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This report chronicles the ANZAC Research Institute’s outstanding record of achievements for the year 2005/06. The Board of the ANZAC Health & Medical Research Foundation and I congratulate the Director, Professor David Handelsman and the fine team of scientists, medical professionals and students working at the Institute on their accomplishments.

This year has built on the performance of the previous three years and has allowed the Institute to consolidate its position as the fastest-growing medical research institute in NSW. The rate of growth has brought both the opportunity to achieve synergies in research effort and create a fertile student environment in which to encourage and develop future research talent, and also the threat that the Institute’s facilities will not keep pace with its rate of expansion. The Board is therefore looking to commence a new phase in the life of the Institute and has commenced planning for major expansion of the facilities over the next few years in conjunction with the development of the new Asbestos Disease Research Institute to be built on adjoining land on the campus of the Concord Repatriation General Hospital.

The Board and management are keenly aware of the strong support for the Institute receives from its major institutional stakeholders and were very pleased to note several tangible expressions of that support during the reporting year. In particular, we note a significant increase in funding under the NSW Medical Research Support Program and the revised financial arrangements under the new Memorandum of Understanding with the Faculty of Medicine of The University of Sydney. The University has also indicated its willingness to support further development of the Institute’s facilities and we look forward to securing similar promises of support from other stakeholders.

I would like to thank the members of the Board for their continuing commitment and dedication to the interests of the ANZAC Research Institute and to pay tribute to the members who retired from the Board during the reporting year. In particular I would like to acknowledge the significant role that Professor Diana Horvath AO played since the inception of the Foundation, to thank Mr Paul McClintock for his valuable support as Deputy Chairman and Mr David MacGowan for the important contribution he made as Chairman of the Finance Committee. The Institute has been well served by their participation. This year the Board has also been pleased to welcome new members Mr Michael Wallace, Mrs Eve Bosak and Professor Kerry Goulston and we look forward to the coming year with every anticipation of further success.

Felicity Barr
Chairman
Welcome to the ANZAC Research Institute’s 6th Annual Report. It’s a pleasure once again to report a very successful year with the Institute continuing its growth and scientific productivity. From our opening in late 2000, the ANZAC Research Institute now provides a research home to nearly 100 scientists within 8 research group, all working closely with affiliated departments of Concord Hospital and attracting over $5 million of external grant funding income. Over the same year, Institute scientists produced over 200 scientific papers in many areas of medical research and continued its research training program of nearly 30 graduate students. Beyond these broad measures of success, you will find details on the wide variety of cutting edge projects the Institute’s scientists are working on later in this Annual Report.

A major highlight this year was the Institute’s successful renewal of its State infrastructure funding under the NSW Medical Research Support Program (MRSP) for the 2006-9 triennium. The Institute’s daily operations are critically dependent on this funding source. While total state-wide MRSP funding was capped and most Institutes experienced stand-still funding, the ANZAC Research Institute won a 50% increase reflecting our growth rate over the last 3 years, the fastest of all NSW medical research institutes.

This year the Institute also signed a new Memorandum of Understanding with the University of Sydney’s Faculty of Medicine. Prompted by the Faculty of Medicine wish to provide fairer and more consistent return on external research funds earned by its affiliated research institutes, this new MOU also improves our Institute’s financial position.

In fulfilling our Institute’s role to provide dedicated, state-of-the-art medical research infrastructure for the whole of the Concord Hospital campus, the Institute has spearheaded efforts to develop a new research facility, the Asbestos Disease Research Centre, on the Concord campus adjacent to, and operationally integrated with, the Institute. This year these efforts reached fruition with the Premier’s announcement, accompanied by his Ministers of Industrial Relations and of Health, at a ceremony held at the Institute to commit capital funding to construct the new Asbestos Disease Research Institute. This project with an overall value of over $15 million aims to have the new building completed by mid 2008. To cap this, the University of Sydney has now also committed a further $3 million for the partial construction of a second floor above the new Asbestos Institute to extend the ANZAC Research Institute’s laboratory facilities. In total when completed these developments will triple the laboratory space on the Concord campus.

Attracting top students to undertake medical research training with a PhD at the Institute remains a challenge, as it is for all off-campus Institutes. Although we offer outstanding research opportunities the barrier of distance has led us to develop a Summer Scholarship scheme to bring top science and medicine students from around Australia and New Zealand to experience research at the Institute over the summer break. This scheme has been adopted by the University of Sydney Faculty of Medicine to offer 60 summer scholarships each year in a scheme that won a University Vice Chancellors Award for enhancing the student experience. This scheme is now starting to show dividends by providing the Institute with a new crop of graduate students.

It is a pleasure to acknowledge the work of many people contributing quietly but crucially to our success. The office management team that keep the Institute functioning now comprises Annet Doss, Tracey Dent, Pam McDowell and Mamdouh Khalil. To them I am immensely thankful for their unstinting efforts. This year saw the departure of Christine...
Harrison from her role as General Manager to take up new challenges and we thank her for all her efforts over 5 years. We have been very fortunate to have such strong and committed organisational support for the Institute’s overall goals. My thanks also go to the Foundation’s Board together with our friends and supporters for their continuing goodwill. It is once again a great pleasure to thank Danny O’Connor, General Manager and Margaret Sanger, Director of Medical Services, Concord Hospital as well as Michael Wallace, CEO of the Sydney South West Area Health Service for their enlightened and unwavering practical support. Finally, I also thank Felicity Barr, Chair of our Foundation Board, for her invaluable support in facilitating the Institute’s growth and success.

It’s always a pleasure to pay tribute to the Institute’s hardworking and creative scientists who create such an interesting and vibrant research environment. Combining the best traditions of scientific collegiality, collaborations and intelligent critique, they give the Institute the buzz that comes with the most productive science. We are fortunate indeed to have such highly motivated and skilled scientific staff and I thank them for their fine efforts.

Thanks to many supporters and the hard work of our scientists and staff, the ANZAC Research Institute has become one of the major NSW independent medical research institutes with international recognition. We are proud to present this record of progress in grants, publications and scientific training produced by our scientists in this report. Your support for our future progress will be greatly appreciated and makes a vital contribution to our joint future as only the best medical research can ensure the highest standards for our future health and medical care.

David Handelsman
Director
Andrology is the study of male reproductive health, medicine and biology. The Andrology Laboratory focuses on the biological and clinical effects of androgens (male hormones) on men’s health. The major androgens are testosterone (T) and dihydrotestosterone (DHT) and they fulfill well known roles supporting male reproductive functions such as fertility and sexuality but they also have vital influences on most other tissues especially the prostate, cardiovascular system, bone and the brain. In medicine, androgens are used to treat hormone deficiency states and in men with certain chronic diseases but are also being tested for use in male contraception and for ageing men. In men, the body’s own androgens are also a crucial influence on the development of prostate and cardiovascular diseases as men grow older.

The Andrology group conducts a range of studies spanning basic, clinical and public health research with a focus on male reproductive health across all ages. Combining the Andrology Laboratory at the ANZAC Research Institute and Department of Andrology at Concord Hospital, it features an integrated bench to bedside and beyond approach intended to facilitate successful translational research.

Our research focuses on improvement in four broad aspects of men’s health

- Androgen therapy to improve health and well-being
- Causes, prevention and treatment of prostate disease
- Understanding testicular function, notably hormonal control of sperm production
- Understanding the effect of male hormones in health and in ageing

Physiology and Pharmacology of Androgens

Clinical Pharmacology of Testosterone

S Kelleher, A Conway, PY Liu, L Turner, DJ Handelsman

As the country’s leading clinical research centre in the clinical pharmacology of androgens, our research continues into optimising and understanding how such treatment works. Our work defined the modern clinical pharmacology of depot testosterone implants. This is a highly effective and affordable treatment modality, which was facing deletion from the market as an old, low cost technology to be displaced by newer and more expensive testosterone products which were, however, less satisfactory for lifelong treatment. After its rescue, this treatment is once again among the major forms of testosterone replacement therapy for young men in Australia. Although a convenient therapy with the advantage of long intervals (6 months) between treatments, the minor surgery implantation procedure suffers from the drawback of occasional extrusions. This is where one or more pellets tracks back under the skin to be expelled through the implantation site, often months later. Several clinical research studies have been examining ways to improve implant delivery and prevent extrusions. These studies have further defined how long treatment lasts, why it varies between men and at what threshold of blood testosterone levels people become aware of the symptoms of insufficient blood testosterone levels. Recently, a new 3 month injectable form of testosterone has been marketed and our centre is now conducting a head-to-head comparison study against the 6 month depot implants.

Testosterone, Obesity and Sleep Apnea

PY Liu, DJ Handelsman with Dr B Yee and Prof RR Grunstein (Woolcock Institute of Medical Research)

Both obesity and sleep apnea are strongly associated with lowered blood testosterone concentrations in middle-aged and older men. We have postulated that these two common, adverse health states combine to form an intermeshed vicious cycle which drives down blood testosterone levels and also worsens both the obesity and sleep apnea. Although palliative treatments are available to improve or bypass both obesity and sleep apnea, no treatments are available to provide simple, well-sustained benefits or cure. An effective treatment that rectifies both of these major health problems would be a substantial advance in promoting health male ageing. A randomized, placebo-controlled clinical study is underway to test the hypothesis that testosterone treatment may ameliorate obesity and/or sleep apnea.

Testosterone Changes during Male Aging

PY Liu, DJ Handelsman with C Meir, MJ Seibel (Bone Biology Group), Dr J Beilin, Prof P Leedman (Royal Perth Hospital) and Dr T Nguyen and Prof J Eisman (Garvan Institute)

In men, blood testosterone concentrations fall with age. The rate of this fall in Australian men has not, however, been adequately documented. This decline is likely to impact on male
reproductive and general health and could contribute to the physical frailties associated with older age. We are examining blood testosterone concentrations changes, and their predictors, in two well-defined groups of men who have been followed for up to 15 years and who reside in Busselton (Western Australia) and Dubbo (New South Wales). This epidemiological study will be one of the first to longitudinally assess the fall in blood testosterone in community-living Australian men.

Reproductive Function after Bone Marrow Transplantation
PY Liu, DJ Handelsman with Dr K Bradstock (Westmead Hospital)

Bone marrow transplantation with ablative chemotherapy is a life-saving procedure that cures certain hematological cancers. The chemotherapy administered can, however, adversely affect testicular function, resulting in impaired fertility and testosterone deficiency. The incidence of erectile dysfunction, decreased reproductive capacity and testosterone deficiency in men following bone marrow transplantation is poorly defined, especially in Australian men. We are collecting this information and will also determine the factors which worsen or improve the chances of normal reproductive health post-transplantation. This knowledge will guide medical surveillance of reproductive health in these male survivors of hematological malignancies, and thereby allow timely treatment when necessary.

Androgen Misuse and Abuse: Sports Doping
C Young, I Collins, M Jimenez, DJ Handelsman in collaboration with A Death, L McRobb, K McGrath (Heart Research Institute) and R Kazlauskas, C Howe (National Measurement Institute)

The marked benefits of androgens on muscle strength, energy and quality of life in men with genuine androgen deficiency mean that androgens are particularly liable to overuse. This may be in the form of medical misuse via misguided over-prescribing or as androgen abuse involving the use of illicit androgenic drugs for sports doping and body building.

For testosterone misuse, we have developed a national and state-based surveillance of PBS-funded testosterone prescribing patterns. This has helped to identify systematic deviations that call for heightened surveillance and increased professional and public education with the goal of making clear the differences between valid evidence-based use of testosterone treatment and deterring misguided applications that lack evidence of safety and efficacy. Fortunately, surveys of Australian high school students indicate that androgen abuse has remained at steady, relatively low levels during the last decade.

Androgen abuse is the illicit use of androgens to improve sports performance or for body-building. Such drug doping is banned in sports as it violates the spirit of fair play as well as endangering athlete’s health. Androgens remain the most effective and widely abused drugs for sports doping. Bans by the World Anti-Doping Agency (WADA) and its national affiliates like the Australian Sports Anti-Doping Authority (ASDA) are policed by methods to detect androgens in urine specimens obtained from elite athletes. Although well-known androgens are readily detected by sophisticated and sensitive chemical methods, in recent years new designer androgens have been developed to evade detection. Our group was the first to prove that the designer androgen THG was a potent androgen, evidence that was pivotal to the first successful prosecution for THG use by an athlete. Maintaining effective bans on androgens requires continual improvement in detection of illicit androgens. The Andrology group is now undertaking WADA- and 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.

Androgens and the Testis
CM Allan, P Lim, K McTavish, J Spaliviero, M Jimenez, DJ Handelsman

We study the roles of major reproductive hormones in testis development and function, in particular sperm production (spermatogenesis). Over recent years through NHMRC-funded projects our laboratory has provided important contributions towards understanding the hormonal regulation of testis development and function. We have developed specific customised genetic models to study the effects on and interactions between the two major hormones, FSH and testosterone, that govern the initiation and maintenance of spermatogenesis. Our studies first showed that testosterone alone was sufficient to initiate spermatogenesis. Yet, although testosterone and its androgen receptor (AR) are essential for male fertility and sperm production, the important biological pathways required for androgen-induced spermatogenesis remain largely unknown. Patrick Lim (PhD student) created a mouse model lacking the androgen receptor (AR) in testicular Sertoli cells, which provide the essential infrastructure and nutrition for sperm development. This model showed that the classical AR pathway in Sertoli cells is pivotal in orchestrating the completion of spermatogenesis. In addition, our laboratory pioneered the development of the first genetic mouse model to over-express FSH in otherwise normal mice. This allowed us to identify the major role of FSH in creating a full complement of Sertoli cells, the somatic (non-germinal) nurse cells that support and nourish the germinal epithelium. While this was vital, full spermatogenesis only developed in the presence of both hormones.

More recent studies have investigated the nature of the steroidal regulation of testis development and spermatogenesis. Remarkably and unexpectedly, we have shown that estradiol, the classical female reproductive hormone, can initiate spermatogenesis in a mouse model (hpg mice) lacking all other...
major reproductive hormones including testosterone. Ongoing research is exploring how estradiol activates Sertoli cells either directly or indirectly via stimulating pituitary FSH secretion. Our distinctive array of customised genetic mouse models is being used to identify and characterise the underlying biological pathways essential for FSH and steroid-dependent testicular function. This greater understanding of fundamental testis biology may identify new leads to develop novel male contraceptive approaches, as well as new targets for treatments of male infertility due to spermatogenic defects and for the origins and treatment of testicular tumours.

Male Hormonal Contraception

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

A major practical application of improved knowledge about how hormones control sperm production is the development of a male hormonal contraceptive. Men have a strong interest in effective family planning with over 1/3 of all contraceptive-using couples relying on traditional male methods of contraception. Despite this not a single new male contraceptive method was introduced over the last century while over the last four decades, numerous highly effective, reversible contraceptives for women have been developed in one of the greatest achievements in applied science, which produced profound changes in our society.

Following a decade of preliminary feasibility and path-findings studies, in 2003 the Andrology Department published a proof of principle study establishing very high reliability of a depot combined hormonal male contraceptive. Our approach featured a long-acting injectable (rather than an oral pill) for better safety and reliability as well as a combination of hormones (testosterone plus a progestin, a synthetic analog of the natural pregnancy hormone progesterone, used in female contraception) rather than testosterone alone. In our preliminary studies using a depot form of testosterone, we defined the lowest effective dose with sufficient suppression but without undesirable side effects and tested it with a progestin to identify the best combination. The excellent result for the prototype hormonal regimen was a major advance. The announcement of the very positive findings of this study, funded by CONRAD, an American public sector agency, made international headline news. Our studies have led the world and made great progress in optimising the approach to develop a practical hormonal male contraceptive regimen. The proof of principle re-kindled the faltering interest of major multinational pharmaceutical trials in developing a marketable product that will exploit this approach for an effective, reversible male hormonal contraceptive. Currently, based on the positive findings of our 2003 study, we are extending our clinical experience with the combined depot approach, as the first medical male hormonal contraceptive service offered anywhere in the world.

In studies during his NHMRC Neil Hamilton Fairley Fellowship, Dr Peter Liu was the lead author in a major Lancet publication that will be a major landmark paper in the development of a hormonal male contraceptive. By working with all active groups in the world, Dr Liu was able to obtain the complete primary data of virtually all published studies. Using this unique combined database, he provided convincing evidence that such hormonal regimens were fully reversible, an essential requirement for a practical hormonal male contraceptive.

Suppression of Sperm Output for Male Hormonal Contraception

PY Liu, DJ Handelsman with Prof RS Swerdloff and Prof C Wang (Harbor-UCLA Medical Center, Los Angeles)

Male hormonal contraceptive methods suppress sperm production by feedback inhibition of the signal that the testes receives to produce sperm. This is analogous to the way that the female oral contraceptive pill works. Male hormonal methods are effective provided that sperm output is adequately suppressed. Currently we are unable to predict reliably which men will adequately suppress sperm output, or the time required. This represents an important barrier to widespread utilisation of these methods. To this end, we have collected data from over 1500 men who have received male hormonal contraceptive treatments throughout the world. By analysing this information, which is the largest dataset of its kind, we will identify the factors that cause inadequate suppression of sperm output and enabling us to tailor future treatments.

Androgens and the Prostate

Origins of Prostate Disease

K Griffiths, S Wishart, 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 ~1970 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.

Prompted by the need to improve recruitment, we have developed a novel, less invasive ultrasound method to measure prostate size that avoids the need for a transrectal probe. We have evaluated this new method fully and have shown it to be more acceptable, and as reliable and accurate as the existing invasive, transrectal method. We anticipate that this new ultrasound method may prove useful for studies requiring repeated measurements of prostate size.

Clinical trial of DHT to prevent prostate growth
A Idan, K Griffiths, L Turner, AJ Conway, D J Handelsman

A major advance in understanding the development or prostate development and disease was the recognition that the prostate has an inbuilt amplification system that boosts the androgenic potency of testosterone entering the gland. This is based on an enzyme (5a reductase type 2) expressed in the prostate that converts T to DHT, a more potent androgen. This highly selective expression in the prostate of this enzyme allowed development of specific blockers of this enzyme that reduce both prostate over-growth (the main reason for prostate surgery in older men) and the rate of development of prostate cancer.

With this background knowledge, our own research suggested a reduction in prostate growth rate in otherwise healthy older men who were treated with an androgen that was incapable of such amplification. This clue has led us to develop a major study being conducted at the Department of Andrology, Concord Hospital to evaluate, in detail, the degree to which DHT is effective in preventing prostate growth in middle-aged men without known prostate disease. Sponsored by an overseas pharmaceutical company, this study will also monitor carefully whether the DHT treatment has any adverse effects on bone or the cardiovascular system.

Tissue-selective Role of Androgens in the Prostate
U Simanainen, K McNamara, 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 and/or treatment for prostate diseases including prostate cancer.

Androgens, Ageing and Female Reproductive Physiology

Androgens and the Ovary
K Walters, K McTavish, P Lim, CM Allan, DJ Handelsman in collaboration with P Illingworth (Westmead Hospital), J Zajac(University of Melbourne)

Androgens are essential for male reproduction and traditionally are regarded as a defining characteristic of masculinity. In recent years, however, there has been growing interest in the pharmacological use of androgens in women. In addition, some recent evidence suggests androgens may have a role in normal female physiology. Our project is exploring the possible role of the androgen receptor (AR) in female physiology, notably in the ovary and female reproductive tissues. We have established new transgenic models to selectively inactivate the AR gene, resulting in female mice functionally unable to respond to any androgens including testosterone. Because such females cannot occur in nature, we have created an unique and important opportunity to characterise the role of androgens acting though the AR in female reproductive and non-reproductive physiology. Kirsty Walters (PhD, UK) recently joined the laboratory to study this unique AR-null female model. Her initial findings have revealed defects in ovulation and late-stage follicle growth are the major contributors to the reduced fertility. This has identified previously unsuspected roles of androgens in female reproductive development and function. Dr Walter’s work was awarded the 2006 Young Investigator Award of the Australian Society for Reproductive Biology at its annual scientific meeting.
In women, fertility terminates at mid-adult life with the onset of menopause after which women are estrogen deficient. Menopause signifies the final exhaustion of ovarian follicles (the cells in the ovary that can develop into eggs) following the progressive deletion of the vast majority of these cells, the potential eggs, from birth onwards by a process known as atresia. The rate of atresia therefore dictates the timing of menopause so that altering the atresia rate could modify age of menopause. Changes in the age of menopausal estrogen deficiency could have a major impact on female health and well-being through estrogen dependent health and disorders.

Although menopause is a salient event, human female reproductive ageing begins well before menopause as the depletion of ovarian follicles accelerates towards the complete demise of the ovary. During the later phases of female reproductive life, women have gradually increasing levels of blood FSH and reduced fertility at least a decade prior to cessation of menstrual cycling (menopause). During this period, blood FSH levels gradually increase and it has proved difficult to determine whether this rising FSH causes the terminal exhaustion of ovarian follicle numbers or is a passive reflection of depletion of ovarian follicle (egg) numbers. We, therefore, established an unique mouse model to explore the relationship between FSH and ovarian ageing. Using a combination of our mouse models, we found that although FSH over-expression had no effect upon sperm production or male fertility, it has striking effects upon female fertility. In female mice, transgenic over-expression of FSH (with blood FSH levels rising with age) initially increased litter size of young females, but led to a rapid decline to premature infertility. These features replicate and, therefore, provide interesting models for clinical situations of gonadotrophin-induced hyper-stimulation and menopause, respectively.

Kirsten McTavish (PhD student) continues to explore the aberrant fertility in these transgenic FSH females. In particular whether rising FSH directly contributes to reproductive ageing, or is a passive reflection of ovarian failure, in particular following the loss of follicles. Our current research suggests that premature infertility due to transgenic FSH occurs despite continual estrus cycling, follicle development and ovulation, and appears not to be linked to early depletion of the non-renewable ovarian follicle pool. Failure of post-implantation survival of embryos appears to be the key mechanism of the advanced infertility, suggesting that rising FSH during ageing may have an important impact on the ability of the uterus to accept embryo implantation and to support early fetal growth. We have created a novel paradigm to investigate contributions of elevated FSH to a number of issues including age-related infertility, the consequences of IVF hyper-stimulation in the light of the controversial new concept that early follicles may be capable of “self-renewal” in mature ovaries, as well as conservation of female fertility by preserving or rescuing follicles during ovarian damage due to chemotherapy or radiotherapy for cancer.
Group Leader: Professor David Le Couteur

Senior Scientists: Dr Michael Muller, Dr Victoria Cogger, Dr Rajkumar Cheluvappa, Prof Robin Fraser, Dr Sarah Hilmer, Dr Hamish Jamieson, Jennifer O’Reilly, Mimi Saba, Allesandra Warren.

The Biogerontology Laboratory, the laboratory component of the Centre for Education and Research on Ageing (CERA) at Concord Hospital, studies the biology of ageing and age-related diseases. Our major focus is on age-related structural changes in the liver and the implications these changes may have for the development of vascular disease and drug metabolism in the elderly.

Blood travels through the liver through many small vessels termed sinusoids. These sinusoids differ from normal vascular blood vessels in that they are lined by endothelial cells that are highly perforated by small pores (fenestrae) about 50-100 nm in diameter and which are arranged in structures called sieve plates. The endothelial cells of normal blood vessels are not perforated and form tight junctions between cells to prevent leakage of blood components. In the liver, endothelial fenestrae facilitate the exchange of large proteins and small particles, including lipid-rich blood particles (chylomicron-remnants) between the blood and liver cells (hepatocytes). Our group discovered that with advancing age the number of endothelial fenestrae decreases, a process we have termed defenestration, with the result that the liver sinusoids become more like vascular blood vessels. We have hypothesised that this process results in the altered exchange of substances between the blood and liver.

Recent work has focused on isolating liver endothelial cells and developing techniques aimed at providing more accurate measurements of fenestrae dimensions. We are also investigating the mechanisms of defenestration and the immunology of the liver.

Live Cell Imaging

V Cogger, D Le Couteur, I Arias, J Lippincott-Schwartz

Dr Victoria Cogger spent 12 months on sabbatical in the Cell Biology and Metabolism branch of the National Institute of Child Health and Development (NICHD) in Bethesda, Maryland USA. While at NICHD Dr Cogger developed methods of live cell imaging of the liver sinusoidal endothelial cell (LSEC) and their fenestrae. To date, work with the LSEC has been challenging due to difficulties with cell isolation, survival outside the liver and visualisation. Under the guidance of Drs Irwin Arias and Jennifer Lippincott-Schwartz, Dr Cogger began to investigate ways to observe fenestrae using conventional confocal microscopy. This was accomplished by labelling proteins that are localised to the LSEC fenestrae with green fluorescent protein (GFP) and tetracysteine motif. This combination allowed visualisation of fenestrae with confocal microscopy and transmission electron microscopy. In addition, experiments were performed to examine the LSEC using the PALM microscope, a technology that is currently under development at the NIH.

Dr Cogger returned in July 2006 to take up the position of Associate Lecturer in Biogerontology based at Concord Hospital.

Calorie restriction delays age-related defenestration of the liver sinusoidal endothelium

HA Jamieson, VC Cogger, SN Hilmer, R Cheluvappa, A Everitt, R Fraser, D Abernethy, R de Cabo, DG Le Couteur

Previous work by our group has demonstrated that aging causes changes in the liver sinusoidal endothelium including a loss of sinusoidal fenestrae and an increase in thickness of the endothelium. This delays the clearance of chylomicron-remnants and may partly explain why ageing is a risk factor for the cardiovascular diseases such as strokes and heart attacks.

Limiting the caloric intake of animals by approximately 30% has been consistently shown to extend lifespan and reduce the incidence of age-related diseases. In this collaborative project with the United States National Institute on Aging, we showed that calorie restriction prevented the development of age-related defenestration. This is the first time that a treatment has been shown to prevent defenestration in old animals. This provides a potential mechanism for how calorie restriction extends lifespan in mammals. Future work will assess if calorie restriction affects the clearance of lipid rich blood particles.

Diabetes accelerates age-related defenestration of the liver sinusoid

HA Jamieson, VC Cogger, R Cheluvappa, R Fraser, SM Twigg, SV McClennan, R de Cabo, DG Le Couteur

In this work we demonstrated that diabetes caused an increase in age-related defenestration. This confirms that the age-related loss of fenestrae can be accelerated. We hypothesised that this may contribute to the delayed chylomicron remnant clearance and the increased rate of atherosclerosis that occurs in diabetes.
**Immunology of the Liver**

A. Warren, D. Le Couteur, P. Bertolino (Centenary Institute)

Alessandra Warren completed her PhD entitled, “Hepatic sinusoidal cells in liver immunology and ageing” in 2006. Part of her work focused on understanding a key issue in immune-mediated liver disease: how T lymphocytes interact with hepatocytes in the presence of a sinusoidal endothelial cell barrier. Electron microscopy studies of a murine model, in collaboration with Dr Patrick Bertolino from the Centenary Institute of Cancer Medicine and Cell Biology (Sydney), demonstrated that intrahepatic and naive T lymphocytes present cytoplasmic extensions which protrude through sinusoidal cell fenestrations and contact hepatocyte’s microvilli. Moreover, fenestrations appear to be important for infiltration of inflammatory cells from the circulation into the parenchyma during autoimmune-hepatitis. These findings suggest that hepatic sinusoidal endothelial cell fenestrations have an important role in liver immunology leading to future studies on their therapeutical implications. Further work was undertaken at University of Tromso (Norway) studying endocytosis of bacterial antigens by hepatic sinusoidal endothelial cells.

**Mechanisms of Age-Related Defenestration**

J O’Reilly, M Muller, D Le Couteur

This ongoing project is examining the potential for isolating LSECs from young and old livers in order to provide purified cells for experiments to investigate mechanisms related to defenestration. Previously, we found that depleting isolated LSECs of ATP caused rapid defenestration. Consequently, we compared the ATP status of young and old isolated LSECs. Although we found no significant difference between the ATP levels of these two groups of cells, we did find that within 24 hours of isolation LSECs lose the ability to retain their fenestrae and their viability declines markedly. The poor survival of these cells outside of the liver currently limits their usefulness for defenestration studies.
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 2006, the program has employed three new research assistants, who have come from the Garvan Research Institute (Colette Yee), University of Adelaide (Rebecca Dragovic), and University of Sydney (Sadaf Warraich). Yu Zheng and Mystie Mak have joined the group as PhD students in 2004 and 2005 respectively. Dr Robert Kalak joined the Bone Biology Program as a Postdoctoral Fellow from the Karol Marcinkowski Medical University, Poznan, Poland.

A number of exciting and competitive projects are presently under way. We have established collaborations with research groups in Australia based at the Universities of Sydney, New South Wales, Melbourne, Adelaide, Perth and Brisbane. Internationally, we collaborate with colleagues from Columbia University, New York, USA, University of Wuerzburg, Germany, Aberdeen University, UK, and University of Basel, Switzerland. We have had the opportunity to build research partnerships through attracting visiting scientists to work at the ANZAC Research Institute. In 2005/6 we welcomed Dr Efrat Monsonego Ornan from Israel and in 2006 we welcomed Professor Frank Buttgereit, Humboldt University, Berlin, Germany (Feb-May 2006); Dr Di Chen, University of Rochester, Rochester, New York, USA (Oct-Nov 2006).

This year’s meetings of the European Society for Calcified Tissue, the Cancer and Bone Society and the American Society for Bone and Mineral Research have been successful for our group. From these meetings we had 5 oral presentations and one Young Investigator Award (Yu Zheng) indicating that our young group established place in the international science community.

Our plan is to further develop a comprehensive research program that makes use of the multidisciplinary opportunities provided the ANZAC Research Institute. Our goal is to intensify collaborations with both basic and clinical research groups on the ARI and Concord campus, and to extend our research efforts to other areas relevant to bone biology and disease.

Preventing The Spread Of Malignant Tumours To Bone
Yu Zheng, Julie Blair, Hong Zhou, Sadaf Warraich, Colette Yee, Markus Seibel, Colin Dunstan.

Breast cancer and prostate cancer have a particular preference to form cancer 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. Tumour cells grow in bone and induce normal bone resorbing and bone forming cells of the bone marrow to destroy the surrounding hard bone. It is 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. We are also examining how physiologic bone remodelling may support the earlier stages of bone metastasis of extravasation and formation of micrometastases. We are studying mice with transplanted breast cancer cells to understand what makes the bone marrow a receptive site for breast cancer metastasis. We are manipulating bone remodelling rates in mice see how this impacts the ability of circulating cancer cells to target bone and to establish destructive tumours there. 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. We have discovered that increasing bone resorption through a low calcium diet enhances breast cancer metastasis to bone in a mouse model. This may have clinical implications as many elderly women at risk of breast cancer have secondary hyperparathyroidism and increased levels of bone resorption. The response of tumours to these changes in bone cell activity is being assessed at the cellular and molecular levels to identify genes that may be critical to the metastatic process.
Glucocorticoid-Induced Changes in Bone Metabolism

Hong Zhou, Mystie Mak, Robert Kalak, Rebecca Dragovic, Colette Yee, Colin Dunstan, Markus Seibel

Glucocorticoids (GC) have been proven to be 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. A novel transgenic mouse model is being employed in the Bone Biology laboratory to study the effects of GC treatment on bone. The transgene carried by these mice results in a local inactivation of GC 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. This model allows us to separate effects on bone, which are due to direct action of GC on the osteoblasts, from indirect effects such as reduced absorption of calcium in the gut. We are studying the contribution of factors such as gender, age and diet to GC-induced bone loss and to examine the role of endogenous GC in bone damage caused by inflammation and arthritis. We have identified a delay in the development of the skeleton in newborn mice and have found that cells isolated from these mice have reduced ability to make bone. We are currently investigating the mechanism of these defects. In the long term, we hope that these studies will point the way to strategies for the reversal or even prevention of the detrimental effects of cortisone on the skeleton.

Regulation of osteoblast and adipocyte differentiation from common precursors

Hong Zhou, Robert Kalak, Mystie Mak, Rebecca Dragovic, Colette Yee, CR Dunstan, MJ Seibel

Osteoblasts and adipocytes develop from a common mesenchymal precursor. An inverse relationship between adipocyte and osteoblast differentiation has been suggested by the clinical observation that marrow adipocyte numbers increase while osteoblast numbers decrease during age-related bone loss or after treatment with glucocorticoids. In this study, we aim to identify the factors that control commitment at the branching point between osteoblast and adipocyte differentiation. Steroid hormones play an important role in regulating osteoblast and adipocyte differentiation. By using the transgenic mouse model, we have found that glucocorticoids stimulate mature osteoblast cells produce the molecules to inhibit adipocyte differentiation and promote osteoblast differentiation. Further studies are planned to determine the gene expression profile in this system. With our collaborators, Prof. Franz Jacob and Dr Norbert Schuetze from the University of Wuerzburg, Germany, we have conducted microarray and proteomic studies into signalling between osteoblasts and osteoblast precursors. We will utilise transgenic mice with impaired osteoblast formation to identify specific autocrine and paracrine factors involved in the regulation of osteoblast differentiation.

Study into the genetic determinants of bone loss and osteoporosis in an affected family

Marta Koslowska, C Meier, M Kennerson, G Nicholson, Ian Blair, MJ Seibel

Osteoporosis is a common multifactorial disorder of reduced bone mass. Osteoporosis treatments are currently limited in terms of efficacy and drug classes available. Identification of new therapeutic targets is a high priority. Although multiple environmental factors are involved in the pathogenesis of osteoporosis, genes also play a major role as reflected by heritability of many components of bone strength. The common form of osteoporosis is generally considered to be a polygenic disorder arising from the interaction of common polymorphic alleles at many loci. However, a few recent publications have reported a major gene pattern of BMD inheritance in several ethnic populations. Identification of major genes contributing to osteoporosis would be of value for assessment of risk in individual patients.

In collaboration with Drs Ian Blair and Marina Kennerson, and Professor Garth Nicholson, Neurobiology Laboratory, ANZAC Research Institute and Molecular Medicine Laboratory, Concord Hospital, we are currently studying a large family with an autosomal dominant inheritance pattern of low bone mineral density. We have obtained DNA samples and clinical data from this extensive family and are examining the results to determine the best approach for identification of candidate genes.

Studies on Biochemical Markers of Bone Metabolism

J Modzelewski , C Meier, MJ Seibel

All metabolic bone diseases are characterised by changes in bone formation and in bone re-absorption, 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 world-wide. 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 Professor Philip Sambrook, RNSH), the effect of androgens on male bone health (with Professor David Handelsman and Dr Peter Liu, ARI), the effect of growth hormones and androgens on bone metabolism in elite athletes (with Professor Ken Ho), the effect of anti-epileptic drugs and smoking on bone turnover (with Prof. John Wark, Melbourne), and other topics.

Studies into the influence of serum testosterone levels and its longitudinal changes on different target tissues of androgen action

C Meier, M Jimenez, J deWinter, DJ Handelsman, MJ Seibel

In men, serum testosterone levels decrease progressively with ageing. Physiological 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 Prof JA Eisman, Bone and Mineral Research Program, Garvan Institute of Medical Research, Sydney, we are studying the large population of elderly men contained 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.
Group Leader: Professor Robert Cumming

Co-investigators & Collaborators: 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), Melissa Litchfield, Maggie Hayes, Suzanne Todd, Angeline Koh, Diane Pinkerton, Tamara Ribaric, Anita Sharma, Janice Koh

CHAMP is a population-based longitudinal study designed to provide a wide range of new information about the health of older men. The study is funded by a 5-year NHMRC Project grant.

Despite the fact that men who reach the age of 65 still have much lower life expectancy than women of that age, very little research has been done on the health of older men. CHAMP has been designed to fill this gap and is arguably the world’s most comprehensive study of the health of older men.

All men involved have blood taken for detailed assessment of their levels of reproductive hormones, including testosterone. While it is known that levels of testosterone decline with age in men, whether or not this decline has any major adverse effects on health is unknown. CHAMP will directly address this issue.

Of particular interest are osteoporosis, muscle weakness, urinary symptoms and dementia. Osteoporosis and fractures are often thought of as female health problems, yet 30% of 60 year old men will have a fracture of some type during the remainder of their life. Muscle weakness may be a greater problem in men than women, with some evidence that men lose muscle at a faster rate than do women as they grow older. Dementia is probably the most disabling condition of old age, yet little research has been done on the special features of dementia in men. CHAMP has a particular focus on testosterone levels and the aetiology of Alzheimer’s disease.

Many older men develop lower urinary tract symptoms such as nocturia, weak stream and dribbling. Furthermore, at least 15% of men over 65 years have some degree of urinary incontinence. It is generally believed that urinary problems in older men are due to their enlarging prostates. However, the causes are likely to be much more complex. Urinary function is assessed using a urinary flow metre and bladder ultrasound to measure post-void residual urine. Blood is being collected for measurement of Prostate Specific Antigen (PSA).

About 1,600 men aged 70 years and over who live in the community in the Concord Hospital catchment area will be recruited into CHAMP. The first men were recruited in January 2005 and over 1500 men were involved by December 2006. 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 are done, including dual energy x-ray densitometry (DEXA) to measure bone, fat and lean mass; the Addenbrooke’s Cognitive Examination; tests of muscle strength, balance and gait; and spirometry. Blood tests include assays for reproductive hormones, vitamin D, PTH, and markers of bone turnover. Blood is being stored for DNA testing. Most of the baseline interview and examinations will be repeated after two years. These repeat interviews will begin in January 2007.
The mutation analysis of genes involved with CMT has been expedited by the introduction of a new improved method called High Resolution Melt (HRM) analysis. The LightScanner machine from Idaho Technology USA is the first instrument to be commissioned in an Australian research institute and was the first to be purchased in the world. We have validated this technology in our laboratory using the Cx32 gene and the method has been used to identify mutations in large multi-exon gene for the most common axonal form of CMT (CMT2A; mitofusin MFN2) and the dynamin 2 (DNM2) gene causing intermediate CMT (DI-CMTB). HRM analysis is a simple, sensitive and cost efficient method to alternative gene scanning methods and has the potential to reduce the sequencing burden of a gene discovery project.

**Motor Neuron Disease**

I. Blair, C. Cecere, J. Durnall, S. Gopinath, T. Hayes, 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 is the most common form of MND. ALS leads to death within 3 to 5 years of first symptoms. The main feature of ALS is muscle denervation that gradually worsens. Initially the hands and arms, or feet and legs are affected. Symptoms worsen and spread to involve many muscles in the body. While muscles atrophy, intellect and senses usually remain intact, although a proportion of cases develop subclinical and clinical frontotemporal dementia. The cause of death is usually respiratory failure and pneumonia. The hereditary motor neuropathies (HMN) are a group of slowly progressive non-fatal MNDs that lead to severe lifelong disability.

The prevalence of MND in the overall population is around 5 to 10 per 100,000. However, few cases exist under age 50. The prevalence among Australian’s over 50 is around 1 per 5,000. About 1,300 Australians currently suffer from MND. The prevalence worldwide is similar, with over 300 cases diagnosed every day.

There is no specific test for the diagnosis of 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. The goal of our research is to gain an understanding of the biological basis of MND through identification of defective genes that cause the death of motor neurons seen in both ALS and non-ALS MND. This understanding is a prerequisite to effective diagnosis, treatment and prevention of MND.

Our laboratory works in close association with neurogenetic clinics. For over 10 years, MND families have been identified and recruited through these clinics and through our role as a referral...
centre for MND DNA diagnostic testing. Our current MND family cohort stands as one of the largest worldwide. The causative disease genes remain to be identified in most of these families. We have commenced genome-wide genetic linkage scans in these families in an effort to determine the chromosomal location of new disease genes. This work has led to three discrete projects:

1. Our recent scan in one large non-ALS MND family identified a region on chromosome 7 that harbours a previously unidentified disease gene. Work is now underway to narrow the chromosomal interval and isolate the gene in question.

2. Another of our genome scans has identified a chromosomal region containing a new ALS disease gene that is also associated with frontotemporal dementia. This gene may be responsible for a significant subset of ALS cases that also show dementia affecting frontal function.

3. A further genome scan has provided strong evidence for the presence of a new gene that causes classical ALS at one of two potential chromosomal locations. Identification of one or more of these new MND genes will provide vital clues to the biological pathways leading to premature death of motor neurons seen in both familial and sporadic cases of MND. We envisage that this will lead to the development of new drugs to prevent and treat these devastating disorders.

**Cell Biology Research Program**

S. Myers, B. Kowalski, M. Simone,

The past year has been extremely productive for the Cell Biology Research Program. We have made significant advances in a number of project areas, which have enabled us to establish a number of fruitful national collaborations. The major objective in our projects is to investigate and understand the functional cellular and molecular mechanisms of these neuro-degenerative diseases. Dr Myers was a co-winner of the University of Sydney’s Vice-Chancellor’s award for the student experience for the Summer Research Program in the Faculty of Medicine, in conjunction with Prof. David Handelsman, and Ms Joanne Elliot and Ms Yamin Sandiran from the Faculty of Medicine.

**Dominant Intermediate Charcot-Marie-Tooth Neuropathy**

Mutations have been identified in the dynamin 2 (Dyn2) which cause dominant-intermediate Charcot-Marie-Tooth (Di-CMTB) syndrome, an autosomal hereditary neuropathy. We have shown in Di-CMTB patient lymphoblast cells that the mutant Dyn2 blocks receptor mediated endocytosis (in collaboration with Prof. P Robinson and Dr. C Malladi from the Children’s Medical Research Institute). We have also observed in this disease that the cells have very altered morphology as depicted by scanning electron microscopy (see cover illustration).

**Hereditary Sensory Neuropathy**

Hereditary sensory neuropathy type 1 (HSN1) is one of the most common and best characterised form of peripheral sensory neuron degeneration. Clinically, it is characterised by loss of pain sensation, muscle wasting and weakness. Mutations in the serine palmitoyltransferase long chain subunit 1 (SPTLC1) protein cause HSN1. Pilot studies over-expressing the mutant SPTLC1 gene in human neuronal cells showed altered localisation of the SPTLC1 and changes to the actin cytoskeleton. We have also shown that the HSN patient lymphoblasts do not have blocked receptor-mediated endocytosis. Further investigations will elucidate how these changes attribute to neuronal cell dysfunction in this neurodegenerative disease. Another exciting area for this program was the successful construction and generation of the HSN1 transgenic mouse. We are currently expanding this colony and, in collaboration with colleagues at the Garvan Institute of Medical Research (Dr Tim Karl), have commenced characterisation of these animals for the HSN1 phenotype.

**Students:**

Dr Sumana Gopinath completed her PhD candidature on motor neuron disease and has received numerous travel awards and the prestigious NSW Motor Neuron Disease award for her studies. This year the laboratory had summer research students as part of the Sydney University Faculty of Medicine program. Megan Brewer was successful in obtaining a second summer vacation scholarship. She worked on CMTX3 project and subsequently enrolled in an Honours year. Min Li Huang obtained the Faculty of Medicine Summer Research scholarship. Results from her project showed that there was no alteration to the number, localisation and function of mitochondria in HSN cells.
This group has building up its presence in the ANZAC Research Institute over the past 3 years to now reach 14 people, primarily working in the laboratory, and another 5 with both clinical and laboratory responsibilities. This mix of basic and clinical science is a feature of the group, allowing us to conduct research into clinically important disorders of the heart and blood vessels both in experimental models and patients with coronary heart and other cardiovascular disease. The group has a range of research interests outlined below, with a focus in 3 areas: vascular and heart muscle injury by oxidation or intervention, inflammation and thrombosis, and atherosclerosis.

Heart Attack and Stroke

Paul Witting, Ben Rayner, Natasha Ellis, Andrea Szuchman-Sapir, Hong Duong, Sarah Parry

These studies focus on ischemic injury to the heart (heart attack) and brain attack (stroke). The main research thrust involves design and testing of potential (synthetic antioxidant) inhibitors of damage to myocardial and neuronal tissues in the setting of acute heart or brain attack. The research has gained funding from a variety of sources including philanthropic Foundations, mainstream government bodies and Industry (Eli Lilly). In addition to two PhD students and a postdoctoral researcher, this portion of the group has expanded further in recent times with the recruitment of Andrea Szuchman-Sapir, a post-doctoral researcher from Israel, Sarah Parry, a research assistant who recently completed an Honours degree in the lab as well as another Honours student for 2007.

CT Angiography

Len Kritharides, George Lau, Mimi Sabaretnam, Tommy Chung

Dr George Lau completed a clinical PhD co-supervised by Dr Ridley in Radiology investigating CT angiography, and its potential to study coronary artery bypass graft disease. He has identified that vein graft remodeling is more important than neointimal thickening in the first 12 months after surgery. Mimi Sabaretnam, jointly supervised by Professor Le Couteur of the Biogerontology laboratory, is investigating the fate of apoE in hepatocytes, particularly investigating the effects of ageing and oxidative stress. She has found that there is altered trafficking of apoE under these conditions, and that this may contribute to altered cellular apoE distribution found in vivo. Dr Tommy Chung is completing his PhD investigating reversible myocardial dysfunction. In collaboration with Professor Handelsman’s group Tommy has identified that conventional doses of androgens do not cause significant myocardial injury. He has also identified that cardiac dysfunction caused by pulmonary embolism follows a distinct pattern and time course of resolution, and that there is frequent reversible dysfunction after commonly used chemotherapy. The last of these projects involves collaboration with Drs Cunningham and Trotman of the Department of Haematology.

Gene expression and modification of vascular and myocardial injury

Harry Lowe, Aisling McMahon, Vicky Benson, Rav Bhindi

The group’s principal research focus is in the 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 are being examined. Using a number of in vitro and in vivo animal models we are investigating the use of DNAzyme and other novel gene-targeting approaches to inhibit injury responses.

Inflammatory mechanisms and mediators in acute coronary syndromes

David Brieger, Alice Tiong, Biao Zeng, Paul Witting, Ben Freedman, Changjie Song, Ying Shen, Eric Yamen

Our group has three main research directions:

a) Inflammatory mechanisms in acute coronary syndromes

In our studies over the last 12 months, we have identified a relationship between circulating levels of matrix metalloproteinase 9, a potential mediator of plaque instability in acute coronary syndromes and activated T cells, but not activated neutrophils. This work adds to the weight of evidence...
suggesting that evocation of the adaptive immune response plays an important role in this condition. Consistent with this theme, we have studied an oligoclonal population of NK T cells, CD3+CD28-, known to be elevated in ACS, and found they correlate with chronic T cell activation. This provides insights into the ontogeny of this population of potentially pathogenic cells.

b) Alternative mediators of fibrinolysis

Using the plasminogen knock out mouse as a model, we have identified increased activity in the neutrophils of mice deficient in plasminogen. The fibrinolytic proteases of these cells are being identified. Studies in parallel have isolated several circulating proteases that also have lytic activity in these knock out animals, and these enzymes are being further characterized and identified. The goal of this work is to provide insights into novel mechanisms of fibrinolysis.

c) CRP and Serum Amyloid A as Inflammatory Mediators

Our main aim is to demonstrate novel mechanisms of initiation of inflammation, and to define links between inflammation and arterial thrombosis. We have shown that both CRP (C-reactive protein) and SAA (serum Amyloid A) which are acute phase inflammation markers predictive of death or infarction in both normal populations and those with coronary artery disease, can stimulate blood monocytes to produce tissue factor, the most powerful initiator of coagulation. There is a non-specific up-regulation of monocye responsiveness to both CRP and SAA in patients with coronary artery disease, so the higher concentrations of these proteins seen in patients who have events indicates that both CRP and SAA are not just markers of inflammation, but may play a role in thrombosis which precipitates adverse events. We are further investigating the mechanism whereby SAA is pro-inflammatory, and have found very early and potent up-regulation of inflammatory cytokines by SAA in blood monocytes. This is also seen in monocyte derived macrophages present in atherosclerotic coronary artery vessel walls, and may be an important amplifier of both inflammation and thrombosis in acute coronary syndromes (including heart attack) and sudden coronary death. The group continues its longstanding collaboration with Prof Carolyn Geczy (UNSW) in these projects. In November 2006 Ying Shen was the first graduate student in the VBG to complete a post-graduate (Masters) degree in the ANZAC.
The Australian Vietnam Veterans Health Study is an epidemiological cohort study of a random sample of 1,000 Australian Army Vietnam veterans, examining the long term health effects of war zone exposures and experiences in combat veterans. Based at Westmead and Concord Hospitals, the study began in the late 1980s and the first wave collected data from veterans from 1991-1993. This current wave interviewed veterans during 2005-06 right across Australia, with fieldwork completed in November 2006. The study is concerned with all aspects of health, and is using assessment instruments that are standardized and that have national norms to allow comparison of veterans with the background male population.

The Australian Institute of Health and Welfare searched the National Death Index on behalf of the study to determine mortality in the cohort. Of the original 1000, 8 had died in Vietnam, and a further 117 have been found to have died since their return. This gives a post-war mortality rate of 11.9%. Risk factors for mortality so far emerging from analysis indicate that the deceased are more likely to have been Regular soldiers rather than National Servicemen, to have enlisted in earlier years, to have been older in Vietnam, to have served longer in the Army before Vietnam and overall, and to have had higher ranks and been older at discharge. Analysis of causes of death and the search for risk factors for mortality is continuing.

Because the random sample of veterans resides right across Australia, interviews were conducted in veterans’ homes or worksites. Interview teams located in WA, SA, Victoria, NSW and Qld were supported by Clinical Investigators travelling to rural localities to conduct assessments. The assessments took an average of four hours and consisted of modular interviews: the study was licensed to use the Australian Bureau of Statistics (ABS) software for computer-administered health interviews to assess physical and mental health. The study developed software to administer a clinical assessment schedule for post traumatic stress disorder (PTSD). Psychiatric health was assessed using the Composite International Diagnostic Interview, for which there are Australian population data to compare. Interviews were conducted by CI-A and by part-time counsellors (psychologists or social workers) associated with the Vietnam Veterans Counselling Service and with the National Centre for Veteran and Military Health.

Follow-up of the cohort in Wave 2 was about as expected: of the living members of the cohort, 308 could not be found and a further 99 refused to participate; a number agreed but could not be interviewed for logistical reasons (resident overseas, on extended ‘grey nomad caravan tour’, away on business). Assessments have been conducted with 455 veterans, representing a 53% response rate of living veterans or 80% of locatable veterans.

The first wave revealed a large untreated population of men with PTSD for whom the lifetime prevalence was 20.1% and the current (1-month) prevalence was 10.5%. In a preliminary analysis of the second wave, the prevalence rates were more than doubled - approximately 42% and 32%. For some men, after the war, those who ‘just got on with it’, positions of responsibility combined with workplace stresses caused spectacular breakdowns in later life; other veterans remain undamaged and in healthy mid-life. Still others, who carry most the serious wounds, are reaping the consequences of an angry life of alcohol and penury and passing this down to their children. In this study, we will examine more closely the time-course of the symptoms of PTSD in an attempt to identify factors that may ameliorate the symptoms, or factors that may trigger the symptoms in later life: for about 25% of the men with PTSD, the full syndrome took many years to emerge and in some cases was preceded by a major life change, such as Army discharge, retirement or retrenchment, business problems, or family events such as children’s illness or death. There is evidence from the study that PTSD has an influence on physical health, with PTSD more likely to be associated with conditions for which an underlying inflammatory mechanism is responsible, such as asthma and arthritis.

The study investigators had received funding in 2006 and again in 2007 from the Australian Rotary Health Research Foundation to include veterans’ wives in the study, using exactly the same data collection procedures as used for the men, but with interviews conducted by telephone. This component of the study will assess the effects of veterans’ problems on their wives and partners. In particular, the team has developed an assessment instrument that measures the amount of stress experienced by each woman and relates this to each of her partners’ symptoms of PTSD (if any). This, for example, will give a different view of the effects of recurrent and distressing nightmares on veterans’ wives and partners. This study will also examine the women’s reproductive history and major illnesses and survival of their children.

Group Leader: Dr Brian O’Toole
Collaborators and Staff: S Catts (Univ of Qld), Jill Cockburn (Univ of Newcastle), Kate Pierse

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CANCER PHARMACOLOGY

Group Leader: Professor Stephen Clarke
Senior Scientists: Assoc Professor Graham Robertson

Staff and Students: Filip Bebek, Wei Chua, Anthony Corradin, Haryana Dhillon, Chantal Gebbie, Melissa Lloyd, Lucy Jankova, Marina Kacevska, Andre Mahns, Marko Matic, Viet Phan, Patsie Polly, Jane Reid, Rohini Sharma, Timothy Tan, Lili Truong, Maria Tsoli, Anne Vannaliasinghe, Catherine Xu.

The Cancer Pharmacology research group is the newest addition to the ANZAC Research Institute, following the appointment of Prof Stephen Clarke to the Chair of Medicine at Concord Hospital. This enabled the establishment of a new team comprising 11 research scientists and students in the laboratory, as well as 7 staff with clinical responsibilities. This expansion has lead to a significant increase in cancer research activities on the Concord campus in the last 12 months involving developments in multiple areas including clinical trials of new cancer treatments, nutritional and psycho-oncology research and the establishment of a molecular-based cancer pharmacology laboratory. In addition, a strong collaboration has been formed with the Australian Proteome Analysis Facility at Macquarie University to discover new biomarkers for Colorectal cancer. This has led to a successful Cancer Institute NSW translational program grant for $3.75 million over 5 years for 2007-11.

Colorectal Cancer Biomarker Studies and Clinical Trials

Stephen Clarke, Haryana Dhillon, Chantal Gebbie, Lucy Jankova, Jane Reid, Lili Truong, Catherine Xu, Mark Molloy, Matt Mackay & Mark Baker (APAF).

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 through-put screening using the Concord Colorectal tissue and data banks collected by Profs Bokey, Chapuis and Chan from the Departments of Surgery and Pathology, CRGH.

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. 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.

Do tumour-derived cytokines repress drug clearance in the liver and alter metabolic pathways?

Filip Bebek, Stephen Clarke, Marina Kacevska, Patsie Polly, Andre Mahns, Graham Robertson, Rohini Sharma, Michael Downes (Salk Institute, California)

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. We carried out clinical studies which 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. A major goal of our research, therefore, 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. 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.

By profiling the expression of all 50 nuclear receptors, their cofactors and a representative set of their target genes, we have gained valuable insights into the alterations in many metabolic pathways in the liver due to tumour-derived cytokines. Such changes in hepatic metabolism may contribute to aberrant energy balance leading to cancer cachexia.

Drug clearance and cancer treatments
Stephen Clarke, Graham Robertson, Maria Tsoli, Patsie Polly

Another source of variability in drug clearance is due to the multiple drugs cancer patients are prescribed as well as the common use of herbal remedies. As many drugs and constituents of herbal therapies can themselves alter the clearance of anti-cancer drugs by changing CYP3A4 and drug transporter levels the CYP3A4 transgenic mice can be used to screen for such drug interactions. These complications in drug & herbal use are mediated by a factor in the liver called Pregnane X Receptor (PXR). By sensing the presence of drugs in the body and switching on pathways of metabolism and transport, PXR is the master regulator of drug clearance. We have used cell-based assays of PXR activation and found commonly used cancer drugs such as vinorelbine and etopside as well as the herbals St John’s Wort and Ginkgo may cause drug interactions. We have also developed computer-based molecular modelling to predict which drugs have the potential to activate PXR.
Molecular analysis of nuclear receptors PXR, RXR and HNF4
Filip Bebek, Anthony Corradin, Andre Mahns, Marko Matic, Patsie Polly, Graham Robertson, Timothy Tan, Mark Molloy (APAF)

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 RXRa and HNF4a. 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, RXRa and HNF4a 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.

Role of PXR in protecting cells against radiation damage in radiotherapy.
Graham Robertson, Maria Tsoli, Anne Vanniasinghe, Natalka Suchowerska (Radiation Oncology, RPA Hospital)

In addition to direct damage to the genetic material of rapidly dividing cancer cells, radiotherapy can cause damage to other components of both normal and malignant cells such as cell membranes. Cholesterol embedded in membranes can be chemically altered by radiation to forms, which can be extremely toxic to cells. PXR has evolved to protect cells from such endogenously generated toxic molecules in addition to foreign chemicals. We have investigated the contribution of PXR to the activation of detoxification pathways, which may reduce the efficacy of radiotherapy.
Scientific Staff

Director
Professor David Handelsman MB BS, PhD, FRACP

Scientific Program Leaders
Professor Stephen Clarke MB BS, PhD FRACP, FACHPM
Professor Bob Cumming MB BS, MPH, PhD, FAFPHM
Professor Ben Freedman MB BS, FRACP, FACC, FESC, PhD
Professor David Handelsman MB BS, PhD, FRACP
Professor David Le Couteur MB BS, PhD, FRACP
Professor Garth Nicholson MB BS, PhD
Dr Brian O’Toole PhD, MPH
Professor Markus Seibel MD, PhD, FRACP

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Associate Professor David Brieger MB BS, FRACP, PhD
Associate Professor Ann Conway MB BS, FRACP
Associate Professor Len Kritharides MB BS, FRACP, FAHA, PhD
Dr Stephen Reddel MB BS, FRACP, PhD

Research Fellowships
Dr Harry Lowe MB BS, FRACP, FACC, PhD
Dr Peter Liu MB BS, FRACP, PhD
Dr Paul Witting PhD

Principal Research Fellow
Dr Colin Dunstan PhD
Associate Professor Graham Robertson PhD

Senior Research Fellow
Dr Charles Allan PhD
Dr Ian Blair PhD
Dr Julie Blair PhD
Dr Marina Kennerson PhD
Dr Michael Muller MA, PhD
Dr Asling McMahon PhD
Dr Simon Myers Dip Ed, PhD
Dr Patsie Polly PhD
Dr Paul Witting PhD
Dr Hong Zhou MD (China), PhD

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Melissa Litchfield BAppSc, MPH
Kate Pierse BA, MA

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Mark Jimenez BSc (Hons)
Dr Robert Kalak PhD
Dr Cindy Kok DRS (Netherlands) PhD
Dr Andre Mahns PhD
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Dr Chiangjie Song MD (China), MSc, PhD
Jenny Spalliviero MSc
Dr Ulla Simianinen PhD
Dr Andrea Szuchman-Sapir
Dr Tim Tan MB BS, PhD
Dr Maria Tsoli PhD
Dr Kirsty Walters PhD
Dr Allesandra Warren MSc PhD

Clinical Research Nurses
Maggie Hayes RN
Marina Etherington RN
Melissa McCulloch BNurs

Project Officers
Dr Lam Ly MD (Vietnam), PhD

Research Assistants
Ivy Collins BS (Hons)
Alex Drew BSc (Hons)
Colette Fong-Yee MSc
Keely McNamara BSc (Hons)
Jennifer O’Reilly BA(Mus) BSc (Hons)
Dr Tamara Rubric MD (Austria)
Janine Street MSc
Sadaf Warraich BSc (Hons)

Technical Support
Fay Bacha BSc
Irene Di Pierro Dip Path Tech
Sabina Horky
Daniel Liske Assoc Degree
Angeline Koh
Ljubica Vrga BSc
Matilda Webbey
Veronica Pollero
Christina Nostas

Graduate Students
Vicky Benson MSc
Dr Melissa Baraket MB BS
Dr Ravinay Bhindi MB BS, FRACP
Dr Rajkumar Cheluvappa MD (India)
Dr Tommy Chung MB BS
Hong Duong
Hariyana Dhillon BSc, MAI (Psych)
Dr Sumana Gopinath MB BS, FRACP
Dr Hamish Jamieson MB BS
Mary Jenkins RN MSc
Marina Kacevska BSc (Hons)
Dr George Lau MB BS, FRACP
Patrick Lim BSc (Hons)
Wendy Mak BSc (Hons)
Marko Matic BSc (Hons)
Kirsten McTavish BSc (Hons)
Ben Rayner BBioSc (Hons)
Mimi Saba BSc (Hons)
Dr Anita Sharma DSM, AMC, FRACP
Ying Shen MD (China)
Martin Simone BSc (Hons)
Dr Ray Sy, Masters
Dr Alice Tiong BSc (Hons), MB BS, FRACP
Leo Turner RN
Eric Yamen MB BS (Hons)
Dr Yu Zheng MD (China)

Undergraduate Students
Filip Bebek
Anthony Corridan
Hong Duong
Jameel Khan
Marta Kozlowska
Megan Parry
Dagma Plasmans
Anne Vanniasinghe

Summer Scholars 2005/06
Shane Antao
Megan Brewer
Winnie Cheng
Edward Fitzgerald
Min Li Huang
Cindy Jiang
Maggie Li

2006/07
Shane Antao
Tara Bautista
Febriani Changi
Wing Yee Cheng
Grant Dale
Edmund Fitzgerald
Jianyi Fock
Claudia Husin
Mandy Liu
Matthew Lyle
Annora Thoeng
Tony Wong
On Kiu Annie Yip

Growth at ANZAC Research Institute

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Administrative Staff

Director
Professor David Handelsman MB BS, PhD, FRACP

General Manager
Christine Harrison BSc (Hons), FIBMS, Grad Dip Bus, (till 31 Oct 2006)

Manager, Molecular Physiology Unit
Mamduh Khalil BSc, Ass Dip Animal Technology

Finance Officer
Annet Doss, Dip Acc, Dip Comp Prog

Computer Support
Stefano Bichi Dip Elec Eng, MC SE

Human Resources
Pam McDowell

Receptionist
Tracey Dent
### Peer-Reviewed Grants & Fellowships

<table>
<thead>
<tr>
<th>Source</th>
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<td>Real time PCR with mutation analyser</td>
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<td>A novel pathway of crosstalk between bone cells involving glucocorticoid signalling</td>
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**Industry Contracts**

- **Besins International**: The efficacy and safety of DHT in presenting prostate growth in men over 50 years of age, Andrology 410,891
- **Eli Lilly**: Managing Osteoporosis in patients presenting with minimal trauma fracture, Bone Biology 51,840
- **Aventis Pharma**: Bone-genetic study, Bone Biology 32,251
- **Roche Pharma**: ibandronate in bone metastases, Bone Biology 43,591
- **Astra**: Bone weld project, Burns Unit 56,096
- **Sanofi/Aventis**: Grace Study, Cardiology/Vascular Biology 26,800
- **Sanofi/Aventis**: Synergy Study, Cardiology/Vascular Biology 1,575
- **Hamilton Health Sciences, Canada**: Oasis 5, Cardiology/Vascular Biology 2,464
- **Quintiles**: Amadeus, Cardiology/Vascular Biology 2,419
- **Icon US**: Destiny Study, Cardiology/Vascular Biology 43,636
- **Department of Health Perth**: Practical Study, Cardiology/Vascular Biology 1,000
- **Flinders Medical Centre SA**: Apex Study, Cardiology/Vascular Biology 22,514
- **Roche Pharma**: Perceptorship Programme, Cardiology/Vascular Biology 60,000
- **Astra Zeneca**: Universe Study, Cardiology/Vascular Biology 837
- **Kendale International**: Cibs III Study, Cardiology/Vascular Biology 6,143
- **Sanofi/Aventis**: I Preserve Study, Cardiology/Vascular Biology 3,777
- **Bayside Health**: Chaplis Study, Cardiology/Vascular Biology 6,500
- **Parenix International**: Fusion Study, Cardiology/Vascular Biology 15,585
- **Sorvay**: Beautiful Study, Cardiology/Vascular Biology 9,698
- **University of Sydney**: Field Study, Cardiology/Vascular Biology 16,833
- **Pharmarize**: Illuminate Study, Cardiology/Vascular Biology 36,798
- **Boston Scientific**: A_F Trial, Cardiology/Vascular Biology 62,272
ANZAC Health and Medical Research Foundation

Financial Performance 33
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Donor Honour Roll 36
## Synopsis of Financial Performance


<table>
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<tbody>
<tr>
<td>Peer Reviewed Funding</td>
<td>$1,288,014</td>
<td>$1,508,389</td>
<td>$2,329,584</td>
<td>$2,536,573</td>
<td>$2,280,291</td>
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<td>Clinical Trials</td>
<td>$84,806</td>
<td>$441,435</td>
<td>$253,682</td>
<td>$632,102</td>
<td>$804,033</td>
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<td>State Government Grants</td>
<td>$442,400</td>
<td>$492,400</td>
<td>$532,044</td>
<td>$536,063</td>
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<td>Commonwealth Research</td>
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<tr>
<td>Donations &amp; Bequests</td>
<td>$195,278</td>
<td>$676,161</td>
<td>$203,405</td>
<td>$571,678</td>
<td>$396,357</td>
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<td>Fundraising</td>
<td>$64,842</td>
<td>$94,953</td>
<td>$60,800</td>
<td>$545</td>
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<td>Interest</td>
<td>$110,072</td>
<td>$157,709</td>
<td>$224,973</td>
<td>$295,432</td>
<td>$522,731</td>
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<tr>
<td>Other</td>
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<tr>
<td>Total Income</td>
<td>$2,100,606</td>
<td>$3,014,418</td>
<td>$4,080,011</td>
<td>$4,442,440</td>
<td>$5,168,610</td>
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<tbody>
<tr>
<td>Salary Costs</td>
<td>$725,879</td>
<td>$674,508</td>
<td>$852,884</td>
<td>$1,561,386</td>
<td>$2,093,774</td>
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<td>Scholarships</td>
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<td>$141,707</td>
<td>$257,688</td>
<td>$439,977</td>
<td>$477,047</td>
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<td>Administrative Costs</td>
<td>$327,728</td>
<td>$490,409</td>
<td>$229,686</td>
<td>$439,977</td>
<td>$654,458</td>
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<tr>
<td>Consumables</td>
<td>$141,796</td>
<td>$364,263</td>
<td>$599,811</td>
<td>$650,555</td>
<td>$654,458</td>
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<td>R &amp; M and Renewals</td>
<td>$167,556</td>
<td>$118,436</td>
<td>$146,089</td>
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<td>Depreciation</td>
<td>$258,281</td>
<td>$291,125</td>
<td>$498,928</td>
<td>$387,744</td>
<td>$434,470</td>
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<tr>
<td>Total Expenditure</td>
<td>$1,621,240</td>
<td>$1,938,741</td>
<td>$2,469,105</td>
<td>$3,466,994</td>
<td>$4,226,771</td>
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<tr>
<td>Net increase in funds</td>
<td>$479,366</td>
<td>$1,075,677</td>
<td>$1,610,906</td>
<td>$975,446</td>
<td>$941,839</td>
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</table>

The ANZAC Research Institute continues to expand its research interests attracting high quality scientists and students from around the world. Current success in these research projects in attracting funding is largely responsible for the increases seen in our assets.

Expenditure continues to rise reflecting the continuing growth and diversification of the Institute's research efforts. The funds expended on salary and scholarships reflect of the growth of research and our commitment to ongoing education of future generations of scientists. The purchase, through generous equipment funding, has also increased the facilities for research and the net assets of the organisation.

Detailed, audited financial statements are available in the pocket in the back cover of this report.
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 is Chair of the Board of the War Widows’ Guild (NSW), Honorary Governor of the Ageing & Alzheimer’s Research Foundation, a member of the NSW Ministerial Advisory Committee on Ageing and President (NSW) of the Australian Association of Gerontology.

Danny O’Connor (Deputy Chair)

Danny O’Connor is the present General Manager, Concord Repatriation General Hospital. 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 were he looked at Major investigations into the evaluation of the effectiveness of methadone treatment for opiate dependence. After which he became State Coordinator for methadone treatment in New South Wales. He worked in 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 with Central Sydney Area Health Service as General Manager, Sydney Dental Hospital and Oral Health Services. He currently serves on various committees as Deputy Chair, ANZAC Health and Medical Research Foundation, as a Member of Ministerial Asbestos Diseases Advisory Committee and sits on the Sydney Institutes of Health & Medical Research Board.

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

Emeritus Professor, University of Sydney. Previous Associate Dean, Northern Clinical School; Chair, NSW Greater Metropolitan Clinical Taskforce; Chair, Confederation of Australian Postgraduate Medical Councils; Head, Gastroenterology Unit, Concord Hospital.

Brian Lee

Brian Lee spent his career in the medical supply industry and recently retired as Area Managing Director (Australia and New Zealand) for Baxter Healthcare. He is the serving National President of the Leukemia Foundation of Australia as well as being a long-time advocate and supporter of ANZAC Health and Medical Research Foundation. He is currently a director of Medical Specialities Australia. He has accepted the position to chair the Fundraising Subcommittee on the current 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.

Mike Wallace

Chief Executive of the Sydney South West Area Health Service since 2006. Previously the Director of Clinical Operations of the Area, Deputy Chief Executive Officer of the Central Sydney Area Health Service as well as General Manager of a number of hospitals health networks both in the metropolitan and rural areas.
Corporations

Biogen Idec $5,000.00
Office for Science and Medical Research $1,500.00
The Philip Bushell Foundation $56,667.00
Wyeth Australia Pty Ltd $2,570.36
Australian Rotary Health Research Fund $13,500.00
Beta Sigma Phi, Delta Master Sydney $600.00
CASS Foundation Limited $17,500.00
Charcot-Marie-Tooth Association of Australia INC $3,000.00
HSP Research Foundation Inc $13,750.00
Volunteer Services Auxiliary of Concord Hospital $20,000.00
Canterbury Hurst House Park RSL $5,000.00
Mr Neville Jeffrey $3,000.00
Myasthenic Association in NSW $2,000.00
Dr William Regan AM $1,000.00
Sir Bruce Williams KBE $1,000.00
Kingscliff Beach Club $500.00

Community Organisation

Bondi Junction Sub Branch RSL $1,000.00
Burwood RSL Club $110,000.00
Chester Hill – Carramar Sub Branch $1,000.00
Epping RSL Sub Branch $100.00
North Sydney RSL Sub Branch $1,450.00
Pittwater RSL Sub Branch $400.00
Canterbury Hurst House Park RSL $5,000.00
returned & Services League of Aust (NSW Branch) $500.00
Callala Beach RSL Sub Branch $50.00
Concord RSL Club Limited $250.00
Concord District Sub Branch RSL $250.00
Rockdale RSL Sub Branch $200.00
Concord Golf Club $100.00
Combined Services RSL (Sydney) $100.00
Clovelly RSL Sub Branch $100.00
Greenacres Bowling & Recreation Club $50.00
War Veterans Bowling Club $50.00
Taxation RSL Sub Branch $50.00

BEQUEST

David & Helen Jobson $500.00
Pamela Churm Bequest $50,000.00
Estate of Elaine Kendall $254,402.00

FOTARI

Steven Kalowski $1083.29 Mr Alex Marcos $100.00
Dr Charles Pawsey $1040.00 Mr AA Ford $100.00
John Linsley $1008.00 Miranda RSL Sub Branch $100.00
Paul Collett $756.00 Major John P. Kelly (Ret’d) $100.00
Paul Waizer $700.00 Len T & June S Kelsey $100.00
Gregory Falk $600.00 J R Belcher $100.00
Ramon Bullock $550.00 Harry Overton $100.00
Ross Bradbury $520.00 Dr A Bala $100.00
G D Pearce $520.00 Dr Michael Amos $100.00
Sir Ron Brierley $500.00 Dr George R Faithfull $100.00
R. W. Balfour $500.00 Denis Ryan $100.00
Mrs Thelma Ryan $500.00 Allen Mailey $100.00
Mr Paul Eric McClintock $500.00 Mr Desmond W Maguire $80.00
Mr John Murray $500.00 Winifred Keat $50.00
Mr Alex Pirie $500.00 Ron O’Connor $50.00
Majorie J Pink $500.00 Rjacjce Westhead $50.00
Andrew G Richardson $500.00 Ms Elaine Peterson $50.00
Eileen Collins $480.00 Mrs Valerie Allen $50.00
Mr WB & Mrs MJ White $350.00 Mrs Marie Andrews $50.00
Dr Graham Dunn $300.00 Mrs L M Brown $50.00
Mr Joe Cipolla $250.00 Mrs Joan Slater $50.00
Mr Gordon Nelson $250.00 Mrs Gloria J. Batkin $50.00
Mr Alan Davidson $200.00 Mrs EM Fitzgerald $50.00
Mr & Mrs GS Swinbourne $200.00 Mrs Elaine Rand $50.00
Ian F. Stanwell Ed $200.00 Mrs Dorothea Watson $50.00
Elizabeth Starkey $200.00 Mrs A J Blight $50.00
Dr J Prowse $200.00 Mr Walter J. Bellman $50.00
Mr John McEvoy $150.00 Mr R Burgess $50.00
Mr Steve Willcock $110.00 Mr Patrick Warren $50.00
M W Hayes $104.00 Mr Leonardi Karpin $50.00
V J Eastment $100.00 Mr Leonardi Coleman $50.00
RS Bateup $100.00 Mr K N Payn $50.00
Rose Bay RSL $100.00 Mr John M White $50.00
NJ Anderson $100.00 Mr John G Lewis $50.00
Ms Barbara Merran $100.00 Mr Ian Brennan $50.00
Ms Alice Kang $100.00 Mr Graham Chudleigh $50.00
Mrs Miriam Atkinson $100.00 Mr FJ Colwell $50.00
Mr William E Carter $100.00 Mr D Curtin $50.00
Mr Thanh Mai $100.00 Mr Arthur Murray $50.00
Mr Stewart Moyer $100.00 Mr Alex Schmierer $50.00
Mr Ron Avis $100.00 Mr AF Niken $50.00
Mr Roger Jacobs $100.00 Mr A McLeod $50.00
Mr R V Pearce $100.00 Mr A Jones $50.00
Mr Phillip Driessler $100.00 Mr & Mrs P & M Yvanovich $50.00
Mr Michael Kinninmont $100.00 Mr & Mrs Doris Zammit $50.00
Mr JL Atteave $100.00 Major General G L. Maitland $50.00
Mr HE Brennan $100.00 JD Smith $50.00
Mr David Clappison $100.00 J Searle $50.00
Mr CS Hughes $100.00 Dr Author Everitt $50.00
Mr Brian Stockwell $100.00 Cecil Hinck $50.00
Mr B J Harrison $100.00 Brigadier RW Morris $50.00
Mr Alfred Derricott $100.00