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.
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This will be my final report to you as Chairman of the Board of the ANZAC Health & Medical Research Foundation. In accordance with our Constitution, I will retire from the post at the forthcoming Annual General Meeting in November 2011. A number of others who have been long-term members of the Board will also retire over the coming months. This is an opportunity for renewal and reinvigoration of the Board to lead the ANZAC Research Institute forward to a successful second decade of operations.

On commencing the second decade, the Board held a strategic planning day in May 2011 to reflect on its present arrangements and to develop responses to the changing environment in the education, healthcare and research sectors. The Board noted with appreciation the strong statements by the incoming Board and CEO of the Sydney Local Health District of their commitment to support hospital-based research and, in particular their ongoing support for the ANZAC Research Institute as the hub for research on the campus of Concord Repatriation & General Hospital. With these assurances, the Board re-committed the Institute to its goal of providing research facilities to serve the needs of the hospital’s clinicians and to its principal aim to achieve excellence in research.

The Board remains concerned with the difficulty of securing adequate infrastructure funding to support the scientists in their work, however we note recent positive developments in both Commonwealth and State funding programs for medical research. We have been happy to participate in the work of the Australian Association of Medical Research Institutes in presenting persuasive arguments to convince governments of the need to support the outstanding research conducted in Australian MRIs with adequate infrastructure funding. We look forward to continuing our contribution to this work and to the AAMRI campaign to build public awareness of and support for Australian medical research.

I would like to acknowledge the fine contributions made by the retiring Board members and to thank them for their work. Professor David Cook assisted us to build strong relationships with the University of Sydney; Professor Kerry Goulston brought great wisdom to his role as Scientific Adviser and later as Board member; Mr Brian Lee took on the frustrating role of chairing the fundraising committee; Mr Rusty Priest AM maintained our ongoing relationship with the veteran community; and Messrs Danny O’Connor and Gary Miller ensured robust relationships with the local hospital and wider health service. The ANZAC Research Institute is better for their service.

Professor Diana Horvath AO joined the Board during the year and has taken on the role of Deputy Chair. Her long-standing commitment to the interests of the ANZAC Research Institute has strengthened the Board’s deliberations and I am sure she and other incoming members will ensure effective governance of the Institute for the future. 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 year now ended. I would also like to thank the administrative staff for their support to the Board, especially the Secretary Julie Taranto, Tracey Dent, Annet Doss and Candice Chang.
Welcome to the Institute’s Annual Report. For the 11th year we again report a very successful year for every dimension of our goals – making research discoveries, winning external grant funding, publishing influential papers in major scientific journals and training the new generation of medical researchers. Since opening in 2000, ANZAC Research Institute quickly joined the ranks of Australia’s top medical research institutes. We now provide a scientific home to over 135 scientists including over 40 graduate (PhD, Masters) students. Annually, the Institute’s scientists earn over $9 million maintaining a higher than average success rate for NHMRC grants and publish over 200 peer-reviewed scientific papers in top journals. We manage this with minimal overhead costs to keep the doors open and maintaining the specialised scientific facilities and services required for such high quality/impact research to flourish. The following pages provide an outline of the innovative work of the Institute’s research groups. Each group leads their field, a challenge they only meet by constantly renewing their research and restlessly striving to innovate at the frontlines of knowledge.

As Concord Hospital’s own medical research institute, the ANZAC Research Institute has earned a reputation for scientific excellence in diverse areas including andrology, burns, cancer, cardiovascular disease, immunology/hematology, osteoporosis, neurodegenerative diseases, and population research into ageing and the health of veterans. The ANZAC Research Institute was created by the foresight of its two key founders, the late Professor John Young, then the University’s Dean of Medicine and Pro-Vice Chancellor (Health Science) who became our first Chairman, together with Dr Diana Horvath as CEO of the Central Sydney Area Health Service, the predecessor of the Sydney South West Area Health Service. Their remarkable shared and co-operative vision set a solid foundation for the Institute’s success. As we enter our second decade, what they foresaw, a dedicated, state-of-the-art facility for high impact medical research at Concord Hospital as a teaching hospital of the University of Sydney Medical School has come to fruition. The ANZAC Research Institute’s serves to align medical research with the best interests of Concord Hospital and the wider medical community. Our research group have close linkages with Hospital departments and ensure the best translational of research to and from clinical practice of medicine. Such tight integration of active medical research into a modern teaching hospital is the key to maintaining highest standards of medical care through continual fresh input from discoveries all over the world. A medical research institute with high academic standing serves a Hospital by attracting top academic physicians, researchers and trainees from around the country and overseas. Doing high quality medical research is costly but it provides an exceptional long-term return on investment in better health and medical care. Only strong community support through governments which recognizes the value of medical research can keep the Institute going strong. Our development required another vital ingredient, support by the NSW government for the high costs of doing top quality medical research. Then as now hospital-based organisation are not eligible for Commonwealth infrastructural support provided solely to Universities for doing the same medical research. In recent years the Commonwealth has widened this artificial distinction between Universities and medical research institutes conducting medical research. This creates perverse incentives and drives apart natural research partners rather than unifying and maximising our joint efforts. In this increasingly difficult climate for maintaining vital support for our medical scientists doing high quality research, we have to dip into savings to maintain operations let alone investing in the new ventures and natural expansion that successful research makes essential. The good news is that there are very positive signs that the Commonwealth and NSW governments are making imaginative plans to sustain medical research for the coming decade. This Report provides the opportunity to thank the many who make the Institute work so efficiently and yet
make it look easy. The skill, commitment and hard work of our superlative administrative team - Julie Taranto, Annet Doss, Candice Chang, Tracey Dent, Mark Jimenez, Mamdouh Khalil, Justin Crosbie, Pam McDowell, Rachelle Innes, and Amy Ng – can’t be praised enough. They make the necessary work go lightly – the scientists owe them a lot and on their behalf I can hardly thank them enough. The Institute’s researcher-friendly atmosphere, one of the Institute’s objectives, is largely due to their sustained efforts.

Also on behalf of the Institute’s scientists, grateful thanks go to the General Manager of Concord Hospital, Gary Miller as well as Michael Wallace, CEO of the Sydney South West Area Health Service and his successor Teresa Anderson as CE of the Sydney Local Health District, for their consistent and constructive support without which ANZAC Research Institute would not function. Similarly, the ongoing support of the Sydney Medical School, Professors Bruce Robinson and Bob Lusby, is gratefully acknowledged. Thanks are also due to John Gatfield for editing of our newsletter Discovery. Finally, it is a pleasure to thank Dr Felicity Barr personally and the Board she Chairs so well, for their unwavering support and enlightened commitment to making the Institute as good as it can be. Above all, it is always a privilege to work in the challenging and productive environment created by the Institute’s scientists - I remain humbled and ever encouraged by their quiet, inspiring efforts which make all hurdles worth surmounting.
Personnel:

Group Leader: Professor David Handelsman
Senior Scientists: Dr Charles Allan, Reena Desai, Dr Ulla Simanainen, Dr Kirsty Walters
Visiting Scientists: Dr Thilee Sivananathan, Dr Thomas Travison

Staff and Students: Omar Akram (with Heart Research Institute), Lydia Andres, Fay Bacha, Frank Bathur, Jaesung (Peter) Choi, Assoc Prof Ann Conway, Lisa Corcoran, Irene Di Pierro, Carolyn Fennell, Yan ru (Ellen) Gao, Rasmani Hazra, Amanda Idan, Maria Jähne, Dr Veena Jayadev, Mark Jimenez, Shai Joseph, Patty Kappelaris, Pekka Keski-Rahkonen, Sarah Lamb, Lucy Liu, Dr Lam Ly, Keely McNamara, Basil Psarommatis, Tayebeh Rastegar, Jennifer Spaliviero, Sasa Spasevska, 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.

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 also in 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.

Highlights:

- Dr Charles Allan et al, PNAS publication: Follicle-stimulating hormone increases bone mass in female mice, 2010

Grants: 2010-11

Andrology Australia- Sivananathan. “Andrology Australia Training Fellowship” $15,000
ARC Discovery- Allan, Handelsman, Griswold, Denyer. “Steroidal control of male meiosis” $82,642
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.” $15,000
MBF Foundation- Handelsman, Liu, McLachlan. “Development of valid diagnostic criteria for age-related androgen deficiency in men (the Healthy Man study)” $130,417
NHMRC- Allan, Handelsman. “The Sertoli cell: master regulator of hormone-induced spermatogenic development” $182,000
NHMRC- Walters, Handelsman, Allan. “Androgen receptor mechanisms in female reproductive physiology.” $173,500
NHMRC- Liu, Grunstein, Handelsman. “Obstructive sleep apnea and androgen dysregulation.” $167,375
NHMRC- Allan, Handelsman, Dunstan. “FSH and female aging.” $127,013
NHMRC- Simanainen, Handelsman. “Intraprostatic androgen signalling as a target in prostate cancer.” $119,736
NHMRC- Allan, Handelsman, Walters, Howell. “FSH control of ovarian function.” $107,508
United States Anti-Doping Agency- Handelsman, Idan.
“Detection of DHEA augmentation doping: Pilot study.” $35,000
University of Sydney Bridging Grant- Simanainen, Handelsman, Harwood. “Steroid activation and androgen signalling as targets in prostate cancer.” $50,000
University of Sydney NHMRC Equipment Grant- Allan, Handelsman, Zhou, Seibel, Kennerson, Nicholson, Blair, Le Couteur, McMahon, Hart, Clark, Simanainen. “Molecular Imager Chemdoc XRS system & miniprotein gel/transblot cell system” $36,975
University of Sydney- Travison. “Population based studies of hormone decline and physical function in older men.” $8,500

Prizes:

• Prof David Handelsman: RFD Award and Plenary Lecture, Society for Reproductive Biology, 2010
• Dr Charles Allan: POC Chair, Society for Reproductive Biology Annual Meeting, 2010-12; Chair of Joint ESA/ SRB LOC for Annual Meeting 2010; POC Member, 2nd World Congress on Reproductive Biology 2011; Working Party Member, Sydney Medical School - Reproductive, Maternal and Child Health Theme - Inaugural Meeting 2011.
• Ms Keely McNamara, University runner-up Three Minute Thesis Competition, 2010

Research:

Physiology and Pharmacology of Androgens

Clinical Pharmacology of Testosterone
A Conway, C Fennell, 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 a steroid reference laboratory for highly sensitive analysis of serum androgens and estrogens in serum samples from a wide variety of human and animal studies.
Androgen Misuse and Abuse: Testosterone Overprescribing & 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 Kazlausakas, G Trout, C Howe (National Measurement Institute)

Androgens play a major role in muscle strength, energy and quality of life in men. This can be dramatic in men with testosterone deficiency where testosterone replacement therapy often provides striking benefits. Androgens, synthetic forms of testosterone, have major effects on muscle size and strength so that abuse of these well known effects has become entrenched in small pockets of the community among men and women seeking performance or image enhancement or as a panacea against ageing.

As a result of these properties, androgens remain 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 are now undertaking 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.

We have continued to undertake national surveillance of PBS-funded testosterone prescribing patterns. This has identified patterns of over-use that call for heightened vigilance and increased professional and public education to reduce wasteful and misguided over-use of testosterone.

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 aims 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 men, this study will also evaluate the prospects for age-specific reference ranges for testosterone in an “elite” healthy male population. This project will extend our established reference panel methodology from our study of young men to middle-aged and older men with the addition of multiple sampling and use of a reference testosterone assay using our new tandem-mass spectrometry method.

Measuring Progress of Puberty
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.

Androgens and the Prostate
Dihydrotestosterone (DHT) Efficacy and Safety Study
A Idan, K Griffiths, L Turner, AJ Conway, D J Handelsman

A major research project was completed to evaluate
whether DHT, the most potent natural androgen, is effective in preventing prostate growth in middle-aged men without known prostate disease as well as determining whether high doses of androgens have any detrimental effects on bone or the cardiovascular system. This randomised, double blind placebo controlled study was recently published in the prestigious journal Annals of Internal Medicine showing that prostate growth was more influenced by ageing than even high dose androgen administration; however potentially harmful effects on bone were also discovered.

Intraprostatic Androgen Signalling and Androgen Sensitivity of the Prostate

U Simanainen, 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 steroidal 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.

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-progestin 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, T Rastegar, S Lamb, L Corcoran, J Spaliviero, M Jimenez, DJ Handelsman, CM Allan

Collaboration: J Couse, K Korach (National Institute of Environmental Health Sciences, Research Triangle Park NC, USA) & M Griswold (Washington State University, Pullman USA); G Denyer (University of Sydney); P Stanton (Prince Henry’s Institute of Medical Research)

Reproductive hormones such as sex steroids (eg. androgen) and gonadotrophins control testis development and sperm production (spermatogenesis). These major hormone pathways converge upon Sertoli cells, a unique cell in the testis vital for spermatogenesis and male fertility. Our major research focus (NHMRC-funded) aims to understand how different hormones control normal Sertoli cell development and function. In particular, we have established novel genetic models to study the role of the androgen receptor (AR) in Sertoli cell maturation and function. A loss-of-function approach has removed a site in the AR essential for DNA binding, revealing that the DNA (genomic) interaction of AR is vital for sperm development. A gain-of-function approach targeted premature expression of Sertoli cell AR to study its role during pre-pubertal development (research by Rasmani Hazra, new PhD student).

Another research focus (supported by ARC Discovery grant) is the role of estradiol in testicular development and function. We investigated the paradoxical induction of sperm production by estradiol, the classic female sex steroid. Collaborative studies with the US National Institute of Environmental Health Sciences (NIEHS) showed that estradiol-induced spermatogenesis involved secretion of follicle-stimulating hormone, the presence of AR, and a specific estradiol receptor (ERalpha), showing a complex interaction of hormonal pathways. A visiting PhD student Tina Rastegar (Tehran University of Medical Sciences, Iran) showed that Sertoli cell AR DNA binding is required for estradiol-induced sperm production. Combined, these research projects are increasing our fundamental knowledge of the underlying biological pathways that control (or inhibit) spermatogenesis and male fertility. Such research is predicted to provide valuable genetic targets for therapy (eg. infertility) or for the treatment of testicular tumours, or to develop novel strategies for male contraception.

Androgens and Post-testicular Control of Male Fertility

U Simanainen, K McNamara, E Gao, DJ Handelsman

Action of male hormones, androgens, is essential not only for maintenance of spermatogenesis, but also in the post-testicular control of fertility. So far, it has not been possible to dissect in vivo the role of androgens in post-testicular fertility due to the close relationship and high androgen dependency of spermatogenesis in the testis. We have created a mouse model with tissue-selective androgen receptor (AR) inactivation in prostate, seminal vesicle, epididymis and vas deferens, while the testis is unaffected displaying normal spermatogenesis and testosterone production. This model will provide novel, in vivo information of androgen action in post-testicular male fertility, with specific data on molecular mechanisms underlying the reduced function of androgen deprived, post-testicular glands.

This new knowledge could make new inroads into the detection, diagnosis and treatment of unexplained male infertility as well as in developing new male-based, hormonally targeted but non-hormonal contraceptives (neo-hormonal) for both human and animal application.

Androgens, Ageing and Female Reproductive Physiology

Androgens and the Ovary

K Walters, L Middleton, CM Allan, DJ Handelsman

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. These may provide long overdue new insights into the basis of the timing of menopause and androgen associated female reproductive disorders such as polycystic ovary syndrome.
(PCOS). Polycystic ovary syndrome (PCOS) is one of the most common causes of anovulation, infertility and hyperandrogenism 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. Androgens have been implicated in the development of PCOS with hyperandrogenism being the most consistent PCOS trait.

Currently we are identifying the precise mechanism how the AR influences female reproductive physiology. We have created unique transgenic models whereby the AR gene has been selectively inactivated (ARKO) resulting in female mice functionally unable to respond to any androgens. Using this novel model Dr Walters has revealed defects in ovulation (Fig. 1) as the major cause of the observed sub-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
S Lamb, K Walters, DJ Handelsman, CM Allan. Collaborations: R Kalak, H Zhou, M Seibel, C Dunstan (Bone Biology, ANZAC); 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 were proposed to accelerate the loss of ovarian eggs and decrease eggs quality. We established a model with rising levels FSH that displays premature female infertility. Research by Kirsten McTavish (during a PhD candidature, now a postdoctoral fellow with Prof Shunichi Shimasaki at UCSD, San Diego) showed that premature infertility due to elevated FSH occurs despite egg development and ovulation. Despite exhibiting reduced fertility, our FSH model had significantly higher numbers of early eggs (primordial follicles), demonstrating high FSH enhances rather than diminishes follicular reserve. Furthermore, we revealed that embryos derived from eggs exposed to high FSH levels displayed normal uterine implantation rates and unexpectedly increased survival levels during development. This beneficial effect of high FSH levels may have relevance to FSH treatments during assisted reproduction. Higher levels of FSH produced earlier infertility as well as ovarian cysts, and a new collaboration with Dr Howell is creating models to study FSH actions in ovarian dysfunction, including polycystic developmental and tumorigenesis.

We also investigated the role of elevated FSH in bone loss, in light of a controversial proposal that high FSH can induce bone loss in ageing women, a major problem in our ageing population. Using our high FSH model, we determined age-related changes to bone structure due to elevated FSH (in collaboration with Bone Biology). We revealed that FSH dose-dependently increased (rather than decreased) bone mass. Furthermore, FSH stimulated a striking gain of bone mass in the presence of reduced estradiol levels. Higher FSH levels further increased bone volume, an effect which was correlated positively with ovarian hormones (inhibin A, testosterone). No detectable FSH receptor in bone showed that FSH did not directly stimulate bone. Therefore, contrary to proposed FSH-induced bone loss, our findings show that FSH has positive effects on bone via an ovary-dependent mechanism, which is independent of estradiol levels, and found no evidence for direct FSH actions on bone cells. Our findings were published in a prestigious journal (Proc. Natl. Acad. Sci. USA.), and have major clinical relevance to the onset of age-related diseases (eg. osteoporosis) associated with loss of ovarian function (eg. estradiol deficiency) due to menopause.

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)
C Goebel, A Cawley, R Kazlausakas, G Trout, C Howe (National Measurement Institute)
Prof RI McLachlan (Prince Henry’s Institute of Medical Research, Melbourne)
J Couse, K Korach (National Institute of Environmental Health Sciences, Research Triangle Park NC, USA)
M Griswold (Washington State University, Pullman USA)
D Robins (University of Michigan, Ann Arbor USA)
G Denyer (University of Sydney);
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)
R Kalak, H Zhou, M Seibel, C Dunstan (Bone Biology, ANZAC)
V Howell (Kolling Institute of Medical Research, University of Sydney)

LIST Registrars/Trainees in Dept of Andrology 2010 - 11
Rashmi NARAYANAN
Praseetha AHANMUGALINGHAM
Kirtan GANDA
Lisa SIMMONS
Kiernan HUGHES
BIOGERONTOLOGY

Personnel:

**Group Leader:** Professor David Le Couteur  
**Scientists:** Dr Victoria Cogger, Dr Alessandra Warren, Dr Aisling McMahon, Dr Dmitri Svistounov, Dr Svetlana Zykova, Samantha Solon, Vicky Benson, Jennifer O’Reilly, Sarah Mitchell, Shajjia Razi, Professor Arthur Everitt, Professor Robin Fraser.

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.

Highlights:

- The group established the role of lipid rafts in maintaining the structure of fenestrations in the liver sinusoidal endothelial cells. This provides the first time a proximal mechanism for regulating fenestrations and pore formation has been identified. The results also provide the first ever high definition three dimensional figures of lipid rafts.
- Our group collaborated with Dr Patrick Bertolino at the Centenary Institute to identify a unique mechanism of peripheral deletion in which naïve autoreactive CD8 T cells are rapidly eliminated in the liver after intrahepatic activation, published in the Proceedings of the National Academy of Science USA.
- In collaboration with Professor Stephen Simpson, we completed a very large nutritional study on ageing at the ANZAC Research Institute. This study of nearly 1000 mice is investigating the effects of macronutrients, particularly protein, on ageing and age-related diseases. Analysis of tissue and genes is underway.
- Dr Cogger was promoted to Senior Lecturer with the Sydney Medical School
- Drs Cogger and Svistounov edited a special issue of Current Gerontology and Geriatrics Research on the aging liver, and Professor Le Couteur edited a special volume on aging pharmacology in the Journal of Gerontology.
- Professor Le Couteur was elected as President of the Australasian Society for Clinical and Experimental Pharmacology and Toxicology, is the ASCEPT Speaker at the British Pharmacological Society ASM in London
- Dr Sarah Mitchell won a four year NHMRC post doctoral fellowship to continue her studies of ageing and the liver at the National Institute on Aging USA.

Grants: 2010-2011

NHMRC- Simpson, Le Couteur, Raubenheimer, Ballard. “Nutrition and ageing “ $313,017
NHMRC- Le Couteur, Cogger, Lebel, Quinn, Hilmer, McCuskey. “Ageing, Werner syndrome and Pseudocapillarization” $245,375
NHMRC- Hilmer, Jones, Cogger, de Cabo. “Hepatic drug clearance and drug induced liver disease in ageing” $183,500
NHMRC- McLachlan, Naganathan, Le Couteur, Hilmer, Gibson. “Pain control in older people” $131,250
NHMRC- Hennessy, O’Connel, Rasko, Twigg, D’Aspice, Le Couteur. “NHMRC National Baboon Colony” $120,000

Prizes:

Professor Le Couteur was awarded the ASCEPT Visiting Speaker award to present at the British Pharmacological Society ASM in London.

Travel grants to Dr Warren, Dr McMahon and Dr Svistounov to attend the International Society for Hepatic Sinusoid Research conference in Florence.

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. The major focus of our research is to develop therapies to prevent these ageing changes, primarily in order to prevent cardiovascular diseases caused by the age-related impairment of lipoprotein metabolism. We are
attempting to do this by increasing our understanding of the regulation of the liver sinusoidal endothelial cells with the cutting edge technology, structured illumination three dimensional microscopy, as well as utilizing a high throughput screening strategy in an genetically manipulated immortal cell line. Recently we have established that the key mechanism for regulating fenestrations is lipid rafts, and we are undertaking a drug screen to find novel drugs that 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. Our research is being conducted in a very large cohort of mice subjected to about thirty different dietary regimes. The research will examine a wide variety of ageing outcomes and in particular we are investigating which cellular pathways mediate the beneficial effects of these nutritional interventions. 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
Personnel:

**Group Leader:** Professor Markus J Seibel

**Senior Scientists:** A/Prof Hong Zhou; A/Prof Colin Dunstan (associated)

**Staff and Students:** Dr Yu Zheng, Dr Tara Brennan-Speranza, Dr Aiqing Li, Dr Rowan Hardy, Dr Karin Lyon, Trupti Trivedi, Jinwen Tu, Yaqing Zhang, Colette Yee, Julian Kelly, Jane Chapman, James Modzelewski, Elysia Neist, Holger Henneicke, Katja Boernert, Uta Heinevetter, Dennis Basel, Katharina Blankenstein, Difei Deng, Sunny Ye, Jason Wang.

**Visiting Professors:** Professor Guoxian Ding, Nanjing Medical University, Jiangsu, China; Dr Mark Cooper, Birmingham University, UK; Professor Iraj Nabipour, Busheer University, Iran.

Role:
The Bone Research Program pursues Basic research in Bone Biology, Bone Metabolism and Clinical Research in Metabolic Bone Disease. In addition, we have a strong interest in the development and evaluation of transgenic models of bone disease.

In 2010/2011, the program has supported postgraduate and doctoral studies of Trupti Trivedi, Jinwen Tu, Yaqing Zhang; Exchanging doctoral students of Holger Henneicke, Katja Boernert, Uta Heinevetter, Dennis Basel, Katharina Blankenstein (Humboldt University, Berlin) Shaoxun Yu (Shanghai Jiao Tong University, Shanghai). Sunny Ye and Weiqi Jason Wang participated as Honours students and Difei Dong participated as an undergraduate summer student.

Highlights:
Our group is well represented at national and international scientific meetings (e.g. American Society for Bone and Mineral Research (ASBMR), European Calcified Tissue Society (ECTS); Australian and New Zealand Bone and Mineral Society (ANZBMS); International Conference on Osteoporosis and Bone Research (ICOBR) and others). At all of these meetings, our group has had multiple oral presentations, reflecting the high standard and international recognition of our research. In 2011, our group’s research has been selected for seven oral presentations at international conferences. In addition, we received the “Most Outstanding Basic Abstract Award” of the 2011 ASBMR, the world’s prime scientific society in the bone field.
**Grants: 2010-2011**

NHMRC Project Grant: Seibel, Zhou, Gundberg, Dunstan. “Role of osteoblast in mediating glucocorticoid-induced metabolic dysfunction.” $197,225

NHMRC Project Grant: Zhou, Seibel, Stewart, Buttgereit, Cooper. “Role of endogenous glucocorticoids in inflammatory arthritis” $165,650

NHMRC Project Grant: Zhou, Seibel, Chen, Dunstan. “Osteoblast control of mesenchymal progenitor cell differentiation: The role of glucocorticoids & Wnt signalling.” $141,125

NHMRC Project Grant: Duque, Zhou, Drissi, Li. “Role of lamin A/C in osteoblastogenesis and age-related bone loss” $152,850

NHMRC Project Grant: Armstrong, Kedda, Smith, Steginga, Kricker, Kimlin, Seibel, Clements. “Sun exposure, vitamin D and the outcome of prostate cancer” $112,494

NHMRC Project Grant: Eisman J, Center J, Nguyen T, Seibel MJ, Sambrook PN, Elder G. “Vitamin D, bone loss, fracture and mortality outcome” $166,659


NHMRC Training Fellowship: Speranza. “The influence of cortisone on the synthesis and signaling of osteoblastic-derived mediators of metabolic dysfunction” $72,508

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

Prostate Cancer Foundation of Australia, Concept Grant: Seibel, Zheng, Dunstan, Zhou. “Vitamin D deficiency and prostate cancer metastasis to bone” $137,661

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

**Prizes:**

University of Sydney Postgraduate Award, to Trupti Trivedi 2009-2012

International Postgraduate Award, to Jinwen Tu 2010-2012

**Our 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 $9,300,000, including 5 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. Therapeutic glucocorticoids also exert numerous deleterious effects on bone resulting in osteoporosis and disorders of energy metabolism.

The Bone Research Program investigates the effects of glucocorticoids on bone using novel genetically modified mouse models. One of these models is characterised through a transgene that results in local inactivation of glucocorticoids in the bone forming cells, the osteoblasts, by directing these cells to produce an enzyme known as 11beta hydroxy-steroid dehydrogenase type 2, normally found in the kidney. We have established a range of cell-targeted GC receptor (GR) knock-out mouse models resulting in GR-deficient fibroblasts, osteoblasts, chondrocytes and adipocytes. Using these genetically modified mouse models, we are currently working on the following research projects:
The Role of 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 (Zhou et al 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 (Zhou et al. Development 136: 427-436, 2009).

In a current NHMRC funded project, 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.

The Role of Endogenous Glucocorticoids in Immune Arthritis

J Tu, Y Zhang, R Hardy, M Cooper, P Stewart, F Buttgereit, MJ Seibel, H Zhou
Synthetic glucocorticoids (GC) are of great importance in the treatment of rheumatoid arthritis (RA) and other inflammatory rheumatic diseases. The role of endogenous GC action in contributing to the susceptibility and/or severity of RA remains to be fully elucidated. In a collaboration led by Prof Frank Buttgereit at Humboldt University, Berlin, Germany, we investigated the effect of osteoblast-targeted transgenic disruption of GC signalling on joint inflammation and bone catabolism in the serum transfer model of autoimmune arthritis. We made the surprising observation that arthritis was attenuated in the transgenic mice, indicating that endogenous glucocorticoids modulate inflammatory responses through direct effects on osteoblasts and pointing to a central role of local endogenous GCs in arthritis (Arthritis & Rheum 60:1998-2007, 2009).

In a current NHMRC funded project, in collaboration with Prof Buttgeret (Humboldt University, Berlin, Germany), Prof Stewart and Dr Cooper (University of Birmingham, UK) we are investigating the mechanisms involved in the attenuation of arthritis. In particular we will focus on cross talk between osteoblasts and synovial fibroblasts that play a crucial role in the recruitment, survival and retention of infiltrating leukocytes populations that drive active inflammation in RA. The isolation of these cells in such inflammatory models has been developed in-house and phenotype determined through expression of the stromal markers fibronectin, CD90 and CD248.

Changes in Bone and Fat Metabolism Induced by Exogenous Glucocorticoids

TC Brennan-Spranza, H Henneicke, C Dunstan, H Zhou, MJ Seibel
The bone-related effects of exogenous glucocorticoids at pharmacological levels are of major research interest. Continuous glucocorticoid delivery at a constant rate is a major requirement for this research. We have developed a method of long-term glucocorticoid treatment that enables us to deliver a sustained pharmacological dose of corticosterone, the major glucocorticoid in mice (Steroids. 74:245-9, 2009). Using this method in our transgenic mice where osteoblast GC signalling is interrupted, we found that exogenous glucocorticoid-induced bone loss could be prevented. We also found, that the transgenic mice lacked the body fat deposits normally seen during high-dose exogenous glucocorticoid treatment. These findings indicate that osteoblasts are an important cellular target for exogenous glucocorticoids, mediating not only the deleterious effects of glucocorticoids on bone but also those on fat metabolism. We will utilise these mouse models to identify the mechanisms that govern the changes in bone and fat metabolism induced by exogenous glucocorticoids.

The Role of Glucocorticoid Receptors in Bone, Joints and Other Organs

A Li, Y Zhang, J Tu, C Dunstan, J Tuckermann (Germany), MJ Seibel, H Zhou
In collaboration with Prof Jan Tuckermann (Germany) and Prof Di Chen (USA), we have established a range of cell-targeted GC receptor (GR) knock-out mouse models resulting in GR-deficient mesenchymal cells, fibroblasts, osteoblasts, chondrocytes and adipocytes. By characterising these condition GR knock-out mouse lines our preliminary data showed that 1) knock out of GR in mesenchymal cells causes a defect of abdominal wall closure during development, similar to
the clinical gastroschisis symptoms and abnormal lung development; 2) knock out of GR in adipocytes causes a pleiotropic phenotype with significant growth retardation and pronounced alopecia followed by premature death within 2 weeks of birth. These findings indicate that glucocorticoid signalling in mesenchymal cells and adipocytes is essential for normal mice development.

Preventing the Spread of Malignant Tumours to Bone
Y Zheng, K Bornert, T Trivedi, D Basel, 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 in bone is associated with bone destruction that frequently results in significant pain and disability. Prostate cancer cells in bone induce high rates of bone formation and bone resorption, resulting in disorganisation of bone structure and severe pain. In both cancers, tumour cells grow in bone and induce normal bone-resorbing cells of the bone marrow to destroy the surrounding bone. It has been proposed that destruction of bone releases factors that help cancer cells grow faster, thus creating a vicious cycle that contributes to the serious consequences of bone metastases.

In this study, we are studying mice with transplanted breast cancer cells to understand what makes the bone marrow a receptive site for breast cancer metastasis. We are manipulating bone remodelling rates in mice see how this impacts the ability of circulating cancer cells to target bone and to establish destructive tumours there. To date, we have determined that anti-resorptive treatments inhibit tumour growth in bone indirectly through effects on osteoclasts, rather than directly through effects on tumour cells (Zheng et al. Bone 2007). After discovering that increasing bone resorption through a low calcium diet enhances breast cancer metastasis to bone in mouse models (Zheng et al, Cancer Res 2007), we are now investigating how vitamin D deficiency affects the growth of breast cancer metastasis to bone. It appears that low Vitamin D levels enhance human breast cancer growth in the bone of mice through both indirect and direct effects (Ooi et al, Cancer Res 2010). This may have clinical implications as vitamin D deficiency contributes to the risk of developing breast cancer and to its progression to metastatic disease.

Furthermore, we have identified a novel role of Vitamin D Receptor (VDR) in breast and prostate cancer cells. Our preliminary research indicated that the VDR itself may exert direct control over the behaviour of primary and secondary cancers: By knocking down the VDR in human breast cancer (MDA-MB-231) cells, we found that these cells had reduced proliferation in vitro, but increased expression of markers of malignancy. These results pointed to a ligand-independent role of the VDR to increase proliferation and to inhibit cell migration (i.e. ‘malignant potential’) in cancer cells. Further studies are planned to investigate the mechanisms by which the VDR controls human prostate cancer growth in vitro and in vivo.

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.

Atypical Femoral Fractures and Bisphosphonate Use
C Girgis, D Sher, MJ Seibel
Together with Drs Girgis (Endocrinology) andSher (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 bisphos-phonate 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

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 Geriatr. 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)

Health and Ageing in Older Men: The CHAMP study

MJ Seibel, I Nabipour in collaboration with the CHAMP investigators

The research focus of the bone group within the CHAMP study is obviously bone health. This year, two major projects have led to a better understanding of the impact of socioeconomic status on bone health (Nabipour et al. Osteoporosis Intl, 2010) and the role of serum uric acid as a predictor of bone health in older men (Nabipour et al., submitted).

For more information on the CHAMP study, see page 32.

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 had the opportunity to build productive scientific partnerships and collaborations with international researchers: Prof Frank Buttgereit, 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, Fritz Lipmann Institute, Germany, Prof Teresa Guise, Indiana University, Indiana, 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. Some of these collaborations have in the past lead to important publications and successful grant applications, including NHMRC Project Grants.

Our collaborations with Australian groups include those of Prof. Phil Sambrook, RNSH, Sydney; Prof. John Eisman and Dr Paul Baldock, The Garvan Inst of Medical Research, Sydney, Profs Bruce Armstrong, Rebecca Mason, Robert Cumming, David Handlesman, Arthur Conigrave and Gustavo Duque, The University of Sydney, Prof. John Wark and Terrence O’Brien, The University of Melbourne, Dr Tania Winzenberg, The University of Tasmania, Prof Chris Nordin, 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 Anthony Weiss, Jelena Rnjak, Jessica Almine, Amy Lee, Dr David Millis, Nicola Clayton, Vlad Illie, Mohammad Mohaghegh, David Goltsman, Cassandra Chong, Rae Johnson and Rana Saheb

Role:

Cultured Epithelium Autografts (CEA) is a well established technique to create large numbers of skin cell for resurfacing of wounds. Unfortunately these cultured cells do not have the same physical properties as normal human skin cells as they are missing the interaction with deeper tissue layers. The group researches all aspects of Burn Care and specialises in tissue engineering of 3 dimensional skin substitutes for severe burns patients.

Objectives:

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 this year, we had three summer research students, Sarah Kim, Eric Lee and Tomasz Szczesnik completed their research projects on bio-film, wound healing and skin tissue engineering projects. Three Master of Surgery candidates, Mohammad Mohaghegh, Vlad Illie and David Goltsman, and an honor student Cassandra Chong joined our research team. Mohammad and Vlad are working on animal model based projects examining angiogenesis and wound healing, and scar formation and wound contracture using their surgical expertise. Cassandra works on fabricating novel bio-scaffolds for skin regeneration using electron spinning nanotechnology. David, a medical student with mathematician background focuses his study on the epidemiology of burns injury to establish models of burns analysis with geo-spatial imaging, attempting to identify on a map of NSW correlations between geographic regions and specific burns types.

The Sydney Burns Foundation keeps working hard to raise fund to support burns research, education and scholarship. The main objective is to assist researchers at Concord Hospital’s Burn Unit to develop a fully-functioning skin equivalents for burn patients.

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, 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.

Identifying the Diffusible Factor(s) Produced by Skin Cells Grown on Tropoelastin Scaffolds

Almine j, Li Z, Maitz P and Weiss AS

The main aim of this project is to study the cell-scaffold interaction and identify the diffusible factor(s) produced by skin cells cultured on the scaffold, which promotes cell proliferation and possible keratinocyte differentiation. Identifying the diffusible factor(s) responsible for the proliferation of keratinocytes and fibroblasts would be important progress in the treatment of burns and the development of a suitable skin graft. The treatment of burns patients involves the rapid coverage and closure of the wounds, which is dependent on skin cell proliferation and differentiation. This process can be facilitated by the addition of a diffusible factor(s); consequently achieving rapid wound closure, reducing the chance of infection and re-forming skin with minimal scarring.

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 polycaprolatone 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, Rnjak J, Maitz P and Li Z

The advance in biotechnology 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 process. 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 substitute and wound dressings will need to be tested in an animal model before proceeding to any clinical trial.
The aim of this study is to assess the role of engineered skin products or dressing in wound healing using an established mouse model. The animal 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.

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 sounded 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: Identifying Ideal Scaffold Morphology and Co-Culture Conditions for Cellular Interactions with Electrospun Scaffolds
Chong C, Wang Y, Maitz P and Li Z

Development of a living 3D skin replacement is urgently needed for treating severe burn injury. Collagen-polycaprolactone (PCL) skin substitutes are fabricated by electrospinning resulting in soft, flexible, fairly porous scaffolds which have a characteristic fibrous surface morphology (Fig 1). Fibre diameter, pore size and scaffold thickness can be precisely controlled and defined according to clinical demands. This study will characterise the optimal internal
structures of electrospun scaffolds for skin cell interactions, responses and behaviours (Fig 1), and to identify the ideal conditions for keratinocyte and dermal fibroblast co-culture on these scaffolds. This study will advance the development of a full-thickness, living 3D skin substitute for skin regeneration, wound healing and minimised scar formation.

Angiogenesis of two different dermal regeneration template, Integra 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.
Personnel:

**Group Leaders:** Professor Stephen Clarke and A/Prof Graham Robertson

**Scientists and Students:** Dr John Allen, Dr Lucy Jankova, Dr Maria Tsoli, Dr Dominic Burg, Phuoc Huynh, Arran Painter and Ryland Taylor.

**Clinical Trials Nurse:** Catherine Xu

**Research Assistant:** Candice Clarke

**Project Co-ordinator:** Jennifer White

Role:

Cancer Pharmacology Unit under Professor Stephen Clarke 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. In 2011 we welcomed Dr John Allen from the Centenary Institute who has 15 years of experience in molecular biology, drug resistance and pharmacokinetics.

Objectives:

To identify prognostic and predictive biomarkers for clinical use in colorectal cancer.

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

Highlights:


- Stephen Clarke. Invited Speaker. ARCS Australia Annual Scientific Congress. (Sydney, May 2011): Therapeutic Area Training for Clinical Researchers – Oncology session: Predicting outcomes of cancer treatment


- Graham Robertson et al. (Invited oral) Tumour-derived Cytokines as a Key Determinant of Drug Clearance in Cancer. ISSX 2011 meeting. Atlanta.


- Ryland Taylor et al. Cancer Cachexia Syndrome: Impact of tumour-derived IL-6 on nuclear receptors and circadian regulation of metabolic pathways in livers of cachectic mice. Cold Spring Harbor 2010 Symposium on Nuclear receptors and Disease, Cold Spring Harbor Laboratory NY. Concord Hospital Travel Award.

Grants: 2010-2011

Cancer Institute NSW- Clarke, Robertson, Baker, Molloy, Bokey, Chapuis, Chan, Lin, Christopherson, Lee, Hong, Kohonen-Corish, Beale, Salomon, Horvath, McKay ‘Use of proteomic analysis to improve the management of colorectal cancer’ $749,100
NHMRC- Clarke, Robertson, Piquette-Miller, McLachlan, Baker, Katsifis ‘Improving the use of chemotherapy by targeting the inflammatory response’ $183,500

NHMRC- Clarke, McLachlan ‘Inter-ethnic differences in tolerance of anti-cancer drugs.’ $107,375

Research:

Colorectal Cancer (CRC) Biomarker Studies and Clinical Trials

S Clarke, G Robertson, L Jankova, D Burg, C Xu,
Collaborators [R Christopherson, L Belov, J Zhou – SMB USyd; M Molloy, M Mackay - APAAF Macq Uni; G Sinclair, P Chapuis, C Clarke, C Fung, C Chan & B Lin - Depts of Surgery & Pathology, CRGH; B Oldfield, S Lockie, Monash University; G Cooney, N Turner, Garvan; M Wilkins - UNSW; F Sladek, Uni of California, Riverside and O Dent - Consultant Biostatistician]

As part of a Cancer Institute NSW program grant for colorectal cancer we have identified a number of proteins in tumours that may act as biomarkers for survival and response to treatment in individual CRC patients. In conjunction with the Australian Proteome Analysis Facility (Macquarie University), we have characterized the protein composition (ie the proteome) of CRC tumours using iTRAQ mass spectrometry. Proteomic profiling for stages A-D CRC tumours identified a number of differentially expressed proteins. A subsequent study of only stage C CRC tumours, identified approximately 30 other proteins that were changed between patients who survived or not. Using surgical cancer tumour (adenocarcinoma) samples, we have identified proteins (fascin1 and GST-Pi) with independent prognostic significance in ~500 stage C CRC patients, with GST-Pi expression also distinguishing those patients who will benefit from adjuvant chemotherapy from those who will not respond. We are currently confirming these findings using large patient cohorts and targeted mass-spectroscopy based SRM assays are being developed for each of these proteins.

Another set of proteins that we explored has been through collaboration with Prof Frances Sladek, UC Riverside, California. We have found that expression of a specific isoform of HNF4 is highly variable between different patient tumours and low levels of HNF4 are linked with activated Src oncogene. This novel finding gives new insights into links between Src - an important protein in tumour initiation – and HNF4 that is essential for normal colon cell function.

We have collected plasma, demographic and toxicity data from over 250 patients receiving chemotherapy. Our data suggest that changes in plasma Vitamin D binding protein and apolipoprotein B100 over the first 14 days post-treatment are associated with a higher incidence of immune cell defects such as neutropenia. Similarly, we have shown that changes in 9 other proteins are associated with response/non-response to chemotherapy.

We have also undertaken iTRAQ MS proteomic profiling of plasma from weight losing or stable patients with advanced CRC. Analysis of the top 30 most changed proteins identified the main pathway as Acute Phase Response Signalling with, in particular, inter- -trypsin inhibitor heavy chain 4 (ITIH4) consistently elevated in cachectic CRC patients. Increased gene and protein expression of ITIH4 was also identified in tissues of cachectic mice.

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 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 fibers 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.
Personnel:

**Group Leader:** Professor Derek Hart  
Honorary Professorial Research Fellow: Professor Ken Bradstock

**Scientists:** Associate Professor Georgina Clark, Dr Nirupama Verma, Dr Phillip Fromm, Dr Kifah Shahin, Dr Frances Chow, Dr Thi Thanh Vu, Leticia Muusers, Leah Kim (2010 Summer Student).

**Visiting Scientists on Staff:** Assoc. Prof Deok Kwan Yang (Korea),

**Administration:** Angus Hastie (Business and Operations Mgr), Donna Borg/Amanda Afyouni (Exec. Assistant),

Role:

The Dendritic Cell Biology and Therapeutics Group (DCBTG) is discovering key immune markers and biological processes which will, with the appropriate funding and clinical partnerships, 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 and must self-regulate or be down regulated to prevent auto-immune inflammatory diseases and facilitate transplants. 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 the human DC subsets and elaborate their function. The group studies DC surface molecules, how these molecules influence DC function and how antibodies to them might be used in clinical practice.

Objectives:

A major part of our work is aimed at using the patient's immune responses as a new modality to treat cancer. We are testing our findings in preclinical models of stem cell transplantation, leukaemia, multiple myeloma, prostate cancer and other malignancies. We are also continuing to develop novel immunosuppressive strategies and are developing previous work on an anti CD83 antibody as a novel immunosuppressive agent. This improves transplant outcomes but still preserves the patient's ability to fight infections and cancer. Negotiations to support a clinical trial of anti-CD83 in allogeneic stem cell transplantation are underway.

The DCBTG continues to mentor and teach as a key objective. Two PhD Students are due to start in January 2012 and a Summer Student is joining in December 2011.

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:

“DC Down Under” Symposium, August 11th 2011. This was the first of a new series that continues the DC scientific meetings, previously organised by Professor Hart. This year's meeting attracted over 70 registrants and local and international speakers presented key scientific discoveries in the field of dendritic cell molecules and subsets.

The installation of a new BD “Influx” High Speed Cell Sorter (Flow Cytometer). Central to the cell separation and analysis undertaken by the DCBTG this will also be used by other ANZAC researchers.
Dr Phillip Fromm on the new BD Influx Flow Cytometer

Professor Hart presented at the International Stem Cell Therapy (ISCT) Conference at Rotterdam in May 2011 on the subject of “Dendritic cell subsets and cross-presentation: the potential benefits of receptor targeted antigen loading”. This also facilitated international collaborations on therapeutic DC cancer vaccines.

**Grants: 2010-2011**

NHMRC Program Grant - Hart, Bradstock, “The Translation of Dendritic Cell Biology into Clinical Practice” $710,000

Cancer Australia / Cancer Council (PdCCRS) – Hart, “RNA loading of tumour associated antigens and the activation of blood dendritic cells for prostate cancer immunotherapy” $198,000

Cancer Institute NSW Career Development Fellowship - Hart, “Translation of Dendritic Cell Biology into New Therapeutics”, $199,000

Anthony Rothe Trust – Hart, “Clinical Application of Dendritic Cell Immune Therapy for Multiple Myeloma”, $99.5K

**Collaborations:**

- Ms Mary Sartor Blood and Marrow Transplant Service, Westmead Hospital
- Dr Ilona Cunningham, Dr Judith Trottman, 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
- Professor Mark Hogarth, Burnett Research Institute

**Research:**

- **Multiple Myeloma**

  Translation of human blood dendritic cell subset biology in multiple myeloma

  *Phillip. Fromm, Hayley Suen, Ross Brown, Douglas Joshua, Derek Hart*

  The investigation of human blood dendritic cell (DC) subsets and their biology in malignant cancers is proving rewarding. Our recent studies showed a reduction in all DC subsets (except one) in the peripheral blood of MM patients, correlating with increasing disease severity. Bone marrow, i.e. the disease site, was enriched with other DC populations. The biology of one subset in particular, (CD141+ DC) suggests that they may provide an immune response against MM. This makes them attractive to target for MM immune therapy and encourages our ongoing investigation of antibody selected DC populations for therapeutic DC vaccination trials.


  We worked with our collaborators at the Royal Prince Alfred Hospital to investigate the immune mechanisms of disease control, which may contribute to long-term survival in multiple myeloma (MM). 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 multiple myeloma (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 inducing 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**

Expression of the chemokine receptor CCR5 on blood dendritic cells after bone marrow transplantation is predictive for the development of acute graft versus host disease.

Kifah Shahin, Mary Sartor, Leah Kim, Derek NJ Hart, Ken F Bradstock.

Dendritic cells (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 Group has extended its search to another biomarker, CCR5, on other DC subsets. The expression of both markers showed a positive correlation with acute GVHD. As these DC markers can be detected in blood, they are potentially very useful diagnostic indicators of GVHD onset. Over a hundred patients have now been studied.

**Prostate Cancer**

RNA loading of tumour associated antigens into blood dendritic cells

Frances Chow, Deok Kwan Yang, Phillip Fromm, Derek Hart

There is worldwide interest in developing immune therapies, including active vaccination with dendritic cells (DC) to treat cancer. Provenge produced by US-based Dendreon has been FDA approved, after a phase 3 clinical trial showed that vaccination prolonged survival in advanced prostate cancer. This has rekindled worldwide interest in DC vaccination. 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 are testing the ability of different DC populations to take up and present RNA encoded tumour targets in preclinical work to allow this technique to be used for DC vaccination in prostate cancer.

**Discovery (basic) Research**

The potential to control inflammation by modulating CD300a and CD300c biomarkers

Georgina J Clark, Derek NJ Hart

It is clear from our own and others work, that the biomarker CD300a is involved in inflammatory responses. Our effort has focused on their significant control of the human dendritic cells (DC) response to inflammation and their interactions with T cells. We are investigating the hypothesis that inflammatory environments alter the ratio of CD300a and CD300c DC and that the pattern of inflammatory cytokine secreted by DC will depend on the ratio of cell surface CD300a and CD300c. If this is correct, then reagents to CD300a and CD300c 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 and other inflammatory diseases.

**CD300f as a target for the treatment of Acute Myeloid Leukaemia**

Georgina J Clark, Derek NJ Hart, Ken F Bradstock

Whilst some leukemias can be cured as a result of advances in treatment options, at least 60% of patients with the most common form of adult leukemia, 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.
**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), Dr Fiona Blyth (CERA), Professor Hal Kendig (CERA)  
 **Staff and Students:** Melisa Litchfield, Janet Gilchrist, Janice Koh, Golnar Moussavi, Diane Pinkerton, Kerrin Bleicher, Noran Hairi, Chris Hoon, Dafna Meram, Fiona Stanaway

**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 and biogerontology. 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 sirtuin enzymes in the aetiology of frailty and social support networks among older men born in Italy.

**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 continue into 2012. We hope to see more than 1000 men. A total of 19 papers have now been produced. Seven papers were published in 2010 and nine in 2011. A particularly important paper was published in the Journal of Clinical Endocrinology and Metabolism describing the longitudinal relationship between serum testosterone levels and frailty.

**Grants: 2010-2011**  

**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 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 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). Blood is being stored for DNA testing.

**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 frailty is being conducted with Tom Travison from Boston University.
Personnel:

**Group Leader:** Professor Garth Nicholson  
**Principal Scientists:** A/Professor Marina Kennerson; Dr Ian Blair  
**Staff and Students:** Obaid Albulym, Carolyn Cecere, Rabia Chaudhry, Shannon Chu, Alexander Drew, De Lian Goh, Ruvini Fernando, Aditi Kidambi, Angela Laird, Carolyn Ly, Natalie Page, Jennifer Solski, Stephen Reddel, Marion Stoll, Sadaf Warraich, Kelly Williams, Shu Yang, Kristy Yuan, Claire Winnick, Ineka Whiteman.

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 finding gene mutations causing neurodegeneration of peripheral nerve and motor neurons. The identification and characterisation of the genes discovered in our families is has uncovered new mechanisms causing degenerative diseases of nerves.

Objectives:  
To determine the underlying causes of neurodegenerative disease as a prerequisite to the development of diagnostic tools and therapy.

Highlights:  
Identification of a new form of X-linked Charcot-Marie-Tooth neuropathy and the causative gene using next generation sequencing and the identification of a new hereditary sensory neuropathy gene DNMT1 which was published in Nature Genetics.  
Proving for the first time that alterations in the TDP43 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. Marina Kennerson gave an invited platform presentation at the 2010 Copper 10 Meeting in Sardinia, Italy for the ATP7A gene discovery. Ian Blair was an invited speaker at the 2010 Asia Pacific Society for Neurochemistry held in Thailand, the Motor Neuron Disease Symposium, Australian Neuroscience Society satellite meeting 2010, and the Motor Neuron Disease Research Institute Annual meeting in 2009. Sadaf Warraich was a finalist for the Concord Hospital Early Career Research award in basic science 2010 and 2011. Richard Shaw 2010-2011 Summer student was a finalist in the Dean's Presentation Award.

Grants: 2010-2011  
**Bushell Foundation- Chu** ‘What gene mutation causes the death of motor neurons in distal hereditary motor neuropathies?’ $35,000  
**Bushell Foundation** – “Discovering genes for X-linked Charcot-Marie-tooth (CMTX) neuropathy using next generation sequencing technologies” $72,000  
**MDA**- Nicholson, Kennerson, Polly, Chaudhry ‘Analysis of structural and regulatory elements of CMTX3 candidate genes’ $108,115  
**MJD Foundation**- Nicholson ‘Establishment of a model phenotype suitable for Machado-Joseph disease (MJD) drug screening’ $200,000  
**MNDRIA**- Yang. “Bill Gole MND Postdoctoral Fellowship” $72,500  
**MNDRIA**- Blair, Nicholson- “Using next-generation DNA sequencing strategies to identify new MND genes” $73,735  
**NHMRC**: Nicholson, Kennerson. “Discovery of Genes For X-linked Charcot-Marie-Tooth Neuropathy” $207,091  
**NHMRC- Phillips, Reddel, Noakes. ‘How are synapses lost in muscle and does this contribute to the loss of strength with age?’ $192,000  
**NHMRC**: Blair, Nicholson. “Investigating the genetic basis of ALS “ $172,508  
**NHMRC- Blair, Nicholson, Hawke. ‘The role of mutant TDP-43 in ALS’ $135,125  
**NHMRC- Blair. ‘Investigating the molecular basis of motor neuron disease’ $102,250  
**Snow Foundation- Nicholson. ‘Program aimed at curing MND: Screening drugs using an animal model’ $424,000
NORTHCOTT NEUROSCIENCE LABORATORY

Prizes:
- PRSS Scholarships to: Alex Drew, Shannon Chu, Obaid Albulym, Kelly Williams, Sadaf Warraich 2010
- James Kentley Memorial Scholarship (Travel Scholarship) to Kelly Williams 2010
- Major Patrick Hore-Ruthven Foundation Scholarship (Gowrie Scholarship Trust Fund) to Kelly Williams
- MNDRIA Bill Gole Fellowship to Dr Shu Yang 2010-2012
- Australian Neuroscience Society conference travel scholarship to Sadaf Warraich
- 3rd Protein Misfolding Conference travel scholarship to Sadaf Warraich
- Concord Repatriation General Hospital Travel Stipend to Marina Kennerson 2010
- National Institutes of Health (NIH) Copper 10 Conference Stipend to Marina Kennerson 2010

Research:

Inherited Peripheral Neuropathies

M Kennerson, O Albulym, A Aziz, R Chaudhry, S Chu, C Ly, A Kidambi, S Reddel, G Nicholson

Charcot-Marie-Tooth (CMT) disease is a degenerative disorder of the peripheral nerve affecting both sensory and motor neurons. It is the most common inherited peripheral neuropathy with one in 2,500 people affected. Motor and sensory neurons represent a unique cell type 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) and is a common feature of many neurodegenerative disorders. 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.

Our work continues 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.

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 we have identified a new unreported locus for a 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.

Motor Neuron Disease

I Blair, S Yang, C Cecere, K Williams, J Solski, A Drew, S Warraich, R Fernando, V Thomas, 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 Zebra Fish Models
I Whiteman, C Winnick, D Goh, A Laird, Jr 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 ‘proteinopath’ 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.

Machado Joseph Zebra Fish Models
A Laird, K Yuan, G Nicholson

Machado Joseph Disease (MJD, or spinocerebellar ataxia-3) is a fatal disease characterised by neurodegeneration within the cerebellum and spinal cord, which leads to a lack of coordination, paralysis and death. MJD affects people of all ages and is particularly prevalent in Indigenous communities in Arnhem Land and Groote Eylandt. Because there is currently no treatment for MJD, we are developing an zebrafish model to study the disease and screen for potential drug therapies. Zebrafish, are well suited for use in these studies because they are transparent during development allowing observation of their neuroanatomy and pathology in vivo. We have genetically modifying zebrafish to express the mutated human gene that causes MJD and we are currently observing the fish for signs of neurological dysfunction. Following the characterisation of the disease features expressed by the fish we will commence screening drug treatments in the fish, aiming to reverse signs of the disease. This research is supported by the MJD Foundation.

Parkinson’s Disease
N. Page 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.

Myasthenia Gravis
Myastheniagravis is a chronic muscle disease that produces muscle weakness. The cause of this disorder is unknown but the muscle weakness occurs because the electrical signal between the nerve and the muscle is disrupted. In a collaboration between Stephen Reddel (ANZAC) and Bill Phillips (Physiology) their team have examined how autoantibodies from patients with Myasthenia Gravis disrupt the neuromuscular junction in a mouse passive transfer model. This work is supported by grants from MDA (4172), NHMRC Australia (570930), the Australian Myasthenic Association in NSW and the Brain Foundation of Australia. The figure shows anti-MuSK antibodies result in fragmentation of the acetylcholine receptor (AChR) cluster, loss of AChR and separation of the synaptophysin labelled nerve terminal from the post synaptic AChR labelled synapse.

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).

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 Gitler, (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 Wayne State University (Mike Shy), Rochester University (Jim Garbern) University of Antwerpen (Vincent Timmerman; Peter De Jonghe); Baylor Medical College (Jim Lupski); University of Miami (Stephan Zuchner); National Institute of Health NIH/NINDS (Kenneth Fischbeck); Murdoch Childrens Research Institute (Eppie Yiu, Monique Ryan, Kate Pope). Through our work with the ATP7A gene we have collaborations with Professor Julian Mercer and Sharon La Fontaine (Deakin University, Melbourne).
Personnel:

**Group Leader:** Professor Ben Freedman

**Senior Scientist:** Prof Len Kritharides, Prof David Brieger, A/Prof Harry Lowe, Dr Jenny Curnow

**Staff and Students:** Dr Julie Redfern, Dr Raymond Sy, Dr Gabrielle Pennings, Dr Wei Zhao, Dr Caroline Reddel, Dr Vincent Chow, Dr Andy Yong, Dr James Edelman, Dr Clement Wong, Dr Tommy Chung, Dr Austin Ng, Dr Mohammed Aziz Moharram, Anu Shanu, Lis Neubeck, Vicky Benson, Alana Mohamed, Rhoda Ascanio, Anna Jackson, Vincy Li, Roshanak Aran, Marzy Nikanami, Rajesh Gounder, Corine De Graaf, Stefanie Reuslaars, Justine Siegwald, Bernadette Aliprandi-Costa, Aileen Siney, and Nicole Lowres.

Role:

Cardiovascular disease relates to disease of the heart and blood vessels. This can cause heart attack, stroke, heart failure and poor blood supply to the legs. It causes 30% of deaths worldwide according to the World Health Organization, and 34% of deaths in Australia.

Objectives:

Research within the Vascular Biology Group incorporates a mixture of basic and clinical science aimed at understanding, preventing and treating cardiovascular disease and its complications. Areas of interest in relation to include:

- Inflammation in cardiovascular disease
- 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 trouble using cardiac rehabilitation Choice of Health Options In Preventing Cardiac Events (CHOICE Study)

Highlights:

Supporting young undergraduate and postgraduate researchers, with Dr Andy Yong graduating with a PhD from the USyd; Alana Mohammed graduating with a Masters from the USyd and Ben Rayner and Vicky Benson submitting their respective PhDs for assessment. Dr Yong’s recent publication (in the journal Blood), received editorial commentary and was co-awarded the Dean’s prize for best postgraduate student publication in the Faculty of Medicine for 2010. Dr Caroline Reddel was awarded the early-career postdoctoral award for an outstanding poster presentation at the 18th Australian Vascular Biology Society Annual Meeting for 2010.

Grants: 2010-2011

- ARC Discovery: Witting. ‘Cellular response to pro-oxidative myoglobin’ $140,000
- HCF Grant-in-aid: Freedman. ‘Choice study for secondary prevention of heart disease’ $228,012
- Heart Foundation: Yong. “Heart Foundation Travel Grants” $2,000
- NHMRC: Yong ‘Medical Postgrad Scholarship’ $35,000
- Pfizer CVL- Ng, Chung, Kritharides ‘Long-term mortality and late pulmonary hypertension after acute pulmonary embolism’ $55,000
- Pfizer CVL- Yong, Kritharides, Lowe, Ng ‘Intracoronary upregulation of platelet P-selectin in patients taking aspirin and clopidogrel’ $53,492
- Servier Grant - Witting. The Heart Rate-Lowering Drug Ivabradine Protects the Myocardium from ischemia reperfusion injury $48000

Research:

Inflammation involves the activities of white blood cells and their interaction with the tissues of the body. Inflammation is promoted and sustained by a number of factors and is very relevant to cardiovascular disease and its complications of heart attack and stroke. There are several lines of work relating to inflammation in our group. Two of these are summarised below.
Inflammation-Serum Amyloid A (SAA)

One aim is to define links between inflammation and damage of the endothelium – the lining of arteries. We have shown that SAA (Serum Amyloid A), which is an inflammation marker predictive of death or heart attack in both normal populations and those with CAD, can stimulate endothelial cells to produce tissue factor, the most powerful initiator of clotting. SAA also increases the production of inflammation molecules on endothelial cells, which are key in initiation and progression of atherosclerosis. SAA may play a role in endothelial dysfunction and blood clotting which precipitates adverse events. We have also demonstrated an important protective effect of HDL, part of the 'good cholesterol' that has other protective actions against the harmful effects of SAA. atherosclerosis. Major contributors to this work are Professor Freedman, Dr Paul Witting, Prof Carolyn Geczy (UNSW), and Professor Kerry-Anne Rye.

Inflammation- Platelet and Leukocyte Activation in CAD

White blood cells are the major inflammation-mediators, however their role is closely linked to that of another cell type called platelets. Although platelets are primarily known for their capacity to promote the clotting of blood, they also promote inflammation and the development of cardiovascular disease. 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.

We have found that levels of EMMPRIN or CD147, which has previously been studied as a cancer marker, are increased on both white blood cells and platelets in patients with coronary disease. We have also found that the tightness or severity of a narrowing in a coronary artery in itself causes the activation of white blood cells and platelets as detected using the platelet marker P-selectin and the white cell marker CD11b. This work has been greatly enhanced by directly measuring shear stress across coronary lesions in collaboration with post graduate students co-supervised by Professor M Behnia from the Faculty of Engineering at the University of Sydney, and ongoing studies of soluble GPVI with Drs E Gardiner and R Andrews (Centre for Blood diseases, Monash University). In collaboration with Dr Michael Vallely and the RPAH Baird Institute, Dr James Edelman has been investigating the profiles of inflammation after cardiac surgery. He has found both similarities and differences in the inflammatory response to conventional on-pump surgery and to off-pump surgery. He has also identified sustained abnormalities of coagulation in patients after surgery. Major contributors to this work are Professor Kritharides, and Drs Yong, Pennings, Reddel and Curnow,

Novel Intravascular Imaging Using Optical Coherence Tomography (OCT)

We are using the novel technique of Optical Coherence Tomography (OCT) to image coronary arteries in vivo and in ex vivo experiments. OCT uses light to image coronary arteries in exquisite detail and is giving unrivalled information regarding the processes of atherosclerosis and the results following coronary stenting and other interventions. The group has particular interest in the assessment of atheromatous lesions in the setting of coronary stenting and is part of an international multicentre longitudinal study of outcomes following OCT from Massachusetts General Hospital, Boston, USA. Lead investigator for this work is Associate Professor Lowe.

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 for clotting include the Overall Haemostatic Potential (OHP) assay and Calibrated Automated Thrombogram (CAT). 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 Reddell, in collaboration with Professors Brieger and Kritharides.

Echocardiographic evaluation of cardiac dysfunction

Patients with clots in the lungs (pulmonary embolism) or high blood pressure in the lungs (pulmonary hypertension) commonly have problems with the right side of the heart. We are investigating the acute and long term effects on the heart, and whether we can detect improvements more accurately using new ultrasound techniques. These studies are being undertaken by Drs Vincent Chow, Wei Zhao and Len Kritharides in conjunction with Drs Ng
and Chung from the Department of Cardiology, and Professor Peters and Dr Seecombe of the Dept of Respiratory Medicine at CRGH. In conjunction with colleagues from Croydon and Burwood psychiatric units, we are investigating the incidence of cardiac dysfunction in patients taking clozapine. Using state of the art echocardiographic analysis Dr Chow is identifying subclinical cardiac dysfunction in these patients and is investigating is investigating the effects of androgen receptor expression and androgen deficiency on myocardial function in mice.

**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, which can be reduced by effective programs of secondary prevention like cardiac rehabilitation. Unfortunately, 70% of survivors do not access formal cardiac rehabilitation, and their risk factor levels are much higher than those who do attend. 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. The program was extremely effective and results persisted for 1 year. Our follow up of the original cohort indicated the effect was long lasting and little diminished at 4 years. Current studies will extend the program and examine 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.

In our current study we have enrolled almost 300 patients who have survived a coronary event but elected not to participate in traditional cardiac rehabilitation and we have completed baseline and one year follow ups. 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 Ms Neubeck
Personnel:

Group Leader: Dr Brian O’Toole

Co-investigators: Professor Stanley Catts (Univ of Qld), Dr Sue Outram (Univ of Newcastle), Professor Mark Dadds (UNSW and Institute of Psychiatry, Kings College London)

Role:

The Australian Vietnam Veterans Health Study was begun at Sydney University in the late 1980s and has followed a cohort of veterans for over 30 years, with significant support from Concord over the years. With Army assistance, a random sample of 1,000 veterans was identified and, with assistance of the Australian Bureau of Statistics and the Department of Veterans Affairs, the first health assessments were undertaken in 1990-92 with funding received from the NHMRC. Over 25 publications have come from the first wave of the study, the most recent in 2008, which continues to provide a solid evidential base for data analysis into the future.

In 2005-06 the study assessments were repeated, again with funding from NHMRC. This has added to the data cache and opened up a much richer prospect for scientific contributions to the knowledge about the long term effects of war service. In 2006-07 the study was expanded to include wives and partners of the veterans, with additional funding support from the Australian Rotary Health Research Foundation. In this study, veterans’ wives/partners were assessed using the same procedures as used for the veterans, and the assistance of the Bureau of Statistics was also made available to the study. In late 2010 the group learned of success in grant application to NHMRC, which has provided nearly $¾M in funding support to extend the study to veterans’ children. This has been supplemented by a generous private donation of a six-figure sum. This Veteran Sons and Daughters Project is as large as the veteran and wives studies combined, and completes a family health study first envisioned nearly ten years ago.

Many discrete projects are under way, supported by modern and sophisticated data analysis techniques and using the veteran cohort study as a base. Each comprises a project that is aimed at providing important insight into the aetiology, maintenance and treatment of war-related illnesses and the warriors who endure them, and allows the incorporation of veteran cohort data into data arising from the companion study of veterans’ wives and partners. The future collection of data from veterans’ now grown sons and daughters will permit a series of important but complex analyses, to assess the effects of war on veterans’ offspring, and to determine the inter-relationships of their mothers and fathers in the psychological development of the children.

Objectives:

To determine the long-term effects of war service on Australian veterans and their families and to provide the best scientific evidence on which to base policy and treatment decisions and the timing of interventions that will enhance the health and welfare of veterans and their families.

Grants: 2010-2011

NHMRC: O’Toole, Catts “Does PTSD in a parent increase the risk of mental health disorders in their offspring?” $222,656.

Research:

Several lines of research are progressing, into the general and specific associations of war service with a large range of outcomes in both veterans and their partners. Examples include explaining the associations we observed between veterans’ levels of combat exposure and their partners’ marital adjustment three decades later, or the association we detected between partners’ PTSD status and her veteran partners’ PTSD, or the factors that predict ongoing PTSD rather than resolution in veterans, or the longitudinal assessment of the appearances of various diagnoses and the factors contributing to these, and the physical and mental comorbidities associated with PTSD in both veterans and their partners.
Table 1. Prevalence of thoughts of death, suicidal ideation, suicide planning and suicide attempt in Australian Vietnam veterans and their partners, expected prevalence from Australian National Survey of Mental Health and Wellbeing (NSMHWB 1997), and relative prevalence (ratio of observed to expected) and 95% confidence interval of veterans and their partners compared with the Australian population.

<table>
<thead>
<tr>
<th></th>
<th>Observed Prevalence</th>
<th>Expected Prevalence</th>
<th>Relative Prevalence</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Veterans</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoughts of death</td>
<td>13.1%</td>
<td>4.8%</td>
<td>2.95</td>
<td>2.25 – 3.65</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>9.8%</td>
<td>1.5%</td>
<td>8.07</td>
<td>5.81 – 10.33</td>
</tr>
<tr>
<td>Made suicide plan</td>
<td>5.6%</td>
<td>0.9%</td>
<td>7.94</td>
<td>4.91 – 4.91</td>
</tr>
<tr>
<td>Attempted suicide</td>
<td>2.4%</td>
<td>0.1%</td>
<td>13.15</td>
<td>5.75 – 10.96</td>
</tr>
<tr>
<td>Thoughts of death</td>
<td>30.0%</td>
<td>7.6%</td>
<td>3.96</td>
<td>3.19 – 4.73</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>15.2%</td>
<td>2.5%</td>
<td>6.24</td>
<td>4.36 – 8.12</td>
</tr>
<tr>
<td>Made suicide plan</td>
<td>5.1%</td>
<td>1.4%</td>
<td>3.53</td>
<td>1.58 – 5.48</td>
</tr>
<tr>
<td>Attempted suicide</td>
<td>2.5%</td>
<td>0.3%</td>
<td>5.99</td>
<td>1.26 – 10.73</td>
</tr>
<tr>
<td><strong>Partners</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

One specific project is examining the issue of suicidality in veterans and their partners. In the course of the psychiatric diagnostic interviews, in the depression module there is a set of hierarchical questions regarding personal thoughts of death, thoughts of suicide (suicidal ideation), making a plan, and attempting to commit suicide. Comparison of the veteran and partner cohorts with the background Australian population show the following results:

These are remarkable findings: As expected, the prevalence of each of the suicidality items decreases as the seriousness of the items increases. However, thoughts of death are alarmingly high among veterans’ partners (30% where only 7.6% is expected based on the population data from the Australian Bureau of Statistics), much higher than background rates (3.96 times higher, with 95% confidence interval 3.19 – 4.73). The incidence of suicide attempts is more than 13 times higher than expected for veterans, and nearly six times higher for partners.

This information alone should really set alarm bells ringing for government. These data were collected more than 30 years after the war. While it is broadly accepted that suicide risk in war veterans peaks about 5 years after the war and then declines, these results show that there is a swell of suicidality present among veterans and their partners that does not necessarily result in a completed act. When the items are summed, to produce a “suicidality index”, there is a clear statistically significant relationship between the total suicidality score and veteran combat, and this relationship is apparent for both veterans and their partners.

The results of the study go beyond the general measures of psychological distress of war veterans’ partners reported by other studies. They show that the partners of veterans are not just struggling with their impaired partner but are suffering elevated rates of serious psychiatric illness, even 30 years after the war. The disparity between rates of psychiatric disorder and healthcare utilization suggests greater attention to ensuring adequate assessment and treatment of partners is required. We expect that these higher rates of mental ill-health in both veterans and their partners will have major implications for the mental health of their offspring.

**Developments:**

Results like those above uncover the need to extend the research effort to encompass the effects of military and war service on the people who serve their country and their families. Efforts are proceeding to get the attention of the Government including the Department of Veterans Affairs and the range of Ex-Service Organisations including Legacy, to work to establish a Centre devoted to health research applied to the families of current of former members of the Armed Forces.

**Collaborations:**

Dr O’Toole has been invited to join the Consortium on Emerging Technologies, Military Operations, and National Security (CETMONS) based in the USA. Dr O’Toole has been invited to join the National Peace Academy in the United States.
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FINANCIAL PERFORMANCE

Income & Expenditure 2001-2011

Millions

$10

$8

$6

$4

$2

$-


Income  Expenditure
Felicity Barr (Chair)

Dr Felicity Barr’s career included senior executive appointments in charge of national veterans’ health services and as Deputy Commissioner for NSW veterans’ services. Since leaving the Australian Public Service in 2003 to pursue her interests in the social issues of ageing, her research has earned her master’s and doctoral qualifications. She currently chairs the Advisory Board for the Research Centre for Gender, Health & Ageing, at the University of Newcastle, serves as a member of the Governing Council and the Audit & Risk Management Committee of Hunter New England Health, Councillor of the Ageing & Alzheimer’s Research Foundation, and President (Hunter Chapter) of the Australian Association of Gerontology.

Danny O’Connor (Deputy Chair)

Danny O’Connor is the Chief Executive of Western Sydney Local Health District. His previous experience includes working as a clinician with the Community Drug Advisory Service in Surry Hills, Sydney, a research officer with the New South Wales Drug and Alcohol Authority and then State Coordinator for methadone treatment in New South Wales. He worked in the public health division of the NSW Health Department as a senior policy analyst before becoming Director of Drug Health Services in Central Sydney Area Health Service. He later moved into hospital management as General Manager, Sydney Dental Hospital and then General Manager of Concord Repatriation General Hospital. Prior to his present role he was Chief Executive of Greater Western Area Health Service.

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.

Prof Diana Horvath

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 Assocn (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 Asssoc 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.
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 Heath 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 David Cook

Professor David Cook currently holds the Chair of Cellular Physiology at The University of Sydney. He was awarded an MD in 1995, the Gottschalk Medal of the Australian Academy of Science in 1996 and became University of Sydney Medical Foundation Fellow of the Faculty of Medicine in 1997 when he was also promoted to professor. His research interests are in the role of ion channels and other transporters in the cell membrane and how control membrane transport activity. In addition to his research and teaching within the Department of Physiology, he serves as Deputy Chair of the Central Sydney Area Health Service Human Ethics Committee and chairs the Clinical Trials Subcommittee at Royal Prince Alfred Hospital.

Professor Bruce Robinson

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.
Professor Robert Lusby

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.

Emeritus Professor Kerry Goulston

Kerry Goulston is Emeritus Professor of the University of Sydney. Previous experience includes being Associate Dean of the Northern Clinical School of the Sydney Medical School and Chair of the NSW Greater Metropolitan Clinical taskforce (GMCT). He has been a practising Gastroenterologist for many years and has a longstanding record in research and teaching. Currently Deputy Chair of the Australia Vietnam Medical Foundation (Hocmai).

Brian Lee

Brian Lee spent his career in the medical supply industry and retired as the Area Managing Director (Australia and New Zealand) for Baxter Healthcare. He was the past National President of the Leukemia Foundation of Australia and former director of Medical Specialties Australia. Brian has been a long-time advocate and supporter of ANZAC Health and Medical Research Foundation and currently chairs the Fundraising Subcommittee on the current Board.

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 Gary Miller

General Manager, Director, Operations, Sydney Local Health District. Gary is a registered nurse with both mental health and general nursing experience and holds a Bachelor of Business with a major in Management. Prior to his appointment as Director, Operations he held the position of General Manager at Concord Repatriation General Hospital. He has previously held a number of senior positions including General Manager at Canterbury Hospital and with the then Central Sydney Area Mental Health Service and at Rozelle Hospital.

Godfrey (Rusty) Priest AM

Rusty Priest was an inaugural member of the AH&MRF serving as its Deputy Chair from 1995 to 2003. He enlisted in the 2nd AIF in June 1945, serving with British Commonwealth Occupation Forces from 1946 to 1948, the Australian Regular Army from 1946 to 1967 and the Emergency Reserve until 1975. Then he held a management position at the University of Sydney, retiring in 1990. A past President (1993-2002) of the Returned and Services League of Australia (NSW Branch) and extensively involved in all matters affecting the welfare of veterans and their dependants. He serves currently as Chairman of the Board of Directors of the Kokoda Track Memorial Walkway Ltd.
### Corporations
- Bartent Pty Ltd: $50,000
- Gwynvill Trading Pty Ltd: $25,000
- Arnmore Pty Ltd - Ray White South Brisbane: $15,000
- Lin Corporation Pty Ltd: $3,500

### Community Organisations
- Charcot-Marie-Tooth Association of Australia INC: $22,000
- Enfield-Croydon Park RSL Sub-Branch: $10,000
- Chester Hill -Carramar Sub Branch RSL: $1,000
- Beta Sigma Phi, Delta Master Sydney: $700
- Warringah Council: $200
- Returned & Services League of Aust (NSW Branch): $500
- City of Canada Bay: $200
- Clovelly RSL Sub-Branch: $100
- Combined Services RSL (Sydney): $100

### Bequest
- Avern McIntyre & Co: $86,093
- University of Sydney: $50,000

### FOTARI
- Clare Loudon: $70,000
- Dr Garth Nicholson: $23,000
- Mrs A Mildenhall: $10,000
- Ms M Graham: $8,000
- Andrew G Richardson: $1,000
- John C Gordon: $1,000
- Lily Matic: $1,000
- R. W. Balfour: $1,000
- Raymond Davis Paul: $960
- Dr Charles Pawsey: $720
- Gregory Falk: $600
- Ross Bradbury: $580
- Asbestos Diseases Foundation of Australia Inc: $500
- Beacon Hill Youth Club: $500
- Garrard Desmond Pearce: $460
- Steven Kalowski: $333
- Ramon Bullock: $300
- Cegedim Strategic Data Australia Pty Ltd: $250
- Dr Kerry J Goulston: $250
- Major John P. Kelly (Ret’d): $200
- Mr Alan Davidson: $200
- Mr R D Butcher: $200
- Mrs Wendie-Sue Lyons: $200
- Angela D’Amore MP: $150
- Brigadier RW Morris: $150
- Dr Graham Dunn: $150
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- Beryl Elliott: $100
- J & A Collins: $100
- Mrs Therese Cashman: $100
- Mr FJ Colwell: $100
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Date: ______________________________

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www.anzac.edu.au
Email: anzac@anzac.edu.au

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