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**ANZAC Research Institute Research Reports**

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**ANZAC Health and Medical Research Foundation**

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The ANZAC Research Institute has gone from strength to strength during 2006/07. The Board of the ANZAC Health & Medical Research Foundation notes with satisfaction the achievements of the Director, Professor David Handelsman and the research scientists, medical professionals and students associated with the Institute.

The Institute continues to build its international reputation as a centre for excellence and is achieving an outstanding record for securing grant funding for its work from government and non-government sources. In today’s competitive environment, the success rate of the ANZAC Institute’s grant applications is a phenomenal achievement. A high rate of publications in best-quality journals and a number of awards to individual scientists provided further recognition of the quality of the research conducted at the Institute under the capable leadership of our Director, Prof David Handelsman.

Such success brings with it an increase in the pressure to provide additional capacity for expanding research commitments and to maintain the laboratories and facilities at international standards. The Board was delighted to receive a commitment from one of our key stakeholders, the University of Sydney to provide $3m to allow co-development of additional research laboratories and offices for the ANZAC Research Institute in the building under construction for the Asbestos Diseases Research Institute, adjacent to our present laboratories. The challenge now facing the Board is to raise funding for the fitout and commissioning of the planned premises.

The Board has been well served during the year under review by the commitment of all members to the ongoing governance of the Foundation. My thanks go to all members of the Board and especially to the Chair of the Finance Committee, Mrs Eve Bosak and the Chair of the Fundraising Committee, Mr Brian Lee. Work underway by both of those committees will strengthen the Institute as it moves forward to the next phase of its development.

Felicity Barr
Chairman
Welcome to the ANZAC Research Institute’s Annual Report. Once again the Institute had a very successful year continuing to grow and produce more than ever in terms of scientific information, winning of grants and awards and training the new generation of medical scientists. Seven years since opening our doors, the ANZAC Research Institute provides a research home to over 100 scientists all closely affiliated with Concord Hospital departments. Each year our scientists earn nearly $6 million of external grant-based funding income, publish approximately 200 scientific papers and provide research training for over 30 graduate students. In the recent 2007 round of grants, the Institute’s scientists were awarded 6 new NHMRC and 3 new ARC grants from 14 submissions, a remarkable success rate compared with the national average of ~20%. 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.

Among the highlights of this year, the Cancer Pharmacology group, headed by Professor Stephen Clarke and Assoc Professor Graham Robertson, won the first ever Program Grant for the Concord campus. Based at the Institute, their NSW Cancer Institute’s Translational Program Grant in Colorectal Cancer provides funding of $3.75 million over the next 5 years. The ANZAC researchers lead a collaboration also involving researchers at the Australian Proteome Analysis Facility, Macquarie & Sydney University, St. Vincent’s/Garvan Institute of Medical Research and Royal Prince Alfred Hospital.

This year we welcome our 9th research group, the Burns Research laboratory, headed by Dr Peter Maitz AM. Within only a few years of migrating from his native Austria, Peter established a world class Statewide Burns Service centred at Concord Hospital and was honored as one of Australia’s medical hero’s for his care of burns victims of the Bali bombings. We look forward to this new group’s research creativity and innovation to improve care for burns victims and for reconstructive surgery in general.

The Faculty of Medicine’s Summer Scholarship Scheme, developed and run from the Institute, won a 2007 Carrick Australian Award for University Teaching for Outstanding Contribution to Student Learning adding to its University of Sydney Vice-Chancellor’s Award. Attracting the best and brightest students to medical research by taking on a PhD at the Institute remains a challenge. The Summer Scholarship scheme brings top science students from Australia, New Zealand and overseas to experience research over the summer break. This scheme is now producing new graduate students for the Institute.

Significant national awards were also won by Dr Ray Sy (Ralph Reader Clinical Science Young Investigator Prize of the Cardiac Society of Australia and New Zealand), Kirsten McTavish (Servier Award of the Endocrine Society of Australia for the best published paper by a young investigator), Dr Kirsty Walters (Young Investigator Award of the Society for Reproductive Biology) and Dr Suman Gopinath (NSW Motor Neuron Disease Award). These important awards reflect the high scientific standards and training provided by the Institute.

The Institute’s leadership in developing state-of-the-art medical research infrastructure on the Concord Hospital campus continues successfully with our spearheading of the $15 million development of an Asbestos Disease Research Institute (ADRI), a world’s first dedicated research facility to this devastating disease, now being built adjacent to, and to be operationally integrated with, the Institute. Due for completion in 2008, we are also grateful for the University of Sydney’s contribution of nearly $3 million to allow co-development of additional research laboratories and offices for the ANZAC Research Institute in the same building. In total, these developments will treble the laboratory space on the Concord campus.
Many people’s hard work and dedication contribute quietly but crucially to our success. On behalf of all the Institute’s scientists it is a pleasure to thank Annet Doss, Tracey Dent, Pam McDowell, Julie Taranto, Justin Crosbie, Mark Jimenez and Mamdouh Khalil, a terrific team who manage the Institute’s administrative functions so well. Our deep gratitude goes to Danny O’Connor, General Manager, Concord Hospital and Michael Wallace, CEO Sydney South West Area Health Service for their enlightened and unwavering practical support, without which the Institute could not operate. The commitment of the new Dean of Medicine, Professor Bruce Robinson, and Professor David Cook to improving Faculty recognition for the ANZAC Research Institute’s activities is much appreciated. Thanks are due again to the Foundation’s Board together with our friends and supporters for their continuing goodwill. The support of John Gatfield and Alice Kang for our fund and profile raising efforts is also much appreciated. Finally, my thanks go again to Felicity Barr, Chair of the Foundation’s Board, for her continued support in facilitating the Institute’s growth and success.

It is a reward in itself to work in the intellectually challenging and creative environment created by the Institute’s terrific scientists. Combining the best of scientific collegiality, collaboration and intelligent critique, they create the wonderful, vibrant atmosphere that surrounds the most productive science. It is a pleasure to pay tribute to their fine efforts.

Thanks to our supporters and the hard work of our scientists and staff, the ANZAC Research Institute is now a major NSW independent medical research institute making an international impact. 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 the Institute’s continued progress will make a vital contribution to our joint future. Only by fostering the best medical research can we ensure the highest standards in our health and medical care; and only strong community support, valuing medical research, can keep the Institute going strong.

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. The body’s own androgens are also a crucial influence on the development of prostate and cardiovascular diseases as men grow older. In medicine, androgens are used to treat hormone deficiency states and androgens can also be used as therapeutic drugs in certain chronic diseases and they are also being tested for use in male contraception and for ageing men.

The Andrology group conducts a wide range of studies spanning basic, clinical and public health research with a focus on men’s reproductive and general 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 how hormones regulate sperm production
- Understanding the effect of male hormones in health and in ageing

Highlights of this year for the group were Dr Charles Allan’s award of the John & Eileen Doddon Memorial Award for Geriatric Research (Rebecca L Cooper Foundation); PhD student Kirsten McTavish won the Eli Lilly Award for best student presentation, Australian Society for Medical Research NSW Scientific Meeting 2007 and the Servier Award for best paper published by a young investigator, Endocrine Society of Australia 2007; Dr Peter Liu was awarded the Outstanding Reviewer Award, Journal of Clinical Endocrinology and Metabolism 2007 and was appointed Associate Professor (Andrology) at the University of Sydney; Dr K Walters won the Young Investigator Award, Society for Reproductive Biology 2006 and Professor Handelsman was awarded a Carrick Institute 2007 Award for Outstanding Contribution to Student Learning for developing the Faculty of Medicine’s Summer Scholarship program.

**Physiology and Pharmacology of Androgens**

**Clinical Pharmacology of Testosterone**

A Conway, PY Liu, C Fennell, L Turner, DJ Handelsman

As the country’s leading clinical research centre in the clinical pharmacology of androgens, our research continues into understanding how well such treatment works and to improving its delivery to make it work better. 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 may be 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. Through these studies we have learned valuable lessons in defining how long the treatment lasts, why and how it varies between men and at what threshold of blood testosterone levels people become aware of the return of symptoms of insufficient blood testosterone levels. As a result of the popularity of such long-term depot treatment, overseas companies have been prompted to develop improvements on their standard products, which last only 2-3 weeks after injection. As a result, recently a new 3 month injectable form of testosterone has been marketed and we are now conducting long-term, head-to-head comparison study against the 6 month depot implants.
ANDROLOGY

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. Peter Liu has postulated that these two common, adverse health states combine to form an intermeshed vicious cycle which drives down blood testosterone levels while also worsening 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 Ageing
PY Liu, DJ Handelsman with C Meir, MJ Seibel (Bone Biology Group), Dr J Bellin, Prof P Leedman (Royal Perth Hospital) and Dr T Nguyen and Prof J Eisman (Garvan Institute)

In men, blood testosterone concentrations fall gradually with age. Such a decline could have impact on male reproductive and general health to make worse the physical frailties associated with older age. As this age-related fall in testosterone production has been almost exclusively studied in the USA, we combined with other colleagues around the country to study this age-related decline among Australian men in more detail. Using 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), we showed that the decline in measured blood testosterone concentrations in Australian men living in regional centres is similar to that in Northern hemisphere urban populations. There was also evidence suggesting Australian men are also subject to the impact of the progressive world-wide temporal trend of increasing obesity.

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 dramatic benefits of androgens to muscle strength, energy and quality of life in men with genuine androgen deficiency mean that androgens are particularly liable to overuse in the community. This may be in the form of medical misuse via misguided over-prescribing or as androgen abuse involving the illicit use of androgens 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 identified patterns of over-use that call for heightened surveillance and increased professional and public education to make clear the differences between valid evidence-based use of testosterone treatment and misguided overuse lacking reliable evidence of safety and effectiveness. Fortunately, surveys of Australian high school students, which we have reviewed, 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 is both cheating 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 were 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 of an athlete for THG use. 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

Hormonal Regulation of Testis Function
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 selective 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. For this work, Pat was selected in 2006 as a finalist for the Novartis Junior Investigator Award of the Endocrine Society. In addition, our laboratory pioneered the development of the first genetic mouse model to examine dose-dependent FSH actions in both and hormone deficient 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. Ongoing research is exploring the combined FSH-androgen responses using microarray technology to identify gene expression patterns that reveal underlying hormonal mechanisms.

More recent studies have investigated the nature of the steroidoal regulation of testsis 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.
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 that subjects undergo an invasive transrectal ultrasound.

Prompted by the need to improve recruitment, we recently published an extensive study in the leading international urology journal proving the validity and reliability of a new, less invasive ultrasound method to measure prostate size. This avoids the need for a transrectal probe and we anticipate that this new ultrasound method may prove useful for studies requiring repeated measurements of prostate size in healthy younger men without known prostate disease during the long time over which prostate disease develops.

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 of 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 (5· 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 J Zajac (University of Melbourne)

Androgens are essential for male reproduction and traditionally are regarded as a defining characteristic of masculininity. 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 reproductive physiology. Our project is exploring the possible role of the androgen receptor (AR) in female reproductive physiology, notably in the ovary and female reproductive tissues (ovary, breast, uterus). 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. Due to the fact that such females cannot occur in nature, we have created an AR-null female model. Her initial findings have revealed that defects in ovulation and late-stage follicle growth are the major contributors to the reduced fertility. Furthermore her most recent work provides strong direct evidence that AR-mediated actions may play a vital role in maintaining female fertility with ageing via hormonal pathways which are likely to have collateral effects on other tissues. This work 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.

Genetic Model to Study FSH and Female Reproductive Ageing
K McTavish, K Walters, DJ Handelsman, CM Allan

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, thereby, 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

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

The Biogerontology Laboratory in the ANZAC Research Institute is the laboratory component of the Centre for Education and Research on Ageing (CERA) at Concord Hospital.

CERA conducts innovative multidisciplinary research into ageing, geriatric medicine and healthy ageing. The driving focus of our research is to develop strategies and therapies to improve the quality of life and health of older people. The research covers an extensive range of methodologies from basic biological research, clinical research, epidemiology, health services and social science.

The Biogerontology Laboratory studies the biology of ageing and age-related diseases with a major focus 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.

Highlights for 2006-2007 include gaining further NHMRC funding to study sirtuin pathways in the ageing liver, co-authorship on a Nature paper studying the effects of ageing and resveratrol on the liver, and an editorial and front cover in Hepatology on immune functions of the liver endothelium.

**Ageing Biology and the Ageing Liver**

D Le Couteur, V Cogger

This research studies the effects of ageing, disease and normal physiology of the hepatic microcirculation. Blood travels through the liver through many small vessels termed sinusoids that differ from normal capillaries. Sinusoidal endothelial cells are perforated by small pores (fenestrations) about 50-100 nm in diameter that regulate the exchange of substrates between blood and liver cells, and the interaction between circulating blood cells and liver cells.

Our group discovered that with advancing age there are major changes in the liver sinusoidal endothelial cells, including a marked reduction number of fenestrations. This is called pseudocapillarization. The changes have been observed in many species including man, and have been subsequently confirmed by others funded by the NIH. Furthermore, it was found that these changes impair the liver uptake of lipoproteins, providing a critical link between ageing, dyslipidaemia and the age-related risk of atherosclerosis. Our research is now aimed at developing therapies to treat pseudocapillarization in order to reduce the risk of vascular disease in older people.

Other related research includes the discovery of changes in the hepatic sinusoid in diabetes mellitus, age-related changes in the liver trafficking of apoE and the effects of fenestrations on the role of the liver in the immune response. We have also been studying the effects of oxidative stress on the liver because of its role in the ageing process.
BONE BIOLOGY

Group Leader: Professor Markus J. Seibel

Senior Scientists: Dr Colin Dunstan, Dr Hong Zhou, Dr Julie Blair

Staff and Students: Dr Robert Kalak, Mystic Mak, James Modzelewski, Li Laine Ooi, Janine Street, Saadaf Warrarich, Colette Yee, Anja Goebel, Dr Yu Zheng, Mandy Liu, Ed Fitzgerald

Visiting Fellows: Professor Frank Buttgereit, Humboldt University, Berlin, Germany (Feb-May 2006); Dr Di Chen, University of Rochester, Rochester, New York, USA (Oct-Nov 2006), Dr Markus Herrmann, University Hospital of Saarland, Homburg, Germany (July 2007 – July 2009), Agnes Weber, Humboldt University, Berlin, Germany, Holger Henneicke, Humboldt University, Berlin, Germany

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 2006/7, the program has two new research assistants, Janine Street from Glaxo-Smith-Kline, Dartford, UK and Anja Goebel from Berlin, Germany, and has supported the postgraduate studies of Yu Zheng, Mystic Mak and Laine Ooi, who joined the group as PhD students in 2004, 2005 and 2007 respectively. Mandy Liu and Ed Fitzgerald participated as an undergraduate summer students.

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 2006 we welcomed Professor Frank Buttgereit from Berlin, Germany, and Dr Di Chen from Rochester, New York. In 2007 we welcomed Dr Markus Herrmann (Homburg Germany), Agnes Weber (Berlin, Germany) and Holger Henneicke (Berlin, Germany). We have also established industry links through research partnerships with Agen, Aventis Pharma (USA and Australia), MSD Merck, Sharp & Dohme (Switzerland), Roche Pharmaceuticals (Switzerland) and Novo Nordisk (Switzerland).

Our research is supported through funding from within Australia and from overseas. With our collaborators, we have current and future funding to a total value of over $5,000,000 including six NHMRC project grants.

This year’s meetings of the European Society for Calcified Tissue, the American Society for Bone and Mineral Research, and the Australian and New Zealand Bone and Mineral Society have been successful for our group. From these meetings, we had 6 oral presentations and 2 Outstanding Abstract Awards (Hong Zhou and Colin Dunstan), indicating that our young group has established a place in the international science community.

Our plan is to further develop a comprehensive research program that makes use of the multidisciplinary opportunities provided by 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


Breast cancer and prostate cancer each have a particular preference to form secondary tumours (metastases) in bone. Breast cancer in bone is associated with bone destruction that frequently results in significant pain and disability. Prostate cancer cells in bone induce high rates of bone formation and bone resorption, resulting in disorganisation of bone structure and severe pain. In both cancers, tumour cells grow in bone and induce normal bone-resorbing and bone-forming cells of the bone marrow to destroy the surrounding bone. It has been proposed that destruction of bone releases factors that help cancer cells grow faster, thus creating a vicious cycle that contributes to the serious consequences of bone metastases.

In this study, we are studying mice with transplanted breast cancer cells to understand what makes the bone marrow a receptive site for breast cancer metastasis. Specifically, we are examining how physiologic bone remodelling may support the earlier stages of bone metastasis of extravasation and formation of micrometastases. We are manipulating bone remodelling rates in mice to see how this impacts the ability of circulating cancer cells to target bone and to establish destructive tumours there.

To date, we have determined that anti-resorptive treatments inhibit tumour growth in bone indirectly through effects on osteoclasts, rather than directly through effects on tumour cells. We have discovered that increasing bone resorption through a low calcium diet enhances breast cancer metastasis to bone in mouse models of both lytic and sclerotic bone metastases (Zheng et al, Cancer Res 67(19):9542-8. 2007). This may have clinical implications for 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
H Zhou, M Herrmann, R Kalak, M Mak, J Street, C Yee, H Hennecke, C Dunstan, MJ Seibel

Glucocorticoids 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 glucocorticoid treatment on bone. The transgene carried by these mice results in a local inactivation of glucocorticoids in the bone forming cells, the osteoblasts, by directing these cells to produce an enzyme known as 11beta hydroxysteroid dehydrogenase, normally found in the kidney. This model allows us to separate effects on bone, which are due to direct action of glucocorticoids 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 glucocorticoid-induced bone loss and to examine the role of endogenous glucocorticoids 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. 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
H Zhou, R Kalak, M Mak, J Street, C Yee, A Weber, C 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 to produce the molecules that 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. We have identified a role for wnt signalling in mediating these effects and are currently defining the critical role of this signalling pathway in more detail.

Evaluation of Bone Effects of an XXY Phenotype in a Mouse Model of Klinefelter’s Syndrome
P Liu, R Kalak, C Wang, RS Swerdloff, C Dunstan, MJ Seibel

In collaboration with Peter Liu of the Andrology Group at the ANZAC Research Institute and with the Harbor-UCLA Medical Center (Torrance California), the bone group has evaluated the phenotype of mice with an XXY karyotype. Similar to human males with Klinefelter’s, syndrome, we have determined that these mice also present with osteopenia. These mice thus provide a much needed animal model for examining the mechanism of bone effects of this syndrome and in particular the genetic vs hormonal factors producing the bone loss phenotype. Further studies are planned to investigate in more detail the mechanism for the bone changes in these mice.

Study into the Genetic Determinants of Bone Loss and Osteoporosis in an Affected Family
M Kozlowska, C Meier, J Modzelewski, M Kennerson, G Nicholson, I 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 Prof Wim van Hul, Belgium, 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, MJ Seibel in collaboration with multiple centres

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

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

Present studies focus on the evaluation of bone turnover in the very elderly (with Professor Philip Sambrook, RNSH), the effect of androgens on male bone health (with Professor David Handelsman and Dr Peter Liu, Andrology, AR), 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 Modzelewski, 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. A first study, on the relationship between serum sex hormone levels and fracture risk, has shown that circulating testosterone but oestradiol levels are associated with incident fractures in older men (Archives of Internal Medicine, 2007, in press).
While autologous skin grafting technique remains the standard method for burns wound management, the lack of available donor sites is always a major problem for treating patient with large and severe burns injury.

Cultured epidermal autograft (CEA), well-established at Skin Culture Laboratory at Concord hospital, is a novel technique by which skin keratinocyte stem cells are isolated from a small skin biopsy from the patient, cultivated into epidermis-like tissue under laboratory conditions so that it reaches over 500 times expansion in size and is then transplanted back to the same patient. As an alternative source of skin grafts, CEA graft provides not only immediate coverage but also living cells and biological factors to facilitate the wound healing and closure. CEA technique shows great potential in treating severe burns because it requires only a small skin biopsy of about 4 cm² therefore creating small donor site wounds.

CEA technology has achieved some excellent results in burns and donor site wound care. But it has limitations in clinical application especially when used for very deep burns involving deep skin damage when it won’t work reliably unless more skin depth can be generated. Even if CEA’s remain viable; the quality of reconstructed skin is not good enough without a better dermal bed to support and facilitate the growth and differentiation of epidermal cells.

Our laboratory is committed to improve the cultured skin autograft technology by developing three-dimensional dermal substitutes and skin equivalents for treating deep burn wounds. Using technologies including tissue culture, cell biology, molecular biology and, cellular and tissue engineering, we have been trying to produce different biological scaffolds that are biologically compatible, safe and suitable for skin cells to attach and grow. The scaffold could be used for repairing the damaged dermal bed or for engineering an autologous skin substitute with skin structures comparable to normal human skin, which includes epidermis, dermal components, pigment cells and microvascular vessels under laboratory conditions. The research and development of tissue-engineered scaffold, dermal and skin equivalents will benefit not only the burns patients but also the patients with other skin defects such as chronic, diabetic and pressure skin ulcers.

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

This trial will compare the efficacy of cultured epidermal autograft (CEA) sheet or suspension in skin grafting for burns injury. Using a randomised comparison design, thin split thickness skin biopsies are taken under sterile conditions from donor sites and biopsies (about 4 cm²) are cultured in the Skin Laboratory at Concord Hospital. Keratinocytes isolated from the separated epidermis following enzymatic digestion will be grown into CEA sheets while other cells will be grown to sub-confluent phase to prepare CEA suspensions. On the day of surgery, both CEA sheet and suspension will be harvested under sterile condition prior to surgery and randomly allocated to regions within the burn. Syringe A and B and a CEA sheet will then be applied to three of the windows and the fourth will receive no additional treatment. The outcome of the grafting will be monitored at 26 weeks and finally at 52 weeks.

Skin Repair: Tissue Engineering using Synthetic Elastin

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

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

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

J Almine, Z Li, P Maitz, AS Weiss

The main aims of this project are to study the cell-scaffold interaction and to identify the diffusible factor(s) produced by skin cells cultured on the scaffold, which promotes cell proliferation and possible keratinocyte differentiation.

Identifying the diffusible factor(s) responsible for the proliferation of keratinocytes and fibroblasts would signify important progress in the treatment of burns and the development of a suitable skin graft. The treatment of burns patients involves the rapid coverage and closure of the wounds, which is dependent on cell proliferation and differentiation, ultimately re-establishing the epidermis and dermis. This process can be facilitated by the addition of a diffusible factor(s); consequently achieving rapid wound closure, reducing the chance of infection and re-forming skin with minimal scarring.

Skin Cell Culture on Hollow Fibre-Collagen Scaffold

C Shu, M Lord, C McFarland, P Maitz, Z Li

Cultured skin substitutes are usually grown on the rigid surface of tissue culture flasks under laboratory conditions. This does not reflect the natural process of human skin development in the dynamic in vivo environment, whereby mechanical loads such as bending, folding, stretching and twisting are continually imposed on the developing tissue. To address this, we have developed a hollow fibre-collagen scaffold system for development of cultured skin grafts. Fibres extracted from plasmapheresis cartridges are incorporated into the scaffold design to allow complete nutrient diffusion to support cell growth. The collagen-hollow fibre scaffold structure has the advantage of flexibility and direct delivery of nutrients through diffusion, which more closely resembles in vivo conditions than a conventional tissue culture flask. This flexible scaffold potentially allows the mechanical manipulation of the three-dimensional cell culture, and may stimulate realistic skin structure formation. We have been investigating the cell growth conditions and to examine cell behaviour in the scaffold system in an attempt to develop a skin substitute for clinical use using this system.

Skin Tissue Engineering using a Biodegradable Polymer

A Taylor, P Maitz, Z Li

The aim of this study is to construct a bio-active scaffold for skin tissue engineering. This project is designed to develop a composite using collagen and polycaprolactone, a FDA-approved biodegradable polyester. The scaffold will be used for regenerate 3D skin substitute. More importantly, the scaffolds will be bio-active as wound healing protein factors such as epidermal growth factor will be included in the scaffold to facilitate wound healing. At this stage, work is focused on characterising structural features of scaffold including pore size, optimizing skin cell growth in the scaffold. Human skin cells including fibroblasts and keratinocytes, obtained from a small skin biopsy and expanded in the laboratory, are seeded into the scaffold to grow. The construct is currently under investigation to determine skin cell proliferation and differentiation and the expression of growth factors and other proteins crucial to wound healing. Long term goals include animal studies and eventually clinical trials.

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

A Taylor, K Neuwiendyk, J Rnjak, P Maitz and Z Li

Lack of an autologous skin graft is always a major problem in treating patients with large and deep burns injuries. Clinically, delayed wound healing is still common and risks wound infection, scar development, deterioration of patient’s well-being and even death. Cultured autologous skin cells or substitutes are emerging as an important alternative for wound coverage and closure. The advance in biotechnology has enabled us to grow different types of skin cells and skin substitutes by skin tissue engineering technology in our laboratory. Skin tissue engineering involves using different biomaterials such as recombinant collagen and elastin or bio-compatible polymers as porous scaffolds to support skin cell attachment, growth and differentiation into skin tissue. Various wound dressing material and dressing regimes designed in our laboratory are trying to provide favourable growth conditions for cultured skin cells and to speed up the wound healing process. Wound healing is a very complicate process in which host factors and metabolisms play critical role. Although the engineered skin looks structurally similar to normal human skin containing epidermal and dermal layers, the bio-safety and efficacy of engineered skin and wound dressing products will need to be tested in an animal model before proceeding to further clinical trials.

The aims of this study are, therefore, to establish a mouse model to assess the role of engineered skin products or dressings in wound healing. The animal host response of each mouse as the recipient of skin products or dressing materials will also be examined at cellular and molecular levels. This study will provide significant information on the efficacy and safety of laboratory-developed bio-scaffolds, skin substitutes and dressing materials.
Toxic Effect of Myoglobin on Kidney Function in Burns Patients

S Perry, Z Li, P Maitz, D Millis, P Witting

Myoglobin is a haem-containing protein that is present in relatively high concentration in cardiac, skeletal and smooth muscle. The role of intracellular myoglobin is generally accepted as that of a passive di-oxygen storage protein. However, cell-free myoglobin can promote damage to lipids and proteins from cells that may be damaging.

Acute renal failure (ARF) is a well-known complication of severe burns and is an important factor leading to an increased risk of death. In patients with significant burns (>25% total skin surface), the incidence of myoglobinuria (excessive concentration of circulating myoglobin) and hypotension during the resuscitation phase is higher in the group who develop early acute renal failure. Extracellular myoglobin is rapidly cleared from the circulation through the kidney, suggesting that the accumulation of myoglobin in the kidney may be responsible, at least in part, for the enhanced acute kidney malfunction. Currently, it is unknown if myoglobin promotes damage to the kidney in burns patient and whether, and if so how, myoglobin contributes to the development of ARF in burns patients.

This study has been designed to investigate the potential effects of extracellular myoglobin on renal function following severe burns.

Biofilm and Infection of Burn Wound

P Kennedy, S Brammah, E Wills

One of the most significant problems in burn care is the problem of infection. Following a burn injury the defensive mechanisms of the skin are impaired or destroyed and colonization by micro-organisms rapidly occurs. Many of the micro-organisms commonly found on the burns wound are known to produce biofilms, a collection of organisms attached to a surface and surrounded by matrix containing polysaccharides known as extracellular polymeric substances. Biofilms are the cause of significant morbidity and mortality in relation to implanted medical devices and septic complications associated with indwelling intravenous catheters. The organisms within biofilms are well known to develop resistance to antibiotics and to the immune system. It is estimated that two third of all chronic disease are biofilm related. Biofilm formation in burn wounds has not been thoroughly examined. This study will help the understanding of the mechanisms of bacterial wound invasion and burn wound sepsis, and therefore help the management of burn wounds.
CANCER PHARMACOLOGY

Head: Professor Stephen Clarke
Senior Scientists: Assoc Professor Graham Robertson
Staff and Students: Dr Wei Chua, Anthony Corradin, Haryana Dhillon, Dr Michael Evtushenko, Dan Gordon, Chantal Gebbie, Melissa Lloyd, Dr Lucy Jankova, Dr Marina Kacevska, Andre Mahns, Marko Matic, Arran Painter, Dr Viet Phan, Dr Patsie Polly, Dr Jane Reid, Dr Annelleise Rittau, Dr Rohini Sharma, Ryland Taylor, Lili Truong, Dr Maria Teoli, Dr Janette Vardy, Catherine Xu

The Cancer research group is a new addition to the ANZAC, following the appointment of Prof Stephen Clarke to the Chair of Medicine. This enabled the establishment of a new team comprising 15 research scientists and students in the laboratory, as well as 9 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. The appointment of Prof Andrew McLachlan (Faculty of Pharmacy, Uni of Sydney) to the Chair of Geriatric Pharmacy on the Concord campus strengthens the pharmacokinetic and analytical expertise required for clinical drug studies in cancer patients.

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

In collaboration with the Australian Proteome Analysis Facility, many potential protein biomarkers have been identified that will provide better assays for diagnosis and prognosis as well as help to predict the response of colorectal cancer patients to anti-cancer agents. Such biomarkers will guide the development of individualised treatment regimes, which will take into account the variability in efficacy and toxicity to drugs experienced by many cancer patients. In addition, some biomarkers will be used to identify patients at risk of developing the muscle wasting associated with the cancer cachexia syndrome. Medium throughput mass spectrometry-based assays have been developed to assess the utility of these proteins before high throughput-put screening using the Concord Colorectal tissue and data banks collected by Departments of Surgery and Pathology, CRGH. Immuno-staining for the presence of specific proteins in colorectal tumours using tissue arrays has commenced and will enable the testing of potential biomarkers for colorectal cancer.

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

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

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

Do Tumour-Derived Cytokines Repress Drug Clearance in the Liver?
S Clarke, M Kacevska, P Polly, A Mahns, G Robertson, R Sharma

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

**Ethnic Differences in Drug Clearance.**
S Clarke, V Phan, A Rittua, C Xu, (Prof A McLachlan - Faculty of Pharmacy, University of Sydney)

Compared to Caucasians, cancer patients from an Asian background have greater difficulty tolerating chemotherapy and suffer from more adverse events due to toxicity. Clinical studies are being carried out in breast and lung cancer patients to examine the genetic differences (SNPs) in genes involved in drug metabolism, which may be related to altered clearance of anti-cancer drugs. Pharmacokinetic analysis of commonly used chemotherapy drugs, such as paclitaxel and doxorubicin, are being developed to determine the rate at which they are eliminated from the body. The inter-patient and ethnic differences in drug clearance will be correlated with genetic differences and toxicity.

**Cancer Cachexia, Cytokines and Altered Metabolic Pathways?**
S Clarke, D Gardon, L Jankova, M Kacevska, A Painter, P Polly, G Robertson, M Tsoli. [M Molloy - APAF; E Hardeman - CMRI Westmead; P Glare – Palliative Care, RPAH; M Downes - Salk Institute, California]

Cancer cachexia is a complex condition involving disturbances in energy balance and metabolism in several organs of the body. The release of cytokines into the blood by tumours is a likely link between tumour cells and the major metabolic tissues of the body – muscle, fat and liver. Mouse tumour models have been used to study the regulation of metabolic pathways during the development of cachexia. As these pathways are primarily controlled by nuclear receptors, we have profiled the expression of all 50 nuclear receptors, their cofactors and a representative set of their target genes in liver as well as a subset in muscle and fat. This has given valuable insights into the alterations in many metabolic pathways due to the impact of tumour-derived cytokines on nuclear receptor expression. Such changes may contribute to aberrant energy balance leading to cancer cachexia.

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

**Molecular Analysis of Nuclear Receptors PXR, RXR and HNF4**
A Corradin, A Mahns, M Matic, P Polly, G Robertson, [F Sladek - University of California Riverside]

To understand the regulation of genes involved in drug clearance pathways, we are carrying out detailed molecular studies into the nuclear receptors PXR, it’s binding partner RXR-alpha and HNF4-alpha. An important step is to identify 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, RXR-alpha and HNF4-alpha 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.**
S Clarke, A Painter, G Robertson, M Tsoli, [N Suchowerska - Radiation Oncology, RPAH]

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 that can be extremely toxic to cells. The nuclear receptor 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 that may reduce the efficacy of radiotherapy. Activation of PXR with the potent ligand, rifampicin, enhanced the survival of colon cells exposed to clinically relevant doses of radiation. At the same time several PXR target genes involved in detoxification pathways are induced by radiation. In addition variable levels of PXR were observed in colorectal tumours from different patients. These exciting results indicate that PXR may be involved in tumour response to radiotherapy.
Highlights

Scholarships

• Rohini Sharma: NHMRC Post Graduate Medical Scholarship, $127,500; 2004-2007
• Rohini Sharma: Cancer Institute NSW Research Scholar, $75,000; 2005-2007
• Marko Matic: APA Scholarship $55,000, 2005-2007
• Anthony Corradin: APA Scholarship $55,000, 2006-2008
• Anthony Corradin: Cancer Institute NSW Research Scholar, $50,000; 2007-2008

Grants

• NHMRC: $296,950, 2007 - 2009
• NHMRC: $495,000, 2005-2007
• Cancer Institute NSW Translational Program Grant: $3.75 million, 2007-2011.
• Cancer Institute NSW Infrastructure Grant: $182,000, 2005-2007.
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. A total of 1705 men were recruited into CHAMP between January 2005 and May 2007. Two year follow-up examinations are currently underway.

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 was designed to fill this gap and is one of the world’s most comprehensive studies of the health of older men. Investigation of the role of reproductive hormones, including testosterone, in ageing in men is an important part of CHAMP.

Among the conditions being studied in CHAMP 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 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.

Men were invited to participate in CHAMP if they were aged 70 years or older and lived in the community in one of three Local Government Areas near Concord Hospital: Burwood, Canada Bay and Strathfield. Just under 50% of those contacted joined the study. To date, over 90% of the 500 men due for a follow-up examination have returned to the study centre.

The study procedures are essentially the same at each clinic visit. 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; spirometry; and uroflowmetry and measurement of post-void residual urines. Blood tests include assays for reproductive hormones, vitamin D, PTH, and markers of bone turnover, and measurement of Prostate Specific Antigen (PSA). Blood is being stored for DNA testing.

Baseline data is now ready for analysis and several papers are being prepared. These include papers on risk factors for falls, the prevalence of Mild Cognitive Impairment, the impact of urinary incontinence on quality of life, and the frequency of the geriatric syndromes of falls, disability, frailty, and cognitive impairment. Some preliminary findings were presented at the Venus and Mars Gender and Ageing Symposium held in Newcastle in June 2007.

There are now seven PhD students involved with CHAMP, as well as two Masters students and two medical students doing Honours projects. Chris Hoon, whose PhD work is on normal cognitive ageing in men, won a prize for his poster at the 2007 scientific meeting of the College of Clinical Neuropsychologists.
The Northcott Neuroscience Laboratory, headed by Professor Garth Nicholson, is internationally renowned in the field of molecular genetics of human hereditary neuropathies. The group has continued to make important contributions to finding gene mutations which cause neurodegeneration of peripheral nerve and motor neurons. The identification and characterisation of these genes is furthering our understanding of the mechanisms causing degenerative nerve disease.

**Gene Mapping and Discovery Program**

**Inherited Peripheral Neuropathies**

M Kenerson, S Reddel, M Brewer, G Nicholson

Charcot-Marie-Tooth (CMT) neuropathy is the most common group of human hereditary disorders. The syndrome is a disorder of peripheral nerve affecting both motor and sensory neurons. CMT is a disabling disorder that afflicts 8000 Australians for their lifetime. It, therefore, has major economic impacts in terms of productive years lost and the requirement for medical, paramedical and pension support, estimated to be $220 million per year.

Approximately 15% of all CMT is inherited on the X chromosome. Only one gene has been identified for the most common form of X-linked CMT (CMTX1) and is caused by mutations in the connexin 32 (Cx32). We are currently working to identify two additional genes for X-linked CMT with families that link to the CMTX3 locus and the CMTX1 locus respectively. All the known candidate genes at the CMTX3 interval on chromosome Xq26.3-q27.1 have been excluded for a pathogenic role and work is continuing to obtain DNA samples from the family first reporting the CMTX3 locus back in 1991. We have shown that our two largest families and the original US pedigree share a common founder haplotype indicating the gene mutation in these families is from a common ancestor. In collaboration with our US colleagues from Wayne State University School of Medicine, Detroit we are mapping a gene for an X-linked spinal form of CMT. The family shows linkage to the CMTX1 locus however analysis of the entire Cx32 gene has failed to identify any mutation. This may suggest that the mutation in this family may be caused by another gene residing in the CMTX1 region.

High Resolution Melt (HRM) analysis has continued to be an important technology utilised by our group for gene discovery and gene mutation scanning. The method is proving to be simple and cost effective while providing the sensitivity and specificity required for detecting alterations in DNA sequence. Diagnostic screening for three of the most common hereditary spastic paraplegia genes has been developed this year and we routinely use HRM analysis for single nucleotide polymorphism (SNP) analysis in our mapping projects (Figure 1). In collaboration with colleagues from the Sultan Qaboos University, Muscat, Oman, we are also using HRM analysis to develop a method for detecting haplotypes of drug resistance in malaria.

**Motor Neuron Disease**

I Blair, C Cecere, J Durnall, A Drew, J Crawford, A Thoeng, K Williams, 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 weakness and wasting 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. 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.

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 diagnostic test for MND and treatment is extremely limited. The only known causes of MND are mutations in particular genes that lead to death of motor neurons. The known MND genes only account for about 2% of all cases. 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. A further 18 families were recruited in the last 12 months bringing the total to around 200. The causative disease genes remain to be identified in most of these families. We have commenced genetic and functional studies in these families in an effort to identify new MND genes and elucidate the molecular mechanisms that lead to motor neuron death. The following projects are under way:

1. Our genetic studies have identified a region on chromosome 7 that harbours a previously unidentified MND gene. Work is now underway to narrow the chromosomal interval and isolate the gene in question.

2. We have also 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.

3. Our genetic studies have identified and provided strong evidence for the presence of a new gene that causes classical ALS at one of three potential chromosomal locations.

4. Novel mutations in two functional candidate genes have been identified in our cohort of MND families. Work is underway to determine the functional consequences of these mutations in patients and cell models. This will give us insights into the biological basis of the disease.

Identification of new MND genes and mutations 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, ML Huang, T Bautista

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.

**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.

**Hereditary Sensory Neuropathy**

Hereditary sensory neuropathy type 1 (HSN1) is one of the most common and best-characterised forms 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 contribute to neuronal cell dysfunction in this neurodegenerative disease. Recent preliminary studies have indicated that mitochondria play a role in HSN1. This exciting new area of research will be a strong focus area for our HSN1 projects (Figure 2). 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.

**Parkinson’s Disease**

N Page, M Kennerson, G Nicholson

Parkinson’s disease (PD) is caused by the progressive degeneration of dopaminergic neurons in the brain that leads to the characteristic disabling motor manifestations of the disease. Recently, the importance of genetic factors in causing familial and some seemingly sporadic cases of PD has been realised, with identification of a growing number of genes harbouring causative mutations. It is anticipated that genetic testing for these known mutations in familial PD patients may, in the future, assist with diagnosis, prognosis, medical decision making, and the ability of the patient to plan for the future. However, due to the high cost and technical difficulties of mutation detection methods, to date no single screening procedure has been developed to identify all known variants in PD genes.
The aim of our project is to develop an affordable, efficient screening procedure for detection of mutations known, or suspected, to cause PD. For this purpose, the Institute has purchased the newly developed technology platform BeadXpress (Illumina). Screening familial PD patients for mutations in this project using the BeadXpress will allow a correlation between genotype and the resulting PD phenotype to be established, thereby aiding physicians in better disease diagnosis. In the long term, it is also hoped that this project will lead to the identification of targets for therapeutic intervention that could prevent the neurodegeneration seen in PD.

**Students:**

Dr Sumana Gopinath completed her PhD candidature on motor neuron disease and received numerous travel awards and the prestigious NSW Motor Neuron Disease award for her studies. The laboratory had three summer research students as part of the Sydney University Faculty of Medicine (2006-2007) program. Megan Brewer was successful in obtaining a second summer vacation scholarship (2005-2006). She worked on mutation screening genes in the CMTX3 interval and enrolled in an Honours year (2006) to continue this project. Both Megan Brewer and Alexander Drew were awarded Australian Postgraduate Research Awards and commenced their PhD candidatures in 2007. During 2007, Ms Min Li Huang and Ms Tara Bautista have been undertaking their Honours year with Dr Myers. Min Li’s project has been to characterise the cell biology of CMT2A, whilst Tara has been characterising the expression of SPTLC1 and ATF3 in HSN1. Both students obtained First Class Honours and Tara was the winner of the David Monk-Adams Award from Dept of Physiology, University of Sydney. Mr Martin Simone, a PhD candidate is working on characterising the cytoskeletal changes in HSN neuronal cells.

**Figure 1:** Analysis of a single nucleotide polymorphism (rs1012777) using high resolution melt curve analysis. The figure demonstrates the separation of samples into groups based on the genotype present in the sample. The separation into groups based on the genotype is facilitated by HRM analysis detecting changes in the melt curve shapes (difference curves).

**Figure 2:** Transmission electron micrograph of HSN1 EBV transformed lymphoblasts showing abnormal accumulation of mitochondria that also have discontinuous or broken membranes causing depolarisation of the mitochondrial membrane (arrows denoting mitochondrial within the cell).

This group has built up its physical presence in the ANZAC Research Institute over the past 3 years to 14 people primarily working in the laboratory, and another 4 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 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 particular areas of cardiovascular research: vascular and heart muscle injury by oxidation or intervention, inflammation and thrombosis and atherosclerosis. In 2007, we have had several researchers invited to present their data at the World Congress on Heart Disease (Kritharides, Lowe and Witting) and work has been published in several prominent cardiovascular journals. Two of the three finalists in the prestigious Ralph Reader Young Investigator prize (Clinical) at the 2007 Cardiac Society of Australia and New Zealand meeting in Christchurch (Ray Sy and Julie Redfern) were students of Kritharides and Freedman, and Ray Sy was the winner. Two members have taken up office in this society with Len Kritharides as Chair of its Scientific Committee, and David Brieger as Hon Secretary. Harry Lowe was appointed Associate Professor of Medicine.

Heart Attack and Stroke

The general interest of the Senior Investigator and his research staff include ischemic injury to the heart (heart attack) and brain attack (Stroke) and effects of myoglobinurea on kidney function. 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. This area of research has gained momentum with the collaboration of a synthetic organic chemist from the United States (Associate Professor Brian Salvatore). A/Prof Salvatore has synthesized a series of analogues derived from a lead compound identified by Dr Witting and his research team. These analogues are now to be tested for their cardio- and neuro-protective efficacy in relevant animal models of acute disease. The research has gained funding from a variety of sources including philanthropic Foundations, mainstream government bodies and Industry (Eli Lilly). Importantly, the lab continues to support young undergraduate and postgraduate researchers with Dr Witting acting as supervisor for three PhD students and an Honours student in 2007. In 2006, Ms Sarah Parry, an Honours student (working under the supervision of Dr Witting), was awarded the Concord Clinical Week basic science award. Sarah was also awarded Honours (Class I) from the University of Sydney for this work within the department.

CT Angiography

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, and his PhD was awarded in 2007. Mimi Sabaretnam, jointly supervised by Professor Le Couteur of Gerontology, has confirmed her earlier findings that oxidative stress affects apoE localization in hepatocytes, and that these changes are replicated in vivo by ageing. In 2007, Dr Tommy Chung completed his PhD investigating reversible myocardial dysfunction, describing the natural history of cardiac dysfunction caused by pulmonary embolism. In collaboration with Drs Cunningham and Trotman of the Department of Haematology, Dr Chung has also described a high incidence of reversible dysfunction after commonly used chemotherapy. Dr Ray Sy commenced a PhD project in 2006 investigating the predictors of adverse outcome in infective endocarditis. His research was awarded the Ralph Reader Young Investigator award (Clinical Section) for 2007 at the Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand.

Gene Expression and Modification of Vascular and Myocardial Injury

H Lowe, A McMahon, V Benson, R Bhindi

The group’s 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.

We are particularly interested in diabetic heart disease and are currently investigating how diabetic heart muscle responds to ischemia-reperfusion injury compared with non-diabetic heart muscle. We have recently established a novel model of heart attack in diabetes, which allows us to examine both early and late responses to injury over several weeks. We are also interested in methods of protecting the diabetic heart from oxidative stress using novel antioxidant compounds developed within the group.

In related studies, we are investigating the effect of chronic kidney failure on heart function using an established model of renal impairment, and the involvement of oxidative stress in this disease.

Our students have had a great deal of success over the last year: Dr Ravinay Bhindi, jointly supervised by Dr Lowe, was awarded his PhD by Sydney University and Dr Ju-Chiat Tan (a student at the Victor Chang Cardiac Research Institute) jointly supervised by Dr McMahon was awarded his PhD by UNSW.
Inflammatory Mechanisms and Mediators in Acute Coronary Syndromes

D Brieger, A Tiong, P Witting

Our group has two main research directions:

a) Inflammatory mechanisms in acute coronary syndromes.

Our studies in this area 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. These cells, when extracted from patients with coronary disease both, directly elaborated and potentiated the ability of other inflammatory cells to release MMP-9 in response to inflammatory stimuli. This work adds to the weight of evidence suggesting that evocation of the adaptive immune response plays an important role in acute coronary disease. 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 in to 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. Developing on this work we have found an important role for plasminogen itself in the regulation of neutrophil function. As local concentrations of plasminogen vary significantly in vascular and tissue beds, both in the presence and absence of disease, this provides a novel avenue for research into inflammatory cell function.

Dr Alice Tiong was recently awarded her PhD from the University of Sydney for work completed within the Vascular Biology Group.

CRP and Serum Amyloid A as Inflammatory Mediators

B Freedman, C Song, Y Shen, E Yamen

Our main aims are 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 monocyte 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, particularly TNF. 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 completed a post-graduate (Masters) degree. Eric Yamen joined the group with CVL grant to continue work in this area.

L to R: Aisling McMahon, Eric Yamen, Vicky Benson, Shane Antao, Paul Witting, Ben Freedman, Chiangjie Song, Hong Duong, Sarah Parry.
WAR VETERAN’S HEALTH EPIDEMIOLOGY: AUSTRALIAN VIETNAM VETERANS HEALTH STUDY

Group Leader: Dr Brian O’Toole

Collaborators and Staff: Prof Stan Catts (Univ of Qld), Prof Jill Cockburn (Univ of Newcastle, deceased), Dr Sue Outram (Univ of Newcastle), Kate Pierse, Dianne Swinsburg, Meredith Kearney, Dr Martin Howell

The Australian Vietnam Veterans Health Family Health Study is an epidemiological cohort study that is based on a random sample of 1,000 Australian Army Vietnam veterans. It examines the long-term health effects of war zone exposures and experiences in combat veterans and their families. Originally based at Westmead and Concord Hospitals, the study began with a study of the veterans in the late 1980s and the first wave collected data from veterans from 1991-1993. A second wave interviewed the veterans again during 2005-06 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.

Vietnam Veteran Cohort

The Australian Institute of Health and Welfare searched the National Death Index on behalf of the study to determine mortality in the cohort of veterans. 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%. The pattern of deaths was similar to the Australian population for the age group of the veterans: 31% died of cardiovascular disease, 25% died of cancer, 11% died of suicide. 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. No single psychiatric diagnosis that was assessed at Wave 1, including PTSD, was associated with mortality between the time of Waves and 2, nor was the amount of combat exposure in Vietnam associated with mortality.

Follow-up of the veteran cohort in Wave 2 was good for a study extending over a further 14-15 years: 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 the lifetime prevalence of PTSD in Vietnam veterans 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% lifetime and 32% current. 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 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 first wave of 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. Future analysis will be directed to examining this association more closely in Wave 2 data.

Papers reporting the preliminary findings for veterans were presented to the Australasian Society for Psychiatric Research Conference in Sydney, and addressed the issues of the increased prevalence of PTSD and the stability of memory of war trauma. Data analysis suggests that, when asked about their traumatic exposures in Vietnam, soldiers recall even the smallest detail and report the same stories consistently even when questioned over clinical interviews some 14 years apart. In particular, the stability of the intrusion phenomena of PTSD (nightmares, flashbacks, etc) is remarkable – the brain won’t let traumatic memories be erased – although it seems that some of the other features of PTSD, such as anger and arousal symptoms, may reduce over time.

Co-morbidity with alcohol disorders is being examined by Doctor of Public Health student, Dr Martin Howell. There is an intricate relationship between combat experiences, alcohol and PTSD, that needs to be unravelled, especially in light of the prevalence changes in PTSD and alcohol use disorders seen over Waves 1 and 2. The role of combat, alcohol, and PTSD in the genesis of diabetes risk factors is being examined to assess the role of war service in the observed excess of diabetes among Vietnam veterans.
Vietnam Veterans’ Wives/Partners
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 is assessing the effects of veterans’ problems on their wives and partners. The study also includes veterans’ ex-wives, where possible. Attention is focused on PTSD and alcohol use disorders, which are the two most prevalent disorders among the veterans. The study has developed an assessment instrument that measures the amount of stress experienced by each woman and relates this to each of her partner’s 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. Fieldwork interviews will be completed by the end of 2007.

Vietnam Veterans’ Children
The Vietnam Veterans Federation contributed a small grant in 2007 to the study team to further develop procedures for assessing the health of veterans’ children and, together with a research grant to Dr Outram from the Hunter Mental Health Research Institute, will enable feasibility studies to be completed, testing for ways to improve participation rates, and for various essential components of the assessments.

New Publications:
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
Dr Peter Maitz AM, MD, PhD, FRACS
Professor Garth Nicholson MB BS, PhD
Dr Brian O'Toole PhD, MPH
Professor Markus Seibel MD, PhD, FRACP

**Clinical Research Associates**
Associate Professor David Brieger MB BS, FRACP, PhD
Associate Professor Ann Conway MB BS, FRACP
Dr Peter Haertsch AM, MB BS, FRACS, FRCSEd (Edin)
Dr Peter Kennedy AM, MB BS, MDS, FRACS
Associate Professor Len Kritharides MB BS, FRACP, FAHA, PhD
Dr David Millos MB BS, FANZCA, FJFICM, MHP
Dr Alaina Taylor MB BS, BMedSc
Dr Edward Wills MB BS, FRACPath

**Research Fellows**
Dr Charles Allan PhD
Dr Ian Blair PhD
Dr Julie Blair PhD
Dr Colin Dunstan PhD
Associate Professor Harry Lowe MB BS, FRACP, FACC, PhD
Associate Professor Peter Liu MB BS, FRACP, PhD
Dr Marina Kennerson PhD
Dr Aisling McMahon PhD
Dr Michael Muller MA, PhD
Dr Simon Myers Dip Ed, PhD
Dr Patsie Polly PhD
Stephane Rochat
Associate Professor Graham Robertson PhD
Dr Paul Witting PhD (ARC Fellow)
Dr Hong Zhou MD (China), PhD

**Project Managers**
Dr Michael Evtushenko BTech Mgt, PhD
Melisa Litchfield BAppSc, MPH
Kate Pierce BA, MA

**Clinical Research Nurses**
Marina Etherington RN
Carolyn Fennell RN
Maggie Hayes RN
Amanda Idan RN
Tom Leong B Health Sc (Nursing), M. Health Sc (Nursing)
Diane Pinkerton RN
Sue Taggart B Health Sc (Nursing)
Leo Turner RN, MSc (Med)
Sue Todd RN
Catherine Xu CNS

**Research Assistants**
Ivy Collins
Jennifer Durnall
Colette Fong-Yee
Ellen Gao
Janice Koh
Bartosz Kowalski
Golnar Mousavi
Natalie Page
Sarah Parry
Janine Street
Sadaf Warraich
Kelly Williams

**Technical Support**
Lydia Andres
Fay Bacha
Vicky Benson
Annette Berryman
Carolyn Cecere
Candice Clarke
Irene Di Pierro
Sabina Horky
Angeline Koh
Ashley Latimer
Daniel Liske
Christina Nostas
Veronica Poliero
Dianne Swinsburg
Ljubica Vrga
Matilda Webbey
Overseas Visiting Fellows/Students
Anja Goebel
Dr Markus Herrmann
Holger Henneiche
Dr Hassan Nabavi
Dr Gideon Sartorius
Agnes Weber

Graduate Students
Jessica Almine BSc(Hons)
Kerrin Blicher
Vicky Benson MSc
Megan Brewer
Anthony Corradin
Dr Rajkumar Cheluvappa MD (India)
Dr Tommy Chung MB BS
Haryana Dhillon BSc, MAI (Psych)
Hong Duong
Alex Drew BSc (Hons)
Dr Hamish Jamieson MB BS
Marina Kacevska BSc (Hons)
Curtis Kuo
Dr George Lau MB BS, FRACP
Wendy Mak BSc (Hons)
Marko Matic BSc (Hons)
Keely McNamara BSc (Hons)
Kirsten McTavish BSc (Hons)
Jennifer O’Reilly BA(Mus), BSc (Hons)
Li Laine Ooi
Alicia Neuback
Dr Viet Phan MD MPH
Ben Rayner BBioSc (Hons)
Jelena Rnjak BSc (Hons)
Mimi Saba BSc (Hons)
Dr Anita Sharma DSM, AMC, FRACP
Martin Simone BSc (Hons)
Fiona Stanaway
Dr Alice Tiong BSc (Hons), MB BS, FRACP
Dr Eric Yamen MB BS (Hons)
Dr Yu Zheng MD (China)

2007/08
Dan Gardon
Min Li Huang
Arran Painter
Ryland Taylor

Undergraduate Students
Filip Bebek
Jennifer Crawford

Honours Students 2007
Shane Antao
Tara Bautista
Jennifer Crawford
Dan Gardon
Min Li Huang
Arran Painter

Summer Scholars 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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<td>NHMRC</td>
<td>Project</td>
<td>Concord health and ageing project in men (CHAMP)</td>
<td>Cumming, Handelsman, Seibel, Creasey, Sambrook, Wate</td>
<td>300,000</td>
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<td>NHMRC</td>
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<td>Sunlight andfalls</td>
<td>Sambrook, March, Cameron, Cumming, Seibel, Simpson</td>
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<td>Hormonal control of Sertoli cell maturation and function</td>
<td>Allan, Handelsman</td>
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<td>Impact of tumours on levels of human drug metabolizing enzymes</td>
<td>Robertson, Clarke, Liddle, Polly</td>
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<td>Glucocorticoid effects on bone: The role of the osteoblast</td>
<td>Seibel, Zhou, Dunstan, Kroczowski</td>
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<td>AED’s and fracture risk.</td>
<td>Ward, O’Brien, Sambrook, Seibel, Herkes</td>
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<td>Inflammation-associated S100 proteins: links between arthritis and atherosclerosis</td>
<td>Geczy, McNeil, Freedman, Hsu</td>
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<td>Pharmacogenetics of tissue androgen activation</td>
<td>Handelsman, Reichardt, Yu, Seibel</td>
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<td>Bone resorption in breast cancer metastasis</td>
<td>Dunstan, Seibel, Zhou, Blair</td>
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<td>Mechanisms for ageing changes in the hepatic sinusoid</td>
<td>Le Couteur, Fraser, Cogger, Muller, Harris, Sullivan</td>
<td>134,250</td>
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<td>How is lipoprotein disposition influenced by fenestrae in the hepatic sinusoidal endothelium?</td>
<td>Le Couteur, Fraser, Cogger, Muller, Sullivan</td>
<td>102,000</td>
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<td>Geriatric pharmacology</td>
<td>Le Couteur, Cumming, McLean</td>
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<td>Le Couteur, de Cabo, Cogger, Hilmer, Fraser</td>
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<td>Effects of androgenic hormones and exercise on male agein</td>
<td>Liu</td>
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<td>Equipment</td>
<td>Illumina BeadXpress Reader</td>
<td>Nicholson, Kennerson, Seibel, Handelsman, Freedman, Le Couteur, Muller</td>
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<td>Equipment</td>
<td>Twister microplate handle: A robotic system for the Bruker HTS-XT infrared module.</td>
<td>Lay, Hunt, Grau, Sorrell, Witting</td>
<td>81,520</td>
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<td>Equipment</td>
<td>Cell culture quarantine and storage facility</td>
<td>Dunstan, Allan, Witting, Myers, Handelsman, Seibel, Nicholson, Zhou, Kennereson, Freedman, Le Couteur, Muller</td>
<td>68,967</td>
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<td>QPMI dissecting microscope with imaging box</td>
<td>Witting, Handelsman, Lowe, Le Couteur, Muller</td>
<td>27,820</td>
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<td>NHMRC</td>
<td>Equipment</td>
<td>MyoCam CCD camera anddonoptix digital image acquisition software</td>
<td>North, Gunning, Winnal, McMahon, Thomas, Butler</td>
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<td>Expanding the animal surgery facility</td>
<td>Witting, McMahon, Lowe, Muller, Witting, Handelsman</td>
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<td>NHMRC</td>
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<td>Biochemical properties of 5-nitrososomoglobin and its role in regulating nitric oxide bio-availability</td>
<td>Witting</td>
<td>321,519</td>
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<td>Fellowship</td>
<td>Early Career Development Fellowship</td>
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<td>MNDRI</td>
<td>Fellowship</td>
<td>Identification of novel genes involved in motor neuron degeneration</td>
<td>Blair</td>
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<td>NSW Health BioFirst</td>
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<td>Dunstan</td>
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<td>Nicholson, Blair</td>
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<td>Novel vitamin E analogues with enhanced specificity for malignant cells</td>
<td>Neusti, Witting, Salvatore</td>
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<td>ARC Discovery</td>
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<td>Steroidal control of male meiosis</td>
<td>Allain, Handelsman, Gregson, Denyer</td>
<td>41,321</td>
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<td>Australian Rotary</td>
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<td>The Australian Vietnam Veterans’ Health Study: Wives’ Cohort:</td>
<td>O’Toole, Cat, Outram</td>
<td>59,885</td>
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<td>Identifying new genes for familial motor neuron disease</td>
<td>Blair</td>
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<td>Guided choice for prevention of future heart disease</td>
<td>Freedman, Redfern</td>
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<td>How do mutations in SPTLC1 causing hereditary sensory neuropathy affect the cell cytoskeleton?</td>
<td>Myers, Kenneross</td>
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<td>CMRI</td>
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<td>How defective dynamin 2 activity causes Charcot-Tooth Disease</td>
<td>Robinson, Nicholson, McCluskey</td>
<td>74,222</td>
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<td>Commonwealth Institute, London UK</td>
<td>Project</td>
<td>Lifestyle of our kids. A longitudinal investigation of the influence of lifestyle and health.</td>
<td>Bass, Daly, Siebel, Norton</td>
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<td>Cure Cancer Australia Foundation</td>
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<td>The role of androgens in prostate physiology and pathology</td>
<td>Handelsman, Simanainen</td>
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<td>Dept. of Communications, Information Technology and the Arts</td>
<td>Project</td>
<td>Use of an in vitro androgen bioassay for universal detection of illicit androgen use: A pilot feasibility study for an androgen gap assay project</td>
<td>Handelsman, Death, Kazlaukas</td>
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<td>Diabetes Australia Research Trust</td>
<td>Project</td>
<td>Gene targeting to treat heart attack in Type 2 diabetes</td>
<td>Lowe, Khachigian, Witting, McMahon</td>
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<td>Diabetes Australia Research Trust</td>
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<td>Lowe, Khachigian, Witting, McMahon</td>
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<td>Diabetes Australia Research Trust</td>
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<td>Design and evaluation of a new model of in-stent re-stenosis in diabetes</td>
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<td>Oxidative mechanisms that cause endothelial dysfunction.</td>
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<td>Eli Lilly Diabetes Research Grant</td>
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<td>Projects focusing on the understanding or treatment of patients with diabetes mellitus</td>
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<td>Eli Lilly Diabetes Research Grant</td>
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<td>Diabetes Research Grant-in-aid</td>
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<td>Hunter Medical Research Foundation MDA</td>
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<td>Health and wellbeing of partners of victims of trauma:</td>
<td>Outram, O’Toole, Catts</td>
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<td>A vulnerable group in the community</td>
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<td>Effects of mutant SPTLC1 on the cell biology of neuronal cells</td>
<td>Nicholson, Myers</td>
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<td>Finding the gene causing X-linked Charcot-Marie-Tooth (CMTX3)</td>
<td>Nicholson, Kennerson</td>
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<td>National Heart Foundation Grant-in-aid</td>
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<td>Serum amyloid A as a mediator of thrombotic risk in coronary</td>
<td>Freedman, Geczy</td>
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<td>Novel catalytic oligodeoxynucleotides to treat acute myocardial</td>
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<td>Investigation of local inflammatory process in coronary</td>
<td>Yamen, Freedman</td>
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<td>Metabolic and psychomotor changes after continuous positive</td>
<td>Liu, Yee, Phillips, Berend, Handelsman</td>
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<td>Steroidal regulation of meiotic development</td>
<td>Allan, Handelsman, Griswold, Deryer</td>
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<td>Finding the gene mutations causing X-linked Charcot-Marie-Tooth</td>
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<td>Identification of a novel gene for progressive motor neuron</td>
<td>Nicholson, Blair</td>
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<td>Bone and tumour necrosis following anti-resorptive treatment</td>
<td>Seibel, Dunstan, Blair</td>
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<td>Managing osteoporosis in patients presenting to CRGH with</td>
<td>Clarke, Robertson, Baker, Molloy, Rokey, Chaquis,</td>
<td>750,000</td>
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<td>Lin, Christopherson, Lee, Hong, Kohonen-Corish, Beale, Solomon, Horvath, McKay,</td>
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<td>Investigator initiated study</td>
<td>A randomised placebo-controlled trial of TU in obese men as</td>
<td>Liu, Grunstein, Handelsman</td>
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<td>Schering Pty Ltd</td>
<td>Investigator initiated study</td>
<td>Efficacy and acceptability of TU injections compared with</td>
<td>Handelsman, Kelleher, Conway</td>
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<td>Seibel, Blair, Zhou, Blair</td>
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<td>Rebecca Cooper Research Foundation</td>
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<td>Dunstan, Seibel, Zhou, Blair</td>
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<td>Allan, Cummings, Handelsman, Seibel</td>
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<td>Ion optix fluorescence and contractility measurement system</td>
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<td>North, Wintow, Gunnin, Thomas, McMahon</td>
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<td>KODAK image station 2000mm multi-modal imager</td>
<td>Seibel, Zhou, Handelsman, Allan, Nicholson, Witting, Le Couteur, Freedman, Dunstan, Blair, Kennerson, Robertson, Muller</td>
<td>29,873</td>
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<tr>
<td>Major Equipment Grant</td>
<td>KODAK image station 2000mm multi-modal imager</td>
<td></td>
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<tr>
<td></td>
<td>Leica CM350 S cryostat</td>
<td></td>
<td>Seibel</td>
<td>26,608</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Global: Small animal surgical equipment.</td>
<td></td>
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**Infrastructure**

<table>
<thead>
<tr>
<th>Source</th>
<th>Grant Type</th>
<th>Title</th>
<th>Investigators</th>
<th>$</th>
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</thead>
<tbody>
<tr>
<td>OSMR</td>
<td>Infrastructure</td>
<td>Medical Research Support Program 2006 – 2009</td>
<td>ANZAC Research Institute</td>
<td>689,330</td>
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<tr>
<td></td>
<td>Centre for the preclinical pharmacokinetic and pharmacokinetic evaluation of cancer drugs, nutritional interventions &amp; complementary therapies.</td>
<td></td>
<td>Clarke, McLachlan, Robertson, Liddle</td>
<td>91,000</td>
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</table>

**Scholarships**

<table>
<thead>
<tr>
<th>Source</th>
<th>Grant Type</th>
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<tbody>
<tr>
<td>NHMRC</td>
<td>Neil Hamilton Fairley Scholarship</td>
<td>Role for Myoglobin in myocardial ischemia reperfusion injury.</td>
<td>Rayner</td>
<td>22,000</td>
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<tr>
<td></td>
<td>Brewer</td>
<td>How do mutations in serine palmitoyltransferase long chain sub unit 1, causing hereditary sensory neuropathy, affect the neuronal cell cytoskeleton</td>
<td>Brewer</td>
<td>30,000</td>
</tr>
<tr>
<td></td>
<td>Simone</td>
<td>What is the gene mutation causing an X-linked form of Charcot-Marie-Tooth neuropathy (CMTX3)? (Stipend for PhD)</td>
<td>Simone</td>
<td>30,000</td>
</tr>
<tr>
<td></td>
<td>Duong</td>
<td>What role for the oxygen-carrying neuroglobin in the pathogenesis of stroke?</td>
<td>Duong</td>
<td>26,670</td>
</tr>
<tr>
<td>National Heart Foundation of Aust</td>
<td>Project</td>
<td>Novel catalytic oligodeoxynucleotides to treat acute myocardial</td>
<td>Lowe, Khachigian</td>
<td>62,000</td>
</tr>
<tr>
<td></td>
<td>infarction via Egr-1</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>


THE FOUNDATION

ANZAC Health and Medical Research Foundation

Financial Performance 37
Board 38
Donor Honour Roll 40
### Synopsis of Financial Performance

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Peer review 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>
<td>3,266,110</td>
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<tr>
<td>Clinical Trials</td>
<td>84,806</td>
<td>441,435</td>
<td>253,682</td>
<td>632,102</td>
<td>220,260</td>
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<tr>
<td>State Government Grants</td>
<td>442,400</td>
<td>492,400</td>
<td>532,044</td>
<td>536,063</td>
<td>804,033</td>
<td>893,690</td>
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<tr>
<td>Commonwealth Research</td>
<td></td>
<td>107,500</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>
<td>288,417</td>
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<tr>
<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>
<td>786,775</td>
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<tr>
<td>Other</td>
<td></td>
<td>287,770</td>
<td>248,470</td>
<td>425,596</td>
<td>842,226</td>
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</tr>
<tr>
<td>Total Income</td>
<td>2,100,606</td>
<td>3,014,418</td>
<td>4,080,011</td>
<td>4,442,443</td>
<td>5,168,610</td>
<td>6,361,414</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<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>
<td>2,737,452</td>
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<tr>
<td>Scholarships</td>
<td>-</td>
<td>141,707</td>
<td>257,688</td>
<td>198,460</td>
<td>212,959</td>
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<tr>
<td>Administrative Costs</td>
<td>327,728</td>
<td>490,409</td>
<td>229,686</td>
<td>439,977</td>
<td>477,047</td>
<td>500,456</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>
<td>620,871</td>
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<tr>
<td>R&amp;M and Renewals</td>
<td>167,556</td>
<td>118,436</td>
<td>146,089</td>
<td>169,644</td>
<td>368,562</td>
<td>201,198</td>
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<tr>
<td>Depreciation</td>
<td>258,281</td>
<td>291,125</td>
<td>498,928</td>
<td>387,744</td>
<td>434,470</td>
<td>477,048</td>
</tr>
<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>
<td>4,749,984</td>
</tr>
<tr>
<td>Net Increase in funds</td>
<td>479,366</td>
<td>1,075,677</td>
<td>1,610,906</td>
<td>975,449</td>
<td>941,839</td>
<td>1,611,430</td>
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</tbody>
</table>
Felicity Barr (Chair)

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

Danny O’Connor (Deputy Chair)

Danny O’Connor is the 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 and then State Coordinator for methadone treatment in New South Wales. He worked in the public health division of the NSW Health Department as a senior policy analyst before becoming Director of Drug Health Services in Central Sydney Area Health Service. He later moved into hospital management 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 retired as the Area Managing Director (Australia and New Zealand) for Baxter Healthcare. He was the past National President of the Leukemia Foundation of Australia and former director of Medical Specialties Australia. Brian has been a long-time advocate and supporter of ANZAC Health and Medical Research Foundation and currently chairs the Fundraising Subcommittee on the current Board.

Dr Charles Pawsey

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

Godfrey (Rusty) Priest AM

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

Professor Bruce Robinson

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

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

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
- The Philip Bushell Foundation: $56,667.00
- Esanda/Cancer Council Raffle Committee: $28,120.00
- HSP Research Foundation Inc: $27,500.00
- The Rebecca L Cooper Medical Research Foundation: $31,100.00
- Charcot-Marie-Tooth Association of Australia INC: $3,750.00
- Mr Neville Jeffress: $3,000.00
- AXA Australia: $145.78

### Community Organisation
- Rotary Club of Caringbah Inc: $17,500.00
- Volunteer Services Auxiliary of Concord Hospital: $16,880.00
- Chester Hill - Carramar Sub Branch: $1,000.00
- Enfield-Croydon Park Sub-Branch: $1,000.00
- North Sydney RSL Sub Branch: $1,000.00
- In Touch Business Results Pty: $500.00
- Stockwell International: $200.00
- Epping RSL Sub Branch: $100.00
- Taxation RSL Sub Branch: $100.00
- North Ryde Community Uniting Church: $50.00

### BEQUEST
- David & Helen Jobson: $500.00

### FOTARI
- Dr Charles Pawsey: $1,040.00
- Andrew G Richardson: $1,000.00
- John C Gordon: $1,000.00
- John Linsley: $924.00
- Paul Collett: $924.00
- Davis Paul Raymond: $880.00
- Steven Kalowski: $833.30
- Ramon Bullock: $650.00
- Gregory Falk: $600.00
- G D Pearce: $520.00
- Ross Bradbury: $520.00
- Dr Margaret Haylen: $500.00
- R. W. Balfour: $500.00
- Sir Ron Briersley: $500.00
- Bradford Gambetta: $440.00
- Eileen Collins: $440.00
- Merrin Hodgson: $440.00
- Paula Fengler: $440.00
- Keely Lammers: $400.00
- Tony Moran: $325.00
- JA & MA Todd: $300.00
- Allan Maidment: $265.00
- Barbara Roff: $265.00
- Dr George R Faithfull: $250.00
- Charles R Waud: $200.00
- Major John P. Kelly (Ret’d): $200.00
- Mr Alan Davidson: $200.00
- Mr WB & Mrs MJ White: $180.00
- Wendy Young: $180.00
- Rhonda Cloak: $145.00
- M W Hayes: $104.00
- Elizabeth Perosh: $100.00
- Jean Elizabeth Blair: $100.00
- Mr B J Harrison: $100.00
- Mrs Valerie Allen: $100.00
- Neville J Anderson: $100.00
- Peter Heany: $100.00
- Peter Robinson: $100.00
- R. J B & A L Bradley: $100.00
- Reg Elliott: $100.00
- Ross L & GC Jones: $100.00
- RS Bateup: $100.00
- S J Sassine: $100.00
- William James Forbes: $100.00
- Davis Paul Raymond: $80.00
- Joan Larking: $75.00
- Peter Maher: $75.00
- Beverley Turner: $50.00
- Brigadier RW Morris: $50.00
- Bryn Jones: $50.00
- Dr Aruthur Everitt: $50.00
- Mr K N Payn: $50.00
- Mr R V Pearce: $50.00
- Mrs Joan S Perry: $50.00
- Ron O’Connor: $50.00