

Centenary
Institute
research
for life



Annual Report 2007

The Centenary Institute is an independent medical research institute, forming a critical point of contact and intellectual engagement between the University of Sydney and the Royal Prince Alfred Hospital.

Our unique blend of highly skilled staff and state-of-the-art equipment and facilities has allowed us to become world leaders in the following critical areas of medical research:

- cancer
- cardiovascular disease
- infectious diseases

Our history

The Centenary Institute opened in 1989 under the stewardship of founding director Professor Antony Basten, to commemorate the centenaries of the University of Sydney Medical School and the Royal Prince Alfred Hospital. Formal working relationships with the University and Hospital have provided unique opportunities for students to become involved in research as well as the translation of basic discoveries into clinical practices.



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Chairman's Report



This was a pivotal year for the Centenary Institute

There has been a major change in the look and feel of the Centenary Institute; we have increased our peer reviewed research funding by more than \$2 million (representing an increase of more than 40 per cent) and there is a strong feeling of collegiality in our continuous output of superb medical research. This new feel is evident in the appearance of this Annual Report which presents a new look, emphasising the importance and relevance of our work for people of all ages – and the fact that many adult diseases do begin in childhood.

Our new Director, Professor Mathew Vadas, assumed leadership of the Centenary Institute at the beginning of the year. He has made his mark felt in a very short time, which is evident in the growth of staff from 103 to 134 during the year. This growth, together with the vibrancy of the artwork lent by the Watters Gallery, has generated a very positive and energetic feeling that reflects the Institute's enormous potential.

This potential, of course, comes from an already excellent base. The Board undertook a benchmarking exercise comparing the Centenary Institute with other similar research enterprises, and I am pleased to note that, whilst we were smaller than many, our output per capita was amongst the top half dozen.

I was delighted to welcome as guest of honour The Hon Tony Abbott, Minister for Health and Ageing, to the first Annual General Meeting. This will become an important occasion in the Centenary calendar as it will promote integration of the Centenary in the community and improve our communication with our supporters.

One of the other major initiatives during the year was a partnership between the Centenary Institute and Sydney Cancer Centre to establish a new cancer research enterprise. This will be part of a new Comprehensive Cancer Centre on the campus, which will comprise of two buildings; one devoted to research, with a working name of Centre for Basic and Translational Cancer Research (CBTCR), and another devoted to clinical care and clinical trials. The CBTCR, housing approximately 350 – 400 scientists with a floor area of some 17000m², will be built adjacent to the Centenary Institute. The CBTCR

will be a joint enterprise between the Centenary and SCC, but will be run by the Centenary Institute.

The fundraising for the CBTCR is well on its way, with significant boosts from grants from the Federal Government of \$10 million and a peer reviewed and competitive award from the Australian Cancer Research Foundation for \$5 million. In addition, the University of Sydney has also expressed its strong support.

Needless to say, in addition to government and institutional support, our own efforts in raising funds from the general community will be critical, both for the new Centre and for the Institute's existing research. In this regard, I am very pleased that Sally Castle, our new Fundraising and Marketing Manager has joined the Institute.

The Board welcomes Professor Mathew Vadas, Professor Bruce Robinson, Mr Geoff Dixon and Associate Professor Kelly-Anne Phillips and farewells Professor Andrew Coats, Professor John Mathews, Ms Sam Mostyn and Professor Mick Reid. We congratulate Neil Lawrence for becoming the 2007 Marketer of the Year, and thank him for agreeing to Chair the Foundation of the Centenary Institute.

I am also very grateful to Dr Nick Pearce, our Chief Operating Officer, for the great assistance he provides in keeping the business and administrative side of the Centenary Institute running smoothly.

The Centenary is extremely fortunate to have great researchers and great staff. I thank all of them for their continuing commitment to a great cause.

The Hon Michael Egan

Executive Director's Report

In leading an organisation such as the Centenary Institute one is conscious of an enormous privilege.



The Centenary Institute celebrates a key event in the history of medical research in Australia, that of the 100th birthdays of Sydney University Medical School and the Royal Prince Alfred Hospital, and is situated ideally on the cusp between these two great institutions. Its history and location dictates the Centenary Institute's focus on diseases of adults of all ages, and its emphasis on relevance in translating its discoveries for the clinical good.

One of our tasks is to make certain that our colleagues, donors and the whole community clearly recognise the distinctiveness and outstanding past and future achievements of the Centenary.

We, with the help of one of our Directors, Mr Neil Lawrence, and Yello have established a new look for the Centenary. This emphasises our goals: "Research for Life" as well as the idea that adult health begins in childhood and that we work on the whole continuum. The readers will note some aspects of this new brand in this Annual Report as well as on our website.

As noted by the Chairman of our Board, a major priority has been the recognition of the outstanding cancer research ongoing in the Centenary Institute and plans for its further strengthening. The joint initiative with the Sydney Cancer Centre (SCC) to build a new cancer research building is therefore a very welcome development. This has been a rapidly evolving enterprise for which support has been evident from all quarters. Importantly, a major Federal Government grant of \$10 million supporting this research initiative and support by the University of Sydney, Australian Cancer Research Foundation (ACRF) and the Sydney South West Area Health Service (SSWAHS), has allowed rapid progress towards our target of \$81 million.

I would especially like to emphasise the importance of the ACRF: this award of \$5 million was strictly peer reviewed and was the biggest given

by the ACRF in 2007. This success was a result of intense cooperation between the scientists and clinicians – not only from the Centenary Institute but also University of Sydney, Royal Prince Alfred and Concord Hospitals, who participated in the application, and our management team led by Nick Pearce. I thank all of them and especially Professors Michael Boyer and Bruce Armstrong – my co chief investigators on the application.

In order to support and advise on our scientific effort, the Centenary Institute has established a Scientific Advisory Board (SAB). Professor Axel Ullrich is its Chairman and it has as its other members, Professors Valerie Beral, Michael Good, Marc Feldman, Ian Fraser and David Hunter. We have already had some excellent meetings with individuals in our SAB, and look forward to our first full meeting in 2009. I want to take this occasion to thank all members of the SAB, especially its Chairman, for their generous support.

The growth in our staff both scientific and administrative has been striking – not only for the numbers but also for their excellence. I welcome Professor Wolfgang Weninger, who leads the Immune Imaging laboratory and also has been given the Chair of Dermatology in the University of Sydney; Professor Jennifer Gamble, who leads the Vascular Biology laboratory and was given the University of Sydney Medical Foundation Chair of Vascular Biology; Associate Professor Pu Xia, who leads the Signal Transduction laboratory; Dr Milka Jormakka who is the new head of Structural Biology; and Ms Sally Castle, our new and energetic Fundraising and Marketing Manager.

A landmark was our success in securing, in partnership with the SCC, the Cancer Institute NSW Cancer Leaders Fellowship for a Chair in Cancer Biology. Together with the Medical Foundation of the University of Sydney we have put together a most attractive package for this prestigious position. In addition, we are in the midst of advertising for a Chair of Endothelium, for which Dr Tom Wenkart has donated not only his vision in identifying endothelial cells, cells which form the lining of the wall of the blood vessels as an essential conduit to health and disease, but also the funds to support this new position.

Executive Director's Report

Increased numbers at the Centenary Institute were also paralleled by an increase in activity. Our Seminar program was revitalised under the leadership of Professors Gamble and Rasko; a series of one day Colloquia were initiated – each, in order to emphasise future collaborations, were entitled “Opportunities in ...”. In 2007, there were three of these: “Opportunities in MicroRNA Research, Vascular Biology and Systems Biology.

Another initiative has been a new series of seminars being organised by Professor Fazekas de St Groth. The seminars are entitled “Science and Commerce” and cover issues of patenting, commercial agreements and funding of commercial ventures. We look forward to a vibrant set of talks in this series over the coming years.

Another priority is the intensification of our fundraising efforts to support our many excellent scientists. This area has been revitalised under the most capable leadership of Ms Castle, who has introduced new donor acquisition and retention programs. In addition, she played a central role in the production of the new brand.

In order to engage our community we initiated an Annual General Meeting, allowing an opportunity to showcase our achievements. We

were delighted that The Hon Tony Abbott, Minister for Health and Ageing, accepted our invitation to be guest of honour. In addition, I have begun a series of “Director’s Lunches”. The guest of honour for the first of these was Professor Valerie Beral, Director Epidemiology Unit, University of Oxford, a world renowned epidemiologist, responsible for the famous ‘million women’ study. Her work on the risks and benefits of hormone replacement therapy were discussed in depth.

On the commercial front the Centenary Institute has concluded a licensing agreement with Becton-Dickinson Inc. that has resulted in significant up front and continuing income tied to commercial milestones. The Centenary Institute has also joined the Medical Research Commercialisation Fund (MRCF), an initiative of the NSW and Victorian Governments that allows commercial projects to be put in front of an expert panel and supported at an angel-mezzanine level to reach the next milestones.

Scientifically, some of the many highlights were Professor John Rasko receiving the Roche Medal awarded to an outstanding Australian biochemist or molecular biologist, and Associate Professor Semsarian’s publication in *Journal of American*

Medical Association. This publication for the first time documents the utility of implanted defibrillators in the prevention of sudden death in patients with genetic disorders of the heart.

We have also been active in standardising appointments to the Centenary Institute. Now we have three substantive levels: our Members of the Faculty of the Centenary Institute are our internationally prominent senior scientists; our Associate Members of the Faculty of the Centenary are our superb scientists en route to full membership; and our Staff Scientists are recognised appointments primarily working in association with the Faculty.

In summary, 2007 has been an intense year. Not only has the Centenary Institute embarked on an ambitious program of focusing its research, growth and rebranding, it also continued to strengthen its relationships with the University of Sydney and the SSWAHS and began a process of engaging with the community – for whom we work and whose support we seek.

I finally wish to thank all of our donors and supporters and hope to be able to welcome you to our Institute in the near future.

Professor Mathew Vadas

The Centenary Institute is joining with the Sydney Cancer Centre to build the Centre for Basic and Translational Cancer Research (CBTCR).



Board of Governors

The Honourable Michael Egan (Chair)

Appointed Chair in September 2005, nominated by Gavin Brown, Vice Chancellor of the University of Sydney

Mr Egan is currently the Chancellor of Macquarie University and is a former Treasurer of NSW. During his 25-year parliamentary career, Mr Egan held a number of ministerial positions and still remains the longest serving Treasurer of NSW (1995-2005).

Dr Teresa Anderson

Appointed Governor in 2007

Dr Anderson is the Director of Clinical Operations, Sydney South West Area Health Service. She is on the State Surgical Taskforce and a Board member of the Centre for Primary Health Care and Equity, University of NSW and was previously the General Manager of Liverpool Hospital.

The Honourable John Brown AO FAMI

Appointed Governor in 2001

Formerly the Member for Parramatta in the Federal House of Representatives for 13 years from 1977, Mr Brown held various Ministerial portfolios including Arts, Sports, Environment and Territories. In 1986, he was named Australian of the Year by *The Australian* newspaper and was the founding Chairman of the Tourism Task Force (now the Tourism and Transport Forum) and is the Founder and Patron of the Sport and Tourism Youth Foundation.

Mr Alastair Davidson MICA (Scot)

Appointed Governor in 2004

Mr Davidson has held executive positions in the banking and financial services industry for 15 years in the UK, US and Australia. He is currently Managing Director of Aurora Funds Management in Sydney. Prior to this, Mr Davidson was at Salomon Smith Barney in Sydney, where he spent eight years as co-head of its new product group, specialising in equity derivatives.

Mr Geoff Dixon

Appointed Governor in 2007

Mr Dixon is the Chief Executive Officer and Managing Director of Qantas. Prior to this, he was Chief Executive Designate (from November 2000), after serving as Deputy Chief Executive for two years. Mr Dixon is a Director of Publishing and Broadcasting Limited, Crown Limited (formerly Arterial Limited), Air Pacific Limited and a number of controlled entities of the Qantas Group. He is on the Governing Board of the International Air Transport Association.

Ms Di Gill

Appointed Governor in 2006

Ms Gill is Executive Director of Royal Prince Alfred Hospital, one of the largest tertiary referral hospitals in NSW. She has extensive experience in health having previously held the position of Director of Nursing Operations at Royal Prince Alfred Hospital. She is a member of the Australian Council of Healthcare Standards, the NSW Health Department Clinical Ethics Advisory Panel and the NSW Health Department Sustainable Access Health Priority Taskforce. In addition, she is an Associate Fellow of the Australian College of Health Service Executives.

Professor John Horvath AO

Appointed Governor in 2007

Professor Horvath is the Chief Medical Officer for the Australian Government. He is the principal medical adviser to the Minister of Health and the Department of Health and Ageing across the full range of professional health issues, including health and medical research, public health, medical workforce, quality of care, evidence-based medicine, biosecurity issues and an outcomes-focused health system. Prior to his appointment as Chief Medical Officer in September of 2003, Professor Horvath was a Professor of Renal Medicine at the University of Sydney and a specialist renal physician at the Royal Prince Alfred Hospital. He was awarded an Order of Australia in January 2001 for his services to medicine.

Mr Graham Kelly

Appointed Governor in 2006

Mr Kelly is non-executive Chairman of Tishman Speyer Office Trust, Centrebet International Ltd, Colonial First State Private Capital Ltd and a non-executive Director of several non-listed companies including FreshFood Australia Holdings Pty Ltd and Oasis Fund Management Ltd. He is a consultant to Freehills law firm, Inspector of the Independent Commission Against Corruption and has been a Director of the Medical Research and Compensation Foundation. Mr Kelly has previously served as Managing Partner of the Sydney/Brisbane/Canberra offices of Freehills and National Chairman of the firm.

Mr Neil Lawrence

Appointed Governor in 2006

Mr Lawrence is currently the Executive Creative Director of Australia's largest advertising group, STW Group, having worked in the advertising industry for over 20 years. His clients include: The Commonwealth Bank, Apple, Sony, Mitsubishi, The Federal Government, Cadbury, Masterfoods, St George Bank, Colgate, American Express, AAPT, FOXTEL, *The Australian*, the *Sydney Morning Herald*, Qantas and many charities such as the Fred Hollows Foundation and the Garvan Institute. In 2007, Mr Lawrence was named Australian Marketer of the Year for his crafting of the Australia Labor Party's successful Kevin07 federal election campaign.

Associate Professor Kelly-Anne Phillips

Appointed Governor in 2007

Associate Professor Phillips is currently the inaugural Colebatch Clinical Research Fellow of the Cancer Council Victoria and a medical oncologist and researcher at the Peter MacCallum Cancer Centre. Her major areas of research are breast cancer genetics and survivorship issues in breast cancer, particularly prevention of chemotherapy-induced menopause and cognitive dysfunction. She leads several international and national studies in these areas.

Professor Bruce Robinson

Appointed Governor in 2007

Professor Robinson is Dean of the Faculty of Medicine, University of Sydney and Head of the Cancer Genetic Laboratory at the Kolling Institute. In 2003, he was awarded the Daiichi Prize by the Asia and Oceania Thyroid Association for this work on the pathogenesis of thyroid cancer. Professor Robinson 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.

Mr John Samaha

Appointed Governor in 2003

Mr Samaha has advised business and government on legal and strategic matters and risk management since 1984. He has represented clients in disputes, Court proceedings, mediations and regulatory investigations. He was at a leading firm, Mallesons Stephen Jaques, from 1988 to 2007 where he was a partner from 1995 to 2007.

Professor Mathew Vadas

Appointed Governor in 2007

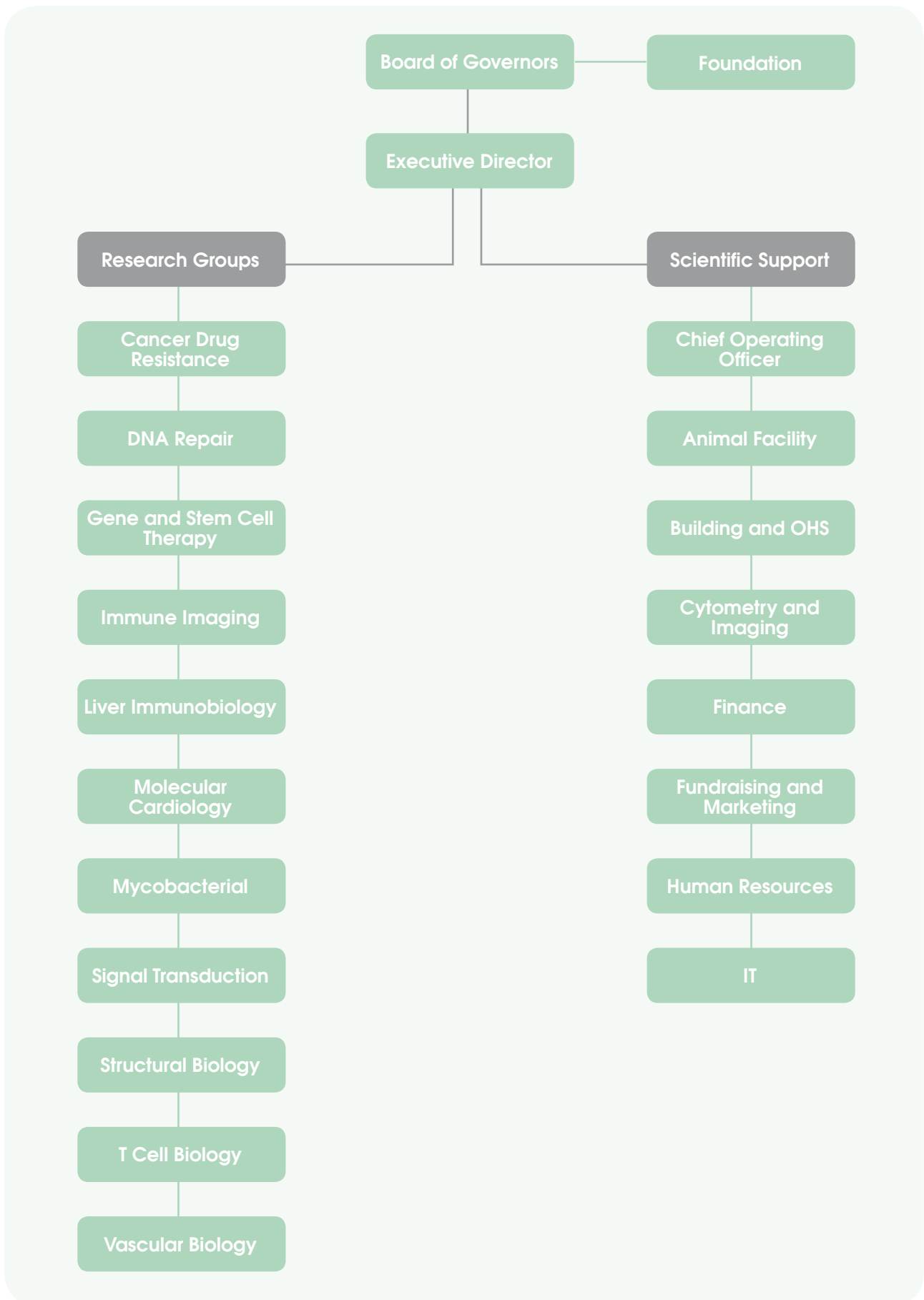
Professor Vadas trained in medicine at the University of Sydney and as a physician at the Royal Prince Alfred Hospital before completing a doctorate at the Walter and Eliza Hall Institute in Melbourne. After postdoctoral work at Harvard, he returned to Australia and built up a significant research enterprise in Adelaide. He was a chief initiator and Inaugural Director of the Hanson Centre for Cancer Research (now Hanson Institute). Professor Vadas has contributed strongly to the Australian biotechnology sector, being involved variously as founder, Chair of the Scientific Advisory Board and acting CEO of two ASX-listed biotechnology companies. He is chair of the Medical Research Advisory Board of the Australian Cancer Research Foundation and on the Board of governors of the SMILE Foundation.

In 2007, there were several changes to the Board of Governors:

- Professor Andrew Coats' term expired and he was replaced by Professor Bruce Robinson.
- Professor Michael Reid's term expired and he was replaced by Dr Teresa Anderson.
- Mr Alastair Davidson's term expired and he was replaced by Professor John Horvarth AO. Mr Davidson was then appointed to a vacant position and remains on the Board of Governors.
- Professor John Mathews' AM term expired and he was replaced by Associate Professor Kelly-Anne Phillips.
- Ms Sam Mostyn resigned and was replaced by Mr Geoff Dixon.
- Professor Mathew Vadas replaced Professor David Burke after taking up his position as Executive Director of the Centenary Institute.

Thank you to these outgoing Governors for their contribution to Centenary over the years of their appointments.

Organisational Chart



Centenary Institute Research Groups

The Centenary Institute's research program focuses on cancer, cardiovascular disease and infectious diseases. Research is carried out by 11 laboratories: Cancer Drug Resistance, DNA Repair, Gene and Stem Cell Therapy, Immune Imaging, Liver Immunobiology, Molecular Cardiology, Mycobacterial, Signal Transduction, Structural Biology, T Cell Biology, and Vascular Biology.

Cancer Drug Resistance – Dr John Allen

On average, 60% of all patients with cancer can currently be cured, usually using a combination of surgery, radiotherapy and chemotherapy. However, in cases where chemotherapy is the main treatment option, such as metastatic cancer or disseminated cancers of the blood, the long-term survival rate is much poorer. We work to improve the scientific basis of chemotherapy by understanding what causes drug resistance in cancer cells.



Tumours often respond poorly to the available drugs or respond at first but then become resistant. It isn't that the drugs are ineffective - we take inspiration from the fact that they sometimes work very well. However, if we understood the reasons for the difference between cancers that respond to chemotherapy and those which don't, then perhaps something could be done about it.

Our Group works to improve the scientific basis of chemotherapy by understanding why cancer cells become drug resistant. When new types of drug resistance are found, we work to evaluate their clinical significance, and to find ways of overcoming them or at least predicting them in advance. We focus on resistance to new and promising anti-cancer drugs that are being applied to treating common, recalcitrant tumours, including melanoma and multiple myeloma.

How will this research impact community health?

Research will lead to improved cancer treatment and better outcomes

for cancer patients. Cancer is now the leading cause of death in the developed world and this trend will continue as the population ages and other causes of death, such as heart disease, decline.

Cancer treatment is rapidly becoming the most prominent concern of our healthcare system, both in terms of the number of people affected and the expense. There is enormous opportunity to improve both the outcomes and the cost-benefit ratio of cancer treatment. It is gratifying that Centenary's results in this field of research are often directly relevant to the clinic and can be translated rapidly into clinical practice. Specific benefits include:

- Providing a scientific basis for optimising drug regimens and drug combinations and thus improving treatment outcomes.
- Predicting resistance or sensitivity to particular drugs in advance, so the best treatments can be tried first.
- Anticipating which cancers might benefit from new anti-cancer drugs.
- Providing a scientific basis for the development of better drugs and identifying targets for new drugs.

Highlights of 2007

In 2007, we found that a particular molecular marker can predict the response or non-response of multiple myeloma patients to a new drug, the proteasome inhibitor Velcade, which is revolutionising treatment of this intractable disease. There has been considerable interest in commercialisation of this development, from pharmaceutical and diagnostic service companies, meaning it should find a place in clinical application of

this drug. Moreover, the marker has given us a handle on why Velcade works so well for myeloma, which was previously unclear, and therefore paves the way for development of even better drugs.

Another new type of drug targets anti-apoptotic proteins and our group confirmed that the sensitivity of melanomas to such drugs depend strongly on the expression of anti-apoptotic protein MCL-1 and its antagonist NOXA. Drugs that respectively repress or induce these proteins are likely to be effective for melanoma in combination with the new the anti-apoptosis agent.

Major projects

Interactions of new anti-cancer drugs with multi-drug transporter proteins

Multi-drug transporter proteins remove toxins encountered in the diet or produced by normal metabolism, from cells, from tissues, organs and the body as a whole. Many anti-cancer drugs resemble such toxins, so the multi-drug transporter proteins interfere with their uptake into the body and into cancer cells. Our group is systematically investigating how these proteins affect the efficacy of promising new anti-cancer drugs.

Drug resistance in melanoma

Australia is the skin cancer capital of the world with the highest incidence of melanoma, one of the cancers most

resistant to chemotherapy. Left too long untreated, melanoma is invariably fatal.

We are interested in the reticence of melanoma cells to undergo apoptosis (an orderly form of suicide) when damaged by anti-cancer drugs. It is an open question how important this resistance is in relation to other forms of drug resistance that operate in melanoma cells.

Analysis of resistance to apoptosis is technically challenging as propagation of melanoma cells in vitro alter their properties. Hence, the focus is on genetically manipulated mouse models of human melanoma, where melanomas develop and can be treated in their natural sites of origin, in the presence of a normal immune system.

Drug resistance in multiple myeloma

Multiple myeloma is an incurable cancer of the blood plasma cells that secrete large quantities of antibodies to fight infection.

The production of antibodies is known to depend on the Unfolded Protein Response (UPR), a system that ensures correct folding and assembly of proteins and the disposal of incorrectly folded or damaged ones – a form of quality control that every complex manufacturing system requires, and cells are no exception.

We suspect that dependence on this system is what makes myelomas resistant to many drugs but, conversely,

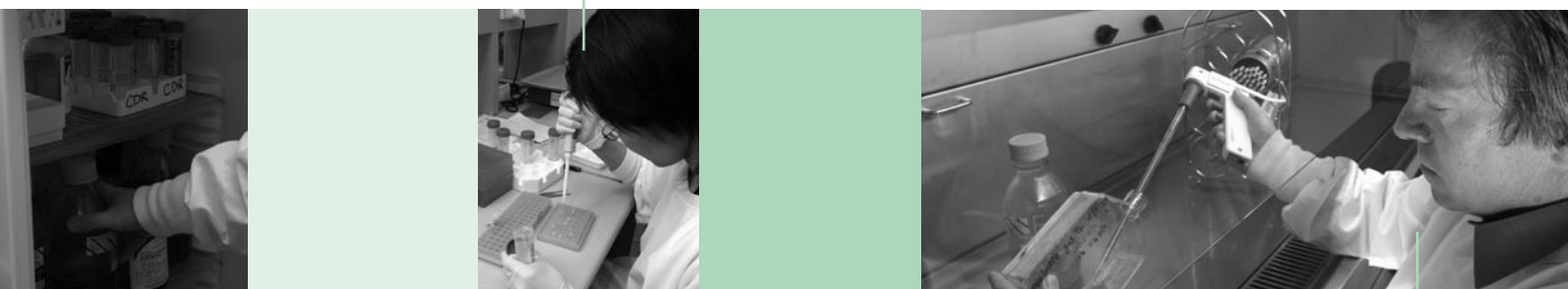
susceptible to a new class of new drugs, the proteasome inhibitors. Initial results indicate that a simple marker of the UPR can predict the sensitivity of myelomas to the proteasome inhibitor Velcade both in vitro and in myeloma patients.

How does the Centenary Institute facilitate this research?

The Centenary Institute provides an ideal setting for the work of the Cancer Drug Resistance Group. The facilities are some of the best in Australia, notably for flow cytometry and the animal house and, more recently, for high-throughput genomics analysis.

Even more important is interaction with talented colleagues and an intellectual environment that promotes an imaginative but rigorous approach to research, inspiring students to excel. The Centenary's precinct offers collaborations with clinicians at Royal Prince Alfred Hospital and with other academics at the University of Sydney that are so important to productive and relevant research.

PhD Scholar, Silvia Ling.



Dr John Allen at work in the Cancer Drug Resistance lab.

Gene and Stem Cell Therapy – Professor John Rasko

The safe introduction of healthy genes into patients with genetic disorders could effectively cure inherited diseases, including some cancers, haemophilia and HIV. We are looking to overcome the barriers to successful gene therapy, develop models to understand the biology of adult stem cells and discover disease mechanisms in diseases such as cancer and genetic disorders.



The Gene and Stem Cell Therapy Group undertakes research in five areas: gene therapy; stem cell biology; gene silencing; genetic disorders; and cancer biology. The focus of the work continues to be to improve gene delivery to the precursor cells of all blood cells, known as haemopoietic stem cells (HSCs) and other adult stem cells such as mesenchymal stem cells.

Understanding the mechanisms by which a normal cell becomes cancerous is a daunting task. By studying proteins and RNA molecules that become up or down-regulated in different cancers, we can study the basic biology of cancer and possible future therapeutic opportunities that will arise as the important molecules are dissected. Studying both the transcription factors and microRNAs will help to define the biochemical pathways and complex inter-molecular machinery involved in neoplasia.

How will this research impact community health?

The safe introduction of healthy genes into patients with genetic disorders could effectively cure inherited genetic disorders such as some cancers, haemophilia and immunodeficiency disorders as well as infectious diseases such as HIV. The focus on improving gene delivery to HSCs and mesenchymal stem cells may assist in both the delivery methods, as well as the targets of gene therapy.

With the development of new therapeutics for cancers including antibodies and small molecules, it has become increasingly important to identify novel targets. These technologies, previously thought to be impractical, have now been proven to provide effective new approaches for the treatment of cancers. For example, the small molecule known as Imatinib (Gleevec) which has revolutionised the treatment of chronic myeloid leukaemia. Our research is exploring new targets involved with the transcription factors BORIS and CTCF, and their interactors, as well as microRNAs and their targets. Using this information, novel therapeutics might be identified in the future along with useful biomarkers for different cancers.

Highlights of 2007

The major highlight of 2007 has been progress towards discovering the genetic cause of another amino acid transport disease, iminoglycinuria. This complex disease is caused by a combination of genes and the results are the culmination of three years of work by the Gene and Stem Cell Therapy laboratory, in collaboration with researchers at the Australian National University.

Other highlights include:

- The development of a luminescent tumour model in mice using the IVIS 100 system.
- Determining proteins that interact with BORIS and CTCF, part of the interactome of proteins regulating methylation in germ and somatic cells. These two proteins become dysregulated in cancer and this interactome are involved in the mechanisms of their action.

Major projects

Stem cells and gene delivery

One of the major problems limiting stem-cell based therapies is the absence of a clear understanding of the composition of the stem cell pool in humans. The right cell must be targeted for the right application or therapy.

HSCs have the capacity to divide to produce countless billions of progeny cells throughout a lifetime and it is these progeny that form the basis

of our immune system. We have established the SCID-repopulating cell (SRC) assay using NOD/SCID mice to evaluate different mobilisation regimens and to investigate the long-term re-populating ability of different HSC subsets, including HSCs purified by the Hoescht side population method. We have developed protocols for differentiating non-human primate mesenchymal progenitors into cells of adipogenic, chondrocytic and osteogenic origin. In both HSCs and mesenchymal progenitors we are working to optimise gene transfer using retroviral and adeno-associated vectors. We have achieved the successful introduction of gene modified cells into small animal models to study therapies for diseases of blood and muscle.

Mechanisms of genetic disease

For the last decade, the group has collaborated with the group of Victor Lobanenkov at the National Institutes of Health (Washington DC, US), examining the role of the tumour suppressor gene CTCF and its related cancer/testis gene BORIS. BORIS is a putative oncogene, which is normally only expressed in the testis, however it is over-expressed in many different types of tumours. During 2007, we have shown that CTCF and BORIS share a number of protein interactors, whilst also having unique binding proteins that may facilitate their opposing effects as a tumour suppressor gene and an oncogene.

Hartnup disorder is an inborn error of renal and gastrointestinal neutral aminoacid transport. In 2004, we described a breakthrough in this field by cloning and characterising the gene responsible for Hartnup disease, SLC6A19. This work was performed by our laboratory in collaboration with Drs Bröer and Cavanaugh in Canberra and its importance has been recognised by successful peer-reviewed grants from both the National Health and Medical Research Council and the Australian Research Council. During the last three years we have studied the genetic cause of other aminoacid transport diseases including iminoglycinuria, hyperglycinuria and dicarboxylic aminoaciduria.

An understanding of the way blood cell production is regulated in the body has immediate relevance to diseases like leukaemia and the way they are treated. MicroRNAs recently identified as part of endogenous gene silencing control have been shown to be intricately involved in the control of cell development and differentiation.

Several years ago, we established an early interest in this area with our report of a highly-specific method to detect microRNAs. We are studying the importance of these regulatory molecules in order to discover their previously hidden functions in normal blood cells and leukaemia in humans. Ultimately this project may lead to novel treatments involving gene therapy and bone marrow transplantation.

How does the Centenary Institute facilitate your research?

The installation of new equipment has been, and will continue to be, very important for our research. This includes the Affymetrix microarray platform, Applied Biosystems 7900HT TLDA low density arrays, re-commissioning of the microinjection facility, and the IVIS100 in vivo bioluminescence imager.

The IVIS100 has been successfully used for our new bioluminescent tumour model, which is being studied by Jessamy Tiffen, a PhD student in the laboratory. It allows tumours in mice to be followed over time, and the effect of over or under-expression of proteins to be assessed on tumour growth and metastasis. The 7900HT will be very important over the coming year for the analysis of microRNAs, allowing the analysis of over 350 microRNAs in a single experiment.

Dr Jeff Holst, Associate Faculty,
Gene and Stem Cell Therapy.



Immune Imaging – Professor Wolfgang Weninger

Cancer and infectious diseases are the leading causes of death in the world. Our novel imaging approach provides a new angle to study basic interactions of the immune system with microbes and cancer cells. Further understanding of these interactions may allow us to develop new targeted therapies for cancer treatment and improve current vaccines or develop new vaccines.

The Immune Imaging Group focuses on the visualisation of white blood cell (leukocyte) migration and interactions in real time within living tissues. Leukocytes are responsible for the recognition and destruction of invading microbes, such as viruses, bacteria and parasites, as well as tumour cells. Therefore, it is important to understand the cellular and molecular mechanisms that regulate their trafficking through the body and their communication with host cells and pathogens.

The principle approach the group uses is a newly-developed imaging technique called multi-photon microscopy. The cutting-edge technology allows for visualisation of fluorescently-tagged cells and molecules within the context of living tissues. This enables studying the dynamics of cell movements at a level of resolution that has not been reached before. Using this approach, the laboratory is investigating fundamental questions related to immune responses against infectious agents and tumours. It is hoped that a better understanding of these processes will, in the future, lead to improved vaccines and immunotherapeutic strategies against disease.

We would like to unravel immunoregulatory mechanisms in infectious diseases and cancer by directly looking inside tissues to see how cells interact with their environment. Using multi-photon microscopy, we will be

able to track cells in living tissues in real time. This will enable us to study how microbes and tumour cells are detected by leukocytes within living tissues. Together, these studies will shed completely new light on disease processes. This information may then be used to develop better vaccines, for example against influenza viruses, or immuno-therapies against cancer.

What impact will your research have on community health?

Cancer and infectious diseases are the leading causes of death in the industrialised world and in developing countries. We still have a very incomplete understanding of the host response against these diseases.

Our novel imaging approach will provide a new angle for studying basic questions related to the interactions of the immune system with microbes and cancer cells. This may lead to a new understanding of the mechanisms mediating the recognition and destruction of infected or tumour cells. This may allow us to construct new targeted therapies against specific molecules involved in cancer growth. We may also be able to improve existing vaccines against viruses or develop new vaccines against microorganisms that have so far escaped vaccination approaches. Together, this will improve the quality of life for all Australians.



Highlights of 2007

A cutting-edge multi-photon microscopy imaging suite was established at the Centenary Institute. The opening of the facility was featured in several news reports, including national television news.

In collaboration with Dr Steve Reiner (University of Pennsylvania), we have discovered that the first division during T cell division occurs in an asymmetric manner (Chang et al. *Science*. 2007; 315:1687). Until now, it has remained a mystery how naïve T cells decide to become effector or memory cells during a primary immune response. We have found that this decision is already made during the first cell division after antigen encounter. Our study showed that the first two daughter T cells displayed phenotypic and functional indicators of being differentially fated towards effector and memory T cell lineages. This suggests a mechanism in which a single lymphocyte can apportion diverse cell fates necessary for adaptive immunity.

This paper is currently the all-time top-ranked article in the Immunology category of the Faculty of 1000 Biology. In addition, it was selected by *Science* as one of the 10 scientific breakthroughs of the year in 2007.

Major projects

Interplay of innate and adaptive immune cells during influenza virus infection

Influenza is an acute febrile respiratory illness caused by influenza virus infection and may trigger potentially life-threatening complications especially in the young and elderly. Immunity against influenza virus involves integration of the innate and adaptive immune system. However, we currently have a poor understanding as to how the interactions between the cellular components of the anti-influenza immune response are orchestrated in space and time.

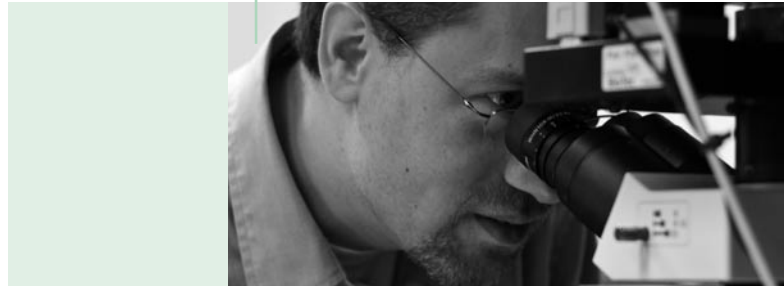
We will make use of intravital multi-photon microscopy to study how innate immune cell subsets, i.e. myeloid and plasmacytoid dendritic cells, induce the activation of antigen specific T cells in the lung draining lymph nodes during infection. In-depth insight into this process is not only important for increasing our knowledge of regulatory pathways of anti-viral immunity, but may, in the long-term, lead to the development of improved vaccine strategies against this important disease. This project is in collaboration with Dr Andrew Caton (Wistar Institute, Philadelphia, US) and Dr Stephen Turner (University of Melbourne).

Mechanisms of T cell migration and interactions in tumours

Tumour cell-host cell interactions are critical determinants for the progression of neoplasms. Of particular importance are cytotoxic T cells, as they may recognise and destroy tumour cells. How T cells navigate within the tumour microenvironment, how they interact with neoplastic cells, as well as their overall contribution to the tumour micromilieu is not well understood.

The project's long-term goal is to define the cellular and molecular cues responsible for the guidance of tumour infiltrating T cells (TIL) through the tumour stroma and mediation of their communication with neoplastic cells. We hypothesise that the quality of TIL migration and interactions with target cells determines whether a tumour is destroyed or grows unimpeded. To test our hypothesis, we will employ multi-photon microscopy in our recently-developed subcutaneous tumour model.

Professor Wolfgang Weninger using the new multi-photon microscope.



Our experiments will provide mechanistic insights into the events leading to tumour cell destruction or tumour immune evasion. Therefore, these studies have important implications for the optimisation of immuno-therapeutic strategies that aim to target cancer. This project is in collaboration with Dr Steve Reiner (University of Pennsylvania, US) and Dr Sarah Russell (Peter MacCallum Cancer Centre, Melbourne).

How does the Centenary Institute facilitate the research?

The new cutting-edge multi-photon microscopy imaging suite features a multi-photon LaVision Biotec TriM Scope with a femtosecond pulsed Ti:Sapphire Spectraphysics MaiTai laser and an APE synchronously pumped Optical Parametric Oscillator system. This system will allow for deep tissue imaging of fluorescently-tagged cells and structures, and enable the real-time tracking of fast moving objects, for example cells in the blood stream.

Liver Immunobiology – Professor Geoff McCaughan

Chronic liver damage affects up to 20 per cent of Australians and liver cancer, often caused by chronic liver damage, is one of the fastest growing diseases in our community. Chronic liver damage has many causes including viral infections (hepatitis B and C), toxins, genetic, metabolic and autoimmune diseases.

The distinct research groups within the Liver Immunobiology program come together through a common link to the liver and models of liver disease including the study of human tissue and blood samples.

Animal models used primarily by one group are often transferable to other experiments. Also, some groups have particular expertise in special techniques such as gene arrays and flow cytometry and advise all groups to enhance experimentation and the understanding of liver disease processes. Furthermore, persistent liver injury is a pre-cancerous state so all groups have an interest in whether particular mechanisms have applicability to liver cancer studies.

The distinct research groups are:

- Liver Immunology lead by Dr Patrick Bertolino
- Molecular Hepatology lead by Associate Professor Mark Gorrell
- Liver Cell Biology lead by Dr Nick Shackel and Dr Fiona Warner

In addition to these project areas, we have a major collaboration with Dr Devanshi Seth and Professor Paul Haber at the Drug Health Services RPA, Sydney South West Area Health Service and University of Sydney in identifying molecular pathogenesis of alcohol induced liver injury.

Alcoholic liver disease (ALD) contributes up to 50% to the total liver disease burden in Australia. We have identified two lead molecular pathways as potential diagnostic and therapeutic targets via our hepatic transcriptome profiling studies. These studies were able to separate out early from advanced injury in ALD. One of the key molecules was Osteopontin (Opn). We have cloned several Opn isoforms and have shown that they are involved in cell growth, migration and tumor development. Current studies are investigating mechanisms of Opn action by using Opn knockouts and Opn si RNA.

One of the other key pathways in ALD seems to be the plasmin and fibrinolysis pathway. We identified several pro and anti-fibrinolytic molecules in human ALD and in experimental in vivo models of ALD. We have shown that two molecules, pro-fibrinolytic annexin A2 and anti-fibrinolytic plasminogen activator inhibitor-1 play a role in regulating fibrinolysis in alcoholic liver injury. We are currently using inhibition by antibodies specific to these molecules (in vitro and in vivo) to study the therapeutic advantage of these targets.

This remains a key collaboration for our program and will be enhanced by participation in an international consortium to establish a genome wide association study for ALD. This is to be the first study of its kind in ALD and has attracted alcohol researchers from USA, UK, Germany, France, Switzerland and Australia.



How does the Centenary Institute facilitate your research?

The facilities, support and expertise located within Centenary Institute allows our program to continue to be productive and maintain a high quality of research output through provision of excellent research facilities, including modern laboratories and state-of-the-art equipment. Of particular note is the clean animal house, irradiator and in-house flow cytometry facility and the newly acquired Genomic facility. Our Program played an important role in obtaining a research grant for this facility and we are playing a major role in setting up and utilising this facility.

Liver Immunology – Dr Patrick Bertolino

The research of the Liver Immunology Group aims to understand the parameters that determine the balance between tolerance and immunity in the liver.

This question is critical in medical research: understanding how to improve hepatic immunity is required to clear some liver-specific viral infections such as those induced by the hepatitis B and C viruses. These viruses are particularly known to persist in the host and lead to a chronic disease. On the other hand favouring tolerance in the liver would improve the outcome of liver and solid organ transplantation: in contrast to other solid organs, liver transplants are spontaneously accepted through unknown mechanisms. Understanding how this tolerance is established would help us to develop new strategies to prevent rejection of other solid organs.

To understand parameters of intrahepatic immunity, we have developed several transgenic mouse models of acute hepatitis in which T cells induce a transient and self-limited damage. Using these well-characterised models we are currently investigating how the liver induces tolerance. With this knowledge, we aim to manipulate these mechanisms to induce a persistent immune response and generate new models of chronic liver disease.

Our results have demonstrated that due to its unique architecture and slow blood flow, the liver can retain and activate naïve CD8+ T cells, therefore acting as a site of primary activation. This finding contradicts the general accepted view that primary T cell responses can only be initiated in lymph nodes (LN).

Our results suggest that the initial activation step programs T cells activated within the liver and LN towards different functions and differentiation pathways: unlike T cells activated in LN, most liver-activated T cells become poor effectors and die rapidly, leading to tolerance. It is the first demonstration that a non-lymphoid organ can be the site of primary activation, a seminal finding with important implications for liver transplantation and hepatitis C virus (HCV) research.



What impact will your research have on community health?

If our model is correct and our strategies in mice successful, we will use similar strategies in humans.

In transplantation, this would mean that we will be able to improve significantly the outcome of liver transplantation. This would provide an extremely important advantage to current therapies that use immuno-suppressive drugs which have side effects and inhibit the whole immune system. It would also be possible to use the ability of the liver to induce tolerance to other solid organ allografts.

In HCV infections, it would be possible to boost the immune system in patients suffering from a chronic disease so that they clear the virus and restore their liver function. In addition, our work could provide new strategies during vaccination of uninfected patients against HCV.

Highlights of 2007

- The Liver Immunology Group had a very productive year in terms of funding, receiving a NHMRC project grant and an International Roche Transplantation Foundation Grant, reflecting the recognition of our work. Dr Bertolino was also awarded a prestigious NHMRC Senior Research Fellowship starting in 2008.
- We have demonstrated that the pro-apoptotic molecule Bim is a critical regulator of T cell death following intrahepatic activation.

- We have shown that T cells activated in the liver are rapidly cleared by hepatocytes. This mechanism might play a very important role in purging the repertoire of antigen-specific T cells during HCV as well as transplantation.

Major projects

Our studies are currently focused on three main aspects:

- Altering the fate of T cells activated by hepatocytes by using mice deficient for genes important for regulating cell death or effector function.
- Investigating the mechanisms responsible for the clearance of recently activated T cells by hepatocytes.
- Developing solid organ transplantation in mice to understand the mechanisms of spontaneous liver graft acceptance and use this knowledge to improve the acceptance of other solid organ transplants.

Molecular Hepatology – Associate Professor Mark Gorrell



Liver fibrosis often leads to severe scarring (cirrhosis) and cancer of the liver. We seek to determine the molecular basis of liver fibrosis and inflammation in order to improve therapy and prevention of chronic liver injury and thus of cirrhosis and cancer. In Australia about 20,000 new hepatitis C virus infections are being diagnosed each year. This infection is the major cause of continuously increasing rates of chronic liver disease and liver cancer. Fatty liver associated with obesity is also increasingly causing chronic liver injury.

We have discovered that in the injured liver genes DDR1, FAP, DPIP, DP8 and DP9 exhibit heightened expression by liver cells and are involved in cell movement and proliferation, and in some glucose homeostasis and tumour growth. DPIP is also interesting because it is the target of a new diabetes therapy. Our discoveries on DPIP and related genes helped the drug development process for this new type 2 diabetes therapy.

Collaborative work with the Pharmacy Faculty at the University of Sydney on the liver/brain enzyme Kynurenine Aminotransferase 1 (KAT-1) is directed towards discovering a chemical

that will control KAT-1 in the brain of Alzheimer's sufferers and thereby alleviate their illness.

Highlights of 2007

Mouse liver scarring related to DPIP or FAP is associated with the density of B lymphocytes in the liver. DDR1 has functions in liver cell behaviour; DP8 and DP9 are in lymphocytes and hepatocytes. DP8 inactivates some molecules called chemokines that are important in cell movement.

Major projects/research focus

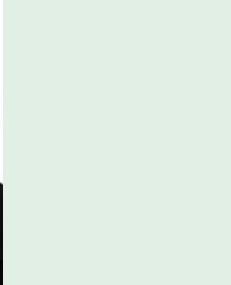
The DPIP family of enzymes consists of dipeptidyl peptidase IV (DPIP), DP8, DP9 and fibroblast activation protein (FAP). We previously found evidence of roles in liver scarring:

- FAP levels increase in human liver in proportion to the extent of scarring.
- FAP causes cells to become less adherent and less motile, these are processes important in healing.
- FAP deficient mice (gene knockout) and DPIP deficient mice exhibit less liver scarring and inflammation than normal mice.

We cloned DP8 and DP9 in the late 1990s. The value of these genes primarily relates to using DP8 and DP9 to reduce risks of drug side effects by ensuring that DPIP inhibitory drugs are DPIP selective. The major use for DPIP inhibitors such as sitagliptin (Januvia) is as a new therapy for type 2 diabetes and we work with pharmaceutical companies to evaluate DPIP inhibitor selectivity. We discovered that DP8 and DPIP inactivate some chemokines. This work was a collaboration with Professor Chris Overall of the University of British Columbia.

DDR1 is a cell surface protein activated by collagen, which is the major component of the liver scarring resulting from long-term liver injury. We have found that hepatocytes express more DDR1 when injured and that differing forms are made in scarred versus non-diseased human liver. We found that DDR1 can make cells of a liver cell line more adherent and slower.

Liver Cell Biology – Dr Nick Shackel and Dr Fiona Warner



The liver is made up of a number of cell types: hepatocytes, stellate cells, cholangiocytes, immune cells and liver progenitor/stem cells. Each of these cell types has distinct roles in normal liver homeostasis and liver disease states. The research projects within our group aim to understand the development of liver disease, particularly the development of inflammation and scar tissue within the liver and the eventual development of liver cancer with particular emphasis on the role of the main cell type, the hepatocyte.

What impact will your research have on community health?

We believe our research will help in understanding the pathogenesis of liver injury, enabling us to develop therapeutic strategies to stop the progression of liver injury and the development of liver cancer (the fourth most common human malignancy).

The therapeutic options in liver disease are limited and frequently not directed to individuals whom it is likely to benefit and we hope our research will help develop novel diagnostic and prognostic tests to enable personalised and tailored therapy in liver disease.

Fibrosis has been previously been considered an irreversible process, however the modern view is that it is a dynamic process that may be resolved in some cases. Our research into the role of the hepatocyte and its role in fibrogenesis will allow us to identify and design more effective forms of treatment for fibrotic diseases.

Highlights of 2007

- Dr Shackel was awarded the Viertel Clinical Investigatorship,
- Dr Warner was awarded an R & D grant scheme from The University of Sydney to study the role of biliary epithelial to mesenchymal transition in liver fibrosis
- Students Melanie Eckersley-Maslin was awarded a University Medal for her honours research project on stem cells and their role in liver injury and Min Zhi Xi was awarded the Dean Prize for Excellence for her research of matrix metalloproteases expression in human liver disease
- Sarah Richardson was awarded an APA PhD Scholarship to study the role of EMMPRIN in liver disease
- Our group also presented our work at the Asia Pacific Association for the Study of Liver Disease in Kyoto Japan, the American Society for the Study of Liver Disease Annual Meeting in Boston USA, and Australian Gastroenterology Week in Perth.

Major projects

Our studies are currently focused on four main aspects of progressive liver disease.

Analysis of liver disease using a functional genomics approach

By utilising functional genomics technologies we aim to understand the development of liver injury with the eventual aim of developing novel diagnostic and prognostic tests. This technology enables us to examine the

whole human genome of over 25,000 genes in a single experiment and we have pioneered the use of both gene arrays and the use of CD antibody arrays in understanding liver disease development.

The role of molecule EMMPRIN and the hepatocyte in extracellular matrix interactions in liver fibrogenesis

We are working to understand the role of the main cell within the liver, the hepatocyte, and its role in the formation of scar tissue and eventual cirrhosis following injury. This injury response is common to many types of liver disease and eventually leads to liver cancer. Our research has focused in particular on a molecule EMMPRIN that we discovered using functional genomics technologies to be instrumental in the formation of liver scar tissue, cirrhosis and liver cancer.

Investigation of novel hormonal/ signalling pathways (renin-angiotensin system and Hedgehog Pathway) and their role in liver injury and cancer

Ultimately we aim to develop therapeutic strategies to stop the progression of liver injury and the development of liver cancer. We are currently studying whether modulation of the renin-angiotensin system and hedgehog signalling are potential avenues for retarding or modulating liver fibrosis and its progression to hepatocellular carcinoma.

Stem cell contribution to liver injury and cancer

We are also looking at the function of stem cells originating from the bone marrow in response to liver injury. In particular, investigating if stem cells have both a role in which they contribute to liver injury as well as having a beneficial task. Our research looks at the possible involvement of bone marrow derived stem cells in the development of liver cancer.

Molecular Cardiology – Associate Professor Christopher Semsarian

Heart disease remains one of Australia's biggest killers, with many of the genetic causes of heart disease still unknown. Understanding the basic biology of heart muscle function and therefore defining novel ways to treat heart muscle disorders clearly has wider implications for a variety of cardiovascular disorders, including cardiomyopathies, heart rhythm disorders and coronary artery disease. The potential therapeutic benefits are limitless.

Integration of molecular biology, genetic technologies and clinical medicine will ultimately reduce human heart diseases and prolong life. We hope through our research to realise these goals in the coming years.

What impact will your research have on community health?

Over the next five to 10 years, our research will likely lead to improved diagnosis of patients with genetic heart disease. Since diagnoses will be based on detection of abnormal genes, this can be done earlier in life, providing a greater therapeutic window for initiation of treatment and prevention strategies.

Our work will also be used to identify those people in our community at a higher risk of developing complications of heart disease, such as heart failure and sudden death, thereby enabling more targeted, personalised therapy. The studies being performed will also facilitate our understanding of the molecular steps which account for how disease develops (pathogenesis), thereby potentially identifying new targets for pharmacological therapy.

Highlights of 2007

In 2007, we completed the largest ever study in prevention of sudden death in young people with hypertrophic cardiomyopathy, which was published

in the prestigious international journal, *Journal of the American Medical Association* and identified key gene defects relating to calcium regulation in families with inherited cardiomyopathies and sudden death.

The establishment of the first ever Indigenous Inherited Heart Disease Clinic in Northern NSW and the clinical and genetic evaluation of hundreds of Australian families with genetic heart diseases, including sudden death, were additional highlights.

Dr Alessandra Doolan became the first PhD graduate from our Group, while we also developed new insights into the causes of sudden cardiac death in young patients with type 1 diabetes.

Major projects

The Agnes Ginges Centre for Molecular Cardiology is focused on the translation of basic laboratory research to improvements in the diagnosis and treatment of patients with heart disease. While there are several lines of integrated research within the program, the unifying focus is the study of cardiovascular disorders which are caused by underlying genetic abnormalities.

There are now over 40 cardiovascular diseases which have been identified to be directly caused by primary genetic abnormalities. Despite the escalation in our knowledge of the genetic causes of cardiac disease, little is known about the molecular steps which determine how a defect in the DNA leads to the clinical disease we see in patients.

Furthermore, studies have shown marked variability in the degree of clinical expression of the abnormal gene. There are many examples of affected individuals within the one family, who are carrying the same gene (DNA) defect, having vastly different clinical features and outcomes. This suggests modifying factors, both environmental (e.g. exercise, diet) and secondary genetic influences, play an important role in modifying the clinical phenotype in genetic cardiac disorders.

The aims of the research program are to identify new gene abnormalities in patients with heart disease, to understand the molecular basis of how these gene mutations lead



PhD Scholar, Christine Chiu,
pipetting samples for testing.



Honours Student,
Ju-En Tan.

to disease and to investigate how these pathogenic mechanisms are influenced by modifying factors. These aims are being addressed in an integrated research program utilising three concurrent sets of studies; in isolated cells, in genetically-modified mice, and in humans with inherited cardiovascular disorders attending the Genetic Heart Disease Clinic at Royal Prince Alfred Hospital.

A number of diseases are being studied, ranging from structural heart disorders such as cardiomyopathies to primary arrhythmogenic diseases such as long QT syndrome. A specific area of study is in sudden cardiac death, particularly in the young. These studies include novel gene discovery, genetic diagnosis, understanding disease pathogenesis and initiation of preventative strategies to reduce sudden death in our community.

An example of one of the key diseases which is a focus of the laboratory is hypertrophic cardiomyopathy (HCM) which is the most common structural cause of sudden death in the young, including competitive athletes.

HCM is characterised by marked thickening of the heart muscle and occurs in approximately one in 500 people, making it the most common genetic heart disorder known. Our research program has seen and collected clinical information and DNA in over 400 HCM families to enable genetic studies to be performed. To complement the studies in humans,

our laboratory has developed two unique transgenic models of HCM, as well as cell culture models to evaluate the cellular effects of specific gene mutations.

How does the Centenary Institute facilitate your research?

Centenary has helped the Molecular Cardiology Group in every way – providing intellectual support, equipment access and a framework for applying for funding.

Mycobacterial – Professor Warwick Britton

Tuberculosis (TB) infects one third of the world's population, causing over two million deaths per year. The Mycobacterial Group aims to contribute to the control of tuberculosis through the development of more effective vaccines and the identification of possible targets for new drugs against *M. tuberculosis* infection.

In addition, as infection with *M. tuberculosis* has such profound effects on the host, we hope to discover new information about how the immune system responds to infection in general. This will be relevant to the control of many different infections of humans.

What impact will your research have on community health?

Eight million new cases of tuberculosis are diagnosed each year and these are often young adults in low or medium resource countries. Given this, tuberculosis has a major impact on socio-economic costs in these countries. With the emergence of new drug resistant strains and the increased spread of HIV, *M. tuberculosis* infection is spreading and major new control measures are needed. Therefore development of more effective vaccines will be of major benefit to human health.

Highlights of 2007

The Mycobacterial Group had many successes throughout 2007, including:

- The demonstration that rBCG expressing the cytokine GM-CSF stimulates increased activation of dendritic cells leading to increased BCG-specific T cell responses. These resulted in increased protection against dissemination of *M. tuberculosis* infection from the lung and we are now testing the effects of rBCG:GM-CSF when given intranasally into the lung.
- The finding that the combination of the gene for Flt3 ligand, a protein which expands dendritic cells, with a mycobacterial antigen in a DNA

vaccine increased the protective effects of the DNA vaccine against tuberculosis.

- We defined the protective effects of a special group of T cells secreting the cytokine, IL-17, which were induced by BCG immunisation of mice lacking the cytokine IL-12 (Wozniak T, unpublished).
- Demonstration that the majority of TB patients and BCG vaccines have T cell responses to the *M. tuberculosis* secreted lipoprotein, Mpt83 (Murmad S, unpublished). In related studies Dr West has shown that this protein is a component of a new vaccine which is partially protective against experimental tuberculosis.
- We published our findings on the human genes which are switched on by *M. tuberculosis* when it infects macrophages.
- Professor Britton's long standing collaboration with Professor Marks on the immunology of asthma resulted in two publications. The first showed the pattern of development of T cell cytokine responses to house dust mite, the major allergen associated with asthma in Australia. The second has defined the early predictors for the development of eczema and asthma in Australian children.
- Professor Britton edited a new book on the Immunology and Cell Biology of Tuberculosis with Professor She Kaufmann (Berlin), published in early 2008. The book was commissioned on the 125th anniversary of the discovery of the bacterium which causes tuberculosis by Robert Koch in 1882.
- Erin Shanahan was awarded a University Medal.

Major projects

Our main focus is to understand how the host responds to infection with *Mycobacterium tuberculosis*, the most successful chronic bacterial infection of humans and how to make more effective vaccines against this infection.

We are also exploring how the bacterium responds to infection in the host by changing the genes it



expresses after it invades host cells, and the function of selected mycobacterial proteins.

In addition, we are studying the function of proteins from *Mycobacterium leprae*, the cause of leprosy in humans, and which stimulate immune responses and could be used to aid the diagnosis of leprosy infection.

How does the Centenary Institute facilitate your research?

The Centenary Institute provides the mycobacterial researchers the only PC3 laboratory which permits work with experimental tuberculosis infection in Australia, essential for our work.

Along with the PC3, Centenary provides a number of other world-class facilities that are essential for our ongoing studies, in particular; excellent animal house facilities to permit breeding of gene deficient mice for TB studies, flow cytometry facilities for cell sorting and the analysis of the inflammatory response to TB infection. The new micro-array facility will allow greater screen of changes in gene expression associated with TB infection.

Most importantly, the Centenary Institute provides a work environment that actively encourages collaborations with researchers in other laboratories at the Centenary, the University, and other research institutions locally, nationally and internationally, all of which are invaluable to our work.

Host Response to Tuberculosis – Dr Bernadette Saunders



TB disease causes damaging lung pathology and new therapies to treat the infection and moderate inflammation are urgently required. We are investigating how protective immunity to tuberculosis is generated and maintained and genetic factors that influence this response.

We hope to uncover new genes that regulate resistance or susceptibility to TB infection and determine how these genes regulate these processes. We are also working to determine how granuloma formation is established and maintained during TB infection and if by over expressing defined cytokines and macrophage effector molecules, we can increase resistance to TB infection.

What impact will your research have community health?

The ultimate aim of our research is to eliminate TB as a human disease. The current vaccine does not provide sufficient long-term protection against TB and antibiotic therapy to treat TB infection requires six to nine months of constant treatment. The focus of our research is to understand the immunological and inflammatory response generated to TB infection and the genes that control this infection. Understanding the factors that control the immune response to TB infection will hopefully lead to new therapies to modulate treatment against TB infection, or to determine who is likely to develop TB disease and would benefit from early therapy before clinical disease is established.

Highlights of 2007

The Mycobacterial Group was awarded a Wellcome Trust grant to identify new genes involved in immunity to TB infection.

We also demonstrated that IDO has dual functions in response to TB infection and found in vitro IDO suppresses T cell activity, while enhancing control of TB infection in infected human macrophages. Interestingly however, mechanisms in vivo compensated for the absence of IDO without altering the resistance of mice deficient in IDO to *M. tuberculosis* infection.

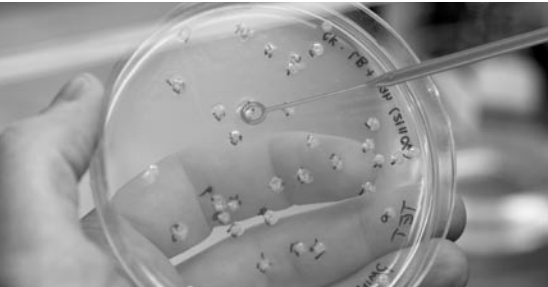
Major projects

Our group is investigating the cellular and genetic factors that regulate protective immunity to TB infection.

At the cellular level we are examining how macrophages, which are the host cell for TB infection, kill the pathogen. In particular we have examined the role the macrophage effector molecules IDO and LRG-47 in control of TB infection. An honours student in the laboratory, Gaya Nagalingam, demonstrated that TB infected macrophages produce large amounts of LRG-47. Studies are underway to determine if overexpression of this molecule will enhance protective immunity to TB infection. It is hoped that this research may lead to the discovery of alternative therapies to treat TB infection.

At a genetic level, we are determining the genetic influences that control susceptibility to TB. Our previous studies have shown that a polymorphism in the P2X7 gene is associated with increased susceptibility to extrapulmonary TB. In 2007, with collaborators at ANU in Canberra, Oxford and France, we were awarded a large five year grant from the Wellcome Trust (UK) to identify genes that influence resistance and susceptibility to TB. It is hoped that this exciting project will uncover new factors that regulate resistance and susceptibility to TB.

Vaccine Development and Pathogenesis – Dr Nick West



Ultimately we hope to prevent the spread of tuberculosis through vaccination and to improve the outcome for those already infected. These two goals may seem unrelated but in fact the first will not be achieved without the second. This is why we must first understand the microbe and the way in which it causes disease.

Research within the group is aimed at highlighting the genetic repertoire possessed by the bacterium, which is essential to survive within the host and cause disease. With this information we will be better placed to make informed decisions regarding drug development. Furthermore, knowing what pathways are essential to the bacterium may also provide new vaccine candidates.

What impact will your research have on community health?

Mycobacterium tuberculosis currently infects one third of the world's population and a large number of these cases result from "reactivation" of the bacterium from a "dormant" state, usually when the individual's immune system, for some reason, is suppressed. It is persistence of the bacterium within the host that is the biggest hurdle for public health as it is this relatively small number of reactivated individuals that are keeping the world infected. In order to curb the number of people becoming infected we need to develop a more effective vaccine to protect uninfected individuals but the world also needs new, effective and affordable drugs to kill the bacteria in its dormant phase before it can reactivate.

A knowledge gap exists in our understanding of the set of genes required by the bacterium to not only infect an individual but also to persist, asymptotically, for decades. Our research is aiming to close this gap and provide the information required to develop new vaccines and new effective drugs.

Highlights of 2007

The highlight for 2007 was the commencement of a grant awarded to Dr West as a NHMRC New Investigator to begin work examining how *M. tuberculosis* causes disease.

Major projects

Our focus is to investigate processes of pathogenesis with the outcome being improved vaccines and treatments for tuberculosis. We are studying this disease from a bacterial prospective in order to improve global public health. This is being achieved in a variety of ways, including, improving our understanding of *M. tuberculosis* microbiology, the discovery and testing of new vaccines and identifying improved vaccine vectors. Research staff and students are actively pursuing programs in each of these broad topic areas.

DNA Repair – Dr Chris Jolly

Understanding of DNA repair pathways is essential to a complete understanding of how cancer arises and may in the future enable us to prevent early stage cancer from progressing.

Both the growth of new tissues and the replacement of old or damaged cells in existing tissues requires controlled cell division and proliferation. During cell division, DNA inside the nucleus has to be replicated perfectly. This is because nuclear DNA carries the genetic information essential for cell function. However, genes in the DNA are continuously damaged by irradiation, chemicals and even by replication mistakes.

The DNA Repair Group aims to understand how the many pathways available to cells to carry out DNA repair interact and how they coordinate to deal with different types of gene damage.

We also hope to identify the steps in antibody hypermutation (a process of DNA damage unique to white blood "B" cells) that are most prone to causing bystander damage of cancer-causing genes.

How will your research impact community health?

Complete understanding of DNA repair pathways is critical to a full understanding of how cancer arises, because damage to DNA and inadequate repair of that damage underlies all cancers. In the future it may be possible to prevent early stage cancers from progressing by identifying the DNA repair defect that has initiated the cancer in the first place.

Highlights of 2007

In 2007, the DNA Repair laboratory achieved three major outcomes:

- We found that an enzyme (DNA-dependent protein kinase) in fact plays an inhibitory role in antibody hypermutation. The

finding implies that antibody hypermutation involves double strand breaks, which are potent inducers of cancer-causing gene rearrangements.

- DNA is made up of four bases: G, C, A and T. We definitively tested and disproved a model (proposed by others in 2005) which explained how mutation of A/T base pairs might occur in hypermutating antibody genes. This work is being published in 2008.
- We discovered that proteins which allow chromosomes to line-up correctly beside each other during cell division ("cohesins") play a critical role in ensuring the fidelity of DNA repair, presumably by ensuring that repair is damaged using the exactly correct DNA sequence as a template.

Major projects

The DNA Repair Group use the mutation of antibody genes in B cells (white blood cells that secrete antibodies) as a physiologically-relevant model of DNA damage. Antibody gene mutation is a natural process of extremely accelerated gene mutation (i.e. hypermutation) that occurs in lymph nodes during immune responses in order to increase the diversity of antibodies able to neutralise an infectious organism. Antibody hypermutation is essential for effective immune responses, but occasionally the antibody hypermutation machinery targets the wrong genes (referred to as "bystander" genes) and causes cancer. In fact, mutation of bystander genes by the antibody hypermutation machinery is implicated in the majority of adult B cell lymphomas and leukaemias.



How does the Centenary Institute facilitate your research?

The Centenary Institute has provided a combination of facilities and personnel absolutely essential to our research - a first-class animal facility to breed transgenic mouse lines in pathogen-free conditions, a first-class flow cytometry facility to isolate rare hypermutating B cells from immunised mice, and quality laboratories and tissue-culture facilities to propagate cells and manipulate and analyse DNA. The seminar program at the Institute provides a forum which promotes collaboration and lateral thinking which has led to unique insights.

Structural Biology – Dr Mika Jormakka

By understanding the structural biology of membrane proteins, we hope to be able to tailor drugs and reduce side effects. We are focused on structural studies of membrane proteins involved in cellular respiration, cell signalling and transport. Of particular interest is transporters involved in cellular drug extrusion, the proteins that ‘pump’ drugs out from the cell and therefore reduce the efficiency of, for example, cancer chemotherapy and antibiotics.

We hope to increase our understanding of these processes by obtaining structural information of these multi-drug transporters, to pave the way for therapeutic design.

In addition, we hope to provide comprehensive structural information of the quinone reduction/oxidation cycle in cellular respiration for continued development of anti-microbial inhibitors and pesticides.

What impact will your research have on community health?

The global effort in structural biology of membrane proteins will provide information in regards to the mechanism of medically important proteins.

The long-term aim is to provide high-resolution structures that will facilitate structure-based drug discovery, enabling us to move away from a trial and error process of drug discovery and design to a scenario where from the structure we can design a ‘perfect’ drug. This would potentially give drugs more specific targets while having fewer side-effects. In addition, structure-based drug design would lead to far cheaper drugs, and shorten the time from research to patient.

Highlights of 2007

The Structural Biology Group solved the 3D structure of a large membrane protein complex involved in cellular

respiration, providing molecular insight to generation of a proton gradient across bacterial and mitochondrial membranes, which is subsequently used to generate cellular energy currency in the form of ATP.

Additionally, we obtained structural information of quinone inhibitor-enzyme complexes, which enables us to understand the generation of reactive oxygen species (causing cellular damage and cancer).

Major projects

The recently established Structural Biology program at Centenary is focused on elucidating 3D structures of membrane proteins involved in fundamental cellular processes by x-ray crystallography. Membrane proteins constitute roughly a third of the genes in genomes and perform a plethora of essential cellular functions. Their importance is reflected in that they represent 50-70 per cent of all pharmacological therapeutic targets.

Structural biology, and the use of X-ray crystallography, provides a precise and detailed model of how a protein is folded in space. This enables us to understand the mechanism by which a protein functions, and also provides a route to structure based drug discovery. Of particular interest to us are structural studies of membrane proteins relevant to human disease and disorders, such as drug extrusion and respiratory disorders.



Membrane transporters are involved in cellular influx and efflux of nutrients, ions and drugs. As such, they fill an essential niche in cellular homeostasis and are, in many cases, implicated in bacterial virulence, as well as drug extrusion, with important implications for cancer and anti-microbial drug resistance. Our studies are focused on multi-drug transporters belonging to the novel 'multi-drug and toxin extrusion' (MATE) family.

Signal transduction at the cellular level refers to the movement of signals from outside the cell to inside. Many disease processes such as diabetes, heart disease, autoimmunity and cancer arise from defects in signal transduction pathways, further highlighting the critical importance of signal transduction to biology as well as medicine.

Central in human signal transduction is G-protein coupled receptors (GPCR). These are receptors localised in the membrane, sensing external stimuli, which is then translated to a cellular response. Of particular interest in our group are receptors involved in regulation of glucose levels in our blood system and their potential as targets for therapeutic drug design.

Respiratory enzymes have their main function in generating a proton motive force (PMF) across the membrane. The PMF has a pH and an electrical component, which is utilised by other membrane processes, such as ATP synthase, membrane transport, and signalling. Aerobic respiratory chain is composed of four large multi-subunit membrane proteins, Complex I-IV, of which II-IV have been structurally determined.

In addition to aerobic respiration, many bacteria are able to induce 'alternative' respiratory pathways using terminal electron acceptors other than molecular oxygen, such as nitrate, sulphur and iron. This enables human pathogens, including enterohaemorrhagic *E. coli* and *Pseudomonas aeruginosa*, to respire in anoxic environments, such as gut and mucus.

We are interested in structural studies of both pathways, where we seek to obtain detailed information of the redox reactions taking place, understanding proton translocation processes, and to acquire detailed structural information of quinone redox reactions, which are ubiquitous for life.

How does the Centenary Institute facilitate your research?

The Centenary Institute has enabled the establishment of an independent research program in structural biology.

Structural Biology Research Officer,
Mikaela Rapp.



T Cell Biology – Professor Barbara Fazekas de St Groth

Allergic, autoimmune and inflammatory diseases affect the majority of the Australian population. We aim to understand the environmental factors needed to prevent these diseases. By modifying these environmental factors, we could re-establish the normal balance of the immune system, thereby stemming the rise of diseases such as type 1 diabetes, rheumatoid arthritis, asthma and inflammatory bowel disease.



The aim of the T Cell Biology Group is to use our knowledge of how T cell responses are controlled in order to design new therapies to prevent and/or treat diseases caused by dysregulated immune responses.

For treatment, we aim to specifically target the immune attack in allergic, autoimmune and inflammatory disease without causing the non-specific immuno-suppression that is a major side-effect of current therapy. To do this, we will need to understand exactly how to manipulate the interactions between dendritic cells and T cells to produce tolerance.

For prevention, our approach is based on the well-documented increase in the incidence of these immune-mediated diseases in populations living under “hygienic” conditions in the developed world. To narrow down the number of possible factors in the “unhygienic” environment that exert a beneficial effect, we are testing whether they act via a small subset of T cells, termed regulatory T cells (Tregs). Our data regarding the factors that control the Treg network in mouse models will be crucial in guiding these studies.

We are also researching new ways to enhance the immune response to cancer by inactivating Treg cells.

What impact will your research have on community health?

Our research has the potential to provide major positive benefits for world health. If we can re-introduce the environmental factors that maintain a normal Treg network in developing countries, we should be able to re-establish the normal balance of the immune system, thereby preventing allergy, autoimmunity and inflammatory disease in the developed world. We could also reverse the current increase in these diseases in rapidly developing countries.

Our research into the control of T cell responses by dendritic cells (DCs) will enhance the ability to produce protective immune responses to major infectious diseases such as tuberculosis, HIV and hepatitis C.

Better means to develop immune responses to cancer would be part of a new multi-pronged approach to long-term control of cancer.

Highlights of 2007

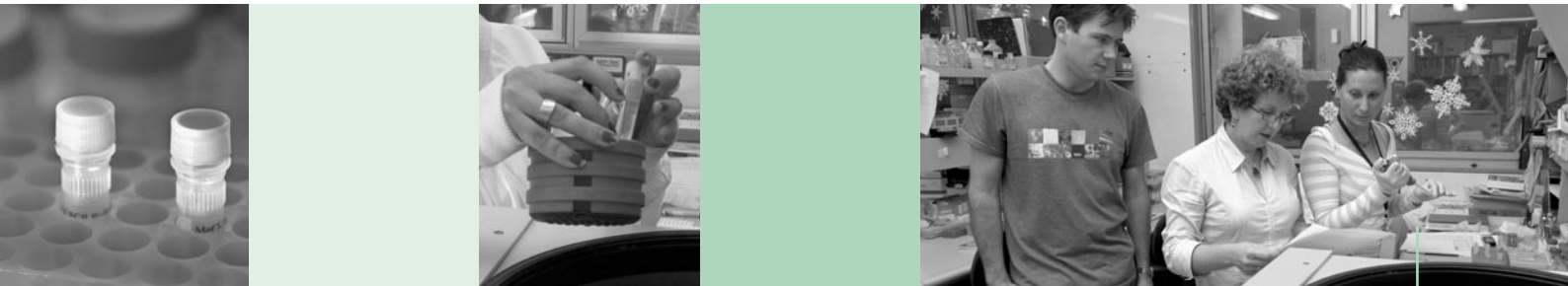
The T Cell Biology Group had many highlights throughout the year, including:

- Showing that Langerhans cells in the skin induce obligatory immune tolerance, even when immuno-stimulatory adjuvant is present.

- Defining the complex phenotype and migratory responses of three previously unknown subsets of skin dermal DCs.
- Demonstrating that Treg cells affect expression of co-stimulatory molecules by DCs during immune responses.
- Demonstrating that Treg selection in the thymus occurs in an avidity window intermediate between that of positive and negative selection.
- Developing a unique murine model of asthma in which the function of transgenic T cells can be suppressed by regulatory T cells.
- Isolating and characterising regulatory T cells from biopsies obtained from the mucosa of patients with inflammatory bowel disease.

Major projects

Diseases resulting from dysregulated immune responses affect the majority of the Australian population, and their chronic nature produces very significant health costs to the community. These diseases include allergies (asthma, hay fever, eczema and anaphylactic shock), autoimmune diseases (type 1 diabetes, thyroid disease, rheumatoid arthritis, multiple sclerosis and systemic lupus



Ben Roediger, Barbara Fazekas de St Groth and Tanya Hartkoph processing immune cell samples.

erythematosis) and inflammatory diseases (coeliac disease, Crohn's disease, ulcerative colitis, atherosclerosis (vascular disease) and type 2 diabetes).

The T Cell Biology Group's research is focusing on two key processes that are involved in dysregulated immune responses. The first is the interaction between CD4 T lymphocytes and DCs. We are using mouse models to understand how the response of transgenic CD4 T lymphocytes can be programmed by different types of DCs. Our recent studies have defined several distinct subsets of DCs in the skin, each with different behaviour and capacity to stimulate T cells.

The second major control on CD4 T lymphocyte responses is via Treg cells which are part of a feedback loop that fine-tunes the immune response and prevents responses against self-antigens. Deficiencies in Treg cells in animal models predispose to the development of autoimmune and inflammatory disease, but also improve immune defence against cancer. Using mouse models, we are defining how Tregs are produced in the thymus, the

factors that maintain their numbers in the periphery, and the mechanisms they use to down-regulate T cell responses. We have shown that Treg cells reduce the stimulatory capacity of DCs by controlling expression of co-stimulatory molecules, and we are currently defining the molecular mechanism involved in this process.

With a view to translating these findings into the clinic, we are testing whether patients with inflammatory bowel disease, systemic lupus erythematosus and Sjogren's syndrome have deficiencies in Treg cells. We are also measuring the effect of chemotherapy on Treg and non-Treg cells, with a view to combining the anti-tumour effects of chemotherapy with therapeutic regimes that have maximum potency against Treg cells but spare the anti-tumour T cell response.

Finally, we are setting up studies to compare human Treg number and function in developed versus developing countries, correlating the Treg data with the incidence of autoimmune, allergic and inflammatory diseases in each population.

How does the Centenary Institute facilitate your research?

Our research cannot proceed without three crucial resources provided by the Centenary Institute: the animal facility, the flow facility, and access to patients at Royal Prince Alfred Hospital.

Our research in murine models uses a large number of genetically modified mouse strains that are bred in the animal facility. We have also been making new transgenic mouse lines in the microinjection facility. We use the multi-parameter LSRII flow cytometer for all our dendritic cell characterisation and rely on rapid cell sorting using the Aria.

Our clinical links are with RPA's Departments of Immunology and Gastroenterology and the Sydney Cancer Centre.

Vascular Biology – Professors Jennifer Gamble and Mathew Vadas

Blood vessels are the major gateways to tissues and are key regulators of cancer growth and spread and are involved in the development of cardiovascular disease. Blood vessels are lined by a continuous layer of cells, called endothelial cells.

The Vascular Biology Group is focused on understanding how mature endothelial cells form from their progenitor cells, the signals that operate to induce new blood vessel formation and ultimately what changes take place in the vessels upon ageing.



What impact will your research have on community health?

The goal is to be able to manipulate the vascular system as an avenue to disease control since inappropriate growth or function of this system is a central feature of most diseases. For example, the cardiovascular complications of diabetes can be partially explained through the failure of endothelial progenitor cells to mature and migrate to damaged sites.

Changes in the normal impermeable nature of blood vessels is an underlying feature of inflammatory diseases, heart attacks, stroke and other forms of infarcts and septic shock, and new blood vessel formation is an essential feature of solid tumour growth.

Highlights of 2007

The control of vascular permeability is a significant unmet clinical need. At present there are no drugs available which target this aspect of disease, yet uncontrolled vascular permeability is an early recognisable feature of a broad spectrum of clinical problems.

The opportunity to develop drugs targeting vascular permeability has come from a refinement of our

understanding of the factors and intracellular signals which maintain the selectively impermeable nature of blood vessels. Our investigations have identified one important signalling enzyme which we have targeted for drug development. In collaboration with Professor Michael Parker of St Vincent's Research Institute in Melbourne, we have commenced development of drugs directed to PKC ζ which will inhibit vascular leak. The approach of *in silico* screening (a process whereby drug design is undertaken by a computer based on the structure of the enzyme and potential drugs that bind to it) has been successful, and we are developing further a set of molecules that are effective both *in vitro* and in mouse models of vascular leak. This work was awarded an NHMRC Development Grant.

Major projects

Blood vessels age

One of the critical features of ageing is the increased incidence of cardiovascular disease and of cancer. Although this has been known for decades, there have been no new ways of studying the process in the test

tube. This type of study is often essential in gaining a deeper understanding. We have discovered a gene (SEN1) that causes endothelial cells to age. This gene causes endothelial cells to increase in size and to express novel surface markers, quite typical of those found in senescence. We have started a major program of research to characterise how this gene is induced (for example, by oxidative stress), what other effects on cellular function it has (for example on vascular permeability) and how it might be regulated.

Blood vessel formation

Angiogenesis is a process of endothelial cell reorganisation and differentiation. miRNAs are endogenous non-coding RNAs which are expressed as long hairpin-forming precursor RNAs that are further processed to 21-23 nucleotide RNA molecules. miRNAs regulate gene silencing generally by post-transcriptional mechanisms.

miRNAs are involved in developmental timing, apoptosis, metabolism and cell differentiation. Recently, abnormal patterns of miRNA expression have been found in disease states, including cancer. We have identified a group of miRNAs which are regulated during blood vessel formation and which control two different but major signalling pathways known to be essential for endothelial cell function. Further work is directed to understanding the impact of these specific miRNAs in normal and tumour associated angiogenesis.

Differentiation of Endothelial Progenitor Cells (EPC)

The EPC reside in the bone marrow and are released into the circulation following stimulation and are now referred to as circulating EPC (CEPC). CEPC can be incorporated into foci of neovascularisation, and functionally contribute to vasculogenesis for example during wound healing, recovery from limb ischemia, postmyocardial infarction and tumourigenesis where they undergo differentiation to mature endothelial cells.

We have demonstrated that the process of differentiation to form the mature endothelial cell is regulated by the enzyme sphingosine kinase-1, which also controls endothelial cell survival. Manipulation of this enzyme system may have potential for the generation of increased numbers of endothelial cells, for example for vascular grafts. Further work is directed to an understanding of the mechanism underlying the regulation by sphingosine kinase.

How does the Centenary Institute facilitate your research?

The Centenary Institute provides the environment essential for medical research. It has excellent facilities, for example, the core cell imaging, animal and gene array facilities.

Most importantly, it provides the critical mass of excellent scientists who have overlapping and complementary interests and skills. This encourages collaborations and the consideration of different approaches in addressing medical problems.



Vascular Biology Research Officer, Carlos Cassano, preparing samples for analysis.



Signal Transduction – Associate Professor Pu Xia

By understanding the role of sphingosine kinase in cancer and diabetes, we seek to develop a new therapeutic strategy to target this enzyme for prevention and treatment of these diseases that account for more than a third of all deaths in Australia.

What impact will your research have on community health?

Our work will provide a better understanding of how cells utilise lipids as a unique language to communicate with each other and how it is misunderstood by the cells causing cell dysfunction, leading to diseases such as cancer and diabetes. Communication between different cells under different conditions are usually in a very specific manner and our proposed development of new therapeutics to target a specific communication pathway, will provide a more effective and safe way for treatment of disease.

Highlights of 2007

The Signal Transduction Group is a recent addition to the Centenary Institute, established in early 2007. The group, together with the staff from Associate Professor Xia's previous laboratory in Adelaide, achieve the following:

- Uncovered a new molecular mechanism through protein S-nitrosylation whereby elevated blood sugar damages blood vessels, resulting in vascular diseases and diabetes.
- Identified a new protein that regulates immune and inflammatory responses is able to induce insulin resistance in liver cells, providing a potential target for treatment of diabetes.

- Identified a role for the enzyme SphK1 in modulating breast cancer cells responding to anti-estrogen drugs, providing a new way to overcome drug resistance and potentially improve the patients' outcomes following treatment.

Major projects

We aim to understand how biological signals communicate between and within cells, and how they go awry leading to the development of human diseases, including cancer, diabetes and heart attack. With a strong research background in the area of lipid signalling, this laboratory continues to play a leading role in defining the signalling mechanisms of sphingolipids and investigating their patho-physiological implications specifically in cancer, diabetes and cardiovascular disease.

Our current research projects include:

- The role of Sphingosine Kinase (SphK) in the development of breast cancer and anti-estrogen resistance.
- The signalling role of SphK in the regulation of pancreatic beta-cell survival and insulin secretion.
- Investigation of inflammatory signalling involved in cardiovascular diseases and diabetic vascular complications.



How does the Centenary Institute facilitate your research?

The Centenary Institute has provided a supportive and stimulating environment for the group. The facilities are an excellent basis for our experimental needs, including the animal house, the flow cytometry and the new imaging and microscopy facility.

The excellent seminar series gives the opportunity for interaction with other researchers within the Centenary and other research institutions around the campus.

Core Facilities

Cytometry and Imaging

Flow Cytometry

Flow cytometry involves the high-speed measurement of multiple characteristics of cells in a stream of fluid that moves past a focused beam of light. As a cell passes the beam, light is both scattered from the cell and emitted from any fluorescent molecules incorporated in or attached to that cell. By collecting this light, information can be gathered about the type of cells that are present and the state they are in. Furthermore, some flow cytometers incorporate the ability to sort the cells into different fractions at high speeds thus enabling the purification of rare cell populations for further study.

Flow cytometry and cell sorting are key technologies that are used extensively by most of the research groups at the Centenary Institute. The cytometry facility at Centenary is well-equipped with three cell sorters and three flow cytometry analysers and offers our researchers unrivalled access to state-of-the-art equipment with wide-ranging applications, along with the technical and scientific support necessary to make optimal use of this significant infrastructure investment.

Flow cytometry highlights in 2007 included increasing the level of technical support through the recruitment of an additional staff member and the addition of new hardware to increase the rate at which samples can be analysed.

Imaging

The Centenary Institute's Imaging Facility encompasses both whole animal and microscopy-based imaging technologies.

The highlight for 2007 was the installation of the LaVision Biotec TriMscope. This cutting edge multi-photon microscope enables researchers unprecedented access to the secret workings of living tissues at the cellular and molecular level. The multi-photon microscope at the Centenary Institute has two unique features, its imaging mode and laser. The unique imaging mode uses multiple laser beams and means fast moving objects and dynamic



Chris Brownlee at work in the Flow Cytometry facility.

processes in living tissue can be viewed, for example, cells in the blood stream. The laser has been enhanced with a unit called an OPO that produces longer wavelengths of light than those used in other microscopes enabling researchers to potentially look deeper into living tissue than ever before.

Throughout 2007, Centenary continued the evaluation and selection process for the upcoming purchase of a state-of-the-art confocal microscope to further enhance the facilities available to Centenary researchers in 2008.

The Centenary's microscopes, small animal imaging and high-level flow cytometry resources directly complement each other. Each technology provides unique, but partial, information about the disease process under investigation. Combining them significantly increases the total value of the research that can be carried out at the Centenary Institute.

Microinjection Facility

The use and development of the latest transgenic (over expression of a single gene) and knockout (deletion of a single gene) technology, collectively called genetically modified, has for many years been a high priority for the Centenary Institute. Centenary's facility is the longest established in the state and one of the most productive in Australia in terms of numbers of mouse strains produced. Centenary's transgenic and knockout mice are the subject of hundreds of scientific publications.

In 2007, the Centenary Institute secured funding from the Cancer Institute

NSW to support the employment of the expert microinjection technician who has made a large number of genetically modified mouse strains. The funding will enable the generation of new genetically modified animals to directly capitalise on the investments made in multi-photon microscopy, small animal imaging and flow cytometry.

Genomics Facility

Cancer genomics represents the new age in how we diagnose, control and assess risk, and treat patients with cancer. Cancer genomics promises to lead to more optimal and cost-effective treatment in patients with cancer and more effective preventative strategies for those at risk.

In 2007, the Centenary Institute purchased the Affymetrix Gene Array platform (supported by funding from the Cancer Institute NSW) to further enhance our genomics facility. The Affymetrix platform will enable a better understanding of the molecular basis of cancer development and will aid in the development of new therapies targeted at these newly recognised molecules. Further, the Affymetrix system will allow us to profile transcriptome response to new therapies, as well as helping to assess treatment efficacy and side effects.

Importantly, this technology promises to be highly significant in realising personalised, pre-emptive, predictive and participatory healthcare.

Mouse Cardiac Physiology and Function Facility

In evaluating the cardiac phenotype in genetically engineered mice, the Agnes Ginges Centre for Molecular Cardiology at the Centenary Institute has developed a facility which allows *in vivo* analysis of several cardiac parameters including:

- blood pressure measurement (tail-cuff);
- electrocardiography (ECG);
- electrophysiological stimulation studies; and
- echocardiography.

In addition, there is a mouse exercise facility (running and swimming) which allows the role of exercise on the cardiac phenotype to be evaluated.

PC3 Laboratory

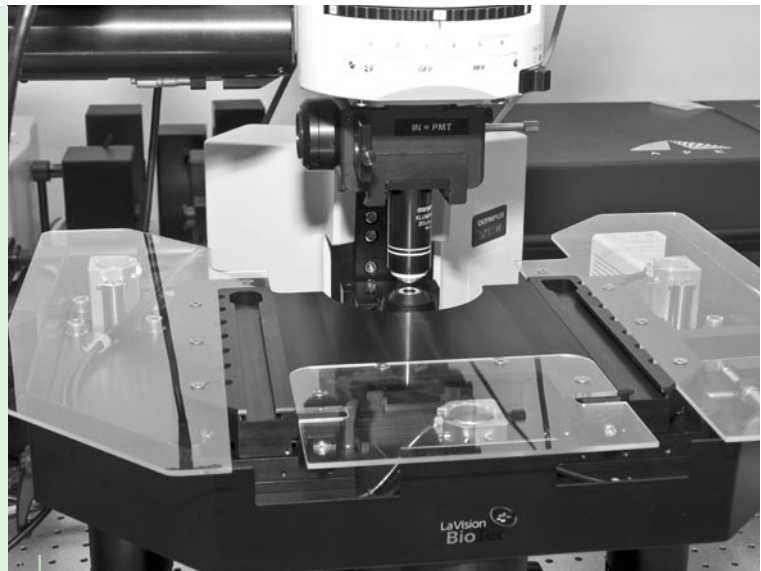
The Centenary Institute houses a PC3 containment facility, the only one in Australia which permits work with experimental tuberculosis infection. This facility is essential for our ongoing investigations examining the immunological and inflammatory response stimulated by *Mycobacterium tuberculosis* infection and the genetic factors that control resistance and susceptibility to tuberculosis.

The facility contains equipment permitting cell culture, genetic manipulation of bacteria and aerosol exposure system for animal infection models.

Animal Facility

Genetically modified mouse lines are bred under Level 2 Specific Pathogen Free conditions in the Centenary Institute Animal Facility. Climate control, strict hygiene and sterilisation procedures, the provision of quality irradiated feed, and environmental enrichment provide an optimal environment for the mice. The PC2 approved facility offers differing levels of containment with dedicated areas for immunodeficient mice, infectious studies and quarantine. The facility is an Australian Quarantine approved premise.

Chris Brownlee gains a unique perspective using Centenary's multi-photon microscope.

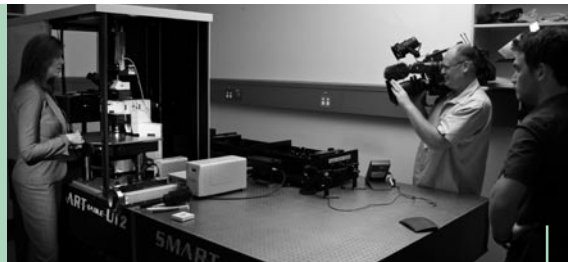


The Centenary Institute unveils its new multi-photon microscope.

Fundraising and Marketing



Centenary Institute scientists gratefully accepting grants for their research.



Channel 9's Jessica Rich at the opening of the Centenary Institute's multi-photon microscope.

2007 saw the Centenary Institute's fundraising efforts take on new energy. With the employment of a new Marketing and Fundraising Manager in April, the Foundation had a new lease of life and is well on its way to building stronger ties with the community.

Over the year our long term supporters continued to be wonderfully generous. We gained eight new Life Members of the Research Society, maintained membership levels and had the highest ever response to our direct mail appeals.

In November, Mathew Vadas sought donations from people with whom the Centenary Institute did not have an existing relationship. The response to this appeal has been heartening and demonstrates that there is a high level of enthusiasm for our medical research amongst the wider community. Centenary's efforts in 2008 will help build our donor numbers even further.

I would like to thank Liz, Aaron and their families for so generously sharing their personal stories with us for the appeals. All at Centenary hold the goal of improving patient outcomes at the very heart of what we do. We wish you all the very best and thank you for your support and inspiration.

The Seat of Knowledge campaign was introduced in 2007. It gives people the opportunity to make a lasting impression in the field of medical research through the purchase of their own personalised seat of knowledge in the Centenary Institute's lecture

theatre. The lecture theatre is where our researchers teach, learn and share their breakthroughs in medical research. The response to this has been heartening with many warm messages in memory of loved ones being placed on the seats and inspiring our staff.

All at Centenary were overwhelmed at the support given to us by new friends and old when our Race Day event was cancelled amidst the equine flu epidemic. Having run for the past 14 years, Race Day is our largest fundraising event, and whilst the horses were struck down, our need for funds continued. On behalf of us all, I would like to say a huge thank you to the individuals and companies who supported us even though the event was cancelled. Thanks to your generosity we were able to meet our income targets for the event.

Finally, a significant communications overhaul was undertaken in 2007. The result is a new look, conversation and logo encompassing a renewed commitment and vitality amongst staff and Board alike to achieve our united vision of Research for Life.

Sally Castle
Marketing & Fundraising Manager

Centenary thanks the following companies for their support:

- Aussie
- Inghams
- MMB Print
- O'Hallorans Corporate Lawyers
- PriceWaterhouseCoopers
- Regional Radio Works
- STW Group
- Swiss Re
- The Wine Society

Staff and supporters enjoy the Wine Society dinner.



2007 Seminar Series and Visiting Speakers

As part of Centenary's commitment to education and development of our staff, we hold regular seminars on current and emerging research topics, promoting interaction between laboratories. The seminar program regularly features visiting speakers, as well as Centenary Institute researchers updating colleagues on developments in their area.

Speaker	Seminar title
Mathew Vadas The Centenary Institute	Sphingosine kinases as an integrator of cellular signalling
Andrew Torda Centre for Bioinformatics, University of Hamburg, Germany	Protein sequence and structure prediction and classification without the ghost of Herr Boltzmann
Gopal Kundu National Centre for Cell Science, India	The role of osteopontin, a member of SIBLING family protein in tumour progression and angiogenesis
Chris Jolly The Centenary Institute	Antibody mutation, DNA double-strand breaks and the cell cycle
John Hamilton Arthritis and Inflammation Research Centre; University of Melbourne	Colony stimulating factors and chronic inflammatory diseases
Brandon Wainwright Institute for Molecular Bioscience	Hedgehog pathway regulation of common human cancer
Antonio Rothfuchs National Institute of Health, Bethesda, US	Visualisation of IL-12p40-producing dendritic cells during mycobacterial infection
Ron Germain National Institute of Health, Bethesda, US	New software for complex multi-scale spatially-resolved modelling and simulation: a focus on the biology, not the math
Peter Koopman Institute for Molecular Bioscience	Molecular regulation of lymphatic development
Matthew Grimshaw Kings College London, UK	Breast tumour micro environment
Pu Xia The Centenary Institute	Sphingosine kinase could serve as a ideal anti-cancer STI target
Peter Currie Garvan Institute	Skeletal muscle growth and regeneration in normal dystrophic development
Martin Lackmann Monash University	Insights into Eph-guided cell positioning: ADAM is turned on by cytoplasmic-relaxed Eph
Barbara Fazekas de St Groth The Centenary Institute	Regulatory T cells in health and disease
Stephen Larsen The Centenary Institute	Stem cell mobilisation and transplantation in non-human primate model
Ranjey Thomas Diamantina Institute, University of Queensland	Development of a therapeutic vaccine for rheumatoid arthritis
David Adams University of Birmingham, UK	Dendritic cell vaccination for hepatocellular carcinoma
Patrick Bertolino The Centenary Institute,	Parameters determining the balance of tolerance and immunity in the liver
Warwick Britton The Centenary Institute	Life on the inside: host-pathogen interactions in tuberculosis infection
John Stambas University of Melbourne	Influenza reverse genetics: a tool for studying CD8+ T cell responses
Jennifer Stow Institute for Molecular Bioscience	Secretion of inflammatory cytokines: new pathways and regulators
Georges Grau University of Sydney	Cell-cell interactions and micro-particles in micro-vascular pathology

2007 Seminar Series and Visiting Speakers

Speaker	Seminar title
Jacqueline Matthews University of Sydney	Regulatory protein complexes in diseases and development
Wolfgang Weninger The Centenary Institute	Real time imaging of immune responses in vivo
Phil Robinson Children's Medical Research Institute	Molecular mechanisms of synaptic vesicle endocytosis: a potential target for new anti-epileptic drugs
Joe Trapani Peter MacCallum Cancer Centre	Structure and function of lymphocyte perforin
Angel Lopez Hanson Institute	Molecular basis for the pleiotropic biological activities of cytokine receptors
Bruce Armstrong Sydney Cancer Centre	Finding causes of lymphoma through international collaboration
Mark Smyth Peter MacCallum Cancer Centre	Cancer inflammation and immune surveillance
Ariel Ruiz i Altaba University of Geneva, Switzerland	Hedgehog-Gli signalling in stem cells, cancer and cancer stem cells
Doug Hilton The Walter and Eliza Hall Institute	Suppressor and enhancer screens in the mouse: shedding light on the control of blood cell number and identifying drug targets
Valerie Beral Cancer Research UK; University of Oxford, UK	Hormones and cancer in women
David Huang The Walter and Eliza Hall Institute	Flipping on the death switch for treating cancers
Sharad Kumar Hanson Institute	Control of protein function by the Nedd4 family of ubiquitin ligases
Julie McMullen The Baker Heart Research Institute	Targeting physiological signalling cascades in the failing heart
David Vaux La Trobe University	IAP's from baculovirus to bedside
David Vaux La Trobe University,	Ten rules for presenting and interpreting data in publications
Roger Reddel Children's Medical Research Institute	Telomere length maintenance in human cancer cells
Phillip Hogg University of NSW	Allosteric disulphide bonds
Mika Jormakka The Centenary Institute	Facing the challenges of membrane protein crystallisation
John Blenis Harvard Medical School, US	mTOR signalling and cell growth control
Gabor Tigyi University of Memphis, US	Lysophospholipid signalling: the good, the bad and the ugly
Axel Ullrich Max Planck Institute for Biochemistry, Martinsried, Germany	Oncogenomics-based cancer drug development
Michael Parker St Vincent's Institute of Medical Research	Thanks for the memories: structure-based drug discovery
Marie Bogoyovitch University of Melbourne	Inhibitors of c-Jun N-terminal kinases: JunK no more?
Gavin Recchia Davies Collison Cave	An introduction to intellectual property issues
Teresa Wozniak The Centenary Institute	Manipulating the cytokine environment for the development of anti-mycobacterial immunity

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Weber-Chrysochoou C, Chrisafullia D, Almquist C, Li Q, Kemp AS, **Britton WJ**, Marks GB. Interleukin-5 T cell responses to house dust mite are associated with the development of allergen-specific IgE responses and asthma in the first 5 years of life. **J Allergy Clin Immunol.** 2007; 120:286-292.

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Xia P. Letter to the Editor: High-Density Lipoproteins and Their Constituent, Sphingosine-1-Phosphate, Directly Protect the Heart Against Ischemia/Reperfusion Injury In Vivo via the S1P3 Lysophospholipid Receptor. **Circulation.** Published online 115:e393.

2007 Invited Presentations

International

Britton W. Upregulation of P2X7 receptor expression and function enhances macrophage control of mycobacterial infection. International Immunology Congress; 2007 Aug; Rio de Janeiro, Brazil.

Britton W. Regulation of protective immunity to anti-tuberculosis subunit vaccines. Department of Immunology, University of Saskatchewan Saskatoon; 2007 Mar; Canada.

Britton W. New solutions to the challenges of vaccines for tuberculosis. Kilimanjaro Christian Medical College; 2007 Oct; Moshi, Tanzania.

Fazekas de St Groth B. 4th International Symposium of the Clinical Use of Cellular Products; 2007; Regensburg, Germany.

Fazekas de St Groth B. EU DC-Thera Network of Excellence Meeting; 2007; Celerina, Switzerland.

Fazekas de St Groth B. 13th Annual Meeting of the International Society for Cellular Therapy (ISCT); 2007 Jun 24-27; Sydney, Australia.

Fazekas de St Groth B. From the laboratory to the clinic: T cells and cytokines. 2007; Oxford, UK.

Fazekas de St Groth B. University of Bristol; 2007; Bristol, UK.

Fazekas de St Groth B. University of Cambridge; 2007; Cambridge, UK.

McCaughan G. Asian Pacific Consensus Statements on Diagnosis, Management and Treatment of HCV Infection. 17th APASL Meeting; 2007 Apr; Kyoto, Japan.

McCaughan G. HBV infection and liver transplantation: burning issues. ILTS Annual Scientific Meeting; 2007 Jun; Rio De Janeiro, Brazil.

McCaughan G. De novo malignancy following liver transplantation. ILTS Annual Scientific Meeting; 2007 Jun; Rio De Janeiro, Brazil.

McCaughan G. The balance between intrahepatic immunity and tolerance: relevance to transplantation and HVC infection. 9th Bannf meeting on Allograft Pathology; 2007 Jun; La Coruña, Spain.

McCaughan G. HCV post liver transplant - host and viral response. ESOT Annual Meeting; 2007 Sep; Prague, Czech Republic.

McCaughan G. Gene array data in PBC. EASL Single Topic Conference on PBC; 2007 Dec; Newcastle UK.

Rasko JEJ. Aminoaciduria Nephrogenetics. ISN - Nature Genetics Forefronts Symposium on Nephrogenetics: from Development to Physiology, Boston USA 2007

Saunders B. Function of P2X7 and IDO in macrophage control of tuberculosis. Infectious Disease Research Institute; 2007 Mar 16; Seattle, USA.

Saunders B. Phagocytosis and Effector Functions; Macrophage and Neutrophil involvement in Innate and adaptive immunity. 9th FIMSA Advanced Training Course and Workshop; 2007 Feb 1-4; Je Ju, South Korea.

Semsarian C. Genetic basis of sudden cardiac death. 55th CSANZ Scientific Meeting. Christchurch, New Zealand 2007.

Seth D. 2nd International Symposium on ALPD and Cirrhosis; 2007 Oct 18-19; Kobe, Japan.

Seth D. National Centre for Cell Science; 2007 Feb 8-9; Pune, India.

Seth D. Research Society on Alcohol and Alcoholism Meeting; 2007 Jul 11-14; Chicago, USA.

Vadas M. Sphingosine kinase in endothelial cell differentiation. 2007 FASEB Summer Research Conference Lysophospholipid Mediators in Health and Disease; 2007 Jun 10; Arizona, US.

Xia P. Role of sphingosine kinase-1 in breast cancer. 10th International Conference: Bioactive Lipids in Cancer, Inflammation and Related Diseases; 2007; Montreal, Canada.

Xia P. The sphingosine kinase signalling pathway and its implications in diseases. Inaugural Australia-China Biomedical Research Conference; 2007; Melbourne, Australia.

National

Allen JD. Understanding response to proteasome inhibitors. University of Sydney Cancer Research Network Mini-Symposium. Cancer Therapeutics: Drug design, resistance and treatment; 2007 Sep 6; Royal Prince Alfred Hospital, Sydney, NSW.

Britton W. Prospects for the control of tuberculosis. FRCPA Annual Scientific Meeting; 2007 Mar; Sydney, NSW.

Britton W. Manipulating host responses to mycobacterium tuberculosis through the IL-12/23 axis and purinergic receptor P2X7. Department of Microbiology and Immunology, University of Melbourne; 2007 April; Melbourne, Victoria.

Britton W. The role of the purinergic receptor P2X7 in the control of tuberculosis. Department of Pharmacology, University of Sydney; 2007 Jul; Sydney, NSW.

Britton W. Do your genes give you TB? Prince of Wales Hospital; 2007 Jul; Sydney, NSW.

Cavanagh L. Australasian Society of Immunology Postgraduate Workshop; 2007 Dec; Manly, NSW.

Fazekas de St Groth B. NSW Animal Ethics Committee Members Meeting; Australian and New Zealand Council for the Care of Animals in Research and Teaching; 2007.

Fazekas de St Groth B. Regulatory T cells in health and disease. 9th MMRI Dendritic Cell Symposium; 2007 Jun 21-22; Brisbane, Queensland.

Fazekas de St Groth B. Flow cytometric identification and isolation of regulatory T cells. Becton Dickinson National Sales and Marketing Meeting; 2007; Hunter Valley, NSW.

Gamble J. Sphingosine Kinase Controls Endothelial Progenitor Cell Differentiation. ComBio; 2007 Sep 22-26; Sydney NSW.

Gamble J. Sphingosine Kinase Controls Endothelial Progenitor Cell Differentiation. Hunter Cell Biology Meeting; 2007.

Gamble J. Control of the Vascular System-implications for understanding and control of arthritis. 49th Annual Scientific Meeting of the Australian Rheumatism Association; 2007 May 26-30; Sydney, NSW.

Haass N. 3D models for the identification of novel candidates for targeted therapy of melanoma. Seminar Series: Centenary Institute; 2007 Nov; Sydney, NSW.

McCaughan G. Pathogenesis of auto immune hepatitis. Melbourne Liver Group Meeting; 2007 Feb; Melbourne, Victoria.

McCaughan G. Hepatitis C infection – from blood donor to allograft failure. Melbourne Liver group Meeting; 2007 Feb; Melbourne, Victoria.

McCaughan G. Autoimmune hepatitis – what to do when the steroids and Azathioprine fail? 3rd Australian Liver Foundation Single Topic Conference on Autoimmunity and the Liver; 2007 Jun; Hunter Valley, NSW.

McCaughan G. HCV post liver transplantation: viral load is important. 9th Annual ANZ Liver Transplant Meeting; 2007 Apr; Melbourne, Victoria.

McCaughan G. HBV infection-evidence for combination therapy. A Debate AGW; 2007 Oct; Perth, Western Australia.

Rasko J. The Carl de Gruchy Memorial Lecture, St Vincent's Hospital, Melbourne, Victoria.

Saunders B. Signalling through the P2X7 receptor aids control of M. tuberculosis infection. ComBio; 2007 Sep 22-26; Sydney, NSW.

Semsarian C. Sudden unexplained death and the molecular autopsy. "Forensic Foray" Meeting, University of Sydney; 2007; Sydney, NSW.

Semsarian C. Genes and sudden death. Nurses Forum, Royal Prince Alfred Hospital; 2007; Sydney, NSW.

Semsarian C. Genetics in heart disease: risk stratification in sudden death. 125th Anniversary Royal Prince Alfred Hospital Clinical Week; 2007; Sydney, NSW.

Semsarian C. How to translate your discovery into a clinical outcome. ASMR Professional Development Program; 2007; Sydney, NSW.

Semsarian C. Genetic causes of sudden cardiac death. PD Heat Meeting and Expo; 2007; Port Douglas, Queensland.

Semsarian C. The increasing role of genetics. PD Heat Meeting and Expo; 2007; Port Douglas, Queensland.

Semsarian C. Getting to the heart of sudden death. Centenary Institute Colloquium II; 2007; Sydney, NSW.

Semsarian C. Research update. 3rd Annual Cardiac Genetics Meeting; 2007; Children's Hospital, Brisbane, Queensland.

Seth D. Bioinformatics Symposium, Bioinformatics & Centre for Mathematical Biology; 2007 Sept 27; University of Sydney, NSW.

Shackel N. Gene Profiling of PBMC in Hepatitis C. Annual Australian Microbiology Meeting; 2007 Jul 9-13; Adelaide, South Australia.

Shackel N. Hepatitis C recurrence post liver transplantation. Annual Roche Pillar Meeting: Case Presentation; 2007; Melbourne, Victoria.

Shackel N. Hepatitis C: It is all about the virus stupid! Annual Roche CARG Transplantation – Controversies in transplantation; 2007; Sydney, NSW.

Shackel N. Nutrition and chronic liver disease. Annual Albion St Clinic Dietician Course; 2007; Sydney, NSW.

Shackel N. Liver transplantation. ASMR Research Week "Science in the Cinema"; 2007; Sydney, NSW.

Shackel N. Gene Array Analysis in Hepatitis C. 2nd Annual Liver Forum; 2007; Canberra, ACT.

Vadas M. Long-lasting quality. Pearls (an initiative of PriceWaterhouseCoopers); 2007 Jun 5; Sydney, NSW.

Vadas M. The role of sphingosine kinase in cancer. University of NSW Cancer Research Centre; 2007 Jun 6; Sydney, NSW.

Vadas M. The role of sphingosine kinase in inflammation in cancer. Children's Institute for Medical Research; 2007 Jul 19; Westmead, NSW.

Vadas M. The role of sphingosine kinase in cancer. ComBio Biomedicine Symposium; 2007 Sep 25; Sydney, NSW.

Vadas M. Imagination and investment in biotechnology. Minter Ellison – AusBiotech Executive CEO Luncheon; 2007 Sep 26.

Vadas M. The role of sphingosine kinase in cancer. Hanson Institute; 2007 Oct 1; Adelaide, South Australia.

Warner F. 2nd Liver Forum; 2007; Australian National University, Canberra.

Weninger W. Annual Scientific Meeting of the Australian College of Dermatologists; 2007 May 13-16; Adelaide, South Australia.

Weninger W. Australasian Society of Immunology Annual Meeting; 2007 Dec; Manly, NSW.

Weninger W. Weekly Seminar Series: Department of Microbiology and Immunology, University of Melbourne; 2007 Sep; Melbourne, Victoria.

Weninger W. Weekly Seminar Series: Peter MacCallum Cancer Centre; 2007 Oct; Melbourne, Victoria.

Weninger W. The Power of One Idea Conference. The Walter and Eliza Hall Institute; 2007 Oct 21-23; Melbourne, Victoria.

Xia P. Role of sphingosine kinase-1 in the vasculature: friend or foe? Centenary Institute Colloquium II; 2007; Sydney, NSW.

Postgraduate Training Program

The Centenary Institute has a strong commitment to the development of the next generation of research leaders. As such, university students make up to a quarter of our research team. Students come from diverse ethnic and academic backgrounds with the common goal of achieving excellence in their chosen field of research.

The Centenary Institute congratulates the following students for their achievements in 2007.

Doctor of Philosophy (Medicine) Awarded (PhDs) 2007

Student	Supervisor	Thesis title
Sioh Yang Tan	Professor Barbara Fazekas de St Groth	In vivo control of regulatory T cell number and function
Stephen Larsen	Professor John Rasko	Stem cell mobilisation and transplantation in a non-human primate model
Vanessa Bryant	Dr Stuart Tangye	The proliferative and differentiation potential of human naïve, IgM memory and isotype switched memory B cells
Anthony Ryan	Dr Jamie Triccas	Utilising recombinant mycobacteria to define vaccine-induced immunity to tuberculosis
Adam Cook	Dr Chris Jolly	DNA repair and antibody gene mutation
Teresa Wozniak	Professor Warwick Britton	Manipulating anti-micobacterial immunity with immune-stimulating cytokines
Alessandra Doolan	Associate Professor Christopher Semsarian	Clinical and molecular basis of sudden cardiac death in the young
Xin Maggie Wang	Associate Professor Mark Gorrell	Fibroblast activation protein in cell biology and liver fibrosis
Denise Yu	Associate Professor Mark Gorrell	Functional studies of dipeptidyl peptidase 8 (DP8) and DP9

Masters of Medical Science Honours (Masters) 2007

Student	Supervisor	Title
Tony Chung	Dr Fiona Warner	Infectious disease and immunology characterisation of HCV receptor, Claudin 1

Grants Awarded 2007

The research undertaken at the Centenary Institute is funded by a diverse range of government and non-government organisations who make our work possible. Our sincere thanks to the following organisations for their continued support of Centenary Institute scientists.

Investigator/s	Title	Granting body
N Shackel, G McCaughan, P Haber, S Strasser	Australian Centre for HIV and Hepatitis Virology Research Grant	Australian Centre for HIV and Hepatitis Virology
S Broer, J Rasko	Amino acids as nutrients – the molecular basis for amino acid absorption in kidney and intestine	Australian Research Council (ARC)
M Jormakka, M Rapp	A rational approach to high-resolution structure of the multi-drug transporter EmrE	ARC
J Rasko, J Holst	Dissecting BORIS function in neoplasia	Cancer Council NSW
A Altaba	Cancer Leaders Program	Cancer Institute NSW
B Fazekas de St Groth, J Rasko, M Vadas, W Weninger, W Dong, Q Ormandy, M Haber, J Allen, P Bortolino, D Seth, P Xia	Expert microinjection technologies for creating genetically modified mice	Cancer Institute NSW
M Maher	Platinum drug resistance: structural and functional studies of the Ctr proteins	Cancer Institute NSW
E McGowan	Identification of new molecular targets for the treatment of breast cancer	Cancer Institute NSW
J Rasko, J Holst	Analysis of the Wnt signalling pathway in cancer	Cancer Institute NSW
J Selwyn	The role of the tumour suppressor CTCF and its paralogue BORIS in carcinogenesis	Cancer Institute NSW
M Vadas, J Rasko, J Allen, G McCaughan, B Armstrong, J Thompson, J Gamble, P Xia, L Horvath, Q Dong, P Hersey, J Arnold, N Shackel	Centenary Centre for Genomic Medicine: Cancer Genomics Gene Discovery Platform (Equipment: Illumina)	Cancer Institute NSW
J Allen, S Ling	Predicting response to proteasome inhibitors	Cure Cancer Australia
S Ling, J Allen	Renewal: Role of XBP-1 in the drug resistance of multiple myeloma	International Myeloma Foundation
S Ling	Predicting and understanding the response of myeloma to proteasome inhibitors	Leukaemia Foundation
T Tsoutsman	Multiple mutations in familial cardiomyopathy: characterisation and treatment studies	National Heart Foundation
T Tsoutsman	Travel grant	National Heart Foundation
P Bertolino	Research Fellowship	NHMRC
D Bowen	Hepatitis C virus-specific cellular immune responses post-liver transplantation	NHMRC
W Britton, J Triccas, N West	Regulation of pulmonary immune responses to subunit vaccines against tuberculosis	NHMRC
M Gorrell	Therapeutic potential of the dipeptidyl peptidase IV in gene family	NHMRC
C Jolly, J Manis, F Alt	Antibody mutation promotes translocation: a natural cause of cancer	NHMRC

Grants Awarded 2007

Investigator/s	Title	Granting body
E Lau	Mechanisms for development of leukaemia via antibody hypermutation	NHMRC
N Shackel, S McLennan, F Warner	Role of the hepatocyte in extra cellular matrix interactions in liver fibrogenesis	NHMRC
W Weninger, L Cavanagh	Interplay of innate and adaptive immunity to influenza A virus	NHMRC
W Weninger, P Mrass	Mechanisms of T cell migration and interactions in tumours	NHMRC
K Morley, P Haber, D Seth, J Whitfield, M Teeson, A Baillie, S Leung	Genetic determinants of the response to pharmacotherapy for alcohol dependence	NSW Health
W Weninger	Real-time imaging of T cells in the tumour micro-environment	Office for Science and Medical Research NSW
N Shackel	Illumina	Perpetual Trustees
J Holst	Role of nutrient amino acids in prostate cancer	Prostate Cancer Foundation of Australia
R Martiniello-Wilks	Tri-modal targeted stem cell gene therapy for prostate cancer metastases	Prostate Cancer Foundation of Australia
J Holst	Gene regulation by nutrient amino acids in prostate cancer	Ramaciotti Foundation
N Shackel	Illumina	Ramaciotti Foundation
S Ling	Predicting response to a new drug for multiple myeloma	RCPA
W Britton, B Saunders	Genetic control of tuberculosis (plate reader)	Rebecca L Cooper Foundation
W d'Avigdor	Understanding the pathobiology and interferon treatment responses in chronic hepatitis C using an analysis of gene expression in peripheral blood mononuclear cells	Rebecca L Cooper Foundation
C Jolly	Development of novel human antibodies for use as therapeutics in arthritis and other autoimmune disorders (Nucleofector)	Rebecca L Cooper Foundation
J Rasko Foundation	Generation of viral vectors for gene transfer (QIAcube)	Rebecca L Cooper
C Semsarian	Clinical and genetic studies in the prevention of sudden cardiac death in the young	RT Hall Trust
N Shackel	Cellcept Australia Research Grant	Roche Australia
N Shackel, S Strasser, F Warner, G McCaughan	Pegasys Initiatives for Learning and Research Awards	Roche Australia
P Bertolino	Understanding the role of resident and donor leucocytes in liver and solid organ transplantation	Roche Organ Transplant Research Fund
B Fazekas de St Groth	Effects of cancer chemotherapy on regulatory T cells	Sydney Cancer Centre
R Martiniello-Wilks	Improving cell-based gene delivery to organ-confined and prostate cancer metastases	Sydney Cancer Centre

Grants Awarded 2007

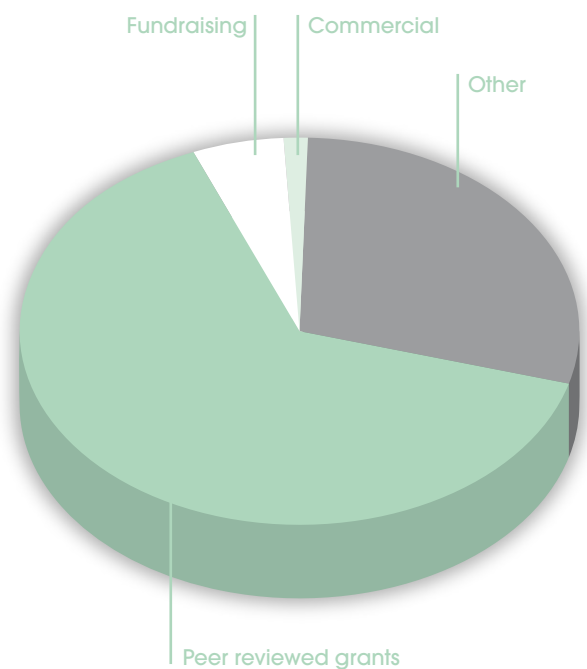
Investigator/s	Title	Granting body
E McGowan, P Xia	The role of progesterone and sphingosine kinase 1 in the regulation of endocrine responsiveness in breast cancer cells	Sydney Cancer Centre
N Shackel, F Warner	Novel gene discovery in progressive liver injury and hepatocellular carcinoma development	Sydney Cancer Centre
N Tran, J Gamble	The expression and function of micro-RNA genes in tumour angiogenesis	Sydney Cancer Centre
N Shackel	Analysis of gene expression in peripheral blood mononuclear cells in chronic hepatitis C infection	Sylvia and Charles Viertel Charitable Foundation
C Jolly	AID-induced DNA damage, DNA repair and the cell cycle	University of Sydney
M Jormakka	Liquid handling robot (equipment)	University of Sydney
A Lay	Role of sphingosine kinase-1 in the dysfunction of endothelial progenitor cells in diabetes	University of Sydney
W Weninger, L Ng	Real-time visualisation of innate immune responses during cutaneous Leishmania infection	University of Sydney
R Cornall, J Bell, C Goodnow, M Lathrop, W Britton, C Vinuesa	Immunity Infection Genomics Consortium	Wellcome Trust
J Young	Regulation of angiogenesis by microRNAs	Wenkart Foundation

Financial Highlights

	2007 '000	2006 '000
INCOME*		
<i>Peer reviewed grants</i>		
Federal – NHMRC + ARC	3,159	3,553
NSW Government	1,193	1,987
Other research grants	2,496	1,396
Total	6,848	5,540
<i>Fundraising</i>		
Donations, events + other	545	484
Bequests	24	950
Total fundraising	569	1,434
<i>Commercial</i>		
	148	45
<i>Other</i>		
	3,042	12,467
Total income	10,607	19,448
EXPENDITURE		
Research activities	7,401	7,686
Foundation	223	269
Administration and infrastructure	1,192	879
	8,816	8,834
Surplus	1,791	10,614

* The complete annual accounts are available on request.

Income 2007



2007 was a year of change for the Centenary Institute. Non-government research grants, in particular funding from the Cancer Institute NSW, grew strongly. NHMRC was stable due to the departure of researchers associated with a program grant. This was offset by the transfer of Professors Vadas and Gamble's program grant. Funding from the NSW Government fell as the current triennium of funding included a supplementary payment in 2006.

The fundraising income grew substantially when bequest income was excluded. Commercial income was stronger in 2007 due to the signing of a license agreement for the regulatory T cell invention with Becton Dickinson Inc. The difference in other income relates to Federal Government construction and fit out grant received in 2006.

Nick Pearce
Chief Operating Officer

Scientific Support Staff

Executive Director

Professor Mathew Vadas

Accounts Officer

Wilfredo Entona

Administration Assistant

Erica Belanger (until Mar)

Anna Marie Slowiaczek (Feb-Sep)

Animal Attendants

Robert Agostino

Mladen Damjancuk

Sandra Martin

Jason Martin-Powell

Claire McGuffog

Karen Ridgeway

Tan Truong

Alyssa White (until Apr)

Animal Facility Technician

Bradley Harper

Assistant Accountant

Chelsea Wang (from Aug)

Building Services Assistant

Bob Thorburn

Chief Operating Officer

Dr Nick Pearce

Communications Coordinator

Simon Milner (May-Jul)

Jane O'Dwyer (from Aug)

Communications Manager

Pearly Harumal (until Feb)

Director's PA/Office Support Manager

Helen Warwick (from Apr)

Donor Services Coordinator

Dianne Missiris (from Nov)

Facilities and Resources Manager

Jeffrey Crosbie

Finance Manager

Viraf Variava

Fundraising and Marketing Manager

Sally Castle (from Apr)

Human Resources Manager

Nanette Herlihen

IT Support

Sam Tardif

Laboratory Assistant**(Animal Facility)**

Ngoc Nguyen (until Feb)

Librarian/Administrative Support

Mary Linnane

Microinjectorist

Michelle Brownlee

Receptionist

Danielle Richards (until Jul)

Catherine Axford (from Nov)

Research Facilities and IT Manager

Dr Adrian Smith

Research Support Officer

Sonja Bates

Senior Technical Support Officer

Christopher Brownlee

Systems Administrator

Robert Middleton

Technical Officer**(Animal Facility)**

Marisa Mourelle

Technical Support Officer

Robert Salomon (from Apr)

Veterinary Manager

Francis Nottle (until Oct)

Maria Wynne (from Nov)

Research Group Staff

Cancer Drug Research

Associate Faculty

Dr John Allen

Research Assistants

Kun Kan (Edwin) Lau
Tsz Tak (Diana) Lau (until Jul)

PhD Scholars

Lye Lin Ho
Silvia Ling
Keryn Lucas

Technical Officer

Thomas Davis

International Work Experience

Anne Dwertmann (until Feb)

DNA Repair

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Dr Chis Jolly

PhD Scholars

Adam Cook
George Sharbeen

Gene and Stem Cell Therapy

Faculty

Professor John Rasko

Associate Faculty

Dr Jeffrey Holst

Senior Research Officer

Charles Bailey

Research Officer

Stephanie Flamant

Editorial Research Officer

Carl Power (from Mar)

Research Assistants

Christina Adler (Apr-Aug)
Fiona Guan (from Apr)
Marcus Hayward (until Mar)
Erin Nelson
Cynthia Ng
Jessamy Tiffen (until Mar)
Sarah Watson (from Oct)

Visiting Scientists

Stephen Larsen
Rosette Martinello-Wilks

PhD Scholars

Megha Rajasekhar
Jennifer Randall
Jessica Selwyn
Shawna Tan
Jessamy Tiffen
Jessica Vanslambrouck

Honours Student

Renuka Balasubramaniam
(Graduate Medical Program)

Immune Imaging

Faculty

Professor Wolfgang Weninger

Senior Research Officers

Lois Cavanagh (from Jun)
Nikolas Haass (from Oct)

Research Officer

Lai Guan Ng (from Jul)

Research Assistant

Mary Mouawad (from Oct)

Liver Immunobiology

Faculty

Professor Geoff McCaughan

Associate Faculty

Dr Patrick Bertolino
Dr Mark Gorrell
Dr Nicholas Shackel
Dr Fiona Warner

Postdoctoral Researcher

Dr Devanshi Seth

Research Officers

Volker Benseler (from Apr)
Peter Stapelberg (from Nov)
Denise Yu

Research Assistants

Betty Chow
William D'Avigdor (from Mar)
Melanie Eckersley-Maslin (from Nov)
Katherine Evans
Rosa Lam
Brenna Osborne
Xin (Maggie) Wang (from Aug)

PhD Scholars

Kathy Ajami
Lauren Holz
Naveed Nadvi
Emilia Prakoso
Sarah Richardson
Sumni Song
Maggie Wang
Sheen Yao

Master Scholar

Tony Chung

Honours Students

Melanie Eckersley-Maslin
Michelle Vo

International Work Experience

Philip Renner (from Oct)

Molecular Cardiology

Faculty

Associate Professor Christopher Semsarian

Research Officers

Joanne Lind
Tatiana Tsoutsman

Research Assistants

Christine Chiu
Matthew Kelly
Emily Tu (until February)

Genetics Coordinator

Laura Yeates

PhD Scholars

Christine Chiu
Jodie Ingles
Lien Lam
Emily Tu

Honours Students

Ju-En Tan
Mark Dennis
(Graduate Medical Program Student)
Trevor Kwok
(Graduate Medical Program Student)

Mycobacterial

Faculty

Professor Warwick Britton – Faculty

Associate Faculty

Dr Bernadette Saunders
Dr Nicholas West

Affiliate Faculty

Dr Jamie Triccas

Research Officer

Erika Heninger (until Jul)
Anthony Ryan (from Sept, casual)
Teresa Wozniak (from Sept)

Research Assistants

Lisa Leotta (from Feb)
Korana Musicki (casual)
Jonathan Nambiar (until Feb, casual)
Angela Pong
Elizabeth Randall (from Feb)
Mark Tan
Erin Shanahan (from December)

Technical Officer

Katie Hall (until Mar)

PhD Scholars

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Frank Kao
Carlyn Kong
Jonathan Nambiar
Anthony Ryan
Teresa Wozniak

Honours Students

Jean-Jacques Fiasson
Gayathri Nagalingham
Erin Shanahan

Structural Biology

Associate Faculty

Dr Mika Jormakka

Research Assistant

Amy Guilfoyle (from Nov)

PhD Scholar

Kimberley Vincent (from Oct)

Signal Transduction

Faculty

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Rhian Shephard (from May)

Technical Officer

Lijun Wang (from Apr)

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Research Officer

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Research Assistant

Ying Lu (from Apr)

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