimise support from the wider community in order to facilitate our vision.

• To provide leadership and excellence in biomedical research in national and international arenas.

• To foster education and training in relevant research and health disciplines.
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Chairman’s Report

This is my first report as Chairman of the ANZAC Health & Medical Research Foundation, the legal structure and board of management for the ANZAC Research Institute (ARI), following the retirement of the previous chairman, Dr Felicity Barr, who served the Institute magnificently over the maximum term allowed by our constitution. She leaves big shoes to fill, both at ANZAC and at the Australian Association of Medical Research Institutes (AAMRI).

The constitution thoughtfully provides for an orderly retirement of long-serving directors and, during the past two years, the board has been able to secure the services of Professors Arthur Conigrave and Ben Freedman from the University of Sydney; Emeritus Professor Michael Field; Dr Teresa Anderson, Chief Executive of the Sydney Local Health District together with Gary Miller, then Matthew Swanborough & now Tim Sinclair in their roles as General Manager of Concord Repatriation General Hospital (CRGH); Ms Kerry Hogan-Ross, a senior solicitor with a major law firm; and Mr Paul Levins, a one-time chief of staff for a NSW Health Minister & now in public affairs & marketing. Such board renewal infuses new ideas and energy into this vital governance function for any medical research institute (MRI).

“It was with great shock that the Board learned of the appalling motor vehicle accident involving Eve Bosak, a stalwart board member, chair of finance subcommittee & all-round tower of strength for the ANZAC Board. During the past 18 months she has gradually been regaining her strength after a gruelling period of intensive care & lengthy rehabilitation. Our thoughts & good wishes are with her husband Myron & family over this difficult time of slow but successful recovery.”

The Board has continued to work closely with CRGH and the Sydney Local Health District at all levels and the University’s Sydney Medical School. In these roles ANZAC Research Institute is somewhat unusual amongst MRIs given that it not only aims to achieve excellence in health & medical research, but specifically provides research facilities to serve the diverse research needs of Concord Hospital’s clinicians and academics. Hence it has avoided binding itself to any restrictive “themes” which form such an important mission of the MRIs clustered around the larger academic campuses.

The Board (along with boards of the other independent MRIs) is involved in ongoing negotiations with the University of Sydney concerning the best way to move forward in the context of the University’s new economic model, and was pleased to contribute to the review of health & medical research at the University of Sydney chaired by Mr Peter Wills AC which highlighted the University’s priority to develop its new Charles Perkins Centre as a centre for wide-ranging medical research into obesity, diabetes and cardiovascular disease.

The Board is pleased to note that SLHD has agreed to accept novation of the contract for construction of the Translational Research Facility (TRF), originally granted by the Commonwealth government to provide a state-of-the-art animal facility for the Bernie Banton Centre building, which houses both the Asbestos Diseases Research Institute (ADRI) as well as ANZAC2 laboratories. SLHD is well suited to handle such capital works, and this will ensure the facilities are built on time and within budget. Both ADRI & ANZAC Research Institute are most grateful for this move and look forward to the timely completion of the project. During the last 2 years, ADRI Board has appointed as its Chairman, J John O’Meally, a retired judge of the NSW Compensation Court and President of the Dust Diseases Tribunal, with whom the ANZAC Board Chairman & Deputy meet regularly.

I would like to register my sincere thanks to Prof Robert Lusby for accepting the Deputy Chairmanship of our Foundation, as well as being the ANZAC nominee on ADRF Board. Without his cheerful dedication we would all be far the poorer.

On behalf of the Board, I congratulate the Director, Professor David Handelsman, the research group leaders and all staff of the Institute on their strong achievements for the period covered by this report. I would also like to thank the ANZAC Research Institute’s administrative staff for their support to the Board, especially Julie Taranto, Tracey Dent, Annet Doss, Candice Chang and Justin Crosbie.
Welcome to our Biennial Report. Now that the ANZAC Research Institute is well into its second decade, it continues to thrive as an independent medical research institute supporting its co-located teaching hospital and affiliated medical school. By all standard global measures of medical research productivity – winning over $11 million annually in external grant income, housing nearly 150 staff including 50 graduate (mostly PhD) students undertaking research training and producing nearly 100 research papers per year – it is a great success. But above and beyond the conventional metrics, proudly it remains a great place for medical researchers to work while making important progress in many fields as outlined further in this Report.

As Concord Hospital’s own medical research institute, the ANZAC Research Institute has earned its reputation for scientific excellence in the wide range of research areas on display in our Report. The Institute was created by the foresight of two key founders, the late Professor John Young, for the University of Sydney, who became our first Board Chair, together with Diana Horvath as CEO of the Central Sydney Area Health Service, the predecessor of the present Sydney Local Health District. Their remarkable shared and co-operative vision set a solid foundation for the Institute’s pathway to success. Now, in a wonderful turn of history, Professor Diana Horvath now serves as our present Board Chair.

Medical care never stands still. Every level of the world of medicine and health care requires an underpinning of thoughtful analytical research and innovation to stay up to date and maintain state-of-the-art medical care for our community. Medical research is a vital and sound investment in the shared health and welfare of our community. Yet undertaking medical research is a very expensive and demanding business. We manage this with minimal overheads needed to keep the doors open while having to acquire expensive scientific equipment and maintain complex research services to allow the highest quality medical research to flourish. In this our main support for operating costs comes from the NSW government together with some returns from the University from its research income earned by our scientists working at the Institute. More direct community support in the form of gifts, donations and bequests is also received with gratitude.

Australia’s 40+ medical research institutes contribute the lion’s share of the highest quality medical research produced in this country. Among various research-active organizations, only medical research institutes offer an un-conflicted focus on excellence in medical research. All Institutes have as their unequivocal highest priority the creation of a researcher-friendly environment providing maximal support for high quality, innovative research including the research training of the next generation of medical scientists. Hospitals are primarily health service providers whereas universities are primarily teaching institutions. Both value medical research, but as an important but secondary objective as supporting top medical research has utilitarian value in attracting prestige and creating the environment required to recruit and maintain the best professional academic or medical staff necessary to fulfill their primary objectives. However, when their primary objectives come into conflict with their secondary interests, their priority for medical research may suffer. So it is only by having strong and successful medical research institutes like ours that our health system and universities can succeed in fulfilling their primary objectives in relation to health care and medical education.

It is a pleasure, once again, to thank the Institute’s management team who make its operations go so smoothly and so well. The skill, commitment and hard work of our terrific team - Julie Taranto, Annet Doss, Candice Chang, Tracey Dent, Mark Jimenez, Mamdouh Khalil, Justin Crosbie, Rachelle Innes and Amy Ng – well deserve the highest praise and thanks from all who enjoy the excellent working atmosphere at the Institute. Achieving the Institute’s researcher-friendly environment, one of our prime goals, is largely due to their sustained efforts.

Thanks also are due to Concord Hospital and the Sydney Local Health District staff – Gary Miller, Matthew Swanborough, Tim Sinclair and the Chief Executive, Teresa Anderson - for their unfailing helpfulness and support without which the ANZAC Research Institute could not operate. Similarly, the ongoing support of the Sydney Medical School, Professors Bruce Robinson, Bob Lusby and Arthur Conigrave is gratefully acknowledged. Thanks also to John Gatfield for editing our newsletter Discovery. Finally, my personal thanks go to Professor Diana Horvath and her predecessor Dr Felicity Barr as Board Chairs together with the Board for the unflagging support and enlightened commitment all geared towards making the Institute as good as it can be. Above all, it remains a privilege to work in the challenging and productive environment created by the Institute’s scientists whose inspiring commitment make all efforts on their behalf worthwhile.
Andrology

PERSONNEL:

GROUP LEADER: Professor David Handelsman

SENIOR SCIENTISTS: Dr Charles Allan, Ms Reena Desai, Dr Ulla Simanainen, Dr Kirsty Walters, Dr Pekka Keski-Rahkonen

VISITING SCIENTISTS: Dr Thilee Sivananathan, Dr Thomas Travison

STAFF AND STUDENTS: Omar Akram (with Heart Research Institute), Lydia Andres, Fay Bacha, Frank Bathur, Aimee Caldwell, Chantall Cerna, Jaesung (Peter) Choi, Assoc Prof Ann Conway, Namita Deo, Irene Di Pierro, Carolyn Fennell, Glenda Fraser, Yan Ru (Ellen) Gao, Rasmani Hazra, Megan Honeyman, Jenny He, Amanda Idan, Dr Veena Jayadev, Mark Jimenez, Nadia Jung, Gurmeet Kaur, Patty Kapelaris, Lucy Liu, Dr Lam Ly, Linda Middleton, Marie Merheb, Tegan Ryan, Jennifer Spaliviero, Sasa Spasevska, Francia Suarez, Win Myatt Theingi, Leo Turner, Ljubica Vrga, Lucy Yang, Bin Zhao.

Role:

Andrology is literally the study of man (Greek andros, man). The medical and scientific discipline is defined as the study of male reproductive health, medicine and biology. Male Reproductive Health involves the overlapping domains of Fertility, Sexuality and Androgenisation which overlap with male general health especially with regard to androgen effects.

The Andrology group focuses on both the biological and clinical effects of androgens on male health, in particular men’s reproductive and general health across all ages. Androgens (male hormones), the main one being testosterone, occur naturally in the body and play far-reaching roles in many body systems, particularly in male reproduction, fertility and sexuality. They exert important influence on most non-reproductive tissues especially the prostate, cardiovascular system, bone and the brain, throughout the entire male lifespan and may also influence women’s health.

Objectives:

The Andrology group is a collaboration of the:

- Andrology Laboratory at the ANZAC Research Institute where the focus is on the physiology and pharmacology of androgens in males and females, by undertaking research using experimental animal models and laboratory bench research

- Andrology Department of Concord Hospital, where patient and community centred research is carried out and translated into improvements in patient care. The focus is on the therapeutic use of androgens such as to treat hormone deficiency states in adolescence and adulthood, in certain chronic diseases, for male contraception and for ageing men. In addition we also study the relatively widespread misuse/overuse and abuse of androgens for many wishful or harmful non-medical reasons as well as in sports doping.
Grants: 2011-2013

Annualised $

Andrology Australia- Sivananathan. “Andrology Australia Training Fellowship.” $15,000

ARC DECRA Fellowship- Walters. “Androgens and ovarian function.” $126,539

Ascend/Besins Pharmaceuticals (France-USA)- Handelsman, Conway “Efficacy and safety of DHT to prevent prostate growth in middle aged men.” $17,700

Australian Rotary Health Research Fund- Gao. “The role of androgen receptor mediated action in breast cancer.” $16,500


NHMRC- Walters, Handelsman, Allan. “Androgen receptor mechanisms in female reproductive physiology.” $181,489

NHMRC- Allan, Handelsman, Walters, Howell. “FSH control of ovarian function.” $110,683

NHMRC- Simanainen, Handelsman. “Intraprostatic androgen signalling as a target in prostate cancer.” $123,272

NHMRC- Walters. “Role of androgens in polycystic ovary syndrome.” $151,810


USyd Bridging Grant/ARI- Simanainen, Handelsman, Zheng. “Androgen signalling as a therapeutic target in breast cancer.” $60,000

USyd Bridging Grant/ARI- Allan, Handelsman. “Dissecting the somatic control of hormone-regulated spermatogenic development.” $60,000

Australian Rotary Health Research Fund- Choi. “Role of androgens via AR in PTEN inactivation induced female reproductive pathology” $16,500

Prizes:

• Mr Peter Choi: Margaret Taylor Scholarship 2012


Research:

Physiology and Pharmacology of Androgens

Clinical Pharmacology of Testosterone

A Conway, C Fennell, S Spasovska, L Turner, DJ Handelsman

The Department of Andrology at Concord Hospital provides testosterone treatment for men who have testosterone deficiency. As an international leader in research into the physiology and pharmacology of androgens, we continue to research the best and most acceptable forms of delivery of testosterone treatment for men who genuinely need this treatment. Our extensive research into various depot forms of testosterone have helped define the best ways to use these treatments to improve quality of life for hormone deficient men.
Measuring Steroids in Serum and Biological Samples
R Desai, T Harwood, P Keski-Rahkonen and DJ Handelsman

Accurate measurement of steroid hormones from clinical and biological samples is essential for the diagnosis and monitoring of reproductive disorders as well as for experimental laboratory studies. For the last few decades, either radioimmunoassay (RIA) or gas chromatography mass spectrometry (GC/MS) have been the standard methods used for these measurements. However, their limitations such as low sensitivity (GC/MS) and non-specificity (immunoassays) together with development of bench-top liquid chromatography (LC) mass spectrometry (MS) methods to measure steroid hormones from biological samples are now accurate and affordable.

We have developed an ultra-sensitive LC-MS/MS method (funded by an ARC LIEF grant). To measure accurately and sensitively androgens (testosterone, dihydrotestosterone and androstanediol isomers) and estrogens (estradiol and estrone) to extremely low levels efficiently and within a single run (Fig 1). The lab now provides the only Australian steroid reference laboratory for highly sensitive analysis of serum androgens and estrogens in serum samples from a wide variety of human and animal studies. The lab has analysed over 15,000 serum and tissue samples from collaborating groups around Australia and overseas and is among the leading labs in the world for steroid MS analysis.

Using our MS estradiol assay as a reference, we have conducted a performance evaluation of the 5 most commonly used direct estradiol immunoassays. We found all 5 were significantly suboptimal in sensitivity and/or accuracy and highlighted the need for improved MS-based estradiol assays in clinical and research practice.

Most recently the lab was awarded an NHMRC grant to develop an ultrasensitive estradiol using LC-MS assays. Dr Keski-Rahkonen has identified a series of promising novel derivatization chemistries to achieve a 10-20 fold boost in sensitivity of our existing sensitive estradiol assay. This new methodology holds great promise to improve the applicability of estradiol assays in clinical and research applications where the existing estradiol assays have proved inadequate.

Androgen Misuse: Testosterone Overprescribing
DJ Handelsman

Androgens play a major role in muscle strength, energy and quality of life in men. This can be dramatic in the small minority of men with genuine testosterone deficiency where testosterone replacement therapy often provides striking benefits. In addition however there is a widespread mistaken belief that testosterone might reverse features of male ageing especially decline in sexual function and energy levels. As a result there is widespread and increasing overuse of testosterone as an anti-ageing and sexual tonic among older men and for performance or image enhancement among young men.

We have continued to undertake national surveillance of testosterone prescribing patterns using both national health service (PBS) as well as commercial wholesales data (IMS) to chart the progress of the epidemic of testosterone overprescribing in Australia and globally. These patterns of over-use call for heightened vigilance and increased professional and public education to reduce wasteful, misguided and possibly harmful over-use of testosterone.

Androgen Abuse: Testosterone & Sports Doping
A Idan, C Fennell, M Jimenez, DJ Handelsman in collaboration with A Death, L McRobb, K McGrath (Heart Research Institute) and C Goebel, A Cawley, R Kazlauskas, G Trout, C Howe (National Measurement Institute)

Androgens, synthetic forms of testosterone, are the most effective and popular drugs abused in sports doping. In recent years new designer androgens and indirect forms of androgen doping have been developed to evade detection of androgen doping. Maintaining effective bans on androgens requires continual vigilance in detection of illicit androgens and of indirect androgen doping. We continue to undertake World Anti-Doping Agency (WADA) and Australian Sports Anti-Doping Authority
(ASDA) supported clinical and laboratory studies to develop new and more powerful detection tests for such novel androgens and other means to evade detection of androgen abuse.

**Healthy Male Ageing: The Health Man Study**

_G Sartorious, S Spasevska, AJ Conway, DJ Handelsman with Prof RI McLachlan and Dr C Allan (Prince Henry’s Institute of Medical Research, Melbourne)_

Why do some men remain healthy well into old age and others do not? Our Healthy Man study aimed to determine the role of circulating androgen levels in maintaining or reflecting good health and to explore the reasons why testosterone concentrations vary in one man compared with another. Through analysis of over 300 very healthy ageing men, this study evaluated the prospects for age-specific reference ranges for testosterone in an “elite” healthy male population. The findings were published in a leading international Endocrinology journal. They showed that there was no apparent decrease in serum testosterone and even mild increases in testosterone metabolites, dihydrotestosterone and estradiol among older men who maintain excellent health. The findings showed that it is most likely that ageing itself does not produce any lowering of blood testosterone as men grow older but that the decreases seen in larger populations of older men are due to their acquisition of age-related diseases (co-morbidities) of ageing.

**Measuring Progress of Puberty**

_G Singh, T Sivananthan, F Bathur, A Idan, A Conway, DJ Handelsman_

Male sexual development and fertility develop relatively rapidly over a few years during adolescence, a period of time known as puberty. The triggers for puberty remain a mystery and the age at which it starts and its rate of progression vary widely between individuals for largely unknown reasons and have hardly ever been studied in the community. The failure of male puberty to occur when expected can cause deep and lasting effects on a developing man’s psyche because of the difficulties it creates in “fitting-in”, being perceived as immature, creating difficulties in finding a social niche and forming life-long partnerships.

The Andrology department is participating in several studies related to male puberty including improving treatment of boys who fail to undergo puberty as well as studying the normal evolution of puberty on the health and wellbeing of young adults in the community. In addition Gurmeet Singh has developed methods to measure the progress of puberty using urine steroid hormone excretion and these methods are being applied to the ARCHER study, a NHMRC funded longitudinal cohort study of adolescents passage through puberty.

**Androgens and the Prostate**

**Intraprostatic Androgen Signalling and Androgen Sensitivity of the Prostate**

_U Simanainen, F Suarez, K McNamara, M Jähne, B Zhao, DJ Handelsman_

_Collaboration: Prof Diane Robins (University of Michigan, Ann Arbor USA); Prof Janet Keast (Kolling Institute of Medical Research, University of Sydney); Dr Stephen McPherson (Australian Prostate Cancer Research Centre, Queensland University of Technology)._

The androgen receptor (AR) has a crucial role in both normal prostate development and the emergence and progression of prostate cancer. We have created a model targeting AR in the prostate epithelium to explore the role of androgen in the prostate development, as well as in prostate proliferative diseases of benign prostate hyperplasia and cancer (transgenic prostate cancer models) that develop in later life. We have demonstrated that while androgens are assumed pro-proliferative in the prostate, the epithelial AR suppresses cell proliferation by keeping the epithelial cells differentiated. In addition, we have shown that the epithelial AR modifies the prostate stromal sensitivity and intraprostatic steroid signalling. Our ongoing research will also investigate the influence prostate disease initiation/progression on steroidal sensitivity and regulation of intraprostatic steroids of the prostate, noting that intraprostatic steroids may have essential roles in the development, but also in the treatment of the prostate cancer later in life. In collaboration with Prof Diana Robins and Prof Janet Keast we have explored the influence of CAG repeat of AR as well as neurotrophic factor Neurturin on androgen sensitivity. Our research may provide new clues for targets for prevention, screening and/or treatment for prostate diseases including prostate cancer. An additional important and novel finding was our proof, for the first time, that the CAG triplet repeat (polyglutamine tract repeat polymorphism) of exon 1 of the androgen receptor does directly modulate androgen sensitivity.
Androgens and the Testis

The Department of Andrology is interested in researching all available avenues to help those men seeking fertility but also the development of safe effective male contraception.

Male Hormonal Contraception

L Turner, C Fennell, AJ Conway, PY Liu, M Jimenez, DJ Handelsman

A major practical application of knowledge about how hormones control sperm production is the development of a male hormonal contraceptive. Following a decade of preliminary feasibility and path-findings studies, in 2003 the Andrology Department published a proof of principle study establishing very high reliability of a depot combined hormonal male contraceptive. Through many preliminary studies using a depot form of testosterone, we defined the lowest effective dose of testosterone having sufficient suppression but avoiding undesirable side effects and tested it with a progestin to identify the best combination. The excellent result for our prototype hormonal combination was a major advance and made international headline news. These path-finding studies have led progress in optimising the approach to develop a practical hormonal male contraceptive regimen. Currently, based on our 2003 study, we are extending our clinical experience with the combined depot approach in providing first medical male hormonal contraceptive service offered anywhere in the world. Furthermore, a major CONRAD and WHO sponsored international multicentre trial is using a similar injectable depot androgen-progesterin combination to extend and refine the findings on contraceptive effectiveness for this “leading candidate” approach for a marketable male hormonal contraceptive.

Hormonal Control of Sertoli Cell Function and Spermatogenesis

R Hazra, D Upton, T Rastegar, L Corcoran, J Spaliviero, M Jimenez, DJ Handelsman, CM Allan

Collaboration: P Stanton (Prince Henry’s Institute of Medical Research)

Reproductive hormones such as sex steroids (eg. androgen) and gonadotrophins control testis development, sperm production (spermatogenesis) and male fertility. These major hormones converge upon unique testis cells called Sertoli cells, which are vital for sexual development and spermatogenesis. A major research focus is to understand how different hormones control postnatal Sertoli cell development and function. Specifically, we created novel genetic models to study the role of the androgen receptor (AR) and follicle-stimulating hormone (FSH) in Sertoli cells. Collaboration with Peter Stanton (PHRI) showed the importance of androgen and FSH actions for the formation of the blood-testis barrier, which is essential for functional spermatogenesis. To target AR actions, we selectively disrupted AR DNA binding in Sertoli cells, which showed DNA (genomic) AR interaction is vital for sperm development. A visiting PhD student Tina Rastegar (Tehran, Iran) showed that Sertoli cell AR DNA binding is vital for the final stages of spermatogenesis. We also investigated the role of estradiol (the classic female sex steroid) in testis function, and showed that the paradoxical induction of sperm production by estradiol requires Sertoli cell AR (ScAR). A new gain-of-function model targeted premature AR expression in Sertoli cells to identify its role during pre-pubertal/pubertal development. Using this model, Rasmani Hazra (PhD student) showed that atypical ScAR expression provides a direct molecular mechanism for premature testicular development, leading to reduced adult testis size and altered spermatogenesis. We also revealed that ScAR activity controls the pubertal maturation of Leydig cells, which is vital for normal androgen production and male fertility. Our studies continue to identify key hormonal-regulated biological pathways in testis cell populations that are crucial for functional testicular development and sperm production. These research projects increase our fundamental knowledge of underlying biological pathways that control (or inhibit) spermatogenesis and male fertility, predicted to provide valuable genetic targets for therapy (eg. infertility), or to develop novel strategies for male contraception.
Androgens, Ageing and Female Reproductive Physiology

Androgens and the Ovary

K Walters, A Caldwell, L Middleton, C Cerna, CM Allan, DJ Handelsman
Collaborations: Dr Jeremy Smith (University of Western Australia)

Enhanced understanding of ovarian function is of great importance as infertility occurs in 1 in 6 Australian couples. Androgens are essential for male reproduction, however, in recent years, we and others have shown experimentally in mouse models, that androgen actions mediated by the androgen receptor (AR) have a previously unrecognized influence on female fertility. Improving our understanding in to the role of androgens in follicle development may provide long overdue new insights into androgen associated female reproductive disorders such as polycystic ovary syndrome (PCOS). Polycystic ovary syndrome (PCOS) is associated with hyperandrogenism and is one of the most common causes of anovulation and infertility in women, affecting between 5-10% of women of reproductive age worldwide. Despite substantial research trying to define the cause of PCOS its origins are unknown.

To identify the precise AR-mediated mechanisms involved in normal ovarian function and the development of PCOS, we are using our novel androgen resistant female androgen receptor knockout (ARKO) mouse models alone, or combined with established rodent models of PCOS. Dr Walters has revealed an important role for AR-mediated actions in ovulation (Fig 1), follicle health and female fertility. Our long term goals are to further enhance our understanding of how androgens regulate female reproductive function, and unravel disruptions in androgenic mechanisms which may be involved in the establishment of androgen-associated reproductive disorders, such as PCOS.

FSH and Female Reproductive Ageing

D Upton, K Walters, S Lamb, DJ Handelsman, CM Allan.
Collaborations: Dr Viive Howell (Kolling Institute, University of Sydney)

In women, reproductive ageing (declining fertility) coincides with an accelerated loss of ovarian follicles (developing eggs). An early sign of reproductive ageing is increasing levels of circulating FSH. High FSH levels are associated with premature ovarian failure or onset of menopause, and may accelerate the loss, or decrease the quality, of ovarian eggs. Dr Allan established a genetic model with rising FSH levels that displays premature female infertility, despite the presence of maturing eggs. Furthermore, we revealed that embryos derived from eggs exposed to high FSH levels displayed normal uterine implantation rates and unexpectedly had increased survival levels during development. This beneficial effect of high FSH levels may have relevance to FSH treatments during assisted reproduction technology (ART). We also plan to use this model to examine the long-term effects of elevated FSH on genetic abnormalities (aneuploidy) in eggs, which increases as egg quality declines during reproductive ageing in women.

We found that higher levels of FSH produced earlier onset of infertility as well as ovarian hemorrhagic cysts. Dannielle Upton (University of Sydney) recently commenced her PhD candidature to investigate FSH actions using these models. Our work has identified FSH-regulated factors which may play a role in the hemorrhagic process, and may provide important insight into the rare but potentially fatal ovarian hyperstimulation syndrome (OHSS) during ART, or due to rare mutations in FSH signalling. High FSH levels may also contribute to ovarian cancer, and a collaboration with Dr Howell has created new models to study elevated FSH actions in combination with the mutation of potential factors (Brcal, Pten, p53) associated with ovarian tumorigenesis. Initial work using these complex genetic combinations shows that the ovary is remarkably resistant to direct or local changes to potential cancer-causing factors, and supports emerging evidence that many ovarian cancers may originate in other tissues or organs.
Androgens and the Mammary Gland

U Simanainen, K Walters, E Gao, P Choi, B Psarommatis, DJ Handelsman

One in nine Australian women will develop breast cancer within their lifetime. Yet for this common, fatal and feared disease, the causes and mechanisms remain elusive. The strongest clues are from sex hormones as epidemiological risk factors with estrogen exposure being widely recognised while the role of androgens, while assumed protective, remains controversial. Our ongoing research utilizes the female androgen resistant mouse models in combination with transgenic and chemical carcinogenesis allowing a direct and versatile experimental approach for analysis of androgen actions in mammary gland development, function (lactation) and tumorigenesis. The knowledge of AR functions at the physiological, cellular and molecular level, modifying breast hormonal sensitivity, will be pivotal to designing novel biomarkers and rational therapeutic or preventative approaches of importance for women’s health, like breastfeeding and breast cancer.

Collaborations:

A Death, L McRobb, K McGrath (Heart Research Institute & University of Technology Syd)
C Goebel, A Cawley, R Kazlausakas, G Trout, C Howe (Australain Sports Drug Testing Laboratory, National Measurement Institute)
RI McLachlan (Prince Henry’s Institute of Medical Research, Melbourne)
D Robins (University of Michigan, Ann Arbor USA)
P Stanton (Prince Henry’s Institute of Medical Research)
L Salamonsen (Prince Henry’s Institute of Medical Research, Monash University)
J Keast (Kolling Institute of Medical Research, University of Sydney)
V Howell (Kolling Institute of Medical Research, University of Sydney)
G Wittert, University of Adelaide
M Grossmann, University of Melbourne
B Yap, University of Western Australia
Andre Araujo, New England Research Institute, Boston, USA
G Jones (St Vincents Hospital, RCPA/AACB)
Julie Newman (Southern Cross Pathology Australia, Monash Medical Centre)
S Franks, K Hardy (Institute of Reproductive and Developmental Biology, Imperial College London, London, UK)

LIST Registrars/Trainees in Dept of Andrology 2011 - 13

Rashmi NARAYANAN, Praseetha AHANMUGALINGHAM, Kirtan GANDA, Lisa SIMMONS, Kiernan HUGHES, Vanita TOOGOOD, Pinar KOZAN, Shanti CHALASANI, Lauren BAKER, Amy HAYES, Timothy MIDDLETON, Avinash SURYAWANSHI, Thilee SIVANANATHAN, Manny MANGAT, Anthony MARREN
Atherosclerosis

PERSONNEL:

GROUP LEADER: Professor Len Kritharides, Professor Wendy Jessup

SENIOR SCIENTISTS: Dr Maaike Kockx

STAFF AND STUDENTS: Matthew Triani, Diana Nawara, Terry Nguyen-Khuong

Role:

Atherosclerosis is the disease whereby atherosclerotic plaques progressively build up inside arteries. It can have serious outcomes such as heart attacks and strokes. Atherosclerosis is the main cause of morbidity and mortality in the developed world.

Objectives:

Macrophages play an important role in the initiation and progression of atherosclerosis. In the atherosclerosis laboratory we study aspects of macrophage biology that are important in atherosclerotic plaque formation using in vitro and in vivo mouse models. Our two main areas of interest are:

• Regulation of macrophage protein secretion
• Mechanisms involved in lipid uptake and removal from macrophages and the artery wall

Grants: 2011-2013

Heart Foundation- Kockx. “Effect of Cyclosporin A on VLDL- secretion in vitro.” $64,500

Heart Foundation- Kockx. “Effect of apolipoprotein infusion on reverse cholesterol transport.” $65,000

NHMRC- L Kritharides, M Raftery.”Biochemistry and functional significance of glycosylation of apolipoprotein E secretion CI.” $156,000

NHMRC- Barter, Rye, Celermajer, Jessup and Kritharides. “Atherosclerosis: Lipoproteins, vascular biology and cellular physiology.” $850,000

Highlights

• Victar Hsieh, Sian Cartland, Virginie DeSwarte and Xianming Du obtained their PhD degrees from UNSW.
• The NHMRC program grant ‘Atherosclerosis’ was successfully renewed (Kritharides and Jessup CIs) for another 5 years (2013-2017)
• Professors Jessup and Kritharides were co-chairs of the HDL satellite (Cairns) of the International Atherosclerosis Society Triennial meeting March 2012.
• Prof Kritharides was appointed Chair of the National Cardiovascular Health Advisory Committee of the National Heart Foundation of Australia effective May 2013)
Research

During plaque formation lipids accumulate in the arterial wall. As a consequence monocytes from the blood will migrate into the arterial wall and take up this lipid rendering them macrophage foam cells, which changes macrophage biology and promotes plaque destabilisation and the complications of atherosclerosis such as heart attacks and strokes. We study how genes expressed in macrophages are modulated by cholesterol loading, novel genes in this process, how protein secretion is affected and how we can enhance removal of cholesterol form these cells and in whole animals.

Dr Mat Traini in our laboratory has recently determined that the expression of a novel phosphodiesterase enzyme, SMPDL3A, is strongly up-regulated after treatments that increase intracellular cholesterol levels in cultured human macrophages. He discovered that cholesterol loading also increases the secretion of SMPDL3A from cultured foam cells, and that SMPDL3A is present in the human circulatory system. Finally, a range of unexpected substrates for SMPDL3A were identified implying that SMPDL3A plays a role in modulating processes directly related to progression of atherosclerosis.

Professor Jessup has led research into the regulation of cellular levels of the cholesterol transporters ABCA1 and ABCG1. Cholesterol affects gene expression but also affects post synthetic degradation and turnover, a finding which has important implications for the determinants of cholesterol clearance from cells.

Secretion of apolipoprotein E from macrophages is anti-atherogenic. Dr Maaike Kockx showed that cholesterol loading of cells decreases the secretion of apolipoprotein E by inhibiting protein transport from the endoplasmic reticulum to the Golgi apparatus and affects the glycosylation profile of secreted apoE. This effect was reversible. Dr Karunakaran in our laboratory identified an important role for the classical isoforms of protein kinase C in regulating apoE secretion, and found that this also had relevance to the secretion of other proteins such as fibronectin and MMP9.

The immunosuppressant cyclosporin A has complex effects on atherosclerosis via its effects on a range of protein secretory pathways. Our previous studies have defined its effects on apoE secretion from macrophages. We have recently commenced studies in whole animal models of hyperlipidemia and atherosclerosis and find LDL-receptor dependent and independent pathways are involved.

Collaborations Atherosclerosis Laboratory

NATIONAL:
Prof Kerry-Ann Rye, Centre for Vascular Research, University of NSW
A/Prof Peter Meikle, Baker IDI, Melbourne
Prof Nicki Packer, Biomolecular Frontier Research Centre, Macquarie University
Prof Andrew Brown, School of Biotechnology and Biomolecular Sciences, University of NSW
A/Prof Nick Di Girolamo, School of Medical Sciences, University of NSW
Prof Phil Robinson, Children’s Medical Research Institute, Sydney
Prof Stewart Cordwell and Dr Melanie White, School of Biochemistry University of Sydney
Prof Mark Raftery, Biomedical Mass Spectrometry Facility, University of NSW

INTERNATIONAL:
Prof Sean Davidson, Metabolic Diseases Institute, University of Cincinnati, USA
Prof Radislav Sedlacek, Institute of Molecular Genetics of the ACR, Prague, Czech Republic
Professor John Chapman, Dr Anatol Kontush, Dr W LeGoff, INSERM Paris
Dr. Miranda van Eck, University of Leiden, Netherlands
**Biogerontology**

**PERSONNEL:**

GROUP LEADER: Professor David Le Couteur

SCIENTISTS: Dr Victoria Cogger, Dr Alessandra Warren, Dr Aisling McMahon, Mashani Mohamad, Samantha Solon, Jennifer O’Reilly, Sarah Mitchell, Shajjia Razi, Professor Arthur Everitt, Professor Robin Fraser, Rahul Gokarn.

**Role:**

The Biogerontology Laboratory in the ANZAC Research Institute is the laboratory component of the Centre for Education and Research on Ageing (CERA) at Concord Hospital. The Biogerontology Laboratory performs research into the biology of ageing and age-related diseases with a major focus on the effects of old age on the liver and the cells of the hepatic sinusoid.

**Objectives:**

Our objective is to develop strategies to delay and prevent diseases of old age.

**Grants: 2011-2013**

Annualised $ 

NHMRC- Le Couteur, Cogger, Lebel, Quinn, Hilmer, McCuskey. “Old age and the liver endothelium.” $198,000

NHMRC- Hilmer, Jones, Cogger, de Cabo. “Hepatic drug clearance and drug induced liver disease in aging.” $197,476


NHMRC- Hennessy, O’Connel, Rasko, Twigg, D’Aspice, Le Couteur. “NHMRC National Baboon Colony.” $120,000

**Prizes:**

Professor Le Couteur received the American Society for Clinical Pharmacology and Therapeutics 2013 William B Abrams award for his contribution to geriatric clinical pharmacology.

Travel grants to Ms Solon to attend the Gordon Biology of Aging conference in Ventura California and Cold Spring Harbour both in 2012.

Travel grant to Dr McMahon for attendance at the Gerontological Society of America, San Diego.

**Highlights**

- Our work on the role of lipid rafts in maintaining the structure of fenestrations in the liver sinusoidal endothelial cells has been recognised as “a major advance in our understanding of the mechanisms that regulate the formation of sieve plates and fenestrations” by the leading journal in Liver Research- Hepatology

- In collaboration with Professor Stephen Simpson we continue to investigate the effects of macronutrients, particularly protein, on ageing and age-related diseases. Analysis of the tissue is now complete and the work has been presented.

- We have established the essential role of fenestrations in insulin resistance.
• Dr Cogger was appointed Sub-Dean of Postgraduate Research with the Sydney Medical School
• Dr Warren was promoted to Lecturer with the Sydney Medical School
• Ms Solon and Ms Razi won the student prizes for their posters at the Emerging Researchers in Ageing Conference in Brisbane in 2012
• Professor Le Couteur received the American Society for Clinical Pharmacology and Therapeutics 2013 William B Abrams award for his contribution to geriatric clinical pharmacology.

Research

Aging and the liver sinusoid

Our group was the first to discover that old age is associated with major structural changes in the endothelial cells in the liver, called pseudocapillarization. In addition we have established that ageing is also associated with significant changes in the other two cells of the sinusoid, the Kupffer cell and the hepatic Stellate cell. We have shown that pseudocapillarization is associated with impaired hepatic metabolism of lipoproteins and more recently, medications and insulin. The major focus of our research is to develop therapies to prevent these ageing changes, primarily in order to prevent cardiovascular diseases and insulin resistance caused by the age-related impairment of substrate transfer in the liver. To do this we are investigating the regulation of the liver sinusoidal endothelial cells with the cutting edge technology: structured illumination three dimensional microscopy; lipidomics and; proteomics. Recently we have established that the key mechanism for regulating fenestrations is lipid rafts, and we are undertaking further studies to develop therapies to increase fenestrations via their effect on rafts.

Sirtuins and the biology of ageing

The sirtuin pathway is involved with mediating the beneficial effects of caloric restriction, and possibly other nutritional interventions on the ageing process. With our international collaborators we have shown that an agonist of the sirtuin pathway called resveratrol has significant effects on the morphology of the liver and the liver sinusoid. We have also investigated the relationship between blood factors that stimulate the expression of the sirtuin pathway in humans. Our results suggest that these factors are associated with frailty in older men from the CHAMP study, and possibly mortality as well. Once the entire cohort of CHAMP subjects has been analysed we will be able to determine the relationship between sirtuin expression and a wide range of age-related outcomes.
Nutritional influences on ageing

In collaboration with Professor Stephen Simpson, we are studying the effects of nutrition on ageing. Using a complex mathematical tool called the geometric framework developed by Professor Simpson, we can analyse the relationship between nutrition and outcomes such as aging and frailty in a total novel way. This approach has uncovered the importance of protein in the diet on ageing. In addition, we have also commenced an investigation in humans. Using the CHAMP study of older men, we utilizing the geometric framework to investigate the relationship between macronutrients and health outcomes.

Developments:

We are developing nutritional and pharmacological strategies to delay ageing and thereby gain the longevity dividend of a reduction and delay in many age-related diseases and disabilities, and potentially longer healthy lives.

Collaborations:

Dr Rafael de Cabo, National Institute on ageing, USA
Dr Michel Lebel, University Laval, Canada
Dr Thomas Huser, University of California, USA
Professor David Sinclair, Harvard University, USA
Professor Bard Smedsrod, University of Tromso, Norway
Dr Eric Thorin, Montreal Heart Institute Research Centre, Canada
Professor Bill Ballard, University of New South Wales
Professor Ron Quinn, Eskitis Institute, Queensland
Professor Stephen Simpson, University of Sydney, NSW
Dr Patrick Bertolino, Centenary Institute, NSW
Associate Professor Sarah Hilmer, University of Sydney NSW
Bone Biology

PERSONNEL

GROUP LEADER: Professor Markus J Seibel

SENIOR SCIENTISTS: A/Prof Hong Zhou

VISITING SCIENTISTS: A/Prof Jingbao (Jason) Li, North Western Polytechnical University, Xi’an China, Dr Rowan Hardy, University of Birmingham, UK, Dr Connie Spies, Humboldt University, Berlin, Germany, Professor Guoxian Ding, Nanjing Medical University, Jiangsu, China, Dr Mark Cooper, Birmingham University, UK, Professor Iraj Nabipour, Busheer University, Iran.

STAFF AND STUDENTS: Dr Yu Zheng (NHMRC Fellow), Dr Tara Brennan-Speranza (NHMRC Fellow), A/Prof Colin Dunstan (associated), Dr Kirtan Ganda, Ms Trupti Trivedi, Ms Jinwen Tu, Mr Yaqing (Frank) Zhang, Mr Peng (Andy) Zhang, Ms Colette Fong-Yee, Ms Sylvia Gasparini, Mr Holger Henneicke, Mr Tazio Maleitzke, Ms Susanne Schillo, Ms Shihani Stoner, Ms Shu-Oi Chow, Ms Ling Zhuang, Mr Chris Ngan, Ms Sarah Kim.

Role:

The Bone Research Program pursues basic, applied and clinical research in bone health and biology, including osteoporosis and metabolic bone disease. Our basic research has a focus on glucocorticoid action in bone, arthritis and bone metastases (bone cancer), for which we have developed and evaluated transgenic models of bone disease. Our applied and clinical research focuses on the assessment of bone metabolism, the implementation of secondary fracture prevention programs, and male ageing.

The program has supported the postgraduate and doctoral studies of Trupti Trivedi, Jinwen Tu, Yaqing Zhang, Kirtan Ganda, Holger Henneicke and Cristopher Ngan (all Sydney University); Katja Boernert, Uta Heinevetter, Dennis Basel, Katharina Blankenstein, Edgar Wiebe, Claudia Huelso (all Humboldt University, Berlin); Shaoxin Yu (Shanghai Jiao Tong University, Shanghai) and Peng (Andy) Zhang (Shanghai University of Traditional Chinese Medicine). Sunny Ye, Weiqi Jason Wang and Sarah Kim participated as Honours students. Difei Deng and Sarah Kim participated as an undergraduate summer students.

Highlights

The past 2 years saw major progress in our basic and clinical research, as documented by several high-level publications (PNAS, JCI, NEJM; see below) and a number of prestigious awards to our team and its members. For example, A/Prof Hong Zhou received the “Most Outstanding Basic Abstract Award” of the 2011 Annual Scientific Meeting of the American Society of Bone and Mineral Research (ASBMR), the world’s prime scientific society in the bone field. Prof Markus Seibel, Drs Kirtan Ganda and Anna Lih received both the 2012 NSW Health Award and the 2012 NSW Premier’s Award for their work on secondary fracture prevention. In 2011, Prof Seibel was elected ANZBMS President-Elect, and he will take over as President in September 2013. In 2012, A/Prof Hong Zhou was re-elected ICHTS Chair of Board Directors for 2013-2014 and appointed Associate Editor for The Journal of Orthopaedic Research. Dr Tara Brennan-Speranza received an NHMRC Training Fellowship and the University of Sydney Medical School Early Career Research Grant. Dr Rowan Hardy was awarded a Visiting Fellowship by Arthritis Research UK, which enabled him to spend a scientifically and socially active year at our lab.
Grants: 2011-2013

Annualised $

Cancer Council- Seibel, Zhou, Zheng, Dunstan. “Novel Cytoplasmic Functions of the Vitamin D Receptor in Bone Metastases.” $119,891


German Research Council (DFG) Special Program Grant- Buttgereit, Seibel. “The role of endogenous glucocorticoids in bone and cartilage destruction by immunologic processes.” Euro 64,500

NHMRC- Eisman, Center, Nguyen, Seibel, Sambrook, Elder. “Vitamin D, bone loss, fracture and mortality outcome.” $166,000

NHMRC- Zhou, Seibel, Chen, Dunstan. “Osteoblast control of mesenchymal progenitor cell differentiation: The role of glucocorticoids & wnt signalling.” $145,895

NHMRC- Zhou, Seibel, Stewart, Buttgereit, Cooper. “Role of endogenous glucocorticoids in inflammatory arthritis.” $173,754

NHMRC- Seibel, Zhou, Gundberg, Dunstan. “Role of osteoblast in mediating glucocorticoid-induced metabolic dysfunction.” $206,857

NHMRC- Duque (Nepean Clinical School), Zhou, Drissi, Li. “Role of Lamin A/C in osteoblastogenesis and age related bone loss.” $155,696

NHMRC- Brennan-Speranza. “The influence of cortisone on the synthesis and signaling of osteoblastic-derived mediators of metabolic dysfunction.” $73,143

NHMRC- Zheng. “Vitamin D Deficiency and Breast Cancer Metastasis to Bone.” $73,143

Novartis Pharmaceuticals Aust P/L. Seibel. “Managing Osteoporosis in Patients presenting to CRGH with Minimal Trauma Fracture.” $40,000

Rebecca L Cooper Medical Research Foundation- Seibel, Zhou. “The role of endogenous glucocorticoids in inflammatory arthritis.” $20,000

University Sydney- Brennan-Speranza. “How Bone Cells Contribute to the Control of Glucose Metabolism: Investigations into the Protective Effects of Osteocalcin on Glucocorticoid-Induced Insulin Resistance.” $25,000

University Sydney Bridging Grant/ARI- Zhou, Seibel, Cooper, Stewart. “Age-associated changes in body composition and fuel metabolism: The role of the osteoblast and endogenous glucocorticoid signalling.” $60,000

University Sydney - Zheng “Novel cytoplasmic functions of the Vitamin D receptor in prostate cancer and its bone metastases.” $25,000

Scholarships:

- University of Sydney Postgraduate Award, to Trupti Trivedi (2009-2012)
- International Postgraduate Award, to Jinwen Tu (2010-2012)
- International Postgraduate Award, to Holger Henneicke (2013-2015)
- NHMRC Training Fellowship, to Dr Yu Zheng (2012-2013)
- NHMRC Training Fellowship, to Dr Tara C Brennan-Speranza (2011-2014)
- Visiting Fellowship by Arthritis Research, UK, to Dr Rowan Hardy (2011-2012)
Prizes:

- A/Prof Hong Zhou, ASBMR Most Outstanding Basic Abstract Award 2011
- Dr Yu Zheng, ASBMR Young Investigator Travel Award 2011
- Dr Tara C Brennan-Speranza, ANZBMS Best Oral Presentation Award 2011
- Dr Yu Zheng, ANZBMS Young Investigator Award 2011
- Dr Yu Zheng, ANZBMS Young Investigator Travel Award 2011
- Dr Yu Zheng, Concord Clinical Week Research Award 2011
- Dr Yu Zheng, 6th ICOBR Web Jee Travel Award, 2012
- Jinwen Tu, 6th ICOBR Web Jee Travel Award, 2012
- Jinwen Tu, First Prize Excellent Poster Award, 4th ICHTS Webster Jee Histomorphometry & Imaging Workshop, 2012.
- Sarah Kim: Dean’s Prize, Sydney Medical School, 2012
- Sarah Kim: Winner, Concord Hospital Student Research Prize, 2012
- Markus Seibel, Anna Lih and Kirtan Ganda: NSW Health Award 2012
- Markus Seibel, Anna Lih and Kirtan Ganda: NSW Premier’s Award 2012

Research

Our ongoing research is supported through funding from within Australia and overseas. With our collaborators, we have current and future funding to a total value of over $10m, including 6 current and 8 past NHMRC project grants. Following is a short description of our current research projects.

The Role of Glucocorticoids in Bone Metabolism

Glucocorticoids are potent anti-inflammatory steroids that are highly effective in the treatment of diseases such as rheumatoid arthritis, asthma, inflammatory bowel disease, malignancies and in organ transplantation. While the beneficial effects of glucocorticoids are hard to overestimate, their application is limited by numerous adverse (side) effects such as osteoporosis, muscle wasting, diabetes and skin atrophy.

The members of the Bone Research Program have a long-standing interest in the effects of glucocorticoids on bone, both under physiological and pathological conditions. Using cutting-edge techniques such as knock-out, overexpression and gene therapy models, we are investigating the molecular actions of endogenous and exogenous glucocorticoids on bone and beyond. One of the models we have been using extensively is characterised by a transgene that results in the inactivation of glucocorticoids in the bone forming cells (‘osteoblast’) only. The transgene directs these cells to produce an enzyme known as 11beta-hydroxysteroid dehydrogenase type 2, which converts active cortisol into inactive cortisone. This model allows us to study the actions of glucocorticoids on osteoblasts and dissect these from the effects on other cell types. In addition, we have established a range of cell-targeted glucocorticoid receptor (GR) knock-out models, generating GR-deficient connective tissue (fibroblasts), bone forming (osteoblasts), cartilage (chondrocytes) and fat cells (adipocytes). Using these models in vitro and in vivo, we are currently working on the following research projects:

- Effects of exogenous glucocorticoids on bone, fat and muscle metabolism.
- Endogenous glucocorticoids and ageing.
- Endogenous glucocorticoids and wnt signaling in bone development.
- Endogenous glucocorticoids in immune arthritis.
- The glucocorticoid-receptor and its role in skeletal biology.
Effects of exogenous glucocorticoids on bone, fat and energy metabolism

T Brennan-Speranza, S Gasparini, H Henneicke, C Gunurdberg, H Zhou, MJ Seibel

The bone-related effects of exogenous glucocorticoids, particularly when given at pharmacological (therapeutic) levels, are of major interest. Glucocorticoid-induced osteoporosis is the most frequent form of secondary osteoporosis and remains an unsolved medical problem. However, glucocorticoids affect not only bone but also many other systems, including glucose and lipid (i.e. systemic energy metabolism).

Surprisingly, some of these effects seem to be mediated through bone, which makes the skeleton an even more interesting target of research. To study these questions in more detail, we have developed a method of long-term glucocorticoid treatment that enables us to deliver a sustained pharmacological dose of glucocorticoids and hence simulate chronic exogenous glucocorticoid excess (Steroids 74: 245-249, 2009). Using this method in models where osteoblastic glucocorticoid signalling has been interrupted, we established that the osteoblast is the main skeletal target of glucocorticoid action (Bone 49: 733-42, 2011). To our surprise, we also found that the osteoblast mediates not only the deleterious effects of glucocorticoids on bone but also those on systemic energy metabolism. Very recently, we demonstrated that osteoblasts play a central role in the pathogenesis of glucocorticoid-induced diabetes and obesity (J Clin Invest 122: 4172-89, 2012). We established that targeted disruption of glucocorticoid signalling in osteoblasts results in preservation of osteoblastic osteocalcin release, while at the same time preventing the development of insulin resistance, glucose intolerance and obesity in glucocorticoid-treated mice. Nearly identical effects were achieved when we replaced osteocalcin in glucocorticoid-treated animals via gene therapy. Moreover, replacement of osteocalcin resulted in clearance of hepatic lipid deposits and improved phosphorylation of the insulin receptor, despite treatment with high-dose glucocorticoids. These data suggests that the effects of glucocorticoids on systemic energy metabolism are mediated, in significant parts, through their actions on bone cells. We are currently in the process of identifying the mechanisms that govern the changes in bone, fat, muscle and fuel metabolism induced by exogenous glucocorticoids.

Endogenous Glucocorticoids and Ageing

H Henneicke, M Cooper, P Stewart, MJ Seibel, H Zhou

Ageing is associated with well characterised changes in body composition and energy metabolism. These include central obesity, glucose intolerance or diabetes, loss of muscle mass and osteoporosis. Interestingly, however, many of these changes are also key features of glucocorticoid-induced metabolic disease. We therefore reasoned that there could be a mechanistic link between glucocorticoid actions on bone and the changes in body composition and fuel metabolism seen with ageing.

We have now observed that targeted abrogation of osteoblastic glucocorticoid-signalling in mice almost completely prevents the age-related changes in body weight and fat mass seen in aged animals with normal glucocorticoid signalling in bone forming cells. It therefore appears that the changes in body composition occurring with age are related to the actions of endogenous glucocorticoids on osteoblasts. As these findings may have implications for our understanding of ageing in general, we aim to identify the mechanisms that link the skeletal actions of endogenous glucocorticoids with changes in body composition, body weight and systemic energy metabolism during ageing.
Endogenous Glucocorticoids and Wnt signaling in bone development
C Fong-Yee, C Dunstan, D Chen (USA), MJ Seibel, H Zhou

We have discovered a novel mechanism by which glucocorticoids regulate mature osteoblastic control of mesenchymal progenitor lineage commitment, via Wnt signalling pathways (J Biol Chem 283: 1936-45, 2008). Consequently, we identified that blocking glucocorticoid signalling in osteoblasts delayed development of the skull in newborn mice and is thus required for the normal development of calvarial bone structures (Development 136: 427-436, 2009). In collaboration with Prof Di Chen (University of Rochester, USA) we are investigating the interaction of glucocorticoid and Wnt signaling in osteoblastic control of mesenchymal lineage commitment. In the long term, we hope that these studies will lead to strategies for the prevention of the detrimental effects of cortisone on bone.

Endogenous Glucocorticoids in Immune Arthritis
J Tu, R Hardy, Y Zhang, S Stoner, M Cooper, P Stewart, F Buttgereit, MJ Seibel, H Zhou

Synthetic glucocorticoids are of great importance in the treatment of rheumatoid arthritis (RA) and other inflammatory rheumatic diseases. The role of endogenous glucocorticoid action in contributing to the susceptibility and/or severity of RA remains to be elucidated. While investigating the role of endogenous glucocorticoids in immune-mediated arthritis, we made the surprising observation that arthritis was attenuated when glucocorticoid signalling was disrupted in osteoblasts. These unexpected observations suggest that endogenous glucocorticoids modulate the local inflammatory response through direct effects on osteoblasts (Arthritis & Rheum 60:1998-2007, 2009).

In a current NHMRC-funded project and in collaboration with Prof Frank Buttgereit (Berlin, Germany), Prof Paul Stewart (Birmingham, UK) and Prof Mark Cooper (Sydney) we are currently investigating the mechanisms behind our observations. We hope that this work will eventually lead to novel strategies for the treatment of autoimmune arthritis. In particular, we are focussing on the cross-talk between osteoblasts and synovial fibroblasts. The latter play a crucial role in the recruitment, survival and retention of infiltrating leukocyte populations that drive active inflammation in RA. We recently have isolated and characterised these cells (Arthritis Res Ther 15:R24, 2013; online publication) and are currently researching the role of endogenous glucocorticoids in other models of auto-immune arthritis.

The Glucocorticoid Receptor and Its Role in Skeletal Biology
Y Zhang, Hardy R, A Li, J Tu, J Tuckermann, MJ Seibel, H Zhou

In collaboration with Prof Jan Tuckermann (Germany) and Prof Di Chen (USA), we have established a range of cell-targeted glucocorticoid receptor (GR) knock-out models resulting in GR-deficient mesenchymal cells such as adipocytes, fibroblasts and chondrocytes. By characterising these conditional GR knock-out lines we found that knock out of the GR in mesenchymal cells causes abnormal lung development and an abdominal wall closure defect similar to what is known in human newborns as “gastroschisis” (PlosOne 2013; in print). Furthermore, knock out of the GR in the hypothalamus and pituitary causes an increase in circulating glucocorticoid levels which is associated with a complex phenotype of significant growth retardation, alopecia and premature death (manuscript in preparation).
Preventing the Spread of Malignant Tumours to Bone

Y Zheng, L Ooi, T Trivedi, S Chow, C Fong-Yee, C Dunstan, H Zhou, MJ Seibel

Breast cancer and prostate cancer each have a particular preference to form secondary tumours (metastases) in bone. Breast cancer metastases to bone are associated with bone destruction (‘lytic lesions’) which frequently cause significant pain, pathological fractures and hypercalcaemia. Metastases from prostate cancer usually induce high bone formation, resulting in ‘sclerotic’ or ‘osteoblastic’ lesions which consist of disorganised bone and also can cause severe pain and pathological fractures. In both breast and prostate cancers, the tumour cells ‘enslave’ the resident bone cells (osteoblasts and osteoclasts) to destroy the surrounding normal bone. It has been proposed that the destruction of normal bone leads to the release of growth factors stored in the bone matrix that help the cancer cells to grow faster, thus creating a vicious cycle that contributes to the survival and expansion of bone metastases.

The BRP is particularly interested in how the bone microenvironment and its behaviour affect tumour growth in bone. One way of doing this is to manipulate bone remodelling rates and observe how changes in bone turnover impact the ability of cancer cells to target bone and to establish destructive tumours. For example, anti-resorptive treatments inhibit tumour growth in bone indirectly through effects on osteoclasts, rather than directly through effects on tumour cells (Bone 2007). Furthermore, we demonstrated for the first time that dietary calcium insufficiency strongly promotes tumour growth in bone, mainly through a PTH-mediated increase in bone turnover (Cancer Research 2007; Clin Exp Metastasis 2008). In further research, we found that vitamin D deficiency has similar effects on the growth of breast or prostate cancer in bone (Cancer Research 2010, Bone 2010, The Prostate 2011). While the accelerated destructive process is in part due to an increase in osteoclast mediated bone resorption, our results also suggest that vitamin D, and in particular the vitamin D receptor itself exert direct control over breast and prostate cancer progression in primary and secondary tumours (work in progress). Results of these studies may have clinical implications as vitamin D deficiency contributes to the risk of developing breast cancer and prostate and to its progression to metastatic disease.

Effects of FSH on Bone Structure and Metabolism

R Kalak, C Allan, J Kelly, H Zhou, C Dunstan, DJ Handelsman, MJ Seibel

In collaboration with Dr Charles Allan and Prof David Handelsman (Andrology), we are studying the phenotype of female transgenic mice over expressing human FSH. We have determined that these mice develop high bone density. This study shows for the first time an apparent anabolic effect of human FSH on mouse bone (Allan et al., PNAS 2010). Further studies are planned to investigate in more detail the mechanism for the bone changes in these mice.

In addition to basic research, the Bone Research Program has a strong clinical research arm. Most of this research happens at the academic section of the Department of Endocrinology & Metabolism, which is part of both Concord Hospital (Sydney Local Health District) and the ANZAC Institute's Bone Research Program.

The Concord Fracture Liaison Service: A world-class research and clinical program for secondary fracture prevention

K Ganda, A Lih and MJ Seibel

Despite the availability of effective treatments that greatly reduce the risk of re-fracture, most patients with incident osteoporotic fractures are neither investigated nor treated for their underlying condition. World-wide, over 70% of people with osteoporotic fractures go undiagnosed and untreated. This appalling situation led us to implement the “Concord Fracture Liaison Service” at Concord Hospital in 2005, with the aim to significantly improve the care of people with osteoporosis. This patient-focussed service includes targeted case-finding, systematic assessment and evaluation, and pharmacological and non-pharmacological treatment as indicated. Other components include patient self-management education programs and support systems, exercise and nutritional advice, care coordination and access to specialised health professionals.
The structure of the FLS is simple. Patients 45 years or older presenting to Concord Hospital with a fracture are being screened to determine whether the fracture had resulted from inadequate trauma. Patients deemed to have suffered a fragility fracture then undergo a standardized series of assessments and investigations, including a medical history, physical examination, bone mineral density (BMD) scan, thoracolumbar spine radiographs and specific blood and urine tests. Multidisciplinary resources were used as appropriate, including involvement of other specialists, Physiotherapy, Dietetics, nursing teams, Social/Allied Health Services at Concord Hospital. Patients diagnosed with osteoporosis were educated about their condition, the risks and benefits of available treatments, and the need for long-term adherence with their management plan. Patients were offered evidence-based pharmacologic and non-pharmacologic interventions as indicated. All patients had access to government-subsidized medications approved in Australia for the secondary prevention of osteoporotic fractures. Patients were reviewed 3 months after their initial visit, and annually thereafter. Annual follow-up visits included an assessment of medication compliance and adverse effects, a physical examination and follow-up questionnaire, together with serial BMD scans and selected laboratory tests. The FLS worked in close co-operation with chronic care services, primary care, community-based lifestyle services and homecare services which are an integral part of the service.

Outcome data analysed after 4 years, evaluated re-fracture rates in people who underwent standard care (i.e. non FLS care) compared to those managed by the FLS. The analysis included 403 patients (246 in the intervention and 157 in the control group). Both groups had similar baseline characteristics, with no differences in socioeconomic status, clinical risk factors, or the frequency of prevalent osteoporotic fractures (Osteoporosis Intl. 2011). Figure 1 demonstrates the incidence of re-fracture between the two groups: There were 10 (4.1%) new fractures in patients managed by the FLS, and 31 (19.7%) new fractures in the control group (p< 0.001). Thus, the risk of suffering a further fracture over four years was reduced by 80% in the intervention group. In those who suffered a new fracture, the time to re-fracture was significantly longer in the FLS group (26 vs. 16 months). The effect of the intervention was independent of age, gender and fracture type. Thus, the key factor achieving the re-fractures in the MTF group was the intervention itself.

As an outpatient service, the Concord FLS is sustainable with relatively little support. On a wider scale, the Concord FLS is cost-efficient on the basis of greatly reduced cost for treating re-fractures. Health economic modelling demonstrates the cost per QALY delivered ranges between AUD 19,500 and 33,600, well below the $50,000 mark - the commonly accepted Australian threshold indicating health economic cost-effectiveness. This has been published in Osteoporosis International, the leading journal in the field of clinical osteoporosis care (Osteoporosis Intl. 2012).

The Concord Fracture Liaison Service has provided tangible improvements in osteoporosis care to the community, as demonstrated by clinically relevant outcome measures (re-fracture rates). This model of care is not only cost-effective, but applicable to any health care network. In recognition of the innovative achievements of this service, Concord Hospital and the Sydney Local Health District have received both the Baxter Award 2012 and the NSW Premier’s Award 2012.

### Atypical Femoral Fractures and Bisphosphonate Use

K Ganda, A Lih C Girgis, D Sher, MJ Seibel

Together with Drs Girgis (Endocrinology) and Sher (Orthopaedic Surgery), we have studied the potential association between the use of bisphosphonates and the occurrence of subtrochanteric or so called atypical femoral fractures. Based on the review of 152 cases of femoral fractures, we found the risk of an atypical vs. typical fracture in non-bisphosphonate users to be increased 37.4 fold in bisphosphonate users, and the atypical fracture pattern to be 96.7% specific to bisphosphonate users. While there is an association between atypical subtrochanteric femur fractures and oral bisphosphonate use, bisphosphonates also significantly reduce the risk of fragility fractures in patients with osteoporosis. Overall the anti-fracture effects of bisphosphonates far outweigh their potential risks. (Girgis et al. N Engl J Med 2010 May 13;362(19):1848-9)
Sunshine, falls and bone health in the frail elderly

MJ Seibel with PN Sambrook and others

Together with our colleagues at Royal North Shore Hospital and the Institute for Bone and Joint Diseases, we continued to study the complexities of bone health in the elderly. This year’s focus was on the associations between drug burden index and physical function in older people in residential aged care facilities (Wilson et al. Age Ageing, 2010); the attitudes of older people in regards to sun light exposure (Durvasula et al. Arch Gerontol Geriat. 2010), the development of a selection strategy for fracture reduction programs in frail older people (Chen et al. J Clin Epidemiol 2010); excess mortality after hip fracture (Cameron et al. J Bone Miner Res. 2010), and the risk factors for hip fracture among institutionalised older people (Chen et al. Age Ageing, 2009).

The Concord Health in Ageing Men Project (CHAMP)

Epidemiological studies on ageing have tended to focus on women, a phenomenon recognized by sociologists as the feminization of ageing. However, a large percentage of older people are men. For example, in Australia, 44% of those aged 65 and over are male, as are 39% of those aged 75 years and over. Furthermore, the 5–7 year shorter life expectancy for men than women and higher death rates at all ages, including older ages, suggest that more detailed study of the health of older men is essential.

The Concord Health and Ageing in Men Project (CHAMP) was established to investigate health in old men, defined as age 70 years and over. There is no upper age limit for recruitment into CHAMP. The initial chief investigators were Robert Cumming, David Handelsman, Markus Seibel, Helen Creasey, Philip Sambrook, Louise Waite, Vasi Naganathan and David Le Couteur. The study has been funded through several projects grants by the National Health and Medical Research Council of Australia, with additional funding from other competitive sources. Recruitment of study subjects occurred during 2005 and 2006, with the first follow-up assessments in early 2007. Since then, there were two further assessments, producing a wealth of cross-sectional and prospective longitudinal data. Since its inception in 2005, the team has published over 30 original reports on topics relevant to the ageing of older men, including pain, depression and quality of life; psychotropic drug use and alcohol drinking; polypharmacy; ethnicity and falls; the prevalence and treatment of osteoporosis in older Australian men; factors affecting bone loss, muscle strength and fractures, socioeconomic status and bone health; urinary incontinence; frailty and use of health resources, to name a few. see page 40 section on Geriatric Epidemiology.

Developments:

Our plan is to further develop our comprehensive research program, making use of the multi-disciplinary opportunities provided by the ANZAC Research Institute, and to intensify our collaborations with both basic and clinical research groups locally and around the world.

Collaborations:

We make ample use of the many opportunities to build productive scientific partnerships and collaborations with national and international researchers. Over the recent years, we had productive collaboration with the following international partners: Prof Frank Buttgerite, Humboldt University Berlin, Germany, Prof Di Chen, University of Rochester, NY, USA, Prof Paul Stewart and Dr Mark Cooper, University of Birmingham, UK, Prof Caren Gundberg, Yale University USA, Prof Jan Tuckermann, University of Ulm, Germany, Prof Teresa Guise, Indiana University, Indiana, USA, Prof Gang Li, The Chinese University of Hong Kong, Prof Yungjun Wang, Shanghai University of Traditional Chinese Medicine, China, Prof Guoxian Ding, Nanjing Medical University, China, Prof Wim van Hul, University of Antwerp, Belgium, and Prof Iraj Nabipour, Busheer University, Busheer, Iran, Prof Peng Shang, North Western Polytechnical University, Xi’an China. Some of these collaborations have in the past lead to important publications and successful grant applications, including NHMRC Project Grants.

Collaborations with Australian scientists include: Prof. Phil Sambrook (+), Sydney; Profs. John Eisman, Peter Croucher, Jackie Center, Tuan Nguyen and Paul Baldock, The Garvan Inst, of Medical Research, Sydney; Profs Bruce Armstrong, Rebecca Mason, Robert Cumming, David Handelsman, Arthur Connigrave, Gustavo Duque, Christopher Little, David Little, The University of Sydney; Prof. John Wark and Terrence O’Brien, The University of Melbourne, Prof Graham Jones and Dr Tania Winzenberg, The University of Melbourne, Hobart; Prof Chris Nordin and Cory Xian, The University of Adelaide; Dr Robert Day, Medical Engineering & Physics, Royal Perth Hospital. We have also established co-operative industry links through research partnerships with Amgen, Sanofi-Aventis (USA and Australia), MSD Merck, Sharp & Dohme (Switzerland, Germany, Australia), Roche Pharmaceuticals (Switzerland, Australia), Novo Nordisk (Switzerland), Servier (France, Australia) and Novartis Pharma (Australia).
Burns Research and Reconstructive Surgery

PERSONNEL

GROUP LEADER: Professor Peter Maitz

SCIENTISTS: Dr Zhe Li, Dr Yiwei Wang and Kate Nieuwendyk

CO-INVESTIGATORS & COLLABORATORS: Sue Taggard, Tom Leong, Dr Peter Kennedy, Dr Peter Haertsch, Dr John Harvey, Prof Andrew Holland, Jelena Rnjak, Prof Anthony Weiss, Dr David Millis, Nicola Clayton, Rae Johnson and Rana Saheb

STAFF AND STUDENTS: Vlad Illie, Mohammad Mohaghegh, David Goltsman, Cassandra Chong, Jonathan Hew

Role:

Lack of skin donor site, wound infection and scar formation remain the major issues in treating severe burns. Our research covers all aspects of burn care and specialises in tissue engineering of 3 dimensional skin substitutes for severe burn wound healing and skin regeneration.

Objectives:

Our research covers the areas of skin tissue engineering, angiogenesis, wound healing, wound contraction and scarring, nutrition and burn wound healing, epidemiology and wound infection.

Our laboratory is committed to engineered skin equivalents for treating deep burn wounds.

We have been developing biological scaffolds that are biologically compatible, safe and suitable for skin cells to attach and grow. The scaffold could be used for repairing the damaged dermal bed or for engineering autologous skin substitute with skin structures comparable to normal human skin. The research and development of bio-scaffold, and skin equivalents are important for better management of severe burn wound and other skin wounds including chronic, diabetic and pressure skin ulcers.

Highlights

In 2012, Burns research team welcome a new member, Jonathan Hew, Jonathan is a medical student of University of Sydney and has enrolled as a candidate for Master of Philosophy degree studying “nutrition and burn wound healing”. Burns & reconstructive surgery research has now three PhD students, two master-degree students and clinical staff working on various research projects in the areas of wound contraction and scarring, skin tissue engineering, angiogenesis, nutrition and burn wound healing, epidemiology and wound infection.

Dr Yiwei Wang won the most competitive project award at 35th Australia and New Zealand Burn Association (ANZBA) Conference in Brisbane. Both David Goltsman and Cassie Chong won the University of Sydney Postgraduate Research Support Scheme (PRSS) travel scholarship in 2012. The scholarship supported Cassie Chong to attend the 2012 36th ANZBA conference at Hobart and win the young investigator award. In 2013, Cassie was awarded an NH&MRC scholarship after being successful with her application for both APA
and NH&MRC scholarships for her PhD study of skin tissue engineering. In 2012, Dr Zhe Li won a research grant from Sydney Burns Foundation of University of Sydney develop living skin equivalent for burn patients. Together with Dr Wojciech Chrzanowski and colleagues in university, Dr Zhe Li was successful with a NHMRC Equipment Grant through 2013 University of Sydney combined equipment scheme.

The Sydney Burns Foundation has continued working hard to raise fund to support burns research, education and scholarship.

In 2014, the 17th Congress of International Society for Burn Injuries and the 37th ANZBA Conference will be held in Sydney with Professor Peter Maitz as the convener for both conferences.

**Research**

**A Randomized Multi-Centered Trial to Evaluate Efficacy and Safety of Cultured Epithelial Autografts for Burn Wound Healing**

*P Maitz, Z Li, K Nieuwendyk, J Harvey, J Vandervord, S Taggard and P Kennedy*

Lack of skin donor site remains a major issue in treating severe burns. Cultured epithelial autografts (CEA) have been used as an alternative to facilitate burn wound closure and skin regeneration.

In this trial, skin biopsies are taken from severe burn patients and epidermal stem cells will be isolated, proliferated under established laboratory condition. The cells will be induced to differentiate into cultured epidermal autograft (CEA). Harvested CEA sheets or suspensions will be grafted in combination with meshed split skin grafts (SSG). The major aim of this trial is to evaluate the efficacy of CEA in treating severe burns.

**A Clinical Evaluation of Efficacy and Safety of Cultured Epithelial Autograft (CEA) Suspension Applied for Donor Site Healing**

*Maitz P, Kennedy P, Li Z, Taggart S, Leong T and Nieuwendyk K*

A patient with severe burn usually needs skin grafting, a surgical procedure that involves transplanting split skin grafts harvested from healthy donor site to wound area. Rapid healing of the donor sites allows the repeat use of the same donor sites in patients with large burns. But delayed healing could lead to complications such as infection and compromise the recovery process of burns patients. This study is designed to examine if the delivery of cultured autologous keratinocytes to donor site wound could facilitate or speed up its healing process. Wound healing will be evaluated by various methods including the measurement of evaporative water loss on different days post surgery and on each dressing change until the donor site has fully re-epithelialized. Data will be analysed statistically to determine the effectiveness of cultured CEA suspension in donor site healing.

**Skin Tissue Engineering Using a Biodegradable Polymer**

*Wang Y, Chong C, Maitz P and Li Z*

Engineered skin substitutes, resembling natural human skin structure and containing living skin cells, would provide excellent alternatives for severe burn wound management.

The aim of this study is to investigate biodegradable porous scaffolds that can be applied as skin substitutes to promote wound healing and skin regeneration. The skin construct composite of collagen and polycaprolactone is produced using lyophilization technique (Fig 1). The surface morphology and international structure is characterized for skin cell attachment, proliferation and migration (Fig 2). The scaffold is also designed to incorporate with active molecules such as growth factors that can stimulate angiogenesis in wound healing.
Efficacy and Safety of Engineered Skin Substitute and Dressing Materials on Skin Wound Healing: A Mouse Model Study

Wang Y, Chong C, Maitz P and Li Z

The advance in biotechnologies has enabled us to grow different types of skin cells and skin substitutes by skin tissue engineering in our laboratory. Various wound dressing material and dressing regimes are also designed in our laboratory in attempt to provide favorable condition for cultured skin cell growth and speed up the wound healing rate. Although skin cells could attach and grow very well in engineered bio-scaffold under laboratory condition; the bio-compatibility, bio-safety and efficacy of engineered scaffolds, skin substitutes or dressing materials will need to be tested in an animal model before proceeding to any clinical trial.

The aim of this study is therefore to establish mouse models to assess the role of engineered skin products or dressings in wound healing process, including early inflammation, cell recruitment, matrix remodeling and wound contraction. The host response of each mouse as the recipient of skin products or dressing materials will also be examined at cellular and molecular levels. This study will provide significant information on the efficacy and safety of laboratory-developed bio-scaffold, skin substitutes and dressing materials.

Nutritional support on skin formation and wound healing:

Hew J, Wang Y, Li Z and Maitz P

Burn wounds have extremely high nutritional and energy requirements. In current practice patients with burns wounds receive a specialized high energy, high protein diet to support the healing process. This diet supports wound healing by providing patients with essential macronutrients such as amino acids, carbohydrate, fat, electrolytes and micronutrients. Although it is generally known that specialized nutritional support will optimize wound healing, the cellular and molecular mechanisms by which nutrient support and energy intake affect skin formation and wound repair remain unclear.

This ongoing study aims to explore the mechanisms by which macronutrition and energy density effects skin structure and wound healing. This will be achieved through the utilization of histological and immunohistochemistry techniques to analyze skin samples collected from mice fed specific diets. Identifying these cellular and molecular mechanisms will increase our understanding of the known relationship between burn wound healing and nutrition. This knowledge will be instrumental in the advancement of nutritional support in burn injury wound repair.

Biofilm and Infection of Burn Wound

Kennedy P, Brammah S and Wills E

One of the most significant problems in burn care is that of infection. Many of the micro-organisms commonly found on the burns wound are known to produce biofilms(Fig 1 and Fig 2), a collection of organisms attached to a surface and sound by matrix containing polysaccharides known as extracellular polymeric substances (EPS). Biofilms are the cause of significant morbidity and mortality in relation to implanted medical devices and septic complications associated with indwelling intravenous catheters. The organisms within biofilms are well known to develop resistance to antibiotics and to the immune system. This ongoing study will help to understand the mechanisms of bacterial wound invasion and burn wound sepsis, and therefore help the management of burn wound.

The effect of endotracheal tube size on voice, swallowing and laryngotracheal injury in patients intubated for thermal burns: a three year observational study

Clayton N, Cheung W, Maitz P, Milliss D, Thanakrishnan G and Li F

The aim of this study is to assess whether the size of endotracheal tube used to ventilate patients with thermal burn injury whilst in ICU, has an effect upon recovery of swallowing and voice, as well as the incidence of tissue changes in the larynx and trachea. It is anticipated that this study will provide information to facilitate development of recommendations for the selection of appropriate endotracheal tube size in patients with thermal burns requiring ventilatory management.
A new framework for analysis and prevention strategies of severe burns and injuries in NSW

Goltsman D, Li Z and P Maitz

Burn injury remains a common public health issue in Australia. Using advanced statistical and epidemiological methods, this research aims to perform in-depth analysis of all retrospective data of burns injuries in NSW and to identify regions and population which possess a higher occurrence of burns, and also to identify and qualify explanatory variables for the occurrence of these burns. This analysis attempts to further explore methods of constructing logistic multivariate and multinomial models linking the interaction of causative factors to the different types of burns. It also aims to establish new models of burns analysis with geo-spatial imaging, attempting to identify on a map of NSW correlations between geographic regions and specific burns types. This spatial analysis will provide better guidance for health resource allocation and more effective education and interventional strategies for the identified high-risk population and geographic ‘hot-spots’. It further provides a platform for prospective analysis in the future, looking at the effectiveness of the strategies implemented nationally.

Skin Tissue Engineering: Producing the Ideal Electrospun Scaffold with Optimal Skin Cell Culture Conditions for Cellular Interactions

Chong C, Wang Y, Maitz P and Li Z

Treatment of severe burn injuries in the form of a living 3D skin equivalent is of utmost importance. Electrospinning of scaffolds is ideal for fabricating reproducible skin equivalents which can be tailored to clinical demand. Electrospun scaffolds are flexible and porous (Fig 1) and the use of the polymers collagen, elastin and polycaprolactone further promote cellular interactions and improve scaffold strength.

This study aims to produce an electrospun scaffold with optimal structure and composition for basal keratinocyte and dermal fibroblast interactions and behaviours. Promotion of cell interactions will accelerate wound healing and minimise scar formation. This study will provide new information important to the development of a full-thickness, living 3D skin equivalent for skin regeneration.

Angiogenesis of different dermal regeneration templates, Integra, PELNAC and collagen-PCL scaffold: A novel murine model

Mohaghegh M, Wang Y, Li Z and Maitz P

An ideal bio-scaffold will not only support the attachment, growth and differentiation of skin cells but also facilitate the rapid angiogenesis of the engineered skin substitute. Rapid vascularisation is essential to keep the skin substitute graft viable and to ensure its take.

Various bio-scaffolds have been developed for generating 3D living skin equivalent in our laboratory. The aims of this study are therefore to test the angiogenesis property of the novel dermal scaffolds using a mouse model. The host response and angiogenesis process of our novel scaffold in the recipient mice will be examined in comparison with commercial dermal regeneration template. This study will provide significant information on the biocompatibility of the scaffold and also help optimizing the bio-scaffold for skin regeneration.

Study of skin graft contraction

Ilie V, Wang Y, Li Z and Maitz P

Wound contracture following split skin grafting results in bad aesthetic and functional outcome. A variety of skin substitutes or artificial dermal replacements are used not only to decrease morbidity and wound contracture in severely burned patients but also to enhance cosmetics of burn wounds. Although applications of dermal substitutes have been described in the literature and studies were conducted comparing the efficacy of dermal substitutes in respect to wound contraction, the mechanism of contraction inhibition was not clearly interpreted and the intrinsic factors involved has not been defined.
Using an animal model, elements and processes involved in skin graft contraction will be examined by correlating and comparing different wound coverage methods that have macroscopically different contraction rates.

**The role of androgens in wound healing-design of a new wound dressing material to accelerate healing process**

_Wang Y, Cheer K, Maitz P and Li Z in collaboration with Dr Ulla Simanainen and Prof David Handelsman (Andrology Laboratory, ANZAC Research Institute)_

Wound healing is an innate response which involves a number of overlapping phases including inflammation, cell recruitment, epithelialization, matrix synthesis and remodeling. In elderly, impaired wound healing is especially common in men, with additional sex-specific differences in wound healing also supporting a critical role for sex hormones in the healing process. We have created a model targeting androgen receptor (AR) to identify the role of androgens via AR in wound repair, as well as compare the impact of AR-mediated androgen actions in anabolic state wound healing (cutaneous) and catabolic state wound healing (severe burn injury). We have confirmed enhanced wound healing rate in AR-knock out male mice compared to wild-type. To avoid the systemic toxicity, we designed a soft wound dressing scaffold with efficient anti-androgen drug (OH-flutamide) loading (95%) and sustained local drug release over 21days.

This study will provide the most comprehensive evaluation on AR-mediated androgen effects and mechanisms in healing process and provide pre-clinical evident of local targeting of AR to improve delayed wound healing clinically. In addition, the novel dressing will provide a safe and efficient template to assess the new AR-target drugs in healing process.

**A randomised and double-blinded trial to investigate the effects of Clobetasol Propionate cream on skin grafts for burn wounds**

_Rana Hilmi, Rae Johnson, Zhe Li, Samuel Zagarella and Peter Maitz_

Burn injuries result in pain, inflammation and destruction of skin cells. Skin grafting will be required when the depth of the injury destroys the deeper skin layers. Despite grafting, the burn injury continues to produce inflammatory reactions that results in a thickened, raised and hyper-pigmented scar which restricts movement, has an increase in sensitivity and itching as well as implication for body image and a return to normalcy. Current management of scar tissue aims to flatten the scar by wearing tailor made pressure garments and silicone gel sheets for 12 to 18 months.

The aim of this pilot study is to examine the effect of superpotent cortisone cream on the scarring. This double blind, single centre study was designed to compare the effect of Clobetasol propionate cream with common moisturiser on the grafted skin.
Cancer Pharmacology Unit

PERSONNEL

GROUP LEADERS: Professor Stephen Clarke and A/Prof Graham Robertson

SCIENTISTS & STUDENTS: Dr John Allen, Dr Anne Vanniasinghe, Dr Anahid Ehteda.

Role:

Cancer Pharmacology Unit under has significantly increased cancer research activities on the Concord campus in multiple areas. These include clinical trials of new cancer treatments, nutritional and psycho-oncology research and the establishment of a molecular-based cancer pharmacology laboratory. The appointment of Prof Andrew McLachlan to the Chair of Geriatric Pharmacy on the Concord campus has strengthened the pharmacokinetic expertise required for clinical drug studies.

Objectives:

To understand the biology of cancer cachexia and its impact on cancer treatments, including drug efficacy and toxicity.

Grants: 2011-2013

Annualised $

NHMRC- Clarke, Robertson, Piquette-Miller, McLachlan, Baker, Katsifis ‘Improving the use of chemotherapy by targeting the inflammatory response’ $191,946

Research

Cancer Cachexia, cytokines and altered metabolic pathways

G Robertson, S Clarke, M Tsoli, A Painter, R Taylor, P Huynh.

Cancer cachexia is a complex condition involving disturbances in energy balance and metabolism in several organs of the body. Cachexia has a devastating impact on patient quality of life and survival – in fact it is the direct cause ~20% of all cancer deaths. The release of factors called cytokines into the blood by tumours is a likely link between tumour cells and the major metabolic tissues of the body – muscle, fat and liver. We have used mouse tumour models to study the development of cachexia and found major disruptions in the regulation of metabolism. In particular it appears that brown and white adipose tissues (BAT/WAT) exhibit severe lipid depletion and increased expression of regulators involved in fatty acid oxidation. In addition UCP1 - a key protein responsible for BAT activation and heat generation - is up-regulated resulting in a fever and inappropriate energy expenditure. In contrast the liver is unable to process and redistribute nutrients including lipids and carbohydrates. Such dramatic changes may contribute to aberrant energy balance leading to cancer cachexia. The morphology of muscle fibres and fat deposits have been examined to characterize the changes that occur during cachexia. These changes may reflect alterations in metabolism and the molecules that control energy balance in the body.

Impact of cancer-induced inflammation on the pharmacokinetics, efficacy and toxicity of anticancer drugs.

G Robertson, S Clarke, J Allen, A McLachlan, A Painter, M Tsoli, P Huynh.

Treatment of cancer requires careful optimization of drug doses - a balancing act between adequate affect from the drugs in killing tumour cells while avoiding excessive toxicity to the patient. Hence, disturbances of clearance of drugs from the body, like those caused by cancer-induced inflammation, are invariably detrimental, regardless of whether they increase or decrease the effective dose. Such changes in the metabolism and transport of anticancer and other drugs can have a major impact on response to treatment - in particular toxicity.
The goal of this project is to assess changes in anticancer drug clearance caused by inflammation associated with tumours and their impact on toxicity of common anticancer drugs by using C26 mouse tumour models.

We showed previously that changes in expression of liver and kidney drug transporters delays the excretion of methotrexate. The current work extends attention to other sites of drug processing and toxicity in the body including suppression of the immune system by common anticancer drugs in the bone marrow, cardiac toxicity of anthracyclines and lung toxicity of bleomycin. The C26 mouse model used for assessing myelo-suppression display higher neutrophil and monocyte levels in both circulation and the peripheral organs and also, the blood neutrophil:lymphocyte ratio (NLR) is elevated 20 fold; a marker of poor prognosis for many cancers in humans. In collaboration with Professor Donald McMillan from the Glasgow Royal Infirmary, we have recently developed a derived NLR which will allow analysis of data from large randomized trials.

The effects of inflammation on disposition of anticancer drugs is being assessed by SPECT/CT imaging of cachectic mice in collaboration with ANSTO, using the new in vivo imaging cameras at the Brain and Mind Institute. These imaging techniques are widely used in the management of human cancer treatment but have rarely been employed with animal models. They have the advantage of providing real-time whole body quantitative data on drug uptake disposition and excretion. Planned studies will use labelled anticancer drugs to model the clinical situation.
Dendritic Cell Biology and Therapeutics

PERSONNEL:

GROUP LEADER: Professor Derek Hart

HONORARY PROFESSORIAL RESEARCH FELLOW: Professor Ken Bradstock

SCIENTISTS: Associate Professor Georgina Clark, Dr Phillip Fromm, Dr Nirupama Verma, Dr Kifah Shahin, Dr Pablo Silveira, Dr Zehra Elgundi, Leticia Muusers, Phi Ai Vu, Fiona Kupresanin.

STUDENTS: PhD: Christian Bryant, Robin Gasiorowski, Honours: Kevin Lo, Rhonda Adam, Summer: Jeremy Wang, Leon Smith, International: Laura Schenning

VISITING SCIENTISTS ON STAFF: Dr Sebastien Anguille

ADMINISTRATION: James Zagarella, Lyn Schedlich

VISITING SCIENTISTS ON STAFF: Dr Sebastien Anguille.

Role:

The Dendritic Cell Biology and Therapeutics Group (DCBTG) is directed by Professor Derek Hart. They discover key immune markers and biological processes which will provide new diagnostic and therapeutic products for improving patient care.

The immune system controls and regulates our internal and external environmental reactions. It responds by up-regulating or activating cellular and soluble components to fight infection and cancer. Dendritic cells (DC) are unique white blood cells that exist as different subsets throughout the body. They are responsible for initiating and directing immune responses. As one of the pioneering groups in this field, the DCBTG is continuing to define human DC subsets and elaborate their function. The group studies DC surface molecules to determine how these molecules influence DC function and how antibodies targeting them might be used in clinical practice.

Objectives:

A major part of our work is aimed at using the patient’s immune responses to treat haematological cancers. We are testing our findings in preclinical models of stem cell transplantation, leukaemia, multiple myeloma, prostate cancer and other malignancies. We are striving to develop novel immunosuppressive strategies, including our previous anti-CD83 antibody as a novel therapeutic agent. We aim to use this antibody to improve transplant outcomes, whilst preserving the patient’s ability to fight infections and cancer. Negotiations to support a clinical trial of anti-CD83 in allogeneic haematopoietic stem cell transplantation are underway.

To obtain sufficient funds to translate its fundamental scientific advances into the clinic the DCBTG has adopted a novel “hybrid” funding model, which combines 1) peer-reviewed grant funding, with 2) philanthropic funding and 3) third party commercial collaborations (e.g. biotech or pharma) to advance its intellectual property and help fund clinical development. The in-kind support and collaborative input from colleagues at the Concord, Royal Prince Alfred and Westmead hospitals makes an additional major contribution.

Highlights:

ANZAC Research Institute 10th Annual Symposium. This special “DC Down Under” Symposium, held in August 2011, was developed to mark the 10th anniversary of the establishment of the ANZAC Research as part of Concord Clinical Week celebrations. This premier symposium “Immune Therapies for Cancer” attracted delegates from all over Australia to hear talks from national and international speakers on the latest developments in the use of immune therapies for
the treatment of cancer. We were pleased to be able to host two international speakers for this event, Professor Zwi Berneman from the University of Antwerp, Belgium, who spoke on DC vaccination in acute myeloid leukaemia and Dr. David Urdal from Dendreon Corporation, USA, who spoke on the development of the first FDA approved cellular therapy for prostate cancer.

“DC Down Under” Symposia. This 2 day event is a relaxed workshop environment attracting over 80 researchers to discuss DC research and its translation into clinical reality. The second “DC Down Under” Symposium was held in August, 2012 with Professor Angus Thompson (Starzl Institute, Pittsburg as guest speaker) and Dr Elizabeth Jeffries (John Hopkins University School of Medicine, Baltimore) as our international guests.

Translational Research. Two locally trained haematologists started their PhDs with the group at the beginning of 2012. Dr Christian Bryant has a special interest in multiple myeloma whilst Dr Robin Gasiorowski is developing a novel therapeutic antibody for treating patients with acute myeloid leukaemia. Their presence has been marked by the publishing of Christian’s first paper describing a small group of multiple myeloma patients, who survive at least 10 years, whilst Robin has received awards at the Haematology Association of Australia 2012 meeting and the Sydney Catalyst Postgraduate Meeting for his presentations on CD300 molecules.

Publications. Our first clinical research project initiated upon establishing the group in Sydney has been completed and published in Transplantation.

Grants


Cancer Institute NSW: Hart, Bradstock, Joshua. We were awarded a Sydney Catalyst TPG “Enabling diagnostic and therapeutic antibodies for haematological and other malignancies.” $710,899. This will accelerate our development of therapeutic monoclonal antibodies.

Anthony Rothe Memorial Trust: Hart. “Clinical application of dendritic cell immune therapy for multiple myeloma.” $90,000

Cancer Australia/NHMRC: Hart, Bradstock. “RNA loading of tumor associated antigens and the activation of blood dendritic cells for cancer immunotherapy.” $97,497


NHMRC Equipment Grant: Hart. “BD Influx Cell Sorter” $197,000

Rebecca Cooper: Hart. “RNA loading of tumour associated antigens and the activation of blood dendritic cells for prostate cancer immunotherapy.” $24,000

NHMRC-Hart. “Clinical translation and commercialisation of novel therapeutic interventions in haematological malignancy and ASCT.” $176,875

Ramacotti- Hart, Freedman, Handelsman, Nicholson, Seibel, Clarke, van Zandwijk. “BD LSR Fortessa (3 laser, 8 colour) cell analyser with FACS Flow supply system.” $75,000
Collaborations:

- Dr Ilona Cunningham, Dr Judith Trotman, Ms Elizabeth Newman; Haematology Department, Concord Repatriation General Hospital
- Professor Douglas Joshua, Dr Ross Brown, Dr Stephen Larsen Institute of Haematology, Royal Prince Alfred Hospital
- Ms Mary Sartor; Blood and Marrow Transplant Service, Westmead Hospital
- Professor Ian Fraser, Dr Alison Cunningham; University of Sydney
- Professor Mark Hogarth; Burnett Research Institute
- Professor Zwi Berneman, Dr Sebastien Anguille; University of Antwerp

Research:

Basic DC Discovery Research

Antibody engineering to produce “custom made” reagents

Zehra Elgundi, Leticia Muusers, Georgina Clark, Derek Hart

Our program is based on understanding the membrane molecules found on the surface of DC. We generate monoclonal antibodies (mAb) to these biomarkers and when we understand the biology, we develop strategies for using these mAb to treat haematological malignancies. The pathway to using these agents in the clinic requires humanised products. Our approach is to use antibody engineering to produce humanised reagents which are used in our basic science studies. This will enable rapid translation of our findings into the clinic.

The potential to control inflammation by modulating CD300a and CD300c biomarkers

Georgina Clark, Robin Gasiorowski, Leticia Muusers, Derek Hart

Our group discovered a family of biomarkers called CD300 molecules which are found on DC and some other white blood cells. It is clear from our own and others work, that these molecules may act to amplify or dampen wanted and unwanted inflammatory responses. Our effort has focused on their significant control of the human dendritic cells response to inflammation and their interactions with T cells. We are investigating the hypothesis that inflammatory environments alter the expression of CD300 family members. If this is correct, then reagents to them could be developed as biomarkers for monitoring inflammatory disease and potentially as agents to treat it. Products that independently manipulate CD300a or CD300c signalling have the potential to be turned into new drugs for controlling the response to transplants, other inflammatory diseases and possibly sepsis.

CD300f as a target for the treatment of acute myeloid leukaemia

Robin Gasiorowski, Georgina Clark, Derek Hart, Ken Bradstock

Whilst some leukaemias can be cured as a result of advances in treatment options, at least 60% of patients with the most common form of adult leukaemia, acute myeloid leukemia (AML), still die of the disease. Mylotarg, an antibody-toxin conjugate therapy for AML, was a promising drug but its recent removal from the market due to unacceptable side effects reinforces the need for other antibody targeted therapies. We have identified a new AML target called CD300f that may enable us to develop new antibody treatments for AML to replace Mylotarg. By defining how CD300f acts in AML and how to target it with antibodies, we hope to develop a less toxic treatment suitable for wide application.
Determining the function of CD302

Pablo Silveira, Kevin Lo, Nirupama Verma, Ai Vu, Georgina Clark, Derek Hart

To understand the biology of the biomarkers that we have discovered, the DCBTG have developed preclinical models in which the relevant genes encoding the biomarkers have been deleted. One of these models has allowed us to gain insights into the role of CD302 in the migration of DC. This is crucial to understanding how DC based anti-cancer vaccines may move from the site of injection to the site of immune stimulation.

DC in Haematological Diseases

Translation of human blood dendritic cell subset biology in multiple myeloma

Phillip Fromm, Christian Bryant, Fiona Kupresanin, Hayley Suen, Ross Brown, Douglas Joshua, Derek Hart

The investigation of human blood DC subsets and their biology in malignant cancers is proving rewarding. We have continued to question why there are lower DC numbers in the peripheral blood of multiple myeloma (MM) patients whereas the disease site, the bone marrow, is enriched for some DC populations, and how this finding correlates with the disease status. We have focused our studies on the biology of a novel CD2 subset of plasmacytoid DC and how they contribute to the disease. These studies also direct our ongoing investigation of antibody selected DC populations for therapeutic DC vaccination trials.

Ten year survivors of multiple myeloma demonstrate differing expression of immune biomarkers

Christian Bryant, Ross Brown, Shihong Yang, Hayley Suen, James Favaloro, Derek Hart, Phillip Fromm, Harry Illand, John Gibson, P Joy Ho

Our work in collaboration with the Royal Prince Alfred Hospital investigating the immune mechanisms of disease control which may contribute to long-term survival in MM, has recently been published. We analysed relevant biomarkers and DC subsets in all current >10 year survivors and compared the results with a larger all-MM group. This analysis demonstrated a significant increase in many immunologic markers in the survivors. The conclusion that immune mechanisms contribute to long-term disease control encourages our efforts to generate new therapeutic immune approaches to treat MM.

Dysfunctional antigen presentation by malignant multiple myeloma plasma cells changes cytotoxic effector T-cells into acquired regulatory cells

Ross Brown, James Favaloro, Shihong Yang, Hayley Suen, Derek Hart, Phillip Fromm, John Gibson, P Joy Ho

Together with our collaborators at the Royal Prince Alfred Hospital, we are investigating the dysfunctional effects of the malignant plasma cells of patients with MM on the immune system. A phenomenon occurs whereby cytotoxic effector T-cells in these patients acquire a range of molecules from malignant cells which alter their function resulting in the induction of regulatory T-cells. This phenomenon is more common in patients with MM than other chronic B cell disorders. These and other artefacts of malignant plasma cells are associated with poor prognosis and form the basis of our current research.

Graft Versus Host Disease

Identification of blood DC biomarkers that predict the development of acute and chronic graft versus host disease following bone marrow transplantation

Kifah Shahin, Zamil Mattar, Mary Sartor, Leah Kim, Stephen Larsen, Derek Hart, Ken Bradstock

DC are centrally involved in the development of acute graft-versus-host disease (GVHD) following allogeneic hematopoietic cell transplantation (alloHCT). Working with the Blood and Marrow Transplant Service at Westmead Hospital has enabled us to examine various DC biomarkers and DC activation status after alloHCT. GVHD in particular seems to be linked to the expression of the biomarker CMRF-44 on specific DC subsets. The DCBTG recently published work demonstrating that the biomarker, CCR5, on other DC subsets showed a positive correlation with acute GVHD. Preclinical studies are now underway to study whether the absence of CCR5 effects the development of GVHD in allotransplants.
Modulation of dendritic cell function through extracorporeal photophoresis in the treatment of chronic graft verses host disease

Phillip Fromm, Fiona Kupresanin, Georgina Clark, Hayley Suen, James Favorolo, Ross Brown, Stephen Larsen, John Gibson, Douglas Joshua, Derek Hart

For patients with severe chronic GVHD, the use of expensive extracorporeal photophoresis (ECP) twice a week becomes the only option. This treatment serves to induce apoptosis in effector T-cells through a combination of intercalating agents and application of ultraviolet light. We have demonstrated that ECP treatment also serves to modulate activation markers of DC that we have previously shown to be prognostically associated with the onset of acute GVHD. Our current work is focussed on understanding how the induction of apoptosis serves to modulate DC function in these patients.

The use of anti-CD83 antibodies as novel immunosuppressive agents

Nirupama Verma, Pablo Silviera, Ai Vu, Kifah Shahin, Phillip Fromm, Georgina Clark, Ken Bradstock, Derek Hart

The pivotal role of DC in GVHD suggests that their depletion may control GVHD by preventing T-cells from being sensitised to host antigens without impairing immunity. Previously published work from Professor Hart’s group showed that a rabbit polyclonal IgG anti-human CD83 (RAH83) antibody prevented GVHD but maintained protective anti-viral and leukaemic activity in a xenogeneic model. We have been tracking the CD83 target on DC in the xenogeneic model to optimise potential therapeutic strategies. Our recent development of an anti-mouse CD83 antibody will allow us to determine how CD83 depletion controls GVHD in mouse allogeneic transplantation models – including solid organ models. We have re-established collaboration with the Cooperative Research Centre for Biomarker Translation reinvigorating our planning for a clinical trial to test a candidate anti-CD83 human monoclonal antibody as a novel immunosuppressive agent.

Immunotherapy

mRNA loading of tumour associated antigens into blood dendritic cells

Phillip Fromm, Sebastien Anguille, Fiona Kupresanin, Georgina Clark, Elizabeth Newman, Ilona Cunningham, Zwi Berneman, Derek Hart

There is worldwide interest in developing immune therapies, including active vaccination with DC to treat cancer. Provenge, produced by the US based company Dendreon, was FDA approved after a phase 3 clinical trial showed that vaccination prolonged survival in anced prostate cancer. We are developing novel antibody based strategies to purify blood DC and this project is testing the optimal form of tumour target antigen to load into the DC product. Previous work suggested that RNA coding for tumour targets was processed effectively by DC and these generated anti-tumour responses in the test tube. We have shown that primary human DC isolated using a chimeric anti-human CMRF-56 monoclonal antibody, can effectively be loaded with mRNA and is able to generate robust anti-viral and anti-tumour T cell responses. We are testing the ability of different DC populations to take up and present mRNA-encoded tumour targets in preclinical work to determine the optimal clinically relevant strategies to allow this technique to be used for DC vaccination in both multiple myeloma and prostate cancer.
Enteric Neuroscience & Gastrointestinal Research Group

PERSONNEL:

GROUP LEADER: Professor Marc A Gladman

SENIOR SCIENTISTS: Dr David Mahns

VISITING SCIENTISTS: Dr Natasha Nassar

STAFF AND STUDENTS: A/Professor Rupert Leong, Dr Michael Suen, Dr Kheng-Seong Ng, Dr Naseem Mirbagheri, Dr Pramudith Sirimanna, Dr Angela Walker, Ms Noemi Montes, Ms Cathy Lee, Mr Ian Whiteley, Ms Sonia Khatri

Role:

Established in 2012, the Enteric Neuroscience & Gastrointestinal Research Group focuses on clinical, epidemiological and translational research into diseases and disorders of the gastrointestinal tract. The group is a collaboration of expert gastrointestinal surgeons and physicians, epidemiologists, biostatisticians and gastrointestinal scientists, physiologists and neuroscientists.

Objectives:

The mission of the group is to advance our understanding of gastrointestinal diseases and to apply such knowledge to improve the care of patients. The main research themes are:

1. Population-based research to investigate the epidemiological basis of gastrointestinal diseases;
2. Clinical research to strive for new knowledge relating to gastrointestinal function in health and disease to allow the development of novel medical and surgical therapies;
3. Translational enteric neuroscience research to determine the molecular, electrophysiological and neuropathophysiological basis of gastrointestinal conditions; and
4. Health outcomes research to objectively measure the impact of interventions in patients with gastrointestinal disease.

Highlights:

- Development of a novel technique to record from isolated extrinsic nerves innervating the human gastrointestinal tract
- Established International collaborations with:
  - Department of Cell and Molecular Biology, Medical Nobel Institute, Karolinska Institute, Sweden
  - Center for Health Outcomes & Policy, University of Michigan, USA
Grants: 2011-2013

Annualised $

Applied Medical Research Project Grant  $75,000
Colorectal Surgical Society of Australia & New Zealand  $22,000
Karl Storz Research Grant  $60,000
Research Donations  $25,000
Medtronic Australia Educational Grant $80,000

Students:

Australian Postgraduate Award –Ng  $23,728
Australian Postgraduate Award –Mirbagheri  $24,653
NHMRC- Ng. “Medical / Dental Postgraduate Research Scholarship”  $33,132
Royal College of Surgeons- Ng. “Peter King Foundation of Surgery Research Scholarship”  $60,000

Prizes:

Young Investigator Award: Dr KS Ng: Electrophysiological characterisation of human visceral afferent nerves: first in man. Ng KS, Montes-Adrian NA, Mahns DA, Gladman MA. Surgical Research Society, Annual Surgical Research Society Meeting, Adelaide, Australia, Nov 2013

Research:

Electrophysiological characteristics of human rectal and colonic afferent neurons.

Ng KS, Montes-Adrian NA, Mahns DA, Gladman MA

During the last decade, abnormal visceral afferent activity gained recognition as being important in the development of functional gastrointestinal disorders. Since it is not possible to directly measure visceral afferent activity ‘in vivo’ in humans, this study aims to make direct electrophysiological recordings (in vitro) from extrinsic afferents supplying the human colon and rectum. Collection of specimens of normal rectum and colon will be obtained and studied following routine colorectal surgical operations. Mesenteric nerves entering the bowel will then be identified and dissected so that extracellular visceral afferent nerve activity can be recorded. The nerve responses to chemical and physical stimulation will then be recorded for the first time in humans. Ultimately, this technique offers the opportunity to measure electrophysiological properties of extrinsic nerves in disease states.

Phenotypic variation in the central and peripheral mechanisms of sacral neuromodulation.

Mirbagheri N, Ng KS, Macefield V, Gladman MA

Sacral Nerve Modulation (SNM) has revolutionised the management of urinary and faecal incontinence over the past 20 years. However, despite extensive experience with the stimulator and research in the field, its mechanism(s) of action remains elusive, as physiological and anatomical assessment of anorectum before and after sacral nerve stimulation has
failed to show any consistent changes. Recent studies investigating the central effects on animal models and in humans, using functional imaging and cerebral evoked potentials, have suggested a possible ‘reorganisation’ of cerebral cortex in response to sacral stimulation. This has led to the concept of ‘neuromodulation’ as a more plausible pathophysiological explanation. This study aims to investigate the neurophysiological impact of Sacral Nerve Stimulation in faecal incontinence as assessed by alteration in focal cerebral activity in response to a visceral stimuli (rectal distention) using functional MRI.

The impact of sacral neuromodulation on gastric function in patients with faecal incontinence.

Mirbagheri N, Suen M, Nassar N, Marc A Gladman MA

Sacral NeuroModulation (SNM) is a well-accepted treatment modality for urinary and faecal incontinence. Emerging evidence suggests that it also has an impact on the upper gastrointestinal tract, as well as in the hindgut. This study aims to assessing the impact of SNM on gastric function by performing baseline and postoperative sonographic assessment of gastric antrum following administration of a liquid test meal to determine the effect of SNM on gastric emptying.

Variation in outcome following major abdominal colorectal surgery in NSW, Australia: results of 120,000 procedures.

Suen M, Le Y, Nassar N, Gladman MA.

Previous studies have demonstrated considerable variation in hospital mortality following inpatient surgery. However, there have been no previous studies to measure outcomes following surgery in Australia. The aim of this study is to investigate health outcomes and health service utilisation following colorectal resection in an Australian population using record-linked population health data. From 2000 to 2010, 120,000 colorectal operations were performed in NSW. Using detailed record-linked data from hospitals, the cancer registry, emergency departments and death registries it is possible to accurately measure and rank hospitals according to their risk-adjusted overall rate of death and complications.

Myocardial injury and necrosis in patients undergoing major abdominal surgery.

Walker A, Dempster AM, Hillis G, Gladman MA.

Post-operative complications have significant impact on patients’ recovery and up to 15% of patients undergoing inpatient surgery are at high risk of complications, such as organ dysfunction and mortality. Such complications can be attributed to dehydration, surgical complications and infection. Post-operative fluid prescription varies wildly amongst surgical specialties, and even individual medical practitioners. Variation in fluid prescription is associated with metabolic acidosis, acute kidney injury and respiratory failure. This study will provide preliminary data on the role of peri-operative fluid load in determining adverse postoperative outcomes, specifically: mortality, end organ damage including myocardial necrosis, impaired wound healing and infection and unplanned admission to the intensive care unit.

Development and validation of a proficiency-based training curriculum for laparoscopic colorectal surgery.

Sirimanna P, Aggarwal R, Gladman MA

The startling statistic that approximately 10% of all hospital admissions encounters a form of harm is only surpassed by the fact that half of all surgical adverse events are preventable. Proficiency-based training using virtual reality (VR) simulation has been shown to reduce errors and improve performance in the actual operating theatre. For junior surgical trainees, the laparoscopic appendicectomy (LA) is the principal index procedure, which itself is associated with a notable learning curve. The aim of this study is to develop a structured, stepwise VR simulation-based training curriculum to enhance technical skills acquisition for LA surgery using an evidence-based strategy on the LapMentor VR laparoscopic surgical simulator.
Geriatric Epidemiology

PERSONNEL:

GROUP LEADER: Professor Robert Cumming

CO-INVESTIGATORS: Professor David Handelsman, Professor Markus Seibel, Dr Helen Creasey (CERA), Dr Vasi Naganathan (CERA), Dr Louise Waite (CERA), Professor Philip Sambrook (Royal North Shore Hospital), Professor David Le Couteur (CERA), Professor Stephen Simpson (Charles Perkins Centre), Professor Hal Kendig (ANU)

STAFF AND STUDENTS: Kerrin Bleicher, Susan Darling, Janet Gilchrist, Danijela Gnjidic, Vasant Hirani, Ben Hsu, Janice Koh, Melisa Litchfield, Alex Porter, Jean Reid, Rosilene Waern

Role:

Epidemiology is the study of the frequency and causes of disease in groups of people (Greek demos, the people). The Geriatric Epidemiology group is responsible for the Concord Health and Ageing in Men Project (CHAMP), an epidemiological study of health and disease in older men. CHAMP provides a platform to study a wide range of health-related issues in older men. The investigators have skills in epidemiology, andrology, bone biology, dementia, geriatric medicine, rheumatology, biogerontology, nutrition and social science. CHAMP is a real bench to bedside to population study. The data is currently being used to study topics as diverse as the role of testosterone in the aetiology of dementia and identification of factors associated with social participation.

Objectives:

Despite the fact that men who reach the age of 70 still have much lower life expectancy than women of that age, very little research has been done on the health of older men. CHAMP was designed to fill this gap and is one of the world’s most comprehensive studies of the health of older men. Investigation of the role of reproductive hormones, including testosterone, in ageing in men is an important part of CHAMP.

Highlights:

Five year follow-up assessments commenced in mid-2010 and will be completed early in 2013. About 1000 men will be seen. A total of 33 CHAMP papers have been published or are currently in press. Papers in 2012 included one describing prostate specific antigen (PSA) levels in older men and another on predictors of nursing home admission.

Grants: 2011-2013

Annualised $

Research:

Men were invited to participate in CHAMP if they were aged 70 years or older and lived in the community in one of three Local Government Areas near Concord Hospital: Burwood, Canada Bay and Strathfield. Fifty four percent of the men we contacted agreed to participate (1705 men) and 80% (1367 men) returned for 2-year follow-up assessments.

The study involves questionnaires and a wide range of tests. Prior to attending the study clinic in the Medical Centre at Concord Hospital, subjects complete a detailed questionnaire. They then spend two to three hours at the study clinic, where a series of tests is done, including dual energy x-ray densitometry (DEXA) to measure bone, fat and lean mass; the Addenbrooke’s Cognitive Examination; tests of muscle strength, balance and gait; and uroflowmetry and measurement of post-void residual urines. The 5-year assessment includes a detailed diet history. Blood tests include assays for reproductive hormones, vitamin D, PTH, and markers of bone turnover, and measurement of Prostate Specific Antigen (PSA). DNA has been extracted.

Collaborations:

CHAMP investigators are working with Rafael de Cabo at the National Institutes of Health in the United States to investigate the role of sirtuin enzymes in frailty and longevity. Collaborative research on reproductive hormones and longevity is being conducted with Tom Travison from Boston University.
Northcott Neuroscience Laboratory

PERSONNEL:

GROUP LEADER: Professor Garth Nicholson

PRINCIPAL SCIENTISTS: A/Professor Marina Kennerson; Dr Ian Blair

STAFF AND STUDENTS: Obaid Albulym, Rabia Chaudhry, Shannon Chu, Alexander Drew, Michael Efendy, Melina Ellis, Adrienne Grant, Aditi Kidambi, Angela Laird, Carolyn Ly, Natalie Page, Gonzalo Perez-Siles, Jennifer Solski, Stephen Reddel, Sadaf Warraich, Maxinne Watchon, Kelly Williams, Claire Winnick, Shu Yang, Kristy Yuan

Role:

The Northcott Neuroscience Laboratory, headed by Professor Garth Nicholson is internationally renowned in the field of molecular genetics of human hereditary neuropathies and motor neurone disorders. The laboratory has continued to make important contributions to the discovery of gene mutations causing neurodegeneration of peripheral nerve and motor neurons. The identification and characterisation of the genes discovered in our families has uncovered new mechanisms causing degenerative diseases of nerves.

Objectives:

Our laboratory focuses on determining the underlying causes of neurodegenerative disease as a prerequisite to the development of diagnostic tools and therapy.

Highlights:

We have mapped and identification of a new gene for a new form of X-linked CMT (CMTX6). Our discovery of the PDK3 gene highlighted an important causative link between nerve degeneration and an essential bioenergy pathway required for the maintenance of peripheral nerves.

We have implemented a high throughput gene sequencing (whole exome sequencing) and bioinformatics program to screen over 400 index patients with peripheral neuropathy and motor neuron disease. This has led to work that will identify an additional 10 new CMT genes. Proving for the first time that alterations in the TDP-43 gene or changes in its expression, may be a common toxic cause of motor neurone disease.

The laboratory was represented at numerous national and international conferences. Professor Garth Nicholson gave the Mervyn Eadie Oration at the 2010 annual meeting of Australian and New Zealand Association of Neurology in Melbourne and the Plenary presentation at the 2013 5th European and North American Charcot Marie Tooth Neuropathy Consortium. A/Prof Marina Kennerson gave platform presentations for CMT gene discoveries at the World Muscle Congress 2012, the American Academy of Neurology in 2013 and the Gene Mapper Meetings in 2012 and 2013.

Grants: 2011-2013

Annualised $:

CMT Association of Australia- Kennerson, Nicholson “Using Modern Genomics to Identify Novel Genes for Charcot Marie Tooth Neuropathy” $12,500

MDA- Nicholson, Kennerson. “Determining the pathogenic effects of ATP7A Mutations in distal motor neuropathy.” $140,000

MDA- Nicholson, Kennerson, Polly, Chaudhry ‘Analysis of structural and regulatory elements of CMTX3 candidate genes’ $108,115

MNDRIA- Nicholson “Sporadic MND: the contribution of genes, biomarkers and metabolites” $57,670

MNDRIA- Yang. Bill Gole MND Postdoctoral Fellowship. $72,500

NHMRC- Blair. “Investigating the molecular basis of motor neuron disease.” $72,768

NHMRC- Blair, Nicholson, Hawke. “The role of mutant TDP-43 in ALS.” $143,205

NHMRC- Blair, Nicholson. “Investigating the genetic basis of ALS.” $165,632

Philip Bushell Foundation – Kennerson. “Discovering genes for X-linked Charcot-Marie-Tooth neuropathy using next generation sequencing technologies” $72,000

Snow Foundation- Nicholson. ‘Program aimed at curing MND: Screening drugs using an animal model’ $300,000

Prizes:
• PRSS Scholarships to: Alex Drew, Obaid Albulyum, Rabia Chaudhry 2012
• MNDRIA Bill Gole Fellowship to Dr Shu Yang 2010-2012
• European & North American CMT Consortium Travel Scholarships to: Dr Alex Drew, Rabia Chaudhry 2013.

Research:

Inherited Peripheral Neuropathies

M Kennerson, O Albulyum, R Chaudhry, S Chu, A Drew, M Efendy, M Ellis, A Grant, C Healy, A Kidambi, C Ly, G Perez-Siles

Charcot-Marie-Tooth (CMT) disease CMT is a degenerative disorder of the peripheral nerve affecting both sensory and motor nerves. Individuals who suffer from this disorder experience distal muscle weakness of legs and arms, foot deformities and sensory loss. The disorder is currently incurable. Motor and sensory neurons are unique cells with long axons (up to 1 metre) that require continuous maintenance from the cell body to the nerve endings. The breakdown of this maintenance leads to the ‘dying back’ of the nerve ends (axonal degeneration). The long term aim of our research is to identify the biological pathways leading to axonal degeneration with the ultimate goal of developing therapeutic treatments to prevent this process from occurring. Our strategy to identify these pathways is to locate the gene mutations in families with inherited peripheral nerve disease.

Gene identification for CMT disease has entered an exciting era in which availability of next generation sequencing (NGS) and genome technologies is expediting the gene discovery process. Using these technologies and bioinformatics pipelines developed in our laboratory we have identified the PDK3 gene for a new form X-linked dominant CMT on chromosome Xp11.1-p21.3. In collaboration with Dr Chris Klein (Mayo Clinic) a new gene for hereditary sensory neuropathy (HSN) with dementia has been identified. This discovery published in Nature Genetics showed that DNMT1 mutations cause this syndrome possibly implicating methylation pathways in CMT for the first time. In collaboration with Professor Kurt Fischbeck we identified the AIFM1 gene as a cause of CMTX4.
Our work continues in the endeavour to understand how mutations in the copper transport gene ATP7A cause a form of distal motor neuropathy on chromosome X. The ATP7A protein is important for maintaining the balance of copper in our bodies. We are developing an animal model to further understand how incorrect movement of the ATP7A protein can lead to death of the motor nerves.

**Zebrafish models of Machado Joseph Disease**

A Laird, K Yuan, M Watchon, G Nicholson

Machado Joseph Disease (MJD, or spinocerebellar ataxia-3) is a fatal neurodegenerative disease that causes a lack of coordination and paralysis, leading to confinement to a wheelchair and high dependence care. MJD affects people of all ages and is particularly common in Indigenous communities of Arnhem Land in the Northern Territory. We have developed the first zebrafish model of MJD to allow us to study the causes of the disease and test potential drug treatments. Zebrafish, are well suited for use in these studies because they are transparent during development, allowing observation of disease neuroanatomy and pathology in the living animal and they can be treated with potential drugs through simple addition to the water they live in. Our zebrafish carry either the healthy or MJD-causing version of the human ataxin-3 protein. Using an automated movement tracking system we are able to track the swimming movement of our fish over time and also compare the effect of drug treatments on this movement. This research is supported by the MJD Foundation.

**Motor Neuron Disease**

I Blair, S Yang, C Cecere, K Williams, J Solski, A Drew, S Warraich, G Nicholson

The motor neurons are nerves that extend from the brain to the muscles and provide the stimulus through which we move, breathe, eat and drink. The motor neuron diseases (MND) are a group of related neurodegenerative diseases that cause the progressive death of motor neurons. These diseases range from slowly progressive, non-fatal forms to the rapidly progressive
fatal disorder amyotrophic lateral sclerosis (ALS). ALS typically leads to death within 3 to 5 years of first symptoms. ALS causes progressive paralysis and the cause of death is usually respiratory failure.

There are no specific diagnostic tests for MND and treatment is extremely limited. The only known causes of MND are mutations in particular genes that lead to death of motor neurons. The known MND genes only account for about 2% of all cases. We are working to understand the biological basis of MND through identification and analysis of defective genes that cause the death of motor neurons. This understanding is a prerequisite to effective diagnosis, treatment and prevention of MND.

Recent highlights of our research include demonstrating that alterations in genes involved in RNA metabolism may be a common toxic cause of motor neuron disease. Our work identified mutations in two genes that cause familial motor neuron disease. These breakthroughs, in collaboration with other Australian and international MND research groups, have opened new chapters in MND research.

Motor Neuron Disease Zebrafish Models

I Whiteman, C Winnick, D Goh, A Laird, J Solski, I Blair, N Cole, G Nicholson

Neuropathological hallmarks of the disease amyotrophic lateral sclerosis (ALS) include aggregation of the proteins Fused in Sarcoma (FUS) and TDP-43, two related, predominantly nuclear proteins. The discovery of ALS causing mutations in the genes encoding these proteins, FUS and TARDBP respectively, by members of our team and others, has provided compelling evidence for an important role of these proteins in the pathogenesis of ALS.

Our team has created in vivo models of ALS in zebrafish, an animal model that is becoming widely regarded for its advantages in both developmental biology and human disease research. By generating transgenic zebrafish lines expressing specific human FUS or TARDBP mutations identified in ALS families, we are able to investigate in vivo the role of mutant FUS and TDP-43 in the pathogenesis of ALS.

Preliminary studies suggest that our transgenic zebrafish recapitulate some of the ‘proteinopathic’ features and motor neuron defects observed in human ALS, including mislocalization and aggregation of FUS, formation of stress granules and aberrant motor neuron branching. We now aim to investigate the impact of these abnormalities on motor control and behaviour. Further, we will use these transgenic lines to test drug therapies. This research is funded by the Snow Foundation.
Parkinson’s Disease

N. Page, S. Chu and G. Nicholson

Parkinson disease (PD) affects around 80,000 Australians. Mutations in seven genes are known to be involved in the development of PD. These gene mutations are likely to account for at least 17% of disease in early-onset disease and for those with family history of PD. Genetic testing in these cases is an important aspect of patient care, useful for reducing diagnostic uncertainty, clarifying treatment options, family planning, and providing information on prognosis. However, due to high costs and technical difficulties, no screening procedure has been developed to identify all known variants in PD genes. Our aim is to develop this genetic diagnostic test using high resolution melt (HRM) analysis. HRM is highly cost-effective, and can detect both known and novel mutations. We aim to make this test available to clinicians as a genetic diagnostic test for PD, leading to an Australia wide service that will better aid physicians in disease diagnosis and prognosis. This project is supported through donations from Geoff and Clare Loudon.

Developments:

We are building on a longstanding track record in gene discovery in neurodegenerative disease by developing new animal models of disease and fostering international collaborations with world renowned neuroscientists. We are using the latest techniques (exome next generation sequencing) to find new mutations causing disease and developing new models of disease processes to see the effects of the disease in living animals (Zebra Fish). We are developing a conditional knock in mouse model for distal motor neuropathy that harbours the human ATP7A mutation with juvenile onset.

Collaborations:

We have continued to build productive and ongoing collaborations with renowned researchers in motor neuron disease that include Professor Guy Rouleau (University of Montreal) and Professor Robert Brown (University of Massachusetts), A/Prof Aaron Gitter (University of Pennsylvania), Dr Julie Atkin (LaTrobe University), Dr Robyn Wallace (Queensland Brain Institute) Dr Anna King (Menzies Research Institute Tasmania). Strong collaborations continue with our peripheral neuropathy colleagues at University of Iowa (Mike Shy), University of Antwerpen (Vincent Timmerman; Peter De Jonghe, Albena Jordanova); Baylor Medical College (Jim Lupski); University of Miami (Stephan Zuchner); National Institute of Health NIH/NINDS (Kenneth Fischbeck); University of Malaya (Nortina Shahrizaila, Azlina Ahmad Annaur); Murdoch Childrens Research Institute (Eppie Yiu, Monique Ryan, Kate Pope); University of Sydney (Bill Phillips). Through our work with the ATP7A gene we have collaborations with Professor Julian Mercer (Deakin University, Melbourne). Our work on the PDK3 gene was done in collaboration with Professor David Chuang (University of Texas, Southwestern Medical Center, Dallas USA).
**Vascular Biology**

**PERSONNEL:**

**GROUP LEADER:** Professor Ben Freedman and Prof Len Kritharides  
**SENIOR CLINICAL SCIENTIST:** Prof David Brieger, A/Prof Harry Lowe, Dr Jenny Curnow  
**SENIOR SCIENTIST:** Dr Gabrielle Pennings, Dr Caroline Reddel  
**STAFF, STUDENTS AND ASSOCIATES:** Dr Wei Zhao, Dr Vincent Chow, Dr Andy Yong, Dr James Edelman, Dr Clement Wong, Dr Tommy Chung, Dr Austin Ng, Dr Julie Redfern, Dr Julie Redfern, Dr Lis Neubeck, Dr Mohammed Aziz Moharram, Nicole Lowres, Vineta Sahai, Roshanak Aran, Marzy Nikanami, Bernadette Aliprandi-Costa, Aileen Siney, Nicole Lowres, Dr Chris Naoum, Dr Richard Alcock, Dr Jerrett Lau, Justine Siegwald, Kevin Phan and Nathalie Rasko.

**Role:**

Cardiovascular disease relates to disease of the heart and blood vessels. Our group undertakes clinical and translational cardiovascular research undertaken by or in collaboration with the department of Cardiology, Concord Hospital.

**Objectives:**

Areas of interest include:

- Inflammation in cardiovascular disease, particularly platelet mediated leukocyte activation, and inflammatory mediation of endothelial dysfunction.
- Novel intravascular (within arteries) imaging using Optical Coherence Tomography (OCT)
- Novel measures of blood clotting
- Measuring hidden weakness of heart muscle using ultrasound (echocardiography)
- Preventing future heart attacks using alternatives to cardiac rehabilitation Choice of Health Options In Preventing Cardiac Events (CHOICE Study)
- Screening for atrial fibrillation using novel technologies (SEARCH-AF), and reducing risk factors and anxiety in patients with atrial fibrillation (CHOICE-AF)

**Highlights:**

Ben Rayner and Vicky Benson graduated with PhDs from the University of Sydney; Dr James Edelman was awarded a PhD from the University of Sydney. Lis Neubeck was awarded a PhD from the University of Sydney. Nicole Lowres won the Affiliate prize of the Cardiac Society of ANZ, Dr Caroline Reddel and Dr Gabrielle Pennings were awarded travel grants from the ASTH to attend the HAA in Melbourne in 2012. Dr Reddel has also received an Early Career Researcher (ECR) travel grant from USyd to attend the 24th Congress XXIV of the ISTH in Amsterdam, Netherlands in 2013. Kevin Phan and Nathalie Rasko completed their Summer Research Scholarship Programs with us in 2012. Kevin Phan and Nathalie Rasko completed their Summer Research Scholarship Programs with us in 2012. Kevin was awarded the Rob Clarke Award from the Physiological Society to attend the IUPS in Birmingham, UK in 2013.
Grants: 2011-2013

Annualised $

Bayer HealthCare- Freedman. “SEARCH-AF Stoke prevention study” $35,000

Bristol-Myers Squibb - Freedman, Neubeck, Lowres, Bennet, McLachlan, Krass, Redfern, Briffa, Bauman.
“Search-AF Stoke prevention study.” $88,200


Heart Foundation – Yong. “Heart Foundation Travel Grants.” $2,000

Heart Foundation – Lowres. “Screening Education and Recognition in Community Pharmacies of Atrial Fibrillation (SEARCH-AF) for Stroke Prevention.” $26,903

NHMRC- Yong. “Studying Coronary Physiology within Human Coronary Arteries using Computational Fluid Dynamics.” $85,455

NHMRC- Neubeck. “Improving health for patients with atrial fibrillation.” $36,862

USyd- Witting, Freedman, Geczy. “Approaches to inhibit SAA-induced endothelial dysfunction and atherosclerosis.” $65,000

Research:

Inflammation- Platelet and Leukocyte Activation in CAD

We have been studying the activation of white blood cells and platelets in people with coronary disease by taking blood samples from the circulation and from the blood vessels supplying the heart itself.

Dr Gabrielle Pennings has recently been investigating the effect of platelet mediated leukocyte activation in vitro with a specific interest in the effect of shear and the factors regulating CD147. Dr James Edelman has completed his PhD investigating the profiles of inflammation and coagulation after cardiac surgery. He has found both similarities and differences in the inflammatory response to conventional on-pump surgery and to off-pump surgery and sustained abnormalities of coagulation lasting weeks after cardiac surgery.

Inflammatory mediation of endothelial dysfunction

Serum Amyloid A (SAA) is an inflammation marker like CRP, and rises steeply during any inflammatory response. High levels of SAA predict cardiac events. Uncertainty remains as to whether SAA is a marker of risk or actually produces vascular damage. Work at the Anzac in prior years showed that SAA was highly pro-thrombotic and induced monocytes and macrophages to produce tissue factor, the activator of all clotting. SAA was also released from the coronary circulation in patients with coronary artery disease. We have now shown that SAA also induces endothelial dysfunction, an early event and continuing aggravator in the development of atherosclerosis.

Novel Measures of Haemostatic Function in cardiovascular and other diseases

One of our interests is to study new ways of measuring haemostatic (blood clotting) function in patients with coronary disease, and in patients with an increased risk of blood clots such as those with certain kinds of cancer. New tests for platelet function and clotting established in our laboratory include the Overall Haemostatic Potential (OHP) assay, Calibrated Automated Thrombogram (CAT), platelet microvesicle formation, and platelet aggregation Detailed studies are being undertaken of patients having procedures such as coronary angiograms and in patients with multiple myeloma in collaboration with the Peter MacCallum Cancer Centre in Melbourne. These studies are being led by Dr Jennifer Curnow and Dr Reddel, in collaboration with Professors Brieger and Kritharides. The same assays are being successfully applied by Dr Reddel to animal models including tumour-bearing mice and mice subjected to surgical trauma.
Novel Intravascular Imaging Using Optical Coherence Tomography (OCT)

Our ongoing study of the novel technique of Optical Coherence Tomography (OCT) to image coronary arteries in vivo and in ex vivo experiments has led Dr Lowe’s students to investigate ways of “flattening” the OCT images using computer analysis. This allows easy appreciation of the state of arteries, stent deployment and heterogeneity within stented segments.

Cardiac dysfunction after pulmonary embolism and after clozapine

Dr Chow’s long term follow up studies of patients with clots in the lungs (pulmonary embolism) have revealed a significant prevalence of pulmonary hypertension, weakness of the right side of the heart and restricted exercise capacity years after the index event. Our current guidelines for long term review of such patients may need be revised in view of his work undertaken under supervision of Professors Kritharides and Matthew Peters (and Drs Ng and Chung. In conjunction with colleagues from Croydon and Burwood psychiatric units, Dr Chow has investigated the incidence of cardiac dysfunction in patients taking clozapine and has found that mild dysfunction is very commonly seen in association with clozapine use.

Choice of Health Options In Preventing Cardiac Events (CHOICE Study)

Patients who survive a heart attack have a high risk of death or recurrent heart attack. Although this can be reduced by effective programs of secondary prevention like cardiac rehabilitation, many survivors do not access formal cardiac rehabilitation and have inadequately controlled risk factor levels. We developed a simple program called CHOICE, which allows patients to choose which risk factor(s) they will lower and how they will lower it. This very effective program has been extended in current studies examining whether a brief intervention is sufficient to produce long term changes over 2 years, or whether a longer program will be better in maintaining results. We enrolled almost 400 patients who survived a coronary event but elected not to participate in traditional cardiac rehabilitation and we have completed baseline, one and two year follow ups. This study was extended to include patients who are members of a health insurance fund as these funders are likely to provide resources for similar programs for their members. Following these patients will tell us if a brief intervention will have long lasting effects on multiple risk factors. This project is being led by Professor Freedman, Dr Redfern and Dr Neubeck.

Atrial Fibrillation studies – SEARCH-AF and CHOICE-AF

Atrial Fibrillation (AF) is the commonest cardiac arrhythmia, with a high risk of stroke and premature death, which can be largely prevented by anticoagulation. Many patients with AF are asymptomatic and AF is not discovered until they have a stroke. We have initiated a screening programme called SEARCH-AF to screen for AF in community pharmacies, and the study was completed in early 2013, showing that a novel iPhone application can record an ECG in and detect many cases of unknown AF. Another study modelled on the CHOICE program and adapted for patients with AF has been piloted to try to improve patient knowledge reduce anxiety about the condition, and improve compliance with medication.

Collaborators:

National:
Professor Carolyn Geczy (UNSW)
Professor Kerry-Anne Rye (UNSW)
Professor M Behnia (USyd)
Associate Professor Michael Vallely (USyd)
Associate Professor Robert Andrews (Monash)
Dr Paul Witting (USyd)
Dr Elizabeth Gardiner (Monash)
Dr Graham Robertson (Garvan Institute)

International:
Dr Carlos Martinez
Staff & Students 2011-2013

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Prof David Le Couteur MB BS, PhD, FRACP
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Prof Garth Nicholson MB BS, PhD
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Dr David Mahns PhD
A/Prof Graham Robertson PhD
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Dr Anahid Ehteda PhD
Dr Phillip Fromm PhD
Mark Jimenez BSc (Hons)
Dr Maaike Kockx PhD
Dr Angela Laird PhD
Dr Lam Ly MD (Vietnam), PhD
Dr Aiqing Li MBBS (China) MD (China), PhD
Dr Terry Nguyen-Khuong PhD
Dr Gonzalo Perez PhD
Dr Alex Phoon MB BS
Dr Kifah Shahin PhD
Dr Ulla Simanianen PhD
Dr Fiona Stanaway PhD
Jenny Spaliviero MSc
Dr Pablo Silveira PhD
Dr Marion Stoll PhD
Dr Matthew Triani PhD
Dr Niruparma Verma PhD
Dr Kirsty Walters PhD
Dr Yiwei Wang Grad Dip Pharm. Sciences PhD
Dr Allesandra Warren MSc PhD
Dr Shu Yang PhD
Clinical Research Nurses
Amanda Idan RN, BSc (Hons)
Glenda Fraser RN
Jing Prideaux RN
Eileen Siney RN, Registered Midwife
Leo Turner RN

Research Assistants
Chantall Cerna BSc
Jane Chapman Path Tech Cert
Shu Oi Chow BSc
Dr Zehra Elgundi PhD
Melina Ellis BSc(Hons), Grad Dip Ed Sc
Colette Fong-Yee BSc, MSc (Hon)
Jenny He BSc(Hons)
Julian Kelly BSc (Hons)
Aditi Kidambi BSc (Hons)
Fiona Kupresanin BBiomedSc, MDiet
Nicole Lowres BSc (Physio)
Carolyn Ly BMedSc (Hons)
Linda Middleton BSc(Hons)
Marie Merheb BSc
Leticia Muusers BSc
Diana Nawara BSc (Hons)
Dr Natalie Page PhD
Dr Gabrielle Pennings PhD
Alexandra Porter DAA
Dr Caroline Reddel PhD
Jennifer Solski B Medical Sc (Hons)
Shihani Stoner MSc
Danielle Upton BSc
Anne Vanniasinghe BSc
Claire Winnick BSc(Hons)
Lucy Yang MD
Dr Wei Zhao MD (China), PhD
Dr Yu Zheng BMed, MMed, PhD

Technical Support
John Allen BSc PhD
Fay Bacha BSc
Frank Bathur BSc, MHA
Annette Berryman
Donna Bonnici
Sabina Bucik Animal Attendant Cert 3
Shannon Chu MSc
Guy Dernee
Irene Di Pierro Dip Sc
Adrienne Grant BA (USA)
Clare Healy BSc
Patty Kapeleris Business Studies
Alev Kavakci
Melisa Litchfield BAppSc, MPH
Zamil Mattar BSc
Tyler McClelland
Dr Lyn Schedlick BSc PhD
Ljubica Vrga BSc (Hons)
Matilda Web bey Animal Attendant Cert 3
Joshua Webbey
Mari Wright
Jennifer Solski B Medical Sc (Hons)

Overseas Visiting Fellows/Students
Zhao Bin
Dr Rowan Hardy
Pekka Keski-Rahkonen
Claudia Huelso
Tazio Maleitzke
Susanne Schillo
Dr Connie Spies
Edgar Wiebe
Peng Zhang
**Graduate Students**
Obaid Albulym MSc
Dr Christian Bryant  MBBS, FRACP, FRCPA
Rabia Chaudhry BSc (Hons)
Peter Choi BSc (Hons)
Dr James Edelman  BSc (Hons) MBBS (Hons)
Dr Robin Gasiorowski  MA, MBBS, FRACP, FRCPA
Ellen Gao BSc
Rasmani Hazra   BSc
Dr Holger Henneicke MD
Gurmeet Kaur MSc
Mashani Mohamad MSc
Kheng-Seone Ng BSc
Jennifer O’Reilly BA(Mus) BSc (Hons)
Shajjia Razi BSc, MSc
Samantha Solon BSc
Ryland Taylor  BSc (Hons)
Trupti Trivedi MSc
Jinwen Tu MSc
Danielle Upton BSc
Sadaf Warraich BMedSc (Hons)
Kelly Williams BSc (Hons)
Dr Clement Wong  BSc (Med) MBBS (Hons) MMedSc (Clin. Epid.)
Dr Andy Yong MBBS (Hons I), FRACP
Dr Frank Zhang MBBS(Surg)

**Masters Students**
Ann Aziz BSc
Shannon Chu BMedSc

**Summer Scholars**

**2011/12**
Rushad N Bachana
Carina Blaker
Sai Sivananda Chaganti
Harry Crane
Sarah Johnston
Sarah Kim
Desmond Ka Kit Li
Ali Phillip Mourad
Lakshmi Chitra Varanasi
Bianca Varney
Xiaojie Wang
Annie Wen
Laura Myfanwy White

**2012/13**
Doug Drak
Jacky Hanh
Sara Kim
Robert Lu
Eleonora Paulini
Kevin Phan
Roshini Ramkuma
Nathalie Rasko
Katherine Skulte
Leon Smith
Naomi Wu

**Honours Students 2012/13**
Namita Deo BSc
Michael Efundy BSc
Nadia Jung BSc
Sarah Kim  BSc
Tegan Ryan BSc
Win Myat Theingi BSc
Administrative Staff

Director
Professor David Handelsman MB BS, PhD, FRACP

Director, Laboratory Animal Services (MPU), Concord Campus.
Mamdouh Khalil BSc, Ass Dip Animal Technology

Business Manager
Julie Taranto JP, BSc

Finance Manager
Annet Doss, Dip Acc, Grad Cert in Acct & Fin Mgmt

Accounts Clerks
Candice Chang
Amy Ng

Information Systems Manager
Justin Crosbie  BSc Information Technology

Human Resources Manager(s)
Rachelle Innes Dip Bus (HR)

Receptionist/Administration
Tracey Dent
Grants & Contracts 2011-2013

The total annualised 2011-2013 grant income was $11,449,615.

All grants are included with the individual group reports.

Publications

Aggarwal S, Maitz P and Kennedy P


Ahn CS and Maitz PK


Akram OM, Bursili C, Desai R, Heather AK, Kazlauskas R, Handelsman DJ and Lambert G


Alcock RF, Yong AS, Ng AC, Chow V, Cheruvu C, Aliprandi-Costa B, Lowe HC, Kritharides L and Brierie DB


The design and rationale of the Australian Cooperative National Registry of Acute Coronary Care—Guideline Adherence and clinical events (Concordance) Heart Lung Circ. S143-9506(12):0144-2, 2013. PMID:23415708

Allan CM


Allan CM and Handelsman DJ


Erectile dysfunction severity as a risk marker for cardiovascular disease hospitalisation and all-cause mortality: prospective cohort study.” PLOS Medicine 10(1:e1001372, 2013. PMID:3598249


The 6-PACK programme to decrease fall-related injuries in acute hospitals: protocol for a cluster randomised controlled trial. Inj Prev 17 (4): e5, 2011. PMID:21653850

Barroso O, Handelsman DJ, Strasburger C and Thewis M


Baur JA, Ungvari Z, Minor RK, Le Couteur DG and de Cabo R


Bax DV, Wang Y, Li Z, Maitz PK, McKenzie DR, Bilek MM and Weiss AS

Binding of the cell adhesive protein tropoelastin to PTFE through plasma immersion ion implantation treatment. Biomaterials 32 (22): 5100-5111, 2011. PMID:21527206

Belavy DL, Seibel MJ, Roth HJ, Armbrrecht G, Rittweger J and Felsenberg D


Bell JS, Le Couteur DG, Mclachlan AJ, Chen TF, Moles RJ, Basger BJJ and Hilmn SN


Hepatocyte entry leads to degradation of autoreactive CD8 T cells. Proc Natl Acad Sci U S A 108 (40): 16735-16740, 2011. PMID:21933957

Benson VL, McMahon AC, Khachigian LM and Lowe HC

Acute local elevation in monocyte chemoattractant protein-1 (MCP-1), distal to the culprit lesion in acute ST elevation myocardial infarction. Int J Cardiol. 2013. PMID:23618428

Birnirnize V, Meinhardt UJ, Uplemby MA, Handelsman DJ and Ho KK

Interaction between testosterone and growth hormone on whole-body protein anabolism occurs in the liver. J Clin Endocrinol Metab 96 (4): 1060-1067, 2011. PMID:21239519


Briffa TG, Neubeck L, Clark AM, Freedman SB and Redfern J


Brock K, Clemson L, Cant R, Ke L, Cumming RG, Kendi H and Mathews W


Vitamin D status is associated with sun exposure, vitamin D and calcium intake, acculturaton and attitudes in immigrant East Asian women living in Sydney. J Steroid Biochem Mol Biol 2012. PMID:22362263

Brown A and Kritharides L


Buttgereit F, Burmester GR, Straub RH, Seibel MJ and Zhou H
Proteomic comparison of colorectal tumours and non-neoplastic mucosa from paired patient samples using iTRAQ mass spectrometry. Mol Biosyst 7 (11): 2997-3005, 2011. PMID:21808808

Javadzadegan A, Yong AS, Chang M, Ng AC, Yaninikas J, Ng MK, Behnia M and Krittahrides L

Jessup W.

Kacoveska M, Downes MR, Sharma R, Evans RM, Clarke SJ, Liddle C and Robertson GR

Karunakan D, Kockx M, Owen DM, Burnett JR, Jessup W and Krittahrides L
Protein kinase C controls vesicular transport and secretion of apolipoprotein E from primary human macrophages. J Biol Chem. 2013. PMID:23388640


Le Couteur DG, Cogger VC, Dobbs B and Fraser R

Le Couteur DG and Handelsman DJ

Le Couteur DG, McLachlan AJ and de Cabo R

Le Couteur DG, McLachlan AJ, Quinn RJ, Simpson SJD and de Cabo R


Le Couteur DG and Simpson SJD

Lee A, Chick JM, Kolarich D, Haynes PA, Robertson GR, Tsui M, Jankova L, Clarke SJ, Packer NH and Baker MS
Liberation of cholesterol from the nuclear envelope to the cytosol. Mol Biol Cell Proteomics. 2012; PMID:20167946

Li Z, Overend C, Maiz P and Kennedy P


Lloyd B, Matthews S, Livingston M, Jayasekara H and Smith K

Lowres N, Freedman SB, Redfern J, McLachlan A, Krass I, Bennett A, Briffa T, Bauman A and Neubeck L
Screening Education And Recognition in Community Pharmacies of Atrial Fibrillation to prevent stroke in an ambulant population aged ≥65 years (SEARCH-AF stroke prevention study): a cross-sectional study protocol. Trials 12 (2): 2012. PMID:22734120

Lowres N, Neubeck L, Freedman SB, Briffa T, Bauman A and Redfern J

Lowres N, Neubeck L, Freedman SB, Briffa T, Bauman A and Redfern J

Lusk MJ, Konecny P, Nairn ZW, Garden FL, Cuming RG and Rawlinson WD
Mycoplasma genitalium is associated with cervicitis and HIV infection in an urban Australian STI clinic population. Sex Transm Infect 87 (7): 107-109, 2011. PMID:21071566

Magee CA, Holliday EG, Attila J, Krittahrides L, Banks E
Investigation of the relationship between sleep duration, all-cause mortality and pre-existing disease. Sleep Med. doi:10.1016/j.sleep.2012.05.010. 2013. PMID:23517587

Magee CA, Krittahrides L, Attila J, McElduff P and Banks E

Makovey J, Macara M, Chen JS, Hayward CS, March L, Seibel MJ and Sambrook PA
Serum uric acid plays a protective role for bone loss in peri- and postmenopausal women: a longitudinal study. Bone 52 (1): 400-408, 2013. PMID:23113134

Mutational origin of Machado-Joseph disease in the...
Anterior prostate epithelial AR inactivation modifies Androgen resistance in female mice increases muscle wasting

How fast does the Grim Reaper walk? Receiver operating characteristics curve analysis in healthy men aged 60 and over. BMJ. 343: d6779, 2011. PMID:22174324

Stanaway FF, Kendig HL, Blyth FM, Cumming RG, Naganathan V and Walte LM


The study design and methodology for the ARCHER study—adolescent rural cohort study of hormones, health, education, environments and relationships. BMC Pediatr. 12:143, 2012. PMID:22950846


The Relationship between fenestration, sieves plates and rafts in liver sinusoidal endothelial cells. PLoS One 7 (9): e48134. 2012. PMID:22929409

Sy RW, Chawanapipat C, Richmond DR and Kritidis L


Sy RW and Freedman SB


Tan AG, Mitchell P, Rrotchchina E, Hong T, Cumming RG, and Walte LM


Traini M, Jessup W


Travison TG, Nguyen AH, Naganathan V, Stanaway FF, Blyth FM, Cumming RG, Le Couteur DG, Samborn PN and Handelsman DJ

Changes in reproductive hormone concentrations predict the prevalence and progression of the frailty syndrome in older men: the concord health and ageing in project. J Clin Endocrinol Metab 98 (8): 2464-2474, 2011. PMID:21767041

Tsoi M and Robertson G


Research Institute

ANZAC

58


Tailoring the porosity and pore size of electrop spun synthetic human elastin scaffolds for dermal tissue engineering. Biomaterials 32 (28): 6729-6736, 2011. PMID:21883438


Does increased sunlight exposure work as a strategy to improve vitamin D status in the elderly: a cluster randomised controlled trial. Osteoporos Int 23 (2): 615-624, 2012. PMID:21369788

Sambrook PN, Cameron ID, Chen JS, March LM, Simpson JM, Cumming RG and Seibel MJ

Dna2 bifunctional proteins are associated with reduced mortality in frail older people: a prospective five-year study. Osteoporos Int 22 (9): 2551-2556, 2011. PMID:20959983


Serum testosterone, dihydrotestosterone and estradiol concentrations in long-term frozen human urine samples. Drug Test Anal. 2013. PMID:23606665

Solski JA, Williams KL, Yang S, Nicholson GA and Blair IP


Stanaway FF, Blyth FM, Cumming RG, Naganathan V, Handelsman DJ, Waite LM, Samborn PN, Greasy HM, Seibel MJ and Le Couteur DG


Ethnicity and falls in older men: the concord health and ageing in project. J Clin Endocrinol Metab 98 (8): 2464-2474, 2011. PMID:21767041

Tsoi M and Robertson G


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58

Walters KA, Allan CM and Handelsman DJ


Walters KA, Middleton LJ, Joseph SR, Hazra R, Jimenez M, Simanainen U, Allan CM and Handelsman DJ


Warren A, Benseler V, Cogger VC, Bertolino P and Le Couteur DG


Warren A, Cogger VC, Fraser R, Delevé LD, McCuskey RS and Le Couteur DG


Wilders SM, Le Couteur DG and Simpson SJ

Diet mediates the relationship between longevity and reproduction in mammals. Age (Dordr) 2012. PMID:22237559


Williams KL, Solski JA, Nicholson GA and Blair IP


Wilson NM, Hilmer SN, March LM, Cameron ID, Lord SR, Selibet MJ, Mason RS, Chen JS, Cumming RG and Sambrook PN


Wilting PK, Song C, Hsu K, Hua S, Parry SN, Aran R, Geac C and Freedman SB

The acute-phase protein serum amyloid A induces endothelial dysfunction that is inhibited by high-density lipoprotein. Free Radic Biol Med 51 (7): 1390-1398, 2011. PMID:21784147

Wong BX, Kyle RA, Myhill PC, Croft KD, Quinn CM, Jessup W, Yeap BB


Mutation analysis and immunopathological studies of PFN1 in familial and sporadic amyotrophic lateral sclerosis. Neurobiol Aging 2013. PMID:23635659

Yeap BB, Alfonso H, Chubb SA, Handelsman DJ, Hankey GJ, Norman PE and Flicker L


Yiu EM, Gheevasinga N, Nicholson GA, Fagan ER, Ryan MM and Ouvrier RA


Yong AS, Layland J, Fearon WF, Ho M, Shah MG, Daniels D, Whitburn R, Maciasac A, Kritharides L, Wilson A and Ng MK

Calculation of the index of microcirculatory resistance without coronary wedge pressure; measurement in the presence of epicardial stenosis. JACC Cardiovasc Interv 6 (1): 53-58, 2013. PMID:23347881

Yong AS, Ng AC, Briege D, Lowe HC, Ng MK and Kritharides L

Three-dimensional and two-dimensional quantitative coronary angiography, and their prediction of reduced fractional flow reserve. Eur Heart J 32 (3): 345-353, 2011. PMID:20705695

Yong AS, Pennings GJ, Chang M, Hamzah A, Chung T, Qi M, Briege D, Behnia M, Krilis SA, Ng MK, Lowe HC and Kritharides L


Zheng Y, Zhou H, Ooi LL, Snir AD, Dunstan CR and Seibel MJ

Vitamin D deficiency promotes prostate cancer growth in bone. Prostate 71 (9): 1012-1021, 2011. PMID:21541977
Board

Prof Diana Horvath AO (Chair)

Diana retired with over 40 years broad experience in the health care industry. Her appointments & awards included: heading the NSW Community Health Program; Medical Director & then General Superintendent at RPAH; 20 years on the council of the Australian Hospital Asscn (now Aust Healthcare Assn) & held the position of National President; an International Fellow of King’s Fund College in London; Director of Health Services at Eastern Sydney Health; the first woman to chair the NH&MRC; Commissioner with the Health Insurance Commission; appointed a governor of Ascham School in Darling Point; was for 14 years CEO of Central Sydney Health (later Sydney South West); established the Clinical Streams of Care model in Australia for which she was awarded the International Hospital Assocn award for Managerial Innovation; was a member of the Trade Policy Advisory Council of several Federal ministers; as CEO set up the Australian Commission for Safety & Quality in Health Care.

She was made an Officer in the Order of Australia (1995) for her contribution to health & health services management; awarded the Sid Sax Medal; the Centenary of Federation medal, & made an Adjunct Professor at University of Sydney.

Professor Robert Lusby (Deputy Chair)

Professor Robert Lusby is the head of the University of Sydney Clinical School at Concord Hospital and an Associate Dean of the Faculty of Medicine. He is a Vascular Surgeon and heads the vascular surgical department of Concord Hospital. He has been president of the International Cardiovascular Society Australian and New Zealand Society. Professor Lusby has served with the Australian Army Medical Corp with deployments to Rwanda with the United Nations, Bougainville and East Timor with Interfet. Colonel Lusby has been Consultant Surgeon to the Australian Army and the Australian defence Force. Professor Lusby was a Board member of Macquarie and Northern Area Health Services, a councillor of the NSW branch of the Australian Medical Association and chairman of its Ethics committee. He was a foundation member of the Post Graduate Medical Council.

Professor David Handelsman

Professor Handelsman has been Director of the ANZAC Research Institute since its inception in 1998. He is an international expert in Andrology, the study of male reproductive health, medicine and biology. While studying for his PhD, he established the first clinical Andrology centre in Australia that has eventually become the first Hospital Andrology department in the country. He has served as adviser to the WHO Human Reproduction Programme, Secretary of the International Society of Andrology and President of the Endocrine Society of Australia. He was awarded the Susman Prize from the Royal Australasian College of Physicians in 1994 and the inaugural AMA Men’s Health Award in 2003. He was promoted to a Personal Chair at the University of Sydney in 1996 to become the first Professor in Andrology in Australia.
Dr Teresa Anderson

Dr Teresa Anderson has had over 30 years experience in the public health system as a clinician and manager. Extensive experience in the management of health services including General Manager, Liverpool Hospital, Director, Clinical Operations, Former Sydney South West Area Health Service and currently Chief Executive, Sydney Local Health District. Board Memberships include: Ingham Health Research Institute; Centenary Institute; and Centre for Primary Health Care and Equity (CPHC&E).

Eve Bosak

Eve’s professional career in accounting, finance and business strategy includes experience in the public, private, academic and global development sectors. Her current and past international experience includes membership of the International Committee on Agricultural Research in Dry Areas (ICARDA) in Syria; CFO, South Asia region, World Bank Washington DC; Director, Cool Savings Ltd Chicago; and CEO, BII Lend Lease (Financial Services JV, Indonesia). Australian experience includes Chair, Governing Council, Southern NSW Local Health Network; Director and CEO, Governance Asia Pty Ltd; member, Audit and Risk Committee, NSW Department of Community Services; member, Departmental Audit Committee, Department of Environment, Water, Sustainability, Population and Communities; Chair, International Committee of the Board, CPA Australia; and Chair, NSW War Widows’ Guild. She is a member of the Institute of Chartered Accountants in Australia, a Fellow of CPA Australia, and an Associate of the Institute of Chartered Secretaries and Administrators in Australia.

Professor Bruce Robinson AM

Professor Robinson was appointed Dean, Faculty of Medicine, University of Sydney, in May 2007. He is an Endocrinologist and Head of the Cancer Genetic Laboratory in the Kolling Institute. While undertaking studies for a Masters of Science degree he undertook molecular research work at the Brigham and Women’s Hospital and the Children’s Hospital, Harvard Medical School from 1986-1989 and was awarded a Doctorate of Medicine from the University of Sydney in 1990. He has developed and led the Cancer Genetics’ Laboratory since 1990 and has supervised over 20 doctoral and masters students working on the genetic basis for tumour formation and gene therapy. In 2003 Professor Robinson was warded the Daiichi Prize by the Asia and Oceania Thyroid Association for this work on the pathogenesis of thyroid cancer.

Professor Robinson has a strong interest in furthering relations between Australia and Asia and he is the Founding Chairman of Hoc Mai, the Australia Vietnam Medical Foundation, which sponsors and supports medical nursing, allied health and scientific exchanges between Australia and Vietnam. He is a Fellow of the Australian Institute of Company Directors.

Dr Ross Bradbury

Dr Ross Bradbury is a graduate from the University of Sydney, he has held a host of postgraduate appointments in Australia and overseas. He holds several concurrent appointments including Director of Microbiology and Infectious Diseases at Concord Hospital and Clinical Microbiologist and Infectious Diseases Physician at the Sydney Adventist Hospital.
Mr Matthew Swanborough

Matthew Swanborough is the Acting Director of Operations SLHD. Manager General Manager of Concord Repatriation General Hospital. Prior to this Matthew was General Manager at Concord Hospital, he also held a senior manager position at PricewaterhouseCoopers UK, where he worked with a range of hospital and Department of Health clients in the United Kingdom as well as across Europe. Matthew has also held positions within KPMG and the former Central Sydney Area Health Service, where he undertook his health service management training.

Professor Ben Freedman OAM (Alternate for Prof Robinson)

Ben Freedman is Professor of Cardiology at Concord Hospital and Deputy Dean of the Sydney Medical School at Sydney University. He was previously Head of Department of Cardiology at Concord Hospital and is Head of the Vascular Biology Group of The Anzac Research Institute. He is a member of a number of boards including the Heart Research Institute, Bosch Institute, Asbestos Diseases Research Foundation, Centre for Vascular Research, Microsearch Foundation, Sydney Burns Foundation, and the Heart Foundation of Australia Research Committee, and Chairs the advisory boards of the Northern Rivers University Centre of Rural Health (North Coast), Broken Hill University Department of Rural Health, and Dubbo/Orange Rural Clinical School of the University of Sydney. Professor Freedman is a Fellow of the American College of Cardiology (FACC), the European Society of Cardiology (FESC), and the Cardiac Society of Australia and New Zealand (FCSANZ). He was secretary of the CSANZ in the mid 1990s, and was Scientific Chairman of the successful World Congress of Cardiology held in Sydney in 2002. In 2011 he was awarded the Order of Australia Medal (OAM) in honour of his contributions to research, education, and clinical practice.

Professor Arthur Conigrave (Alternate for Prof Robinson)

Prof Arthur Conigrave is: an endocrinologist specializing in disorders of calcium metabolism; a research scientist with internationally recognized expertise in the structure and function of the calcium-sensing receptor and in mechanisms of regulation of parathyroid hormone secretion; Deputy Dean of Sydney Medical School and lectures in Medical Biochemistry for the University of Sydney Medical Program.

Mr Paul Levis

President of the Australia and New Zealand office of Intellectual Ventures, a $5bn Seattle based company that invests in invention. I have worked in the fields of business, communication, negotiation, government and the not for profit sector across a diverse policy field for over 25 years. I am a current board member of auDA (Australia’s .au domain name coordinator).

I am an Honorary Associate and guest lecturer at the Graduate School of Government at the University of Sydney and a Key commentator with the Global Internet Business Coalition.
Ms Kerry Hogan-Ross

Kerry Hogan-Ross is a lawyer and accredited mediator. She was a partner of a national law firm, DLA Phillips Fox and DLA Piper for 12 years. She is also on the board of Force Majeure, a not for profit dance theatre company where she is the company Secretary. Kerry has been a commercial and insurance litigator for more than twenty three ears and advises corporations, insurers, professionals and company directors in a wide variety of areas. Kerry’s professional indemnity practice includes claims against solicitors and doctors.

Professor Michael Field  AM

Professor Emeritus, University of Sydney
Former Head, Sydney Medical School - Northern
Former President, Australian & New Zealand Society of Nephrology
Former Chair, Medical School Accreditation Committee, Australian Medical Council

Vice-President, Association for Medical Education in the West Pacific Region
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For further information contact:

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