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

Mission
• To establish and operate a state-of-the-art biomedical research institute on the campus of Concord Hospital that is affiliated with the University of Sydney.
• To encourage, collaborate in and undertake basic, clinical and epidemiological research, with a particular focus on ageing, that aims to improve health and medical care and is dedicated to the memory of our war veterans and their families.
• To gain and optimise support from the wider community in order to facilitate our vision.
• To provide leadership and excellence in biomedical research in national and international arenas.
• To foster education and training in relevant research and health disciplines.
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With enormous pride, we bring to a close the first decade of operations of the ANZAC Research Institute. All those who have been associated with the creation and development of the Institute from its early beginnings to the present day will find great satisfaction in reading through this Annual Report and learning of the important and excellent research work being undertaken by the ANZAC research groups across their varied disciplines. The current success of the Institute could not have been achieved without the significant support of our key stakeholders, especially The University of Sydney and the Sydney South-West Area Health Service. The Board is particularly grateful for their assistance with the expansion of the Institute to occupy the new laboratories in the Bernie Banton Centre.

Throughout the year, the Board has been concerned by continued uncertainty over the ongoing availability of funding for essential infrastructure. Like most other medical research institutes (MRIs), the ANZAC Institute benefits from its situational relationship with The University of Sydney and Concord Hospital and the Board believes that both hospital and university find the relationship equally beneficial. The downside of the situation is that when funding demarcation occurs, MRIs always find themselves on the wrong side of the demarcation line. When education/research funding is discussed, MRIs become hospital entities; when hospital funding is discussed, they are seen as research entities. The ANZAC Institute has been remarkably successful in attracting high-quality research grants for its work, but only rarely are such grants accompanied by a component for infrastructure support.

The Board has been both disappointed and concerned as the certainty surrounding NSW government programs for infrastructure funding for MRIs has dissipated over recent years. Assurances that the triennial funding regime would be restored have proven inaccurate; forecasts of imminent clarification of state and Federal responsibilities have also proven optimistic. New complications frequently arise by way of reviews of Federal tertiary education funding, COAG agreements on health reforms which fail to clarify funding for MRIs, and of course, the destabilising effect of Federal and State elections. The Board’s concerns have been complicated by the lowered income on the Foundation’s investments as a residual effect of the global financial crisis.

In spite of these concerns, I am pleased to note the satisfactory results, both financial and research outcomes reported in the following pages. On behalf of the Board, I congratulate Professor 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.

Lastly, I must acknowledge the contribution of retiring Board members Ms Kerry Russell, who was replaced by incoming General Manager for Concord Repatriation General Hospital Mr Gary Miller, and Dr Charles Pawsey. In particular I acknowledge the support and involvement of Dr Pawsey during his long term as a Director of the Board and thank him for ensuring the support of the Hospital’s medical staff for the development of the ANZAC Research Institute. We welcomed Mr Miller and Dr Ross Bradbury who has replaced Dr Pawsey as the Director representing the medical staff at CRGH.
Welcome to our Annual Report for this year which marks the 10th anniversary of the ANZAC Research Institute. As has become customary, we can report another very successful year for all our goals – making research discoveries, winning external grant funding, publishing influential papers in major 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 37 graduate (PhD) students. Altogether we earn an annual external grant-based income of over $8 million based on maintaining over double the national average success rate for NHMRC grant and publish 180 scientific papers per year in top journals. We have managed this with minimal overhead costs to keep the doors open and the scientific facilities and services operating as required for top research to flourish. You can see an outline of the innovative work of the Institute’s research groups in the following pages. 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, we have earned a reputation for scientific excellence through work covering a diverse range of areas including andrology, burns, cancer, cardiovascular disease, osteoporosis, neurodegenerative diseases, and population research into ageing and the health of veterans. In the last year we have been joined by a leading immunology group, the Dendritic Cell Biology Group headed by Professor Derek Hart whom we are delighted to welcome. Prof Hart successful recruitment to Sydney from Brisbane brings not only world leading expertise in translational immunology research but also a new NHMRC Program Grant into the ANZAC as well as the University of Sydney.

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 cooperative vision set a solid foundation for the ANZAC Research Institute’s path to success. They foresaw a dedicated, state-of-the-art facility for high impact medical research at Concord Hospital as it became a major teaching hospital of the University of Sydney Medical School and the NSW Health system. But our development could not have been achieved without another vital ingredient, the enlightened support by the NSW government in providing funding for the costs of doing medical research. Then as now hospital-based organisations are not eligible for Federal infrastructural support provided to Universities for doing the same research. However, now as we move into our second decade we are caught in cross-currents. Over the last two years NSW infrastructural support has declined in the expectation that Commonwealth government support will pick up the shortfall. Conversely, the Commonwealth is creating an artificial separation between Universities and medical research institutes and driving apart natural research partners rather than unifying and maximising our joint efforts. These create an increasingly difficult climate for maintaining vital support for our medical scientists doing high quality research. Hopefully a more enlightened framework will prevail soon so we can continue building on success. Currently we have to dip into savings to maintain operations let alone being able to invest in the new ventures and natural expansion that successful research makes possible.

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 government which recognizes the value of medical research can keep the Institute going strong.

Once again the Annual Report gives me the opportunity to express my thanks and real gratitude to the many who make it possible to discharge my pleasant duties. The Institute’s work depends on the goodwill and skilful and diligent work of our terrific administrative team - Justin Crosbie, Tracey Dent, Annet Doss, Candice Chang, Mark Jimenez, Mamdouh Khalil, Pam McDowell, Julie Taranto & Babita Das. They make the necessary work go lightly – it is a pleasure to thank them most sincerely. Thanks are also due to the General Manager of Concord Hospital, Gary Miller, and Michael Wallace, CEO of the Sydney South West Area Health Service for their consistent support without which we could not operate. Similarly, the ongoing support of the Sydney Medical School, Professors Robert Lusby and David Cook in particular, is gratefully appreciated. Thanks are also due to John Gatfield for editing of our newsletter Discovery. Finally, it is a pleasure to thank Dr Felicity Barr, the Chair and her Board, for their unwavering support and enlightened commitment to making the Institute as good as it can be. Above all, it is a privilege to work in the challenging and productive environment created by the Institute’s scientists and I am grateful to them always for 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, Assoc Prof Ann Conway, Lisa Corcoran, Irene Di Pierro, Carolyn Fennell, Ellen Gao, Rasmani Hazra, Amanda Idan, Dr Veena Jayadev, Mark Jimenez, Shai Joseph, Patty Kapelaris, Sarah Lamb, Lucy Liu, Dr Lam Ly, Dr Kisten McTavish, Keely McNamara, Jennifer Spaliviero, Sasa Spasevska, Leo Turner, Ljubica Vrga, Lucy Yang.

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:

- **Prof David Handelsman:** Appointed Associate Editor (Male Reproduction) for the Journal of Clinical Endocrinology, 2009
- **Dr Kirsty Walters:** Young Investigator Award from Australian Menopause Society, 2009

Grants:

- **Andrology Australia- Jayadev:** "Development of a postgraduate education program for a clinical fellow in Andrology" $15,000
- **Anti-Doping Research Panel Grant- Heather, Handelsman:** "Novel androgen bioassay for detection of designer androgens" $131,000
- **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
- **Cancer Australia/NHMRC- Simanainen, Handelsman, Zhou, Seibel:** “The role of intraprostatic glucocorticoid action in prostate physiology and pathology” $73,563
- **Cancer Institute NSW- Simanainen:** “The role of androgens in prostate physiology and pathology” $198,283
- **MBF Foundation- Handelsman, Liu, McLachlan:** “Development of valid diagnostic criteria for age-related androgen deficiency in men” $154,167
- **NHMRC- Liu, Grunstein, Handelsman:** “Obstructive sleep apnea and androgen dysregulation” $170,750
- **NHMRC- Walters, Handelsman, Allan:** “Androgen receptor mechanisms in female reproductive physiology” $173,500
- **NHMRC- Allan, Handelsman:** “The Sertoli cell: master regulator of hormone-induced spermatogenic development” $184,500

NHMRC- Allan, Handelsman. “Hormonal control of Sertoli cell maturation and function” $171,050

NHMRC- Allan, Handelsman, Dunstan. “FSH and female aging” $110,257

University of Sydney- Travison “Population based studies of hormone decline and physical function in older men.” $8,500

University of Sydney Bridging Scheme- Simanainen, Handelsman, Harwood. “Steroid activation and androgen signalling as targets in prostate cancer” $50,000

University of Sydney Bridging Scheme- Walters, Handelsman. “Androgen mechanisms in female reproduction” $50,000

USYD Research Infrastruct Major Equipment Grant- Allan. “Rotor-Gene 6000 Real-time Amplification System” $26,264

WADA- Handelsman, Kazlauskas, Trout, Goebel, Idan, Turner. “Detection of indirect androgen doping with a GnRH analog (Leuprolide)” $200,000

World Health Organisation- Handelsman, McLachlan. “Sperm suppression and contraception protection provided by norethisterone enantate (Net-En) combined with testosterone undecanoate (TU) in healthy men. Master protocol A25165” $125,000

Prizes:
- Prof David Handelsman: RFD Award and Plenary Lecture, Society for Reproductive Biology, 2010
- Dr Charles Allan: Chair of the Joint ESA/SRB LOC a& or POC, Society for Reproductive Biology, 2010
- Ms Keely McNamara, University runner-up Three Minute Thesis Competition, 2010
- Dr Tom Travison (Boston University), US International Travelling Fellowship 2009-10
- Prof David Handelsman: Appointed Associate Editor (Male Reproduction) for the Journal of Clinical Endocrinology and Metabolism, 2009
- Dr Kirsty Walters: Young Investigator Award from Australian Menopause Society, 2009

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, our team continues to research the best and most acceptable forms of delivery of testosterone treatment for men who need this treatment. Our extensive research into various depot forms of testosterone has 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 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 standards used for these purposes. However, there are limitations of these techniques 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. These new generation of highly accurate assays are now affordable and now match the sensitivity of immunoassays while maintaining reference level specificity of MS.

We have developed an ultra-sensitive LC-MS/MS method using a state-of-the-art API 5000 mass spectrometer (funded by an ARC LIEF grant). It can measure accurately and sensitively androgens (testosterone, dihydrotestosterone and androstanediol isomers) and estrogens (estradiol and estrone) to low levels within a single run without derivatization (Fig 1). In fact, we are now able to accurately measure serum levels of testosterone from women and estradiol from men, which have...
traditionally been difficult to measure accurately by previous methodologies. Sample preparation involves a simple liquid-liquid extraction procedure and with an analysis time of less than 10 minutes with potential for higher throughput by using microtitre plate format and with simple adaptation, tissue and non-human samples can be analysed. Most recently we applied these highly sensitive methods to analysis of serum androgens and estrogens in serum samples from a wide variety of animal species with important findings that require re-evaluation of much of the previous knowledge.

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.

Together with our collaborators at NMI, we have completed studies to develop novel methods to detect abuse of other potential anabolic agents that act through increasing androgen output (such as hCG, and recombinant LH) or through other mechanisms (such as insulin). A recently completed pilot study revealed that short term use of an injectable GnRH analog produces a sustained increase in testosterone levels which may not only go undetected using the current method of sports doping urine tests but may also serve to “mask” the abuse of other androgens at the same time. Based on these important findings, a larger WADA-funded study is underway to extend and detail these findings so as to develop more effective detection tests.

We developed a national, state-based surveillance of PBS-funded testosterone prescribing patterns. This has identified patterns of over-use that call for heightened surveillance and increased professional and public education to make clear the differences between valid evidence-based use of testosterone treatment and deterring misguided overuse lacking reliable evidence of safety and effectiveness. Fortunately, surveys of Australian high school students we have reviewed indicate that androgen abuse has remained at steady, relatively low levels during the last decade.

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-
ANDROLOGY

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. When boys pass the usual time for puberty without experiencing the expected body changes, the secondary sexual characteristics (such as voice change and growth of muscle and body hair) that are the distinctive features of a man’s body, this is called delayed puberty. Delayed puberty can have deep and lasting effects on a developing man’s psyche because of the difficulties it creates in “fitting-in”, on how they are perceived as immature by others and themselves, creating difficulties in finding a social niche and forming life-long conjugal partnerships. Delayed puberty in boys is a common problem presenting to paediatricians and treatment is often further deferred while doctors and parents wait in hope that puberty may “catch-up” naturally. More pro-active and effective treatments for delayed male puberty are important area for further study.

The Andrology department is developing several studies related to male puberty. In one, the Department is coordinating a large multi-centre study of pubertal failure involving all major Australia and New Zealand pediatric endocrinology centres to test whether new recombinant gonadotrophin treatment is superior to the conventional form of testosterone treatment currently used world-wide. This study has the potential to change medical practice in the management of delayed puberty in adolescent boys. The Department is also supporting the ARCHER study, a rural community based adolescent cohort study of puberty, its variations and the impact of these on the development of health and wellbeing in young adults.

In order to conduct studies of male puberty in the community, better objective and quantitative measures of progress of male puberty are needed. While blood tests are very useful, they are invasive and hard to get in large community-based studies and they also only provide a single instantaneous measure of hormones levels, rather than an integrated measure over time. Furthermore, it is not possible to tell the onset of male sexual activity or of sperm production by any objective tests. We are therefore developing novel ways to measure these important, but difficult to study, endpoints by examining urine specimens.

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 has been completed to evaluate whether DHT is effective in preventing prostate growth in middle-aged men without known prostate disease. It also aims to determine DHT treatment has any adverse effects on bone or the cardiovascular system. This study also provides unique foresight into the likely benefits and risks of the new class of pure androgens, known as SARMs, for which DHT is the prototype. This randomised, double blind placebo controlled study is investigator-initiated and sponsored by an overseas pharmaceutical company. Our findings show that prostate growth was not influenced by the daily topical administration of DHT over a 2 year period and overall had a variety of expected benefits and remained relatively safe to use. The results have been presented to the US and Australian Endocrine Societies and a manuscript has been submitted to a major international journal.

Origins of Prostate Disease
K Griffiths, G Sartorious, B Jin, L Chan, A Conway, DJ Handelsman

Our clinical studies on the origins of prostate disease have also focussed on early life factors (such as pre-birth or during puberty) that may predestine the development of prostate disease decades later. We are undertaking two long-term clinical cohort studies. In one, we are following a cohort of 570 men studied 5-10 years previously to measure the growth rate of the human prostate by ultrasound and to identify lifestyle, hormonal and genetic factors that may influence it. In the second study, we are focussing on how events before and soon after birth may determine the susceptibility of the prostate to diseases such as prostate cancer and hyperplasia in later life. In this project, we are establishing a birth cohort of young men born in inner Sydney and who are now in their early 30’s. The latter study requires us to trace young men born in Sydney around 1970 using hospital birth records. In contrast to a birth cohort of girls developed
by collaborators in Adelaide, the recruitment of boys in Sydney has proved to be much more difficult, due, at least in part, to the requirement for an invasive transrectal ultrasound. As a response, we developed and validated a new less invasive method, transperineal ultrasound, which we showed to be as reliable as the standard transrectal methods. This new method published in the top Urology journal should facilitate future population studies of healthy men prior to onset of overt prostate disease.

**Tissue-selective Role of Androgens in the Prostate**

*U Simanainen, K McNamara, E Gao, CM Allan, DJ Handelsman*

The androgen receptor (AR) has a crucial role in both normal prostate development and the emergence and progression of prostate cancer. Ulla Simanainen (PhD, Finland) has joined the laboratory to study the AR and prostate function by applying innovative transgenic approaches to selectively disrupt AR function in defined cell types within the mouse prostate. We have created a model targeting AR in the prostate epithelium to explore the role of androgen in the development of structures fundamental to normal functioning prostate, as well as in prostate proliferative diseases of benign prostate hyperplasia and cancer that develop in later life. Our ongoing research will also investigate the influence of selective AR deprivation on long-term steroidal sensitivity of the prostate, noting that early hormonal exposure and deprivation may have long-range influences and essential roles in the subsequent development of prostate cancer later in life. 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.

**Gonadotrophin Replacement Therapy in Treatment for Male Infertility**

*A Idan, A Conway, DJ Handelsman*

Most causes of male infertility are unknown and consequently there are very few treatment with proven effectiveness in treatment of men unable to produce pregnancy in their wives. Gonadotrophin deficiency is the most effectively treatable cause of male infertility. The Andrology Department has published the largest and most detailed analysis of gonadotrophin treatment for this condition. It also was a major participant in the clinical registration studies for the new recombinant (genetically engineered) FSH hormone which is one of two key hormones necessary for treatment of gonadotrophin deficient men.

The other key hormone required for treatment of gonadotrophin-deficient men is human chorionic gonadotrophin (hCG). For the last 5 decades this has traditionally been produced by purifying urine from pregnant women but in recent years it has become possible to produce recombinant hCG commercially via genetic engineering. As this recombinant hCG remains under patent to a single multinational company who market it solely for use in IVF, despite the clinical need it has not been tested in men. To rectify this deficit, the Andrology Department has conducted the only studies of recombinant hCG in men aiming to discover the most effective manner to use it. We recently completed a study to compare the effects of the new recombinant hCG with the older standard form of hCG purified from pregnancy urine. If, as expected, this proves the rhCG as safe and effective in healthy males as the conventional form of purified hCG, this may open the way for this newer form of treatment for men with gonadotrophin deficient and infertility as well as in boys with pubertal failure.
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-finding 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.

Registrars/Trainees in Dept of Andrology 2009 - 10
Rashmi NARAYANAN
Praseetha AHANMUGALINGHAM
Kirtan GANDA
Lisa SIMMONS
Kiernan HUGHES

Hormonal Control of Sertoli Cell Function and Spermatogenesis
CM Allan, S Lamb, L Corcoran, J Spaliviero, M Jimenez, DJ Handelsman

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 and gonadotrophin proteins control testis development and sperm production (spermatogenesis). We have a major research focus (through external NHMRC-funding) on the functional development of Sertoli cells, vital cells that surround and nurture developing sperm cells. Our research has contributed to fundamental understanding of the specific roles of key hormones and their receptors found in Sertoli cells (SC), which coordinate the complex hormonal responses required for spermatogenesis and normal male fertility. New genetic models were created to study the androgen receptor (AR) and its role in SC function, in particular the direct binding of AR to DNA (ie. target genes). The specific loss of AR DNA-binding function in SC revealed that genomic AR interaction is vital for sperm development. In this model, the expression levels of two SC androgen-regulated genes, Rhox5 and Eppin known to be important for full male fertility, were reduced in the pre-pubertal testis. However, in the adult testis, Rhox5 remained low whereas Eppin expression became elevated, revealing differential developmental control for distinct AR-regulated genes. Expression of a known androgen-repressed gene (Ngfr) showed maintenance of a non-classical AR pathway independent of DNA binding, however the incomplete spermatogenesis in this model suggests such pathways are secondary, or play no major independent role in SC function. Other genetic models have been established to study the role of SC AR during development, and will allow the dissection of the AR-regulated pathways essential for initiating normal spermatogenesis and male fertility.

Another key research interest (supported by an external ARC Discovery grant) is to determine the role of sex steroids, such as androgens (eg. testosterone), estrogens (eg. estradiol) and progestins in testicular development and function. We use genetic models deficient in sex steroids (hypogonadal hpg model) or specific hormone receptors such as the AR and estrogen receptors (ERs) to dissect specific roles and actions of these major steroids. A
recent major collaborative studies with the US National Institute of Environmental Health Sciences (NIHES) proved that estradiol, the classic female sex steroid, can stimulate spermatogenesis in gonadotrophin-deficient mice, and requires the presence of ERalpha but not ERLbeta. This rather paradoxical estradiol-induced spermatogenic response also involves follicle-stimulating hormone (FSH) secretion, and requires the presence of a functional AR. In combination, these research projects are increasing our fundamental knowledge of the underlying biological pathways that control (or inhibit) spermatogenic development. Such research is predicted to provide valuable genetic targets for therapy (eg. male 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.

The dichotomy of reduced sex accessory gland structure and functions with normal testis development and function provide a so-far unique opportunity to develop novel insight into the molecular determinants of androgen-dependent, post-testicular sperm functional maturation. This model could identify hitherto unexplained causes of male infertility as well as creating novel targets for development of post-testicular, male fertility regulation mechanisms. 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, S Joseph, CM Allan, DJ Handelsman in collaboration with L Salamonsen (Prince Henry’s Institute of Medical Research, Monash University)

Enhanced understanding of ovarian and uterine physiology and function is of great importance as infertility occurs in 1 in 6 Australian couples, with 50% attributable to female factors. Androgens are essential for male reproduction and traditionally are regarded as a defining characteristic of masculinity. However, in recent years, studies have shown that androgens can influence female reproduction. 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), premature ovarian failure (POF), endometriosis, and uterine hyperplasia, a precursor of endometrial carcinoma.

Currently we are identifying the precise mechanism whereby the AR influences female reproductive physiology, notably in the ovary, brain and female reproductive tissues (ovary, breast, uterus). We have created a unique transgenic model whereby the AR gene has been selectively inactivated (AR KO), resulting in female mice functionally unable to respond to any androgens. Using this novel model Dr Walters has revealed defects in ovulation (Fig. 1) and late-stage follicle growth as the major contributors to the observed reduced fertility. Furthermore, more recent work provides strong direct evidence that as well as intra-ovarian AR-mediated actions, extra-ovarian AR-mediated functions also play a central role via neuroendocrine signalling in maintaining
female fertility. In addition, we have shown a role for AR-mediated actions in the regulation of uterine growth and development, which may have important long-term functional consequences for hormone dependent uterine disorders such as endometrial hyperplasia and cancer. This work aims 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.

FSH and Female Reproductive Ageing

K McTavish, K Walters, DJ Handelsman, CM Allan
Collaborations: R Kalak, H Zhou, M Seibel, C Dunstan (Bone Biology, ANZAC)

In women, reproductive ageing (declining fertility) coincides with an accelerated decline in ovarian follicles (cells that contain the developing eggs). An early sign of reproductive ageing is increasing levels of serum FSH, which may occur several years prior to cessation of menstrual cycling (menopause). High FSH levels are associated with premature ovarian failure or onset of menopause, reduced ovarian reserve and reduced success of assisted reproduction. We established a unique transgenic mouse model with increasing levels of FSH and premature infertility. Current research (via NHRMC funding) employs this model to determine whether or not high FSH is a passive marker or actively contributes to reproductive ageing. Kirsten McTavish successfully completed her PhD investigating this high FSH expressing model, and is now a postdoctoral fellow with Prof Shunichi Shimasaki at UCSD (San Diego). This research showed that premature infertility due to elevated FSH occurs despite estrous cycling, follicle development and ovulation (similar to reproductive ageing in women), but appears not to be linked to early depletion of the non-renewable ovarian follicle pool. Ongoing research is investigating the effects of high FSH on the ovarian follicle reserve. Premature infertility in transgenic FSH females was due to reduced embryo-fetal survival, which can be rescued using pharmacological (anti-progesterone) or genetic (AR-deficiency) approaches showing elevated FSH disrupted progesterone-androgen signalling pathways. Higher levels of transgenic FSH in another line produced earlier infertility as well as ovarian cysts. Thus, our transgenic FSH model provides a valuable opportunity to study female reproductive ageing, gonadotrophin-induced hyper-stimulation and ovarian dysfunction.

Recent research has also focussed on the role of FSH in bone loss, after the recent but controversial proposal that elevated levels of FSH can induce bone loss in ageing hypogonadal women, a major problem in our ageing population. Our recent work has studied age-related changes to bone structure and dynamics in our transgenic FSH female mouse models. This work suggests that increased FSH alone does not directly stimulate overall bone gain or loss but depends on complex ovarian-dependent mechanisms to influence overall bone dynamics. Continued analysis of these models has major clinical relevance to the onset of age-related diseases (eg. osteoporosis) associated with loss of ovarian function (eg. estradiol deficiency) due to menopause.

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)
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)
R Kalak, H Zhou, M Seibel, C Dunstan (Bone Biology, ANZAC)
BIOGERONTOLOGY

Personnel:

Group Leader: Professor David Le Couteur

Scientists: Dr Victoria Cogger, Dr Alessandra Warren, Dr Aisling McMahon, Dr Svetlana Zykova, Dr Dmitri Svistounov, Vicky Benson, Jennifer O’Reilly, Samantha Solon, Sarah Mitchell, 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:

• In collaboration with Professor Stephen Simpson, we established 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.

• We were the first in the world to use structured illumination microscopy to study the morphology of the liver sinusoidal cell and to establish the structure of fenestrations using light microscopy.

• Our group collaborated on two international studies of the effects of resveratrol on ageing. The first study in collaboration with Professor David Sinclair at Harvard University established that resveratrol delayed most age-related conditions in normal mice and reversed ageing changes in the liver. The second study in collaboration with Dr Michel Lebel at University of Laval showed that resveratrol prevents the development of insulin resistance in mice with a premature ageing condition called Werners Syndrome.

• Professors Arthur Everitt and Le Couteur edited and published a book authored by over forty international scientists on longevity and caloric restriction.

• Professor Le Couteur became a councillor of the International Society for Hepatic Sinusoid Research, a member of the International Advisory Panel of Age and Ageing, a Member of Council of the Clinical Division of International Union for Basic and Clinical Pharmacology, a member of the Pharmaceutical Benefits Advisory Committee and Deputy Editor of the Journal of Gerontology.

Grants:

NHMRC- Le Couteur, Cogger, Lebel, Quinn, Hilmer, McCuskey. “Old age and the liver endothelium” $296,000

NHMRC- Hilmer, Jones, Cogger, de Cabo. “Hepatic drug clearance and drug induced liver disease in ageing” $183,500


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

NHMRC- Le Couteur, Fraser, Cogger, Sullivan. “Caloric restriction ageing and the liver sinusoidal endothelium” $104,806

Ramaciotti- Cogger. “The liver, age-related dyslipidemia and atherosclerosis, and novel therapeutic targets in a premature aging mouse model.” $26,000

Prizes:

Samantha Solon was awarded a travel grant by the Gordon Research Conference and the Concord Research Committee to present an oral presentation at the Gordon Research conference on the Biology of ageing in Geneva, Switzerland.

Professor Le Couteur was awarded a travel grant by the NIA to present an oral presentation at the ‘International Workshop on Future Perspectives on ageing Research’ in Sevilla, Spain.

Travel grants were awarded to Dr Warren, Dr McMahon and Dr Svistounov to attend the International Society for Hepatic Sinusoid Research conference in Pasadena, USA.
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. As well as being relevant for ageing, we have found similar changes in diabetes mellitus. 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.

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 ninety 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 aim to develop nutritional and pharmacological strategies to delay ageing and thereby gain the longevity dividend of a reduction and delay in many age-related diseases. Because of the complexity of ageing, this requires increasing collaborations internationally, within Australia, and importantly with the ANZAC Research Institute which has enormous capabilities necessary for such research.

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
Professor Ron Quinn, Eskitis Institute, Queensland
Professor Stephen Simpson, 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 Robert Kalak, Dr Yu Zheng, Dr Tara Brennan, Dr Karing Lyon, Dr Aiqing Li, James Modzelewski, Janine Street, Colette Yee, Elysia Neist, Julian Kelly, Mystie Mak, Li Laine Ooi, Trupti Trivedi, Jinwen Tu, Holger Henneicke, Anastasia Mijuseva, Katja Bornert, Uta Heinevetter, Shaoxin Yu, Difei Dong, Katharina Blankenstein.

Visiting Professor: 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 research in Basic Bone Biology, Applied Bone Metabolism and Clinical Research in Metabolic Bone Disease. In addition, our laboratory has a strong interest in the development and evaluation of transgenic models of bone disease.

In 2009/2010, the program has supported postgraduate and doctoral studies of Mystie Mak (Thesis submitted), Laine Ooi (Thesis submitted), Anastasia Mijuseva (Humboldt University Berlin), Holger Henneicke (Humboldt University Berlin), Katja Bornert (Humboldt University Berlin), Uta Heinevetter (Humboldt University Berlin), and Shaoxin Yu (Shanghai Jiao Tong University). Difei Dong participated as an undergraduate summer student.

Current Grants:

NHMRC Project Grant: Zhou, Seibel, Chen, Dunstan. “Osteoblast control of mesenchymal progenitor cell differentiation: The role of glucocorticoids & Wnt signalling.” $143,625

NHMRC Project Grant: Seibel, Zhou,Gundberg, Dunstan. “Role of osteoblast in mediating glucocorticoid-induced metabolic dysfunction.” $197,000

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

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

NHMRC Project Grant: Cumming, Simpson, Le Couteur, Blythe, Naganathan, Kendig, Seibel “Aging, nutrition and the Geometric Framework”

Prostate Cancer Foundation of Australia, Concept Grant: Seibel, Zheng, Dunstan, Zhou. “Vitamin D deficiency and prostate cancer metastasis to bone” $142,405

Cancer Institute NSW: Armstrong, Seibel, Clements. “Sun exposure, vitamin D and the outcome of prostate cancer” $122,010

Prizes:

ASBMR Young Investigator Award: 30th Annual Meeting of the American Society for Bone and Mineral Research (ASBMR), Denver, USA, to Li Laine Ooi, 2009
University of Sydney Short Term Visiting Fellowship, to Dr. M Cooper (Sponsor: M. Seibel) 2009
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 have been of great benefit to countless patients suffering from diseases such as rheumatoid arthritis, asthma, inflammatory bowel disease and malignancies, or who have undergone organ transplantation. It is, however, well known that glucocorticoids may also exert deleterious effects on bone causing osteoporosis.

The Bone Research Program investigates the effects of glucocorticoids on bone using novel genetic modified mouse models. One of these models is characterised through a transgene that results in a local inactivation of glucocorticoids in the bone forming cells, the osteoblasts, by directing these cells to produce an enzyme known as 11beta hydroxysteroid dehydrogenase, 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 and maintenance

K Lyon, X Shao, C Yee, C Dunstan, D Chen (USA), MJ Seibel, H Zhou

We have discovered a novel mechanism by which glucocorticoids regulate mature osteoblast in their control of mesenchymal progenitor lineage commitment through Wnt signalling (Zhou et al J Biol Chem 283: 1936-45, 2008).

Furthermore, we have identified a delay in the development of the skeleton in newborn mice and determined that glucocorticoid signalling in osteoblasts is required for normal development of calvarial bone structures (Zhou et al. Development 136: 427-436, 2009).

In a current NHMRC funded project, in collaborate with Prof Di Chen (University of Rochester, USA) we are investigating the interaction of glucocorticoid and Wnt signaling in osteoblasts controlling mesenchymal lineage commitment. In the long term, we hope that these studies will point the way to strategies for the prevention of the detrimental effects of cortisone on bone.

The Role of Endogenous Glucocorticoids in Immune Arthritis

A Li, J Tu, R Kalak, 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. However, the role of endogenous GC action in contributing to the susceptibility and/or severity of RA is unknown. In collaborate with 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 auto-immune 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 collaborate with Prof Frank Buttgereit (Humboldt University, Berlin, Germany), Prof Paul Stewart and Dr Mark Cooper (University of Birmingham, UK) we are investigating the mechanisms involved in the attenuation of arthritis, which may point to novel strategies for the treatment of autoimmune arthritis.

Changes in Bone and Fat Metabolism Induced by Exogenous Glucocorticoid-Induced

T Brenna, U Heinevetter, H Henneicke, R Kalak, 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, we found that exogenous glucocorticoid-induced bone loss could be prevented in these mice. 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. This work has been given three oral presentations at ASBMR conference in Denver, and American College of Rheumatology (ACR) conference in Philadelphia, US 2009. We will utilise these mouse models to identify the mechanisms that govern the changes in bone and fat metabolism induced by exogenous glucocorticoids.

Preventing the Spread of Malignant Tumours to Bone

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 to 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.

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 overexpressing 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. Further studies are planned to investigate in more detail the mechanism for the bone changes in these mice. The principle ideas behind this research have been outlined in a letter to Cell (Seibel et al., Cell, 127: 1079. 2006).

Bone effects of the XXY phenotype in a mouse model of Klinefelter’s syndrome
P Liu, R Kalak, C Wang (Harbor-UCLA), RS Swerdloff (Harbor-UCLA), H Zhou, C Dunstan, D Handelsman, MJ Seibel

In collaboration with A/Prof Peter Liu (Andrology) and with the Harbor-UCLA Medical Center (Torrance California), the bone group has evaluated the phenotype of mice with an XXY karyotype. Similar to human males with Klinefelter’s syndrome, we have determined that these mice also have osteopenia. These mice thus provide a much needed animal model for examining how bone is affected in this syndrome (Liu et al., JBMR 2010). Further studies are planned to investigate in more detail the genetic and hormonal mechanisms for the bone changes in these mice.
Atypical Femoral Fractures and Bisphosphonate Use
C Girgis, D Sher, MJ Seibel
Together with Drs Girgis (Endocrinology) and Sher (Orthopaedic Surgery), we have studied the potential association between the use of bisphosphonates and the occurrence of subtrochanteric or so called atypical femoral fractures. Based on the review of 152 cases of femoral fractures, we found the risk of an atypical vs. typical fracture in non-bisphosphonate users to be increased 37.4 fold in bisphosphonate users, and the atypical fracture pattern to be 96.7% specific to bisphosphonate users. Based on the demographics of the Hospital’s catchment area, the mean annual incidence of atypical femur fractures was calculated as 0.23 per 10,000 of the general population, 1.66 per 10,000 in people 65 years or older, 33 per 10,000 in alendronate users, and 7.4 per 10,000 amongst risedronate users. While there is an association between atypical subtrochanteric femur fractures and oral bisphosphonate use, bisphosphonates also significantly reduce the risk of fragility fractures in patients with osteoporosis. Overall the anti-fracture effects of bisphosphonates far outweigh their potential risks. (Girgis et al. N Engl J Med 2010 May 13;362(19):1848-9)

Sunshine, falls and bone health in the frail elderly
MJ Seibel with PN Sambrook and others
Together with our colleagues at Royal North Shore Hospital and the Institute for Bone and Joint Diseases, we continued to study the complexities of bone health in the elderly. This year’s focus was on the associations between drug burden index and physical function in older people in residential aged care facilities (Wilson et al. Age Ageing. 2010); the attitudes of older people in regards to sun light exposure (Durvasula et al. Arch Gerontol 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 30.

Studies on Biochemical Markers of Bone Metabolism
J Modzelewski, MJ Seibel
All metabolic bone diseases are characterised by changes in bone formation and in bone resorption, the two major processes that keep bone alive, healthy and strong. Measurement of specific ‘bone markers’ in serum and urine determines the activity of these processes and the results of these simple tests can help the clinician assess the severity, and monitor the treatment of bone diseases such as osteoporosis.

Although these “bone markers” have been developed only recently and are still being refined, they are already widely used amongst clinicians worldwide. Led by Markus Seibel, we are focussing on the development and experimental and/or clinical validation of novel or improved markers of bone turnover.

Present studies focus on the evaluation of bone turnover in the very elderly (with Philip Sambrook, RNSH), the effect of androgens on male bone health (with David Handelsman, Andrology), the effect of anti-epileptic drugs and smoking on bone turnover (with John Wark, University of Melbourne), and other topics.

Influence of serum testosterone levels and its longitudinal changes on different target tissues of androgen action
C Meier, M Jimenez, J Modzelewski, DJ Handelsman MJ Seibel
In men, serum testosterone levels decrease progressively with ageing. Changes seen with ageing (such as decreased bone mass and decreased muscle strength) are also seen in individuals with hypogonadism. Hence, diminished testosterone levels have been associated with a variety of chronic conditions in elderly men, and formed the basis for trials investigating the effects of androgen replacement therapy in elderly men with partial androgen deficiency.

However, the impact of different degrees of androgen deficiency on age-related conditions remains unclear and, specifically, the influence of longitudinal changes in serum
testosterone on the occurrence of androgen-related diseases is unknown. This includes the effect of partial androgen deficiency on musculoskeletal measures (i.e. fractures, rate of bone loss, muscle strength), quality of life and overall mortality.

In collaboration with John Eisman (Garvan Institute), we are studying the large population of elderly men in the Dubbo Osteoporosis Epidemiology Study. This project, assessing the impact of androgens on men’s health, will help us to understand the physiological role of sex hormones in elderly men and could lead to more effective treatment of osteoporosis in men. A first study, on the relationship between serum sex hormone levels and fracture risk, has shown that circulating testosterone but not oestraadiol levels are associated with incident fractures in older men.

**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 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 Connigrave and Gustavo Duque, The University of Sydney, Prof. John Wark and Terrence O’Brian, 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).
Personnel:

**Group Leader:** Professor Peter Maitz

**Scientists:** Dr Zhe Li, Dr Yiwei Wang and Kate Nieuwendyk

**Co-investigators & Collaborators:** Dr Alex Phoon, Sue Taggard, Dr Peter Kennedy, Dr Peter Haertsch, Dr John Harvey, Dr John Vandervord, Dr Anthony Weiss, Jelena Rnjak, Jessica Almine, Amy Lee, Dr Clive McFarland and Dr David Millis

Role:

The group researches all aspects of Burn Care and specialises in tissue engineering of 3 dimensional skin substitutes for severe burns patients. 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.

Objectives:

Our laboratory is committed to improve the cultured skin autograft technology by developing three-dimensional dermal substitutes and skin equivalents for treating deep burn wounds. Using technologies including tissue culture, cell biology, molecular biology and, cellular and tissue engineering, we have been trying to produce different 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, which includes epidermis, dermal components, pigment cells and microvascular vessels under laboratory conditions. The research and development of tissue-engineered scaffold, dermal and skin equivalents will benefit not only the burns patients but also the patients with other skin defects such as chronic, diabetic and pressure skin ulcers.

Grants:

In last 12 months, our group has received the research funds including $150,000 from Bushell Foundation and $100,000 from The Day of Difference Foundation to support our ongoing research projects and the burns postdoctoral research fellow.

Research:

**A Randomized Multi-Centered Trial to Evaluate Efficacy and Safety of Cultured Epithelial Autografts (CEA) in Combination with a Meshed (4:1) Split Skin Graft (SSG) after Debridement of a Burn Wound.**

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

Thin split thickness skin biopsies are taken under sterile conditions and transported to the Concord Skin Laboratory where the biopsies are processed. A piece of thin-split skin biopsy (about 4 cm²), taken from the available donor site under sterile conditions, will be transported in biopsy transport medium to Skin Laboratory at Concord Hospital. Keratinocytes will be isolated from the separated epidermis following enzymatic digestion. The cells will be seeded into two cell culture flasks and cultivated under established laboratory condition. The cells in one flask as Chairman, Professor Peter Maitz as Deputy Chairman and the Hon. John J Fahey as Patron. The foundation supports research, education and scholarship in the field of burns medicine and reconstructive surgery at the Sydney Medical School, the University of Sydney. The main research objective is to assist researchers at Concord Hospital’s Burn Unit to develop a fully-functioning replacement skin for burn patients.
will be allowed to grow and differentiate into cultured epidermal autograft (CEA) sheet while the cells in another flask will be maintained at sub-confluent phase for preparing CEA suspension.

Prior to surgery the patient will undergo a Laser Doppler on the burn that will be in the study to diagnose depth. The suspension will be randomly allocated to syringe A or B with the control syringe containing only transport media. On the day of surgery, both CEA sheet and suspension will be harvested under sterile conditions one hour before the surgery starts, labelled and then transported to the operating room in an esky with an ice brick.

On operation day (day 0) the burn wound will be debrided and a meshed SSG (4:1) will be applied and secured. Children will be in a separate study group and a suitable mesh size will be chosen by the surgeon. Four 10cm x 10cm window dressings (Surfasoft®) will then cover the SSG. Syringe A and B and a CEA sheet will then be applied to three of the windows and the forth will receive no additional treatment. The wounds will then be covered by a piece of Urgotul® (except the graft with the CEA sheet as Urgotul® is all ready in situ as the carrier dressing) and Surfasoft® secured dressings as per protocol. The dressings will remain intact for 5 days and assessed/redressed until healed. Scarring will then be monitored at 26 weeks and finally at 52 weeks.

A Clinical Evaluation of Efficacy and Safety of Cultured Epithelial Autograft (CEA) Suspension Applied to a Donor Site on a Burn Injured Patient.

Skin Repair: Tissue Engineering using Synthetic Elastin

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. The management of the donor site is, therefore, a very important issue in severe burn patient care. Rapid healing allows the repeat use of the same donor site in patients with large burns. But any delay in donor site 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.

Burn patients with a donor site ≥ 2% total body surface area will be recruited to join the trial subjecting to informed consent. The two donor sites of each patient will be divided into CEA group and control randomly. Participants will consent to a skin biopsy from which keratinocytes will be isolated and cultivated in Skin Laboratory at Concord Hospital. On operation day, the cultured keratinocytes will be harvested and spray-delivered to the donor site in CEA group while control site wound receive control vehicle solution only.

Evaluation of wound healing will occur 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 reepithelialized. Data will be analysed statistically to determine the effectiveness of cultured CEA suspension in donor site healing.

Skin Repair: Tissue Engineering using Synthetic Elastin

J Rnjak, Z Li, P Maitz, AS Weiss

Synthetic human elastin is among a range of bioengineered materials aimed at mimicking native host connective tissue. Synthetic elastin scaffolds (Fig 1), produced by chemically cross-linking recombinant human tropoelastin, and is a logical choice for a skin substitute matrix.

Synthetic human elastin has the potential to overcome difficulties associated with other matrices including animal- derived collagen or irradiated cadaver-derived dermis, as it is a human protein, and therefore not expected to be rejected. An additional benefit is that it is recombinant and therefore not extracted from humans, eliminating the risk of contamination, especially with agents that are difficult to eradicate such as latent viruses and prions.

The current project aims to grow human skin cells on synthetic human elastin scaffold (both sheets and electrosprun 3D structure) in an attempt to develop an autologous skin substitute for treatment of burns injury.
Identifying the Diffusible Factor(s) Produced by Skin Cells Grown on Tropoelastin Scaffolds

J Almine, Z Li, P Maitz, AS Weiss

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 cell proliferation and differentiation, ultimately re-establishing the epidermis and dermis. 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

Yiwei Wang, D Martinez Tobón, P Maitz, Z Li

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 construct a bio-active, hybrid scaffold that is biodegradable, biocompatible and porous in structure to support skin cell growth. This project is designed to develop a composite using collagen, and FDA-approved biodegradable polyester, polycaprolactone. The scaffold will be used to generate 3D skin substitute under laboratory condition. More importantly, the scaffolds will be made bio-active containing protein factors to facilitate wound healing. Porous bio-scaffolds are developed by lyophilization technique (Fig 2) or fabricated by electrospun nano-fibres (Fig 3).

Efficacy and Safety of Engineered Skin Substitute and Dressing Materials on Skin Wound Healing: A Mouse Model Study

Yiwei Wang, J Rnjak, P Maitz and Li Z

Lack of autologous skin graft is always a major issue in treating patients with large and deep burns injuries. Clinically, it is still quite common to observe delayed wound healing, which could lead to wound infection, scar development, deterioration of patient’s well-being and even death.

Cultured autologous skin cells or substitutes are emerging as an important alternative for wound coverage and closure. The advance in biotechnology has enabled us to grow different types of skin cells and skin substitutes by skin tissue engineering technology in our laboratory. Skin tissue engineering involves using different biomaterials such as recombinant collagen and elastin or bio-compatible polymers as porous scaffolds to support skin cell attachment, growth and differentiation into skin tissue. Various wound dressing material and dressing regimes are also designed in our laboratory in an attempt to provide favourable growth condition for cultured skin cells and to speed up the wound healing process. Wound healing is a very complicated process in which host factors and metabolisms play a critical role. Although the engineered skin looks structurally similar to normal human skin containing epidermal and dermal layers, the bio-safety and efficacy of engineered skin and wound dressing products will need to be tested in an animal model before proceeding to further clinical trial.

The aims of this study are therefore to establish a mouse model to assess the role of engineered skin products or dressings in wound healing. 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

P Kennedy, S Brammah, E Wills

One of the most significant problems in burn care is that of infection. Following a burn injury the defensive mechanisms of the skin are impaired or destroyed and colonization by micro-organisms rapidly occurs. Many
of the micro-organisms commonly found on the burns wound are known to produce biofilms, 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. It is estimated that two third of all chronic disease are biofilm related. Biofilm formation (Fig 4 and Fig 5) in burn wounds has not been thoroughly examined. 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.
Personnel:

Group Leader: Professor Stephen Clarke

Scientists: Assoc Professor Graham Robertson, Dr Kellie Charles

Scientists: Phillipa Camilleri, Candice Clarke, Dr Wei Chua, Anthony Corradin, Haryana Dhillon, Dr Michael Evtushenko, Chantal Gebbie, Phuoc Huynh, Dr Lucy Jankova, Dr Marina Kacevska, Dr Stephen Kao, Melissa Lloyd, Marko Matic, Melissa Moore, Anthoulla Mohamudally, Arran Painter, Dr Viet Phan, Dr Jane Reid, Dr Anneliese Rittau, Angie Shum, Cindy Tan, Ryland Taylor, Lili Truong, Dr Maria Tsoli, Dr Janette Vardy, Jennifer White, Catherine Xu,

Role:
The Cancer research group has successfully established itself at ANZAC, following the appointment of Prof Stephen Clarke to the Chair of Medicine. Since joining four years ago, the team 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 (Faculty of Pharmacy, Uni of Sydney) to the Chair of Geriatric Pharmacy on the Concord campus strengthens the pharmacokinetic and analytical expertise required for clinical drug studies in cancer patients. Dr Kellie Charles rejoined the group as a Senior Scientist after 4 years Post-Doctoral Training in London

Objectives:
To have a strong collaboration with the Australian Proteome Analysis Facility at Macquarie University which enabled our scientists to search for new biomarkers for Colorectal cancer. This has led to a successful Cancer Institute NSW translational program grant for $3.75 million over 5 years.

 Grants:

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- Vardy, Clarke, Tannock, Schnitzler, Dhillon ‘Cognitive function and fatigue after chemotherapy’ $77,150

NHMRC- Clarke, McLachlan ‘Inter-ethnic differences in tolerance of anti-cancer drugs.’ $109,686

NHMRC- Geczy, McNeil, Freedman, Hsu ‘Inflammation-associated S100 proteins: links between arthritis and atherosclerosis’ $146,750

University of Sydney Bridging Scheme- Clarke, Robertson, McLachlan ‘Impact of tumour-derived cytokines on drug clearance pathways in cancer.’ $50,000

Research:

Colorectal Cancer Biomarker Studies and Clinical Trials
S Clarke, H Dhillon, C Gebbie, L Jankova, J Reid, G Robertson, L Truong, Maria Tsoli, J Vardy, C Xu, [M Molloy, M Mackay & Baker - APAF; P Chapuis, L Bokey, Owen Dent, C Chan Caroline Fung & B Lin - Depts of Surgery & Pathology, CRGH].

In collaboration with the Australian Proteome Analysis Facility, many potential protein biomarkers have been identified that will provide better assays for diagnosis and prognosis as well as help to predict the response of colorectal cancer patients to anti-cancer agents. Such biomarkers will guide the development of individualised treatment regimes which will take into account the variability in efficacy and toxicity to drugs experienced by many cancer patients. In addition some biomarkers will be used to identify patients at risk of developing the muscle wasting associated with the cancer cachexia syndrome. Medium throughput mass spectrometry-based assays have been developed to assess the utility of these proteins before high throughput screening using the Concord Colorectal tissue and data banks collected by Departments of Surgery and Pathology, CRGH. Immunostaining for the presence of specific proteins in colorectal tumours using tissue microarrays has enabled validation
of potential biomarkers for colorectal cancer. We found that the proteins fascin and GST-pi are prognostic markers for survival while maspin did not show an association with clinical outcome despite previous reports for many cancers including colorectal.

Concord has become a major Australian centre for clinical trials in colorectal cancer patients with particular emphasis on the angiogenesis inhibitor bevacizumab. In nutritional cancer research, we have evaluated the prognostic value of nutritional assessments and demonstrated that patients with advanced colorectal cancer and a poor nutritional status have a shorter survival than well nourished patients. Studies into the cognitive function and fatigue in cancer patients after chemotherapy will be carried out by oncologist Janette Vardy. In psycho-oncology research, among other projects, we are assessing whether education and counselling might improve end of life decision making.

Cancer Pharmacology and Cachexia

The focus of the cancer pharmacology laboratory is to explain inter-patient differences in response and toxicity to anti-cancer drugs. The treatment of cancer patients with drugs is difficult due to the fine balance between killing tumour cells and causing toxicity to normal cells. Therefore the huge variability between patients in clearance of anti-cancer agents has a significant impact on the success of chemotherapy. Anti-tumour action may be lost if the drug is cleared too rapidly, while slow drug excretion may lead to extreme toxicity. A better understanding of the source of this variability should lead to improvements in the manner in which chemotherapy is administered and would represent a welcome advance for cancer patients.

Cancer cachexia is experienced by up to 80% of all cancer patients and involves muscle wasting and depletion of fat reserves. It is directly responsible for the death of 30% of cancer patients. A better understanding of the complex factors responsible for cancer cachexia would help to identify those patients who will be susceptible to developing cachexia as well as better management of this debilitating condition.

Do Tumour-Derived Cytokines Repress Drug Clearance in the Liver?

S Clarke, M Kacevska, M Matic, Arran Painter, Viet Phan, G Robertson, Anneliese Ritau, Prof Andrew McLachlan, Faculty of Pharmacy, USyd

The rate of breakdown and elimination of drugs from the body is largely determined by the levels of enzymes called cytochrome P450s (CYPs) in the liver as well as specific drug transporters which move drugs in and out of cells. In humans CYP3A4 is responsible for the disposal of more than half of all drugs including many important anti-cancer agents. Clinical studies carried out by our group found that CYP3A4 levels are reduced in some cancer patients, leading to greater toxicity. The source of repressed hepatic CYP3A4 levels appears to be linked to tumour-derived cytokines. Therefore a major goal of our research is to study the links between cytokines released by tumours and down-regulation of drug clearance pathways in the liver. Ultimately we hope to be able to predict which patients will suffer toxicity and to develop anti-inflammatory treatments that will normalise drug handling and improve patients’ response to anti-cancer drugs.

As it is difficult to study these processes in the livers of patients, we created a transgenic mouse model of human CYP3A4 regulation. Using these mice we have carried out experiments to analyse the signalling pathways and molecular mechanism involved in mediating the inflammatory response of the liver to tumours. We have found that this process is linked with the growth of several different cancers, including melanoma, breast, colon and sarcoma, indicating that this may be a general feature of many different cancers. In addition to repression of CYP3A metabolism, hepatic drug transporters for several important anti-cancer drugs are also switched off in the presence of cancer, leading to even slower clearance of drugs from the body and greater toxicity. In collaboration with APAF (Macquarie University) we have carried out extensive proteomic profiling and found that all aspects of drug clearance pathways are altered, including many CYP and phase II enzymes and drug transport proteins. Pharmacokinetic and biodistribution studies are underway to assess the impact of these changes on clearance of anti-cancer drugs and probe reagents.

Detailed analysis of cytokine signaling cascades and nuclear receptors which control metabolic pathways has shown that there is crosstalk between IL-6 and impaired nuclear receptor action. The use of mouse tumour models has enabled us to perform pre-clinical testing of anti-cytokine interventions aimed at normalising drug clearance. In preliminary experiments we have found that using antibodies to IL-6 has partially restored the levels of CYP3A.
**Ethnic Differences in Drug Clearance.**  
*S Clarke, V Phan, A Rittau, C Xu, [Prof A McLachlan - Faculty of Pharmacy, University of Sydney, Prof Micheline Piquette-Miller, University of Toronto]*  
Compared to Caucasians, cancer patients from an Asian background have greater difficulty tolerating chemotherapy and suffer from more adverse events due to toxicity. Clinical studies are being carried out in breast and lung cancer patients to examine the genetic differences (single nucleotide polymorphism or SNPs) in genes involved in drug metabolism which may be related to altered clearance of anti-cancer drugs. Pharmacokinetic analysis of commonly used chemotherapy drugs such as paclitaxel and doxorubicin are being developed to determine the rate at which they are eliminated from the body. The inter-patient and ethnic differences in drug clearance will be correlated with genetic differences and toxicity.

**Cancer Cachexia, Cytokines and Altered Metabolic Pathways?**  
*S Clarke, D Gardon, L Jankova, M Kacevska, P Polly, G Robertson, M Tsoli, Ryland Taylor, Anthony Corradin, Marko Matic, Phillipa Camilleri, Angie Shum. [Mark Molloy - APAF; Edna Hardeman - UNSW; Frances Sladek Uni of California Riverside]*  
Cancer cachexia is a complex condition involving disturbances in energy balance and metabolism in several organs of the body. The release of 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. Mouse tumour models have been used to study the regulation of metabolic pathways during the development of cachexia. As these pathways are primarily controlled by nuclear receptors, we have profiled the expression of all 50 nuclear receptors, their cofactors and a representative set of their target genes in liver as well as a subset in muscle and fat. This has given valuable insights into the alterations in many metabolic pathways due to the impact of tumour-derived cytokines on nuclear receptor expression. In particular it appears that brown adipose tissue (BAT) becomes inappropriately activated resulting in excessive energy expenditure while the liver is unable to process and redistribute nutrients including lipids and carbohydrates. Such changes may contribute to aberrant energy balance leading to cancer cachexia.

The morphology of muscle fibres and fat deposits has been examined to characterise the changes that occur during cachexia. These changes in muscle and fat cells reflect alterations in metabolism and the molecules that control energy balance in the body.

**Molecular Analysis of Nuclear Receptors PXR, RXR and HNF4**  
*A Corradin, M Kacevska, M Matic, P Polly, G Robertson, [M Molloy - APAF Macquarie Uni; F Sladek - University of California Riverside]*  
To understand the regulation of genes involved in drug clearance pathways, we are carrying out detailed molecular studies into the nuclear receptors PXR, its binding partner RXRα and HNF4α. An important step is to identifying which domains of the PXR protein are necessary for interactions with other molecules in liver cells after PXR is activation by drugs. We are especially interested in defining specific interactions with other protein co-factors which move PXR into the nucleus and form the active multi-protein complex required to switch on target genes. Specific modifications of the PXR RXRα and HNF4α proteins, such as phosphorylation, are likely to play a critical role in modulating such interactions with other proteins. We anticipate that this information will help to understand how different diseases which have a marked inflammatory component, such as cancer, impact on nuclear receptors by altering their phosphorylation state.
DENDRITIC CELL BIOLOGY & THERAPEUTICS

Personnel:

Group Leader: Professor Derek Hart
Scientists: Prof Ken Bradstock, Dr Georgina Clark, Dr Kifah Shalil

Role:

Dendritic Cells (DC) are unique subsets of white blood cells found throughout the body. They are responsible for initiating and directing immune responses. As one of the pioneering groups in the field, we are continuing to define the human DC subsets and elaborate their function. We aim to learn how DC interact with their environment by studying DC surface molecules and how these molecules influence DC function. Our DC knowledge is then used to benefit patients, by developing new diagnostic and potential therapeutic antibodies, which we test in preclinical models of haematopoietic stem cell transplantation, leukemia, multiple myeloma and other malignancies. Our group has completed a trial of therapeutic DC vaccination in prostate cancer and is evolving further trials of immune therapies in multiple myeloma and other malignancies. We are also developing a CD83 antibody as a novel immunosuppressive agent, which preserves the patient’s ability to fight infections and cancer for clinical trial in allogeneic transplantation.

Objectives:

We want to use our knowledge of DC to develop new diagnostic and therapeutic products. We predict that the ability to analyse DC subsets and their functional status will provide diagnostic information relevant to managing the beneficial and harmful effects of the immune response in cancer, transplantation, autoimmune/inflammatory diseases and vaccinations against the major infectious diseases. Finally, we are now looking to develop new DC based therapeutics in world first clinical trials and our new Sydney home will be ideal for this work.

Highlights:

Participation in the Human Cell Differentiation Antigen Workshop and recent involvement in an international publication on DC nomenclature has highlighted the interest in the DC field.

Our previous work has led to the recent publication defining a new human blood CD141 DC subset (J Exp Med 2010; 207:1247).

Our ongoing collaborative work with Brisbane colleagues has created new fully human antibodies to CD83 that immunosuppress immune responses (J Exp Med 2009; 206:387).

A clinical trial of DC vaccination in hepatitis C was published by our collaborators.

Grants:

NHMRC Program - Hart, Bradstock. “The translation of dendritic cell biology into clinical practice” $672,000
Cancer Australia – Hart, Radford “RNA loading of tumor associated antigens and the activation of blood dendritic cells for cancer immunotherapy” $198,300

Research:

Studies on DC in multiple myeloma and haematopoietic stem cell transplantation are underway via our collaborations at the Royal Prince Alfred and Westmead Hospitals.

We have a novel DC cell surface molecule discovery project. Exciting new studies on the function of DC molecules in gene deleted mice will commence when the mice are transferred from Brisbane.

Our pioneering studies using novel anti CD83 DC agents for immunosuppression will continue and move to clinical application based upon anticipated CRC-BT funding.

Developments:

The group is most grateful for the warm welcome it has had in Sydney and to old and new collaborators for facilitating a quick return to research productivity following the move from Brisbane. This has been supported by ongoing collaborations in Brisbane, Melbourne and Adelaide including those supported by the CRC-BT. The opportunity to coordinate collaborative interests in the DC contribution to the immune response in stem cell transplantation and the haematological malignancies in three major University of Sydney teaching hospitals is a unique opportunity that is already attracting international commercial and academic interest.

Collaborations:

Previous Brisbane DC Program and University of Queensland colleagues.
Royal Prince Alfred Hospital
Westmead Hospital
Centenary Institute
CRC-BT
GERIATRIC EPIDEMIOLOGY

Personnel:

Group Leader: Professor Robert Cumming

Co-investigators: Professor David Handelsman, Professor Markus Seibel, Dr Helen Creasey (CERA), Dr Vasi Naganathan (CERA), Dr Louise Waite (CERA), Professor Philip Sambrook (Royal North Shore Hospital), Professor David Le Couteur (CERA), 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:

NHMRC funding was awarded for 5- and 7-year follow-up assessments. This will ensure that CHAMP provides insights into the mechanisms underlying good health and longevity in men. Ten papers were accepted for publication. These included papers on depression in older men born in Italy; health service use among disabled and frail men; the role of liver function for good health; socio-economic status and osteoporosis; and chronic pain and frailty.

Grants:

NHMRC-Cumming, Le Couteur, Kennerson, de Cabo, Naganathan, Sambrook. “Sirtuins and the molecular epidemiology of frailty in older men.” $259,874


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 most of these have 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; spirometry; and uroflowmetry and measurement of post-void residual urines. 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 Scientist:** Dr Marina Kennerson  
**Senior Scientist:** Dr Ian Blair  
**Staff and Students:** Obaid Albulym, Megan Brewer, Carolyn Cecere, Rabia Chaudhry, Shannon Chu, Gai Diamond, Alexander Drew, Carolyn Ly, Natalie Page, Martin Simone, Jennifer Solski, Shajjia Razi, Stephen Reddel, Marion Stoll, Sadaf Warraich, Kelly Williams, Shu Yang

**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 mutations in the copper transport gene ATP7A as a cause of distal motor neuropathy on chromosome X.  
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 a platform presentation at the 2009 American Society of Human Genetics for the ATP7A gene discovery. Ian Blair was an invited speaker at the Motor Neuron Disease Symposium, Australian Neuroscience Society satellite meeting 2010 and the Motor Neuron Disease Research Institute Annual meeting in 2009. Megan Brewer was a finalist for the Concord Hospital Early Career Research award in basic science 2009.

**Grants:**

ALSA- Nicholson, Blair “Identification of a novel gene causing motor neuron degeneration” $87,370  
Australian Rotary Health Research Fund- Blair, Nicholson ‘Investigating the role of the gene encoding TAR DNA binding protein (TDP-43) in ALS’ $10,125  
Bushell Foundation- Kennerson, Nicholson ‘What is the gene mutation causing an X-linked form of Charcot-Marie-Tooth neuropathy (CMTX3)? (Stipend for PhD)’ $30,000  
Bushell Foundation- Chu ‘What gene mutation causes the death of motor neurons in distal hereditary motor neuropathies?’ $35,000  
James N Kirby Foundation- Kennerson ‘Bell's Palsy’ $22,600  
MDA- Nicholson, Kennerson ‘Finding the gene causing x-linked Charcot-Marie-Tooth (CMTX3) neuropathy’ $45,178  
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- Kennerson ‘Finding genes causing familial motor neuron degeneration’ $13,500  
MNDRIA- Blair, Nicholson ‘Identifying novel genetic loci for familial motor neuron disease’ $34,000  
MNDRIA- Yang. “Bill Gole MND Postdoctoral Fellowship” $72,500  
NHMRC- Blair. ‘Investigating the molecular basis of motor neuron disease’ $102,250  
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, Hawke. ‘The role of mutant TDP-43 in ALS’ $161,674  
Snow Foundation- Nicholson. ‘Program aimed at curing MND: Screening drugs using an animal model’ $424,000
Prizes:
PRSS Scholarships to: Megan Brewer, Alex Drew, Shannon Chu, Obaid Albulym, Kelly Williams 2009
University of Sydney Postgraduate Award to: Kelly Williams 2009
Sydney Medical School Research Top Up to: Kelly Williams 2009
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

Research:
Inherited Peripheral Neuropathies
M Kennerson, O Albulym, A Aziz, M Brewer, R Chaudhry, S Chu, Carolyn Ly, G Nicholson
Charcot-Marie-Tooth (CMT) disease CMT 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. Due to the chronic nature of these disorders, the hereditary neuropathies are a poorly recognised and silent health burden with a lifetime cost to Australians measured in billions of dollars.

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 most recent breakthrough is the identification of mutations in the copper transport gene ATP7A as a cause of distal motor neuropathy on chromosome X. The ATP7A protein is important for maintaining the balance of copper in our bodies. The mutations we have identified result in the protein not trafficking (moving) correctly when cells are exposed to high levels of copper. The figure (right) is a schematic diagram of the ATP7A protein and the location of the mutations we have discovered are shown in red. Our discovery highlights the importance of copper transport in the maintenance of motor neuron function and has significant therapeutic implications for identifying drug targets and preventing axonal degeneration in patients with this disorder. The laboratory led an international collaboration with groups from, Australia, United States, Belgium and Brazil to publish these findings. Our focus is to now understand how incorrect movement of the ATP7A protein in neurons can lead to a length dependent death of the motor nerves.

Motor Neuron Disease
I Blair, S Yang, C Cecere, K Williams, J Solski, A Drew, S Warraich, V Xie, 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 proving for the first time that alterations in TDP43 gene or changes in its expression, may be a common toxic cause of motor neurone disease. Our work first identified a TDP43 gene mutation that causes familial motor neurone disease. We also found new gene mutations in FUS that cause MND. These breakthroughs, in collaboration with other Australian and international MND research groups, were recently reported in the journal Science. We are now working to understand how these mutations lead to cell death in patient tissues. These discoveries have opened new chapters in MND research and offer hope for the development of better diagnostic and therapeutic tools for this devastating illness.

Collaborations:
We have continued to build productive and ongoing collaborations with renowned researchers in motor neuron disease that include Professor Chris Shaw (Kings College, London); Professor Guy Roleau (University of Montreal) and Professor Robert Brown (University of Massachusetts). Strong collaborations continue with our peripheral neuropathy colleagues at Wayne State University (Jim Garbern, Mike Shy), University of Antwerpen (Vincent Timmerman; Peter De Jonghe); Baylor Medical College (Jim Lupski). Through our work with the ATP7A gene we have formed collaborations with Professor Julian Mercer (Deakin University, Melbourne) and Dr Stephen Kaler (National Institutes of Health).

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.
Personnel:

**Group Leader:** Professor Ben Freedman  
**Senior Scientist:** Dr Paul Witting, A/Prof Len Kritharides, A/Prof Harry Lowe, A/Prof David Brieger  
**Staff and Students:** Dr Julie Redfern, Dr Chang-Jie Song, Dr Raymond Sy, Dr Gabrielle Pennings, Dr Wei Zhao, Dr Caroline Reddel, Dr Vincent Chow, Dr Susan Hua, Dr Andy Yong, Dr Mohammed Moharram, Dr James Edelman, Dr Clement Wong, Dr Tommy Chung, Dr Austin Ng, Vicky Benson, Shane Anteo, Ben Rayner, Hong Duong, Anu Shanu, Lis Neubeck, Alana Mohamed, Rhoda Ascanio, Anna Jackson, Vincy Li, Roshanak Aran, Marzy Nikanami, Mimi Sabaretnam, Alex Rosenov and Jasmin Voitl.

Role:

Cardiovascular disease relates to disease of the heart and blood vessels. It is considered to be the leading cause of death world-wide - 30% of deaths occur as a result of cardiovascular disease according to the World Health Organization, and 34% of deaths in Australia. Cardiovascular disease includes coronary artery disease (CAD), heart failure, arteriosclerosis, and hypertension among others. The leading cause of death in Australia in 2008 was coronary heart disease which results from insufficient blood supply to the heart generally due to blocked arteries around the heart (coronary arteries); this can cause angina (chest pain) heart attack, and death.

Objectives:

Research within the Vascular Biology Group incorporates a mixture of basic and clinical science aimed at understanding, preventing and treating CAD and its complications including heart attack and cardiac death. Areas of interest include:

- Investigation of Mediators of Inflammation
- Platelet and Leukocyte Activation and Interactions within CAD
- Heart Attack and Stroke
- Gene Targeting for Heart Attack
- Studies of Saphenous Vein Graft Disease
- Novel Measures of Haemostatic Function in CAD
- Echocardiographic Evaluation of Cardiac Dysfunction
- Risk Stratification in Infective Endocarditis
- Choice of Health Options In Preventing Cardiac Events (CHOICE Study)

Research:

**Investigation of Inflammatory Mediators**

Our main aims are to demonstrate novel mechanisms of initiation of inflammation, and to define links between inflammation and formation of blood clots in arteries. We have shown that both CRP (C-reactive protein) and SAA (Serum Amyloid A), which are inflammation markers predictive of death or heart attack in both normal populations and those with CAD, can stimulate blood monocytes to produce tissue factor, the most powerful initiator of clotting. There is a non-specific upregulation of monocyte responsiveness to both CRP and SAA in patients with CAD, so the higher concentrations of these proteins seen in patients indicates that both CRP and SAA are not just markers of inflammation but may play a role in blood clotting which precipitates adverse events.

We have further investigated the mechanism whereby SAA is pro-inflammatory and found very early and potent up-regulation of many pro-inflammatory molecules by SAA and monocytes are the principle source. This is even greater in monocyte-derived macrophages present in atherosclerotic plaques.

Grants:

- ARC Discovery – Witting. ‘Cellular response to pro-oxidative myoglobin’ $140,000
- Brain Foundation - Reddel. ‘Does chronic upregulation of acetylcholine signalling at neuromuscular junction with pharmaceutical long term inhibition of acetylcholinesterase exacerbate the pathophysiological effects of anti-AChR mediated and anti-MuSK mediated myasthenia gravis?’ $20,000
- Bushell Foundation- Freedman, Reddel. ‘Guided choice for prevention of future heart disease’ $130,614
- DART- Freedman. ‘Proinflammatory activation of endothelial cells by serum amyloid in diabetes’ $30,000
- HCF Grant-in-aid- Freedman. ‘Choice study for secondary prevention of heart disease’ $228,012
- National Heart Foundation- Witting, Corbett, Brieger ‘Neuroprotective antioxidants that synergise with thrombolytic treatments for acute cerebral ischemia’ $64,500
- NHMRC- Yong ‘Medical Postgrad Scholarship’ $34,000
- NHMRC (NICS)- Redfern “Patient-centred modular prevention of heart disease: a program for implementing evidence-based guidelines.” $63,796
- Pfizer CVL- Ng, Chung, Kritharides ‘Long-term mortality and late pulmonary hypertension after acute pulmonary embolism’ $55,000
- Pfizer CVL- Yong, Kritharides, Lowe, Ng ‘Coronary stenosis severity and intracoronary upregulation of platelet P-selectin in patients taking aspirin and clopidogrel.’ $53,492

Highlights:

Supporting young undergraduate and postgraduate researchers with Hong Duong graduating with a PhD from the USyd and Ben Rayner submitting his PhD for assessment.
VASCULAR BIOLOGY

coronary artery vessel walls, appears to be mediated by the nuclear switch NF-κB, and may be an important amplifier of both inflammation and thrombosis in acute coronary syndromes and sudden coronary death. We have also shown that SAA is released into the coronary circulation in patients with CAD. Investigations have shown that exposure of blood vessel lining cells to pathological SAA induces endothelial dysfunction by affecting Ca²⁺ signal transduction pathways, stimulating production of reactive oxygen species, up-regulating expression of pro-inflammatory genes and genes involved in the coagulation cascade, and decreasing cGMP which is involved in the synthesis of the blood vessel vasodilator nitric oxide. Presently, we are using an apoE deficient mouse model to assess the proatherogenic activity of SAA.

We have also demonstrated an important protective effect of HDL, part of the ‘good cholesterol’ that has other protective actions against atherosclerosis. We are beginning to study the protective effect of HDL on SAA-induced endothelial abnormalities, under high-glucose conditions to simulate diabetes. The group continues its longstanding collaboration with Prof Carolyn Geczy (UNSW) in these projects, and in other projects to ascertain the role of S100 proteins in atherosclerosis.

Platelet and Leukocyte Activation and Interactions within CAD

Our aims are to examine the extent and mechanisms of platelet and leukocyte activation occurring due to the presence of CAD both systemically and in the intracoronary tree, as well as interactions between platelets and leukocytes that may be contributing to CAD. By observing the response of platelets and leukocytes in the intracoronary tree we have an in vivo model of activation demonstrating the effect of plaque volume on platelet and leukocyte activation.

Recent work involving a novel platelet marker, EMMPRIN or CD147, shows that despite the lack of response of traditional platelet activation markers, p-selectin and PAC-1, EMMPRIN on the platelet is upregulated systemically, due to the inflammatory state and age of the patient rather than CAD specifically. EMMPRIN expression has been found to be upregulated on monocytes in patients with acute myocardial infarction, our results concur with this finding in the systemic circulation; however, we observed upregulation due to CAD on both the monocyte and granulocyte populations. Upregulation of platelet activation markers across coronary stenoses has been observed. Current work will include continued examination of what occurs within the coronary tree with respect to platelet and leukocyte mechanisms of activation and studies of the regulation in GPVI in collaboration with Drs E Gardiner and R Andrews (Monash University). Dr Yong will be extending his work on intracoronary platelet activation by relating this to the functional severity of coronary stenoses, and computationally modelled shear stress in coronary arteries in collaboration with Professor M Behnia from the University of Sydney.

Heart Attack and Stroke

Dr Witting and his staff and students’ interests include ischemic injury to the heart and brain and effects of myoglobinurea on kidney function. The main research thrust involves design and testing of potential inhibitors of damage to myocardial, renal and neuronal tissues in the setting of acute insult to these organs.

Current work has seen the study in neuronal protection evolve into gene targeting of a novel haem protein called neuroglobin. This protein is expressed in the brain during acute ischemic insult and is believed to play a role in protecting the brain during stroke. Studies using a neuroglobin-transfected neuronal cell line have recently been published in the highest-ranked journal in the field of oxidative stress.

Gene Targeting for Heart Attack

Our focus is gene expression and modification of vascular and myocardial injury - specifically, the contexts of neointimal formation following vein graft and native coronary injury, and myocardial ischemia-reperfusion injury. Using in vitro and in vivo animal models we are investigating the use of DNAzyme and other novel gene-targeting approaches to inhibit injury responses.

We are particularly interested in diabetic heart disease and investigating how diabetic heart muscle responds to ischemia-reperfusion injury compared with non-diabetic heart muscle. We have established a novel model of heart attack in diabetes, which is allowing us to examine both early and late responses to injury, both in recent onset and in established diabetes.

Egr-1-targeting DNAzymes are sequence-specific enzymes that cleave Egr-1 mRNA, thus preventing expression. Using in vitro models of diabetes and myocardial ischemia, and our own animal model of myocardial ischemia in diabetes, we are examining the
effects of DNAzyme delivery on Egr-1 expression, molecular pathways of ischemic injury, and infarct size. This work has the potential to provide novel “diabetes specific” therapies for heart attack.

Studies of Saphenous Vein Graft Disease
Coronary bypass grafts (SVGs) have a tendency to develop narrowings in the years following coronary surgery, leading to further symptoms of heart attack. The nature of these narrowings remains poorly understood, but we believe it is distinct from the atheroma that develops in native coronary vessels. We are trying to determine the nature of atheroma in SVGs and to define the similarities and differences from atheroma in native coronaries. This will help us understand the atherosclerosis process in these conduits in a better way.

Novel Measures of Haemostatic Function in CAD
Our focus is on the utility of novel measures of haemostatic (blood clotting) function in characterising therapeutic responses to anti-platelet drugs in patients with coronary disease. Patients undergoing invasive cardiac procedures like stenting and receiving anti-platelet therapies, have their overall haemostatic function determined by assays, including the Overall Haemostatic Potential Assay and Calibrated Automated Thrombogram. These have been developed in collaboration with the Haematology Departments at Concord Hospital (Dr Jennifer Curnow) and Royal North Shore Hospitals. The impact of different anti-platelet agents on these assays is being evaluated and compared against conventional functional studies of platelet function.

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. Dr Zhao is a highly trained echocardiographer who is applying new speckle-tracking ultrasound techniques to the measurement of the contraction of the right ventricle. She has developed a new measurement which detects recovery of cardiac function before conventional imaging. Dr Chow, is an an Echocardiography fellow in our Department and APA Masters Student at the University of Sydney. Dr Ng and Dr Chung, are evaluating the incidence of late pulmonary hypertension in patients who have previous clots in the lungs. There are very few studies systematically recording the long term effects of pulmonary embolism on the heart and his work will establish important baseline data for the elderly Australian population.

In collaboration with Professor Handelsman, Dr Zhao will be investigating the effects of androgen receptor expression and androgen deficiency on myocardial function in mice. She has established high frequency echocardiography of mice and will use this technique to assess heart response to injury and to treatments that may promote its recovery.

Risk Stratification in Infective Endocarditis
Infective endocarditis is a life-threatening condition, the incidence of which has remained unchanged over the last 20 years. As part of his PhD thesis at the University of Sydney, Dr Ray Sy has completed a series of studies investigating risk stratification, population incidence and the effect of timing on prognostic benefit in patients with infective endocarditis in NSW. Ray found that thrombocytopenia is an important predictor of outcome, and that it remains a predictor even after two weeks of treatment whereas some other factors lose their predictive power over time. Ray found in a linkage study covering the state of NSW that the mortality of infective endocarditis remains alarmingly high and that this condition is affecting an increasingly elderly population. He also found that the prognostic benefits assigned to treatments must take into account the timing of the treatment if they are not to introduce systematic biases.

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 3 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. Following these patients will tell us if a brief intervention will have long lasting effects on multiple risk factors.
VETERANS EPIDEMIOLOGY

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 in the late 1980s and has followed a cohort of veterans for over 30 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 the assistance of the Bureau of Statistics and the Department of Veterans Affairs, and funding from NHMRC. This has added to the data lode and opened up a much richer prospect for scientific contributions to the knowledge about the long term effects of war service. Many discrete projects are under way, supported by modern and sophisticated data analysis techniques. A few of these are described below, and arise from published or under-review manuscripts from the study. Each describes 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.

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 available to the study. Thus, the study has extended from veterans to their wives/partners, and is now seeking funding support to extend the study to veterans’ 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.

Highlights:

Dr O’Toole was interviewed by ABC Radio “Health Report” with Dr Norman Swan in August, 2009, following publication of the initial findings from the veterans study in the American Journal of Epidemiology, and he was subsequently interviewed on camera for ABC1 TV news on 11/11/2009.

The initial findings of the wives and partners study were presented at the December 2009 meeting of the Australasian Society for Psychiatric Research Conference in Canberra.

Dr O’Toole was invited to address the Vietnam Veterans Association of Australia National Congress in Caloundra, Queensland, giving an overview of the studies and results so far.

Dr O’Toole assisted the Vietnam Veterans Federation of Australia in forming a submission to the Repatriation Medical Authority examining the role of the malevolent environment of war in leading to PTSD and other adverse mental health conditions in the absence of direct combat.

Dr O’Toole was invited to participate in the International Summit on Peace and War at Case Western Reserve University in Cleveland, Ohio, in October 2010.

Grants:

Lavasseur Bayley Bequest for veteran-related research: $20,000.

Research:

1. Dispelling the Myths and Legends about Vietnam Veterans:
   1.1 “They would have been like that, anyway”. This particularly cynical view was addressed in research examining the risk factors for posttraumatic stress disorder (PTSD), where information from time periods before veterans enlisted, before they went to Vietnam, and during their Vietnam service was used to
assess their relative contribution to the risk of developing PTSD. Significant associations were found with veterans’ fathers’ own post-WWII mental state, with pre-Vietnam agoraphobia and depression, and with the sustaining of combat casualties, which together contributed about 25% to the risk of PTSD. But the overwhelming association with PTSD lay in the experience of combat. They wouldn’t have been like that, anyway, except for their combat experiences.

1.2 “Vietnam veterans have unhappy unstable relationships and are more likely to be divorced and have multiple marriages”.

Again, findings from the study indicate that the marriage and divorce rates of Vietnam veterans are not very much different from the general Australian population. Indeed, while there is some small effect of PTSD on marital adjustment, the striking finding is that relationships can withstand these effects, that veterans’ wives ‘hang in there’ in support of their husbands/partners, and the general measures of marital satisfaction of both veterans and their partners are not much different from the background Australian population.

1.3 “Vietnam veterans are ‘walking time bombs’ about to explode in rage and perpetrate domestic violence against their wives”.

About one-quarter of Australian women have a history of being on the receiving end of domestic violence. Again, the rates of domestic violence in veterans – as reported both by veterans and their partners – are almost precisely the same as the general Australian population. Moreover, when veterans have succumbed to lashing out, it seems to be associated with early development of PTSD, has happened generally only once, and has occurred a long way in the past.

1.4 “The Natio’s were not as affected by their Vietnam service as they had shorter deployments”.

The data clearly shows that, in both waves of the veteran study, Regular soldiers had somewhat poorer physical health than the National Servicemen, and this is partly accountable by their older ages both in Vietnam and in the study. However, in spite of spending a shorter time in Vietnam, there is no difference between the mental health of Regulars and that of the Natio’s; no differences in depression, nor anxiety, and especially not PTSD. We can conclude that being fit and healthy and having shorter deployments in a war zone like Vietnam does not necessarily provide protection against post-war mental health problems. A soldier can encounter psychologically traumatic events from Day One in a war zone. However, it is true that duration of deployment (for both Regulars and National Servicemen) is one of the key predictors of PTSD as found in our analyses.

2. Understanding the Long Term Effects of War on Warriors

PTSD does not necessarily abate with time; it is a chronic condition that is treatment-resistant. It is often accompanied by a number of comorbidities, both physical and mental. In the physical health domain, the study has uncovered evidence that comorbidity is confined to diseases that may have an underlying inflammatory mechanism, such as asthma, arthritis, and hypertension, which are all associated with PTSD and which appear at greater prevalences than population expectations. We have hypothesised an underlying molecule endothelin-1 may play an explanatory role in these conditions, as epidemiological evidence is brought to bear on biological mechanisms. This inflammatory hypothesis is being examined in relation to long term physical health conditions observed in the second wave of the veteran cohort study, where PTSD has again been implicated in poorer physical health.

PTSD can have a delayed onset. Our research suggests, however, that delayed onset PTSD is much rarer than previously postulated, with symptoms appearing from soon after exposure to a traumatic event. However, it is often the case that veterans, having taken the advice given to “just put it aside and get on with your life, son”, carry on for years with sub-threshold symptoms grumbling along until life events such as marital separation, job loss, adverse family health events, or retirement, “get on top of them” (in the words of many veterans). It is then that the psychological defences that have guarded them against morbidity break down and PTSD appears full blown. More than 60% of veterans reported some form of intrusive symptomatology (nightmares, flashbacks, intrusive memories) in the first wave of the study; in the second wave this had risen to 70%. One third reported emotional numbing and avoidance in wave 1; by wave 2 this had increased to almost half. The arousal symptoms (sleep difficulties, hypervigilance, anger, startle), on the other hand, were relatively stable over the 15 years between the waves of assessment. The prevalence of PTSD had increased from about 20% to more than 30%, with “partial” PTSD (where diagnostic criteria are not quite met but just fall short of the strict criteria) increasing this rate to more than 42%. Our analysis is using sophisticated statistical growth mixture models to examine the longitudinal course of the various PTSD components and the diagnosis itself.

3. Are There “Ripple Effects” of War Service on Veterans’ Families?

The study of veterans’ wives and partners has added an exciting development to the study. More than 250 women were interviewed using the same assessment procedures
as used for the veterans, and the background Australian population data on health compiled by the Bureau of Statistics was also made available to the study. The initial results show that veterans’ wives do not suffer most health conditions at the same rates as the veterans, and are mostly not afflicted any more than the Australian population. However, the same is not true of their mental health: anxiety disorders and severe recurrent depression were among 11 of 17 psychiatric diagnoses that were significantly higher than population expectations. Despite higher diagnosis rates, there was no commensurate increase in health service usage. Veterans’ combat and PTSD were significant predictors of women’s depressive disorders, particularly severe depression. This is evidence that veterans’ war service and their own mental health have demonstrably adverse consequences for their female partners that can be seen three decades after the war. 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. These results reinforce the need to continue surveillance of veteran health and to take into consideration the impact of war service and combat exposure on veterans’ intimate partners when future studies of other veterans are undertaken. Higher rates of mental ill-health in both veterans and their partners may have major implications for the mental health of their offspring.

In spite of this, veterans’ marital relationships seem to withstand these onslaughts: the average length of relationships was more than 31 years, nearly one-quarter of the veterans were married before deployment and most stayed together after the war, and veterans’ marriage rates were not different from the Australian population. Nevertheless, in a Clinical Masters’ project completed by former research assistant Dianne Swinsburg, it was found that veterans’ PTSD and combat exposure were associated with marital cohesion, satisfaction and overall adjustment. Wives’ depression was the strongest predictor of marital adjustment; given that veterans’ PTSD and combat were significant predictors of their partner’s depression, this reveals an indirect link from war service to wives’ marital happiness. In spite of this, veterans’ wives “hang in there”.

Future analyses will be directed to understanding the relationship between development of psychiatric problems in veterans and the reciprocal development of their wives’ problems. In particular, although the actual number of suicide attempts in veterans and their wives is very low, there is a detectable relationship between the two. This issue will be examined in more detail by graduate Psychology Honours student Tammy Orreal-Scarborough during the coming months.

**Developments:**
Grant applications have been submitted to NHMRC and Rotary for funding in 2011-2013 to include veterans’ offspring in the study, to make a ‘family triple’ study that will be unique in Australia and one of the largest to be conducted in the world. If this is successful, it will provide the basis for additional biological research: It has been recently reported in the scientific literature that trauma and PTSD may affect gene expression particularly of immune system functions, and that gene expression may be transmitted to the next generation. Future possibilities of this line of enquiry may provide a firmer biological basis for understanding PTSD and point towards promising lines of treatment.

**Collaborations:**
Dr O’Toole has been invited to join the Consortium on Emerging Technologies, Military Operations, and National Security (CETMONS) based in the USA.
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McLachlan AJ, Hilmer SN and Le Couteur DG

McLachlan AJ, Hilmer SN and Le Couteur DG
FINANCIAL PERFORMANCE

Income & Expenditure 2001-2010

Millions

- $1
- $2
- $3
- $4
- $5
- $6
- $7
- $8
- $9


- Green: Income
- Blue: Expenditure
BOARD

Felicity Barr (Chair)
Felicity Barr’s interest in the issues of ageing developed during her service with the Commonwealth Department of Veterans’ Affairs, including five years as Deputy Commissioner in NSW. She has completed master’s studies in gerontology and is now working towards her doctorate in the Faculty of Health Sciences, University of Sydney. She chairs the NSW Ministerial Advisory Committee on Ageing, is also Chair of the Board of the War Widows’ Guild (NSW), Honorary Governor of the Ageing & Alzheimer's Research Foundation, and President (NSW) of the Australian Association of Gerontology.

Danny O’Connor (Deputy Chair)
Danny O’Connor is the Chief Executive for the Greater Western Area Health Service 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 at Concord Repatriation General Hospital.

Eve Bosak
Professional career in accounting, finance and business strategy for almost thirty years in the public, private, academic and global development sectors. International experience as CFO, South Asia region, World Bank and senior positions with major public and private sector international corporations. Serving on many public and private sector Boards in Australia including CPA Australia and 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 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.

**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 Board.

**Dr Charles Pawsey**

After Charles Pawsey graduated from the University of Adelaide in 1967, he spent three years at Queen Elizabeth Hospital in Adelaide. Later at Greenslopes Hospital in Brisbane he worked as a National Heart Foundation Research Assistant undertaking research into the Renin-Angiotensin system and hypertension. He undertook his physician traineeship at Sydney Hospital in 1972-73 and his Cardiology training at Royal Prince Alfred Hospital in 1974-75 and at Johns Hopkins Hospital in 1976. Since 1977, he has been a Staff Cardiologist at Concord Repatriation General Hospital.

**Godfrey (Rusty) Priest AM**

Rusty Priest was an inaugural member of the ANZAC Health & Medical Research Foundation serving as its Deputy Chair from 1995 to 2003. Rusty enlisted in the 2nd AIF in June 1945, serving in Japan with British Commonwealth Occupation Forces from April 1946 to December 1948, the Australian Regular Army from 1946 to 1967 and the Emergency Reserve until 1975. Then he undertook a management position at the University of Sydney, retiring in 1990. He is a Past President of the Returned and Services League of Australia (NSW Branch), having held office between 1993 and 2002. He is 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.

**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 Daichi 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.

Mr Gary Miller
General Manager, Concord Repatriation General Hospital. 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 appointment as General Manager at Concord, he was the General Manager at Canterbury Hospital. He has previously held a number of senior positions with the then Central Sydney Area Mental Health Service and at Rozelle Hospital.

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.

Clinical Assoc Professor Kerry Russell
Clinical Assoc Professor Kerry Russell is the Area Director of Nursing & Midwifery Services at Sydney South West Area Health Service. She has held a wide range of clinical and management positions and has a keen interest in workforce, particularly staffing and recruitment, continuing education for nurses and midwives and the development of partnerships to achieve mutual benefits.

Over a period of 4 years, Kerry successfully coordinated the overseas recruitment programs for NSW Health. She has undertaken a number of nursing reviews both in NSW and interstate. Kerry is a Board Member of the College of Nursing and is a Surveyor with the ACHS. In 2008, with a colleague, Kerry completed a whole of workforce review in the Greater Western Area Health Service and the North Coast Area Health Service as well as a Nursing Workforce Review for the Fiji Ministry of Health.
## DONOR HONOUR ROLL

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