Centenary Institute

annual report 06

CENTENARY INSTITUTE

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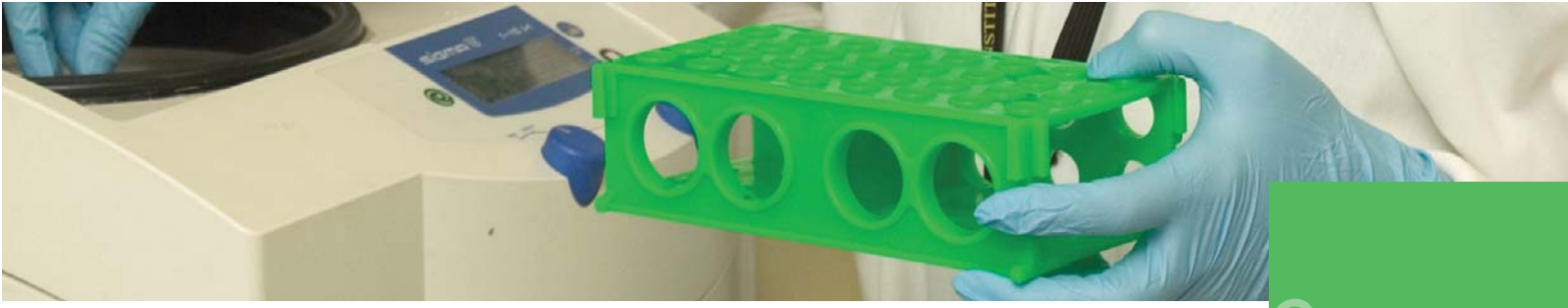
OUR LOGO

The letter “C” set in sandstone in the logo, has dual symbolism. It reflects our commitment to cancer research and, as the Roman Numeral for 100, it represents our association with the Centenaries of the University of Sydney Medical School and Royal Prince Alfred Hospital.

Our mission

To improve the
quality of life
for all Australians through
excellence in medical
research

Centenary Institute Annual Report 2006



Contents

4

2006 Highlights

- Centenary Institute's Agnes Ginges Centre for Molecular Cardiology, headed by Associate Professor Chris Semsarian, have identified several 'killer' genes believed to be responsible for sudden cardiac death (SCD) following tests on more than 400 Australian families with a history of heart disease. The group is amongst the first to report the association between two gene mutations and disease severity and increased risk of SCD.
- Associate Professor Barbara Fazekas de St.Groth, together with colleagues, has developed a new blood test to detect a rare but important subset of white blood cells, known as regulatory T cells. It is possible the test will be used in the diagnosis and monitoring of autoimmune and infectious diseases. The work was published in the *Journal of Experimental Medicine* in July and submitted as PCT patent application in August. License negotiations with a reagent company interested in marketing the kit are ongoing.
- Professor John Rasko, Head of the Centenary Institute of Cancer Medicine and Cell Biology's Gene and Stem Cell Therapy laboratory, reported in *Nature Medicine* the results of an international collaborative study involving Haemophilia patients from the RPAH. The clinical trial demonstrated the safe introduction of a clotting factor gene to achieve a substantial improvement in the levels of the essential protein, Factor IX. Insights into an immune response following the gene therapy may provide opportunities for the ultimate cure of this serious disease.
- Dr Patrick Bertolino and colleagues have shown for the first time how liver cells make contact with disease-fighting T cells in the body. Electron microscopy images captured minuscule extensions produced by the circulating T cells reaching across the openings in the vessel walls to liver cells. In hepatitis infection the openings are closed to protect the liver from damage by the immune system. This research was published in the November issues of the journals *Hepatology and Journal of Hepatology*.
- Professor Warwick Britton's mycobacterial laboratory demonstrated that variations in the purinergic receptor on the surface of a population of human white blood cells called macrophages determines the ability of these cells to kill *M. tuberculosis* and that a genetic variant (polymorphism) of the receptor is associated with the risk of developing tuberculosis in two separate populations of TB patients in Sydney. Purinergic receptors are a family of plasma membrane molecules involved in several cellular functions including vascular reactivity, apoptosis (programmed cell death) and cytokine secretion. This genetic variant of the receptor was associated with reduced capacity of infected macrophages to die through apoptosis and kill mycobacteria. In separate studies the group showed that the recently recognised cytokine IL-23 is effective for increasing the immune response and protective effect of DNA vaccines against TB and that this cytokine can compensate for IL-12 deficiency in controlling TB in mice.

Grants 2006

- NHMRC Project Grant, Genetic Modulation of the host response to pulmonary TB
  - Dr Bernadette Saunders, Professor Warwick Britton and Professor John Rasko
- NHMRC Project Grant, Manipulating immunity to *Mycobacterium tuberculosis* with novel vaccines and immunotherapeutics
  - Dr Jamie Triccas, Professor Warwick Britton
- NHMRC Project Grant, Diseases of Aminoacid Transport: Genetic, Molecular and Biochemical Studies,
  - Professor John Rasko, in collaboration with Dr Juleen Cavanaugh and Dr Stefan Broer from ANU.
- NHMRC New Investigator Project Grant Regulation of Angiotensin-Converting Enzyme 2 Expression in Liver Injury
  - Dr Fiona Warner
- NHMRC Enabling Grant, Genetic Repositories Australia
  - Professor Peter Schofield (University of NSW), Professor John Rasko and colleagues
- Sydney Cancer Centre Grant, Mesenchymal stem cell gene therapy for prostate cancer
  - Dr Rose Martiniello-Wilks
- Sydney Cancer Centre Grant, The role of CTCF and BORIS transcription factors in cancer
  - Professor John Rasko
- National Heart Foundation Project Grant, Novel insights into the genetic basis of hypertrophic cardiomyopathy: candidate genes related to calcium handling
  - Associate Professor Chris Semsarian
- University of Sydney Major Equipment Grant, NHMRC Equipment Grant and a Gift from the Clive and Vera Ramaciotti Foundation for the purchase of IVIS 100 *In vivo* Bioluminescence Imaging System
  - Professor John Rasko, Dr John Allen, Dr Patrick Bertolino, Professor Warwick Britton, Associate Professor Barbara Fazekas & colleagues,

- Perpetual Trust, Equipment Grant Prevention of sudden death in Australian families
  - Associate Professor Chris Semsarian
- Perpetual Trust, Equipment Grant Improving animal models of multi-drug resistant human disease
  - Dr John Allen and Dr Bernadette Saunders
- University of Sydney NHMRC Equipment Grant
  - Prof Geoff McCaughan, Dr Mark Gorrell,Dr Alexandra Sharland, A/Prof Paul S Haber, Dr Bret W Church, Dr Patrick Bertolino
- Rebecca L Cooper Foundation, Live animal imaging for gene expression
  - Professor John Rasko
- Rebecca L Cooper Foundation, Gene expression in pulmonary tuberculosis infection
  - Professor Warwick Britton
- Leukaemia Foundation, Non-coding gene control of myelopoiesis
  - Professor John Rasko

Patents

Hnin Aung, Pat Iversen and John Rasko USA Provisional patent filed by AVI Biopharma, Corvallis, OR, entitled 'Antisense Composition and Method for Inhibition of miRNA Biogenesis'. Inventors, September 2006.

Ling S, Allen JD. Australian Provisional Patent Application. entitled 'Assay for response to proteasome inhibitors'. Centenary Institute of Cancer Medicine and Cell Biology. Reference: 20124AUV00. Filed Dec 8, 2006.

Student Awards:

Ben Roediger (PhD student, T Cell Biology) was selected to give an oral presentation in a Plenary session at the 9th International Conference on Dendritic Cells in Edinburgh. He was awarded a Faculty of Medicine Travelling Fellowship of $5,000 to attend the meeting.

Alex Spencer (PhD student, T Cell Biology) was awarded a Keystone Travel Scholarship to attend the Determinants of Host Resistance, Susceptibility or Immunopathology to Pathogens conference at Steamboat Springs in Colorado.

Sioh-Yang Tan (PhD student, T Cell Biology) was awarded a Keystone Travel Scholarship to attend the Tolerance, Autoimmunity and Immune Regulation conference at Breckenridge in Colorado.

Scholarships

Ms Christine Chiu - NHMRC/National Heart Foundation Dora Lush (Biomedical) (Molecular Cardiology).

Mr Robin Mihrshahi - Alumni Scholarship for Health Sciences and an Australian Postgraduate Award (T Cell Biology).

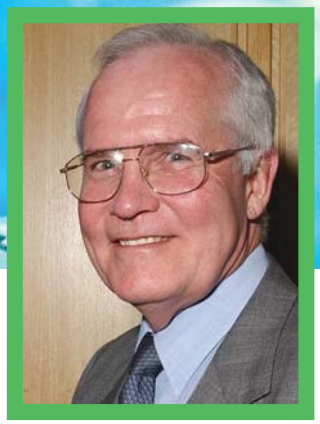
Dr Lye Lin Ho - Research Scholar Award, Cancer Institute NSW (Cancer Drug Resistance)

Dr Silvia Ling - Research Scholar Award, Cancer Institute NSW (Cancer Drug Resistance)

Dr Stephen Larsen - Research Scholar Award Cancer Institute NSW (Gene & Stem Cell Therapy Group)

Publications

2006 was a very successful year for the Centenary Institute with respect to publications in high impact journals. Researchers published a total of 57 manuscripts, books and chapters throughout the year. A detailed list can be found on pages 38 to 40 of this report.



Director's Report

2006 has been a landmark year for the Centenary Institute. The Foundation Director, Professor Tony Basten, AO, FAA, FTSE formally resigned at the end of 2005, having earlier stood down as Executive Director in October. He was appointed Emeritus Professor at the University of Sydney and stayed with Centenary in an honorary capacity until mid 2006, when he left to take up a prestigious Visiting Fellowship at Cambridge University. Professor Basten takes the best wishes and gratitude of all staff and friends of Centenary, and he leaves knowing that he has placed Centenary in a very sound position to face the future.

After an extensive national and international search the Board of Directors of Centenary appointed Professor Mathew Vadas as the new Executive Director, to take up his appointment on December 31, 2006. Professor Vadas and his team are internationally renowned research scientists, who will move from Adelaide to Sydney in the new year. He brings a depth of experience in immunology, molecular medicine and cancer medicine and, with him at the helm, the Centenary Institute is in good hands as it enters a new phase of growth in the service of our community.

2006 brought a number of notable firsts that will allow the Centenary Institute to renovate and refurbish our facilities, so that we can move confidently into the future. Most notable was a $10M capital grant from the Federal Government in the 2006 Budget. This was followed by a substantial grant from the NSW State Government, through its Medical Research Support Program, which helps fund the infrastructure costs of independent medical research institutes in New South Wales.

The formation of the Sydney Institutes of Health and Medical Research (the "Central Research Hub") will allow greater coordination across the different discipline-based research institutes affiliated with University of Sydney and the RPAH. The University is in discussions with St John's College to create a new research building for the Research Hub, on land bordering Johns Hopkins Drive and extending between St John's College and the Veterinary School. This development will create one of Australia's premier research precincts, and Centenary is pleased to be a partner in these plans, appreciating that the new building will provide the capacity necessary for the continued growth of Centenary into the future.

The year has also seen a number of senior scientific and administrative support staff retire or resign to pursue opportunities elsewhere. These include Robert Brink, Stuart Tangye and Pablo Silveira, who left with our thanks for their contribution to Centenary over many years. Their departure, however, creates opportunities for rejuvenation of Centenary's scientific staff and its scientific directions, and new recruits to the scientific staff will be featured in Centenary Newsletters. Centenary's long-standing General Manager, Ms Denyse Bartimote, left Centenary employment in January, and Dr Nick Pearce took on the role of Acting General Manager. Ms Elaine Cook resigned and Viraf Variava has taken on the role of Acting Finance Manager. Ms Judith Barry retired during 2006, and Ms Nanette Herlihen was appointed in her place. Dr Pearly Harumal, who undertook her post doctoral research in Centenary, before becoming Communications Manager and Research Society Manager within Centenary and Ms Stevie Rose, who spent some nine months with us reorganising Centenary fund raising, resigned at the end of the year. Dr Jenny Kingham resigned as Veterinary Manager and was replaced by Dr Frank Nottle.

For those retiring or leaving to take positions elsewhere, we extend our thanks for their dedicated contributions to Centenary over many years, and we welcome those joining Centenary, with a promise of an interesting and exciting life experience.

With changes in scientific staff and changes in the leadership of the Centenary Institute, the Board of Centenary has reaffirmed the place of cancer medicine in our research profile, and has committed the institute to developing greater activity in this important area, while maintaining its internationally renowned strengths in immunology and other areas of molecular medicine. The expansion of research activity will place great pressure on our physical and intellectual facilities. Centenary is committed to doubling it size within the next five years, something that will be achieved only by the availability of new physical infrastructure and the ability to recruit intellectual capital.

David Burke, AO, FAA, FTSE
Interim Executive Director

From the Chairman

2006 was kind to the Centenary Institute in a number of ways.

First, we were fortunate to have the services of Professor David Burke AO as our interim Director while we embarked on an international search for a new permanent Executive Director. David took on this role at the Centenary notwithstanding his already heavy workload as Dean of Research and Development at the University of Sydney.

I am very grateful to him both for his leadership throughout the year and the great assistance he gave us in the successful search for our new Director, Professor Mathew Vadas.

Mathew is an outstanding researcher and clinician. He was the foundation Director of the Hanson Centre for Cancer Research in Adelaide and has an internationally established reputation in the fields of inflammation and cancer. He is one of Australia's most highly cited scientists and has also been a prominent contributor to the Australian biotechnology industry.

During 2006 two of our very valued Governors, Professor Diana Horvath and Mr Paul Harris, retired from the Centenary Board after many years of service. I would like to thank them for their great service, and also welcome Mr Neil Lawrence and Mr Graham Kelly who were appointed as governors in late 2006.

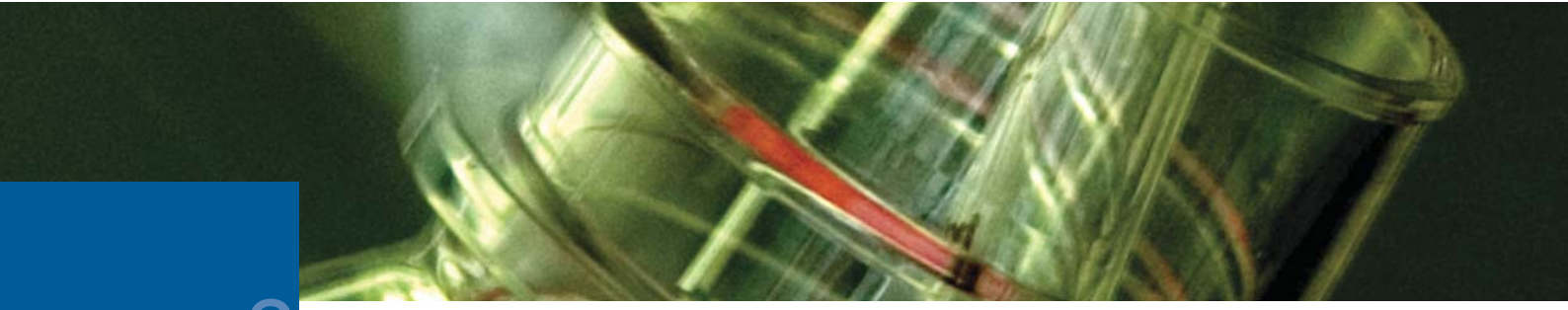
Neil is the Executive Creative Director of one of Australia's largest advertising groups and Graham has a distinguished background in law and commerce. I am sure their skills and experience will be of considerable benefit to the Centenary.

We were also fortunate to have the continued financial and moral support of the State and Commonwealth Governments, the Sydney South West Area Health Service, the University of Sydney and many individual donors. We were especially grateful to receive a $10 million grant from the 2006 Commonwealth Budget to upgrade and expand our facilities, including our animal, PC3 and flow cytometry facilities.

But most important of all, we are extremely fortunate to have the continued support of the Centenary's great researchers and staff who are responsible for the great work that is detailed throughout this report. I thank them for their tremendous dedication and assure them, on behalf of all my fellow governors, that we will do whatever we can to enable their research to flourish.

The Hon. Michael Egan,

Chairman.



Report from Incoming Executive Director

Whilst this Annual report of the Centenary Institute encompasses the 2006 calendar year, and I only started my tenure as Executive Director in January 2007, I felt a short note with glimpses into the future was appropriate.

But first of all I want to note that Centenary has been and still is regarded as one of the leading independent medical research institutes (MRI) in Australia, one with an enormously talented staff, and one with the goodwill of its neighbours and 'shareholders', the University of Sydney and Sydney South West Area Health Service (SSWAHS). To lead such an Institution is thus an enormous responsibility and an honour.

The establishment of Centenary and its maturation to its current prominence was due to Professor Tony Basten's vision and leadership. Tony left behind a tradition of exacting scientific standards, competition on the international stage and of recruiting and retaining the leaders and opinion makers in medical research. Centenary will be always in his debt.

I also wanted to acknowledge the contribution of the Interim Director of Centenary, Professor David Burke, who held the reins for more than a year. David's had an unique ability of understanding the key issues pertaining to the health and prosperity of Centenary, and making the adjustments necessary to hand over a place with a new outlook on the future. I am happy to say that David has continued to be an enormous supporter of Centenary and a wise advisor to its Director from his substantive position of Dean of Research & Development. I look forward to our continual interactions.

Now to the future. The Centenary Institute, soon to be called Centenary Institute of Cancer and Molecular Medicine, addresses many of the important illnesses of adults in the Western and Developing worlds. Its focus on adult diseases should not change. The growing importance of cancer in an ageing population, and being located in a campus that looks after the largest cancer load in NSW, will make cancer research, in all its manifestations, and increasing interest, and one we shall pursue in conjunction with the Sydney Cancer Centre, SSWAHS and the University Sydney.

It will be essential to constantly reinvigorate our science, and this means the recruitment of new talent and using Centenary as a meeting place for not only scientists but clinicians and lay people interested in a longer healthier life. We shall make efforts to increase the frequency and reach of meetings within the Centenary.

Finally the reality of increasing scientific activity and funding the infrastructural needs of Centenary means that the Institute will have to increase from its current staff of 110 to approximately 350-400 over the next years. Our current building has the capacity to hold approximately 170 individuals- hence we shall look at possibilities of adding to our physical size.

I look forward to reporting to you next year with the details of our plans and progress in their implementation.

Professor Mathew Vadas
Executive Director

Board of Governors

The Honourable Michael Egan

The Honourable Michael Egan was appointed as Chair of the Board of Governors in September 2005, as a nominee of the Vice Chancellor of the University of Sydney, Gavin Brown. He is the former Treasurer of NSW and has held a number of ministerial positions. Mr Egan was a Member of Parliament for 25 years and is the longest serving Treasurer of NSW (1995-2005) since the introduction of responsible Government in 1856.

The Honourable John Brown *AO FAMI*

The Honourable John Brown AO FAMI was appointed as a Governor in 2001. Formerly the Member for Parramatta in the Federal House of Representatives for thirteen years from 1977, during which time he held various Ministerial portfolios including Arts, Sports, Environment and Territories. In 1986 Mr Brown was named Australian of the Year by the Australian Newspaper. Mr Brown is the Emeritus Chairman of the Tourism Task Force and is the Founder and Patron of the Sport and Tourism Youth Foundation.

Professor Andrew Coats

Professor Andrew Coats was appointed as a Governor in 2004 in his capacity as the Dean of the Faculty of Medicine, University of Sydney. He is a member of the Board of a number of Institutes affiliated with University of Sydney including the Woolcock Institute, Heart Research Institute, George Institute of International Health and the Menzies School of Health Research and is Chairman of the Australian Health Informatics Council.

Mr Alastair Davidson MICA (Scot)

Mr Alastair Davidson MICA (Scot) was appointed as a Governor in 2004. He has held executive positions in the banking and financial services industry for 15 years in the UK, USA and Australia including Salomon Smith Barney in Sydney for eight years as co-head of its new product group, specialising in equity derivatives. He is currently Managing Director of Aurora Funds Management based in Sydney.

Ms Di Gill

Ms Di Gill was appointed Governor in 2006. She is Executive Director of RPAH, one of the largest tertiary referral hospitals in New South Wales. She has extensive experience in health having previously held the position of Director of Nursing Operations at RPAH. She obtained her Masters of Public Health at the University of Western Sydney and 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 also an Associate Fellow of the Australian College of Health Service Executives.

Mr Graham Kelly

Mr Graham Kelly was appointed as a Governor in November 2006. He is non-executive Chairman of Tishman Speyer Office Trust, Centrebet International Limited, Colonial First State Private Capital Limited and a non executive director of several non-listed companies including FreshFood Australia Holdings Pty Limited and Oasis Fund Management Limited. He is a consultant to Freehills law firm, the Inspector of the Independent Commission Against Corruption and has been a Director of he Medical Research and Compensation Foundation. Mr Kelly served as Managing Partner of the Sydney/Brisbane/Canberra offices of a major Australian law firm, Freehills, from 1991-1995, and also as National Chairman of the Firm from 1993-1995. He was formerly Chairman of Cyptome Pharmaceuticals limited. He has an Honours degree in Law from the Australian National University.

Mr Neil Lawrence

Mr Neil Lawrence was appointed as a Governor in November 2006. He is currently the Executive Creative Director of Australia's largest advertising group, STW Group. He has worked in the advertising industry for over 20 years. Neil's clients include: The Commonwealth Bank, Apple, Sony, Mitsubishi, The Federal Government, Cadbury, Masterfoods, St George Bank, Colgate, American Express, AAPT, FOXTEL, The Australian Newspaper, The Sydney Morning Herald, Qantas and many charities such as the Fred Hollows Foundation and The Garvan Institute. In 1997 the agency Whybin Lawrence TBWA was formed with Neil as its CEO and Executive Creative Director. Between 1997 and 2004 the agency grew from 5 to over eighty staff and was voted 'Emerging Agency of the Year' in 1997 and 'Sydney Agency of the Year' in 1999. He has a Bachelor of Arts (Psychology and Politics) and a Bachelor of Social Work.

Professor John Mathews AM

Professor John Mathews AM was appointed as a Governor in October 2000. He was the Founding Director of the Menzies School of Health Research in Darwin for fifteen years until 2000 when he was appointed Head of the National Centre for Disease Control, Health and Aged Care as well as a Visiting Professor of the University of Sydney. Professor Mathews has been a member of numerous advisory and review groups for the NHMRC and the Federal Government.

Ms Sam Mostyn

Ms Sam Mostyn was appointed as a Governor in 2003. She has an extensive background in law, corporate affairs, human resources and politics, and was a senior advisor (communications) to the former Australian Prime Minister, The Hon PJ Keating. Ms Mostyn is Group Executive of

Culture and Reputation at IAG and serves on the Academic Advisory Board of the Australian Institute of Management and the Boards of the NSW Premier's Council on Active Living and the Sydney Festival. She is a Trustee of the Australian Museum and is a Director of Insurance Australia Group Services Pty Limited, NRMA Life Limited and NRMA Staff Superannuation Pty.

Professor Michael Reid

Professor Michael Reid was appointed Governor in 2005. He was Director General of the Ministry for Science and Medical Research, which has overall responsibility for planning and coordinating science, innovation and medical research in NSW. He was formerly Director of the Policy and Practice Program at the George Institute for International Health, University of Sydney. He held the position of Director General of NSW Health for five years and prior to that was Managing Director of a consulting company with government and NGO projects in Australia, Asia and the Pacific.

Mr John Samaha

Mr John Samaha was appointed as a Governor in 2003. He has an extensive background in law specialising in litigation, regulatory investigations and risk management strategies, which often involve mediation outside the formal court process. He joined Malleson Stephen Jaques in 1998 and in 1992 was seconded to the Chairman's Office, Australian Securities Commission as adviser to the Director of Enforcement. He is Partner in the Dispute Resolution Group, Malleson Stephen Jaques.

Professor Mathew Vadas

Professor Mathew Vadas was appointed as a Governor in January 2007. He trained in medicine at the University of Sydney and as a physician at the RPAH 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). He is one of Australia's most highly cited scientists. He 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 has also served as consultant to several international pharmaceutical companies as well as national biotechnology enterprises. 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.

Our History

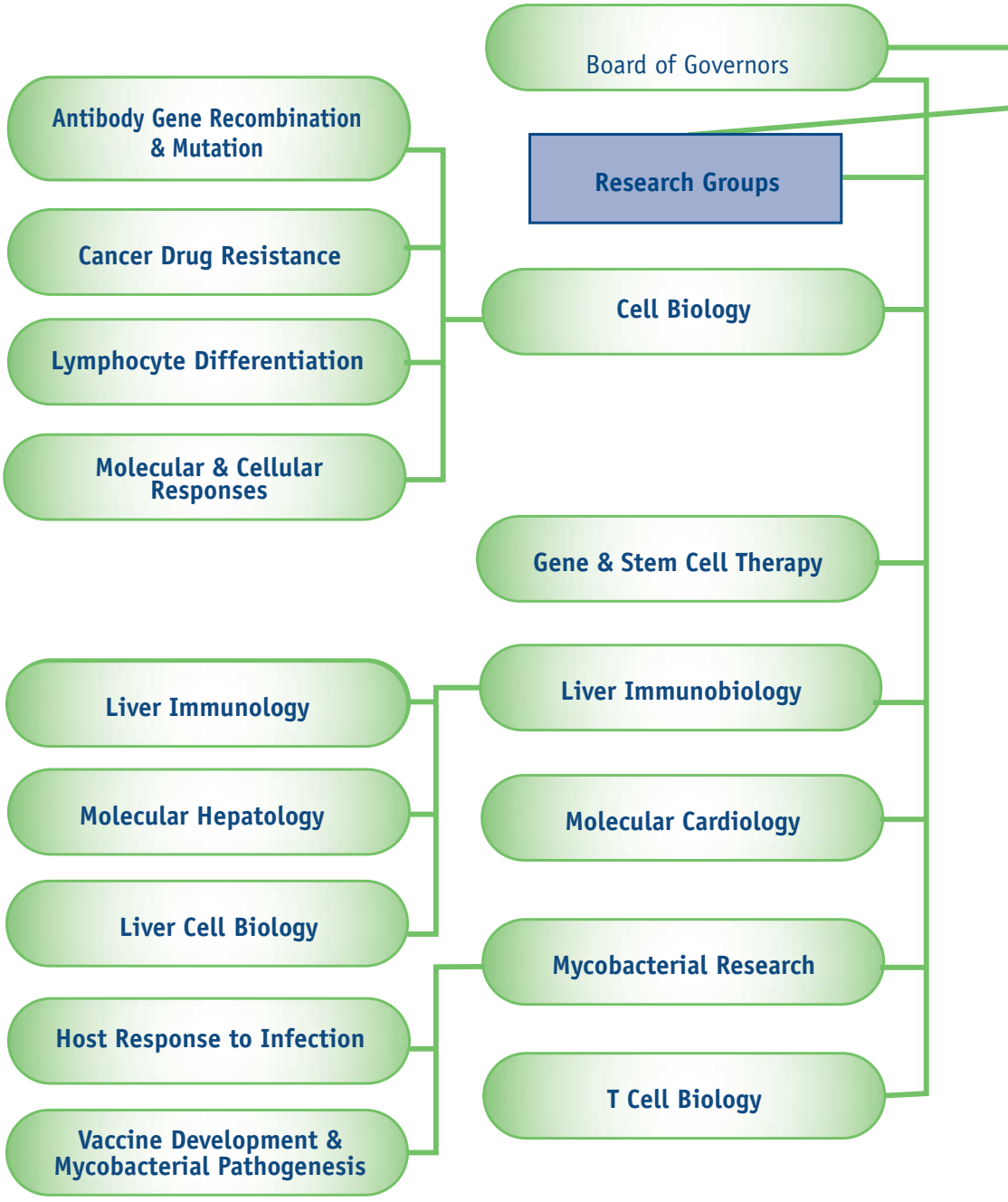
The Centenary Institute was conceived in 1982 to commemorate the centenaries of the University of Sydney Medical School and the RPAH. In 1989 it became a functioning entity under an Act of the NSW Parliament based on the Founding Director's, Professor Antony Basten, Federal Centre of Excellence. In 1994 Centenary moved into its purpose-built facility capable of accommodating a research team of up to 150 career investigators, trainees and support staff. Located in the grounds of RPAH adjacent to the Medical School and University campus, the Institute's facilities include a specific pathogen free grade animal house, mouse cardiac physiology and function facility, physical containment (PC) 3 facilities for working on human pathogens such as tuberculosis, transgenic service, a state of the art flow cytometry facility, library with online capability and a lecture theatre. The Centenary Institute has formal affiliations with the University and Hospital, providing opportunities for students to become involved in research as well as the translation of basic discoveries into clinical practices.

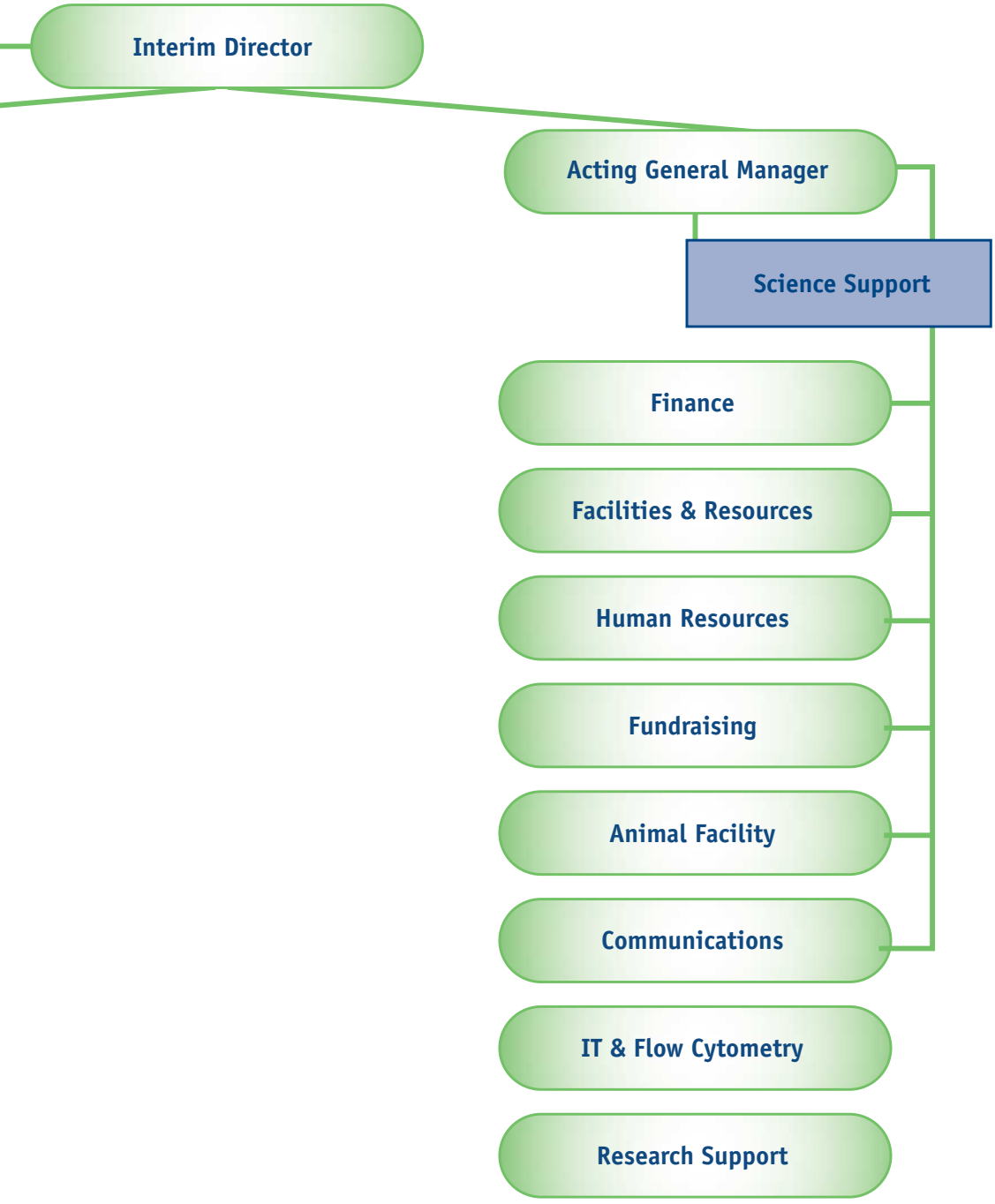
Centenary has an internationally competitive, multidisciplinary research team comprising some of the very best young scientists from major centres overseas as well as Australian researchers who have studied and/or completed fellowships on international campuses. Centenary has published in excess of 780 articles in refereed journals and books, its staff has in excess of 1200 presentations at international and national conferences since 1992, and it has attracted over $100 million dollars in grant funding to the campus.

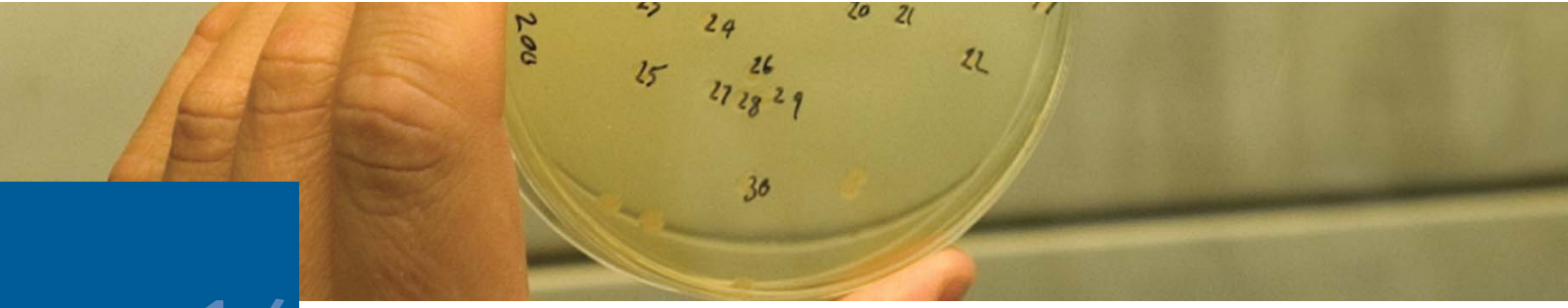
The Centenary Institute has a proud record of training PhD students; since 1992, there has been a total of 48 graduates. On completion of their PhDs, students have gone on to successful postdoctoral studies at many of the world's leading institutions including Oxford, Stanford and Yale Universities.

In 2007, the Centenary Institute enters a new phase of its history with the appointment of Professor Mathew Vadas MB BS, FRACP, FRCPA, PhD, DSc as Executive Director. Professor Vadas trained in medicine (with First Class Honours) at the University of Sydney and as a physician at the RPAH before completing a doctorate at the Walter and Eliza Hall Institute in Melbourne. He was a chief initiator and Inaugural Director of the Hanson Centre for Cancer Research (now Hanson Institute) and is one of Australia's most highly cited scientists with citations in excess of 16,000. He has over 200 publications and 20 patents. Professor Vadas has also contributed strongly to the Australian biotechnology sector, being involved variously as founder, Chair of the SAB and acting CEO in of two ASX listed biotechnology companies.

Organisational Chart




Interim Director
Acting General Manager
Science Support
Finance
Facilities & Resources
Human Resources
Fundraising
Animal Facility
Communications
IT & Flow Cytometry
Research Support



Research Groups

The Centenary Institute's research programme is based on a combination of cell biology, molecular medicine and immunology. Research is carried out by eight teams, namely B Cell Biology, Cancer Drug Resistance, Gene and Stem Cell Therapy, Liver Immunobiology, Lymphocyte Differentiation, Molecular Cardiology, Mycobacterial Research and T Cell Biology.

Cell Biology

Program Head: Professor Antony Basten

The research activities of the Cell Biology Laboratory encompass five different programs managed by independent scientists with the overall support and leadership of the Director. Dr Robert Brink of the Molecular and Cellular Responses Project investigates the signals inside cells, which are responsible for cell survival versus death.

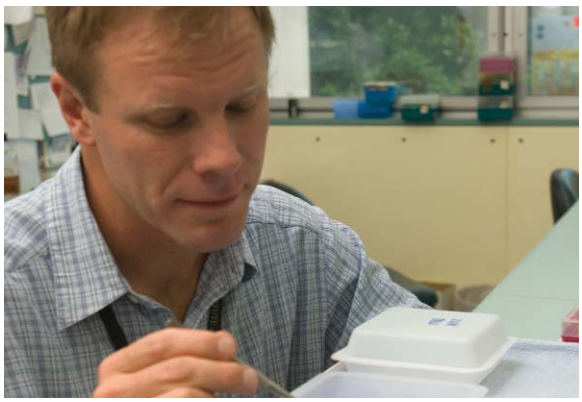
The Antibody Gene Recombination & Mutation Project led by Dr Chris Jolly investigates the mechanisms involved in immunoglobulin class switching and somatic hypermutation, which produce the diversity of antibodies in our immune system. Dr John Allen's Cancer Drug Resistance lab investigates the mechanisms of resistance to anticancer drugs and ways in which this problem can be overcome. The Lymphocyte Differentiation lab led by Dr Stuart Tangye investigates the regulation of the human immune system and how it responds to infection.

Highlights:

- Elected to honorary membership of Australasian Society for Immunology
- Awarded Visiting Fellowship to MRC Laboratory of Molecular Biology and Trinity College, Cambridge to work with Professor Sir Gregory Winter FRS on the role of antibodies in health and disease.

Molecular and Cellular Responses

Dr Robert Brink



The group's work focuses on how B cells first develop in the body and then produce antibodies in response to invading structures (antigens). The major tools used are genetically modified mice. These mice i) allow the visualization of B cells as they develop and respond in the body, and ii) facilitate the manipulation of specific genes in vivo. The laboratory has also recently developed a range of genetically engineered protein antigens (mutated hen-egg lysozyme molecules) that have provided clues on how anti-vaccine antibody production may be optimised.

Highlights:

- demonstration that the TRAF3 protein is a key regulator of B cell development
- publication of our work showing that the strength of the interaction between antigen and B cell controls the speed of antibody production

Antibody Maturation and DNA Repair

Dr Chris Jolly

Antibodies form our first line of defense against most infections by 'tagging' the infectious organism for destruction. Antibody specificities differ, with each antibody matching a different surface 'epitope'. As an immune response against an infection matures, the tagging efficiency of specific antibodies dramatically improves in a matter of only days. This improvement is achieved by the active mutation ('hypermutation') and rearrangement ('class-switching') of antibody genes in B cells responding to the infection. The goal of our research is to understand the molecular mechanism of antibody gene mutation, and to understand how this pro-survival mutation pathway is distinct from mutation pathways that lead to lethal cancer.

Antibody mutation occurs in 2-phases: dC/dG base pairs are mutated first – by the AID protein. Subsequent mutation of dA/dT base pairs appears to occur when the DNA repair machinery attempts to correct the mutations originally made at dC/dG bases by AID. An hypothesis to explain mutation of dA/dT base pairs in antibody genes is that repair of AID-induced dC/dG mutations occurs in G1-phase of the cell cycle when nuclear dUTP levels are high, leading to mis-incorporation of dU bases (in place of dT bases) opposite dA bases in the repaired DNA. In 2006, we focused on testing this hypothesis using recombinant DNA techniques.

Highlights:

- Used retroviral transduction to show that over-expression of a dUTPase enzyme in primary mouse B cells alters the spectrum of antibody gene mutations. This experiment supports the hypothesis that the ratio of dUTP to dTTP in the nucleus influences antibody gene mutation. Experiments are in progress to determine the mechanism by which nuclear dUTP influences mutation.
- Used gene-knockout technology to show that the DNA-PKcs DNA repair protein simultaneously inhibits AID-induced gene conversion and promotes AID-induced point mutation in the chicken DT40 B cell line. This experiment suggests the previously unsuspected possibility that the DNA-PK complex plays a role in antibody gene mutation in mammals. We will test this when we have obtained DNA-PKcs-knockout mice.

Cancer Drug Resistance

Project Leader: Dr John Allen

Averaged across the major forms of cancer, more than half of all patients can currently be cured, mainly by 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. It falls to one in five. Tumours often respond poorly to the available drugs or else respond initially but then become resistant. This doesn't mean that the drugs in themselves are ineffective - we take inspiration from the fact that they sometimes work very well. If the reasons for why they work differently were understood *then something could be done about it*.

It is for the above reasons that the Cancer Drug Resistance Group works to improve the scientific basis of chemotherapy by understanding the cellular and molecular processes underlying drug resistance and related problems of drug toxicity and pharmacokinetics. We aim to identify new mechanisms of anticancer drug resistance, to evaluate their clinical significance, and to identify and pursue ways of overcoming them. We focus on resistance to new and promising anticancer drugs that are being applied to treating common, recalcitrant tumours, including melanoma, multiple myeloma and prostate cancer.

The lab is fortunate to have comprehensive *in vitro* models for investigation of candidate cellular mechanisms relevant to drug resistance. Findings are followed up in preclinical models and by analysis of molecular changes in patient tumour samples that can be related to outcome of drug treatments.

Interactions of new anticancer drugs with multidrug transporter proteins.

Multi-drug transporter proteins remove toxins encountered in the diet or produced by normal metabolism, from cells, tissues, organs and the body as a whole. Many anti-cancer drugs resemble such toxins, so the multidrug transporter proteins interfere with their uptake into the body and into cancer cells. We are systematically investigating how the multi-drug transporter proteins affect the efficacy of promising new anti-cancer drugs. Some of these beneficial new drugs have low toxicity compared to traditional anti-cancer drugs and may be taken daily over long periods of time, with obvious benefits for the management of cancer. Under this type of treatment, however, the eventual emergence of drug resistance is almost inevitable. We collaborate in this work with the Sydney Cancer Centre, RPAH, The Children's Cancer Institute Australia, several other research centres, and pharmaceutical companies.

Regulation of multidrug transporter proteins.

In specific types of cancer the presence of multidrug transporter proteins predicts poor outcomes for chemotherapy. A good example is paediatric neuroblastoma, where high levels of the MRP1 and MRP4 transporters and the NMYC oncogene all indicate a poor prognosis. Cellular and molecular work suggest that the MRP4 transporter is directly upregulated by MYC oncogenes, which are frequently activated in common adult cancers. In addition, MRP4 is a marker of progression in prostate cancer, possibly because its expression turns out to be an androgen-regulated. Elucidating a relationship between drug resistance and commonly activated oncogenes would be very significant for treatment of specific cancers, such as the use of Irinotecan for advanced colon carcinoma. In pursuit of this goal, we collaborate with the Garvan Institute of Medical Research and the Children's Cancer Institute Australia.

The contribution of defective apoptosis pathways to drug resistance in melanoma.

Australia has the world's highest incidence of melanoma. It is one of the cancers most resistant to chemotherapy. Left too long untreated, melanoma is invariably fatal. We focus on the reluctance of melanoma cells to undergo apoptosis when damaged by anticancer drugs. Analysis of resistance to apoptosis is technically challenging because propagation of melanoma cells *in vitro* invariably alters their properties in this respect. Hence we are pursuing 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. At time of writing, we are generating melanomas and about to try treatments that may be prophylactic. This work is in collaboration with leading apoptosis groups at the Walter and Eliza Hall Institute in Melbourne and the melanoma group at the University of Newcastle.

Drug resistance in haematological cancer

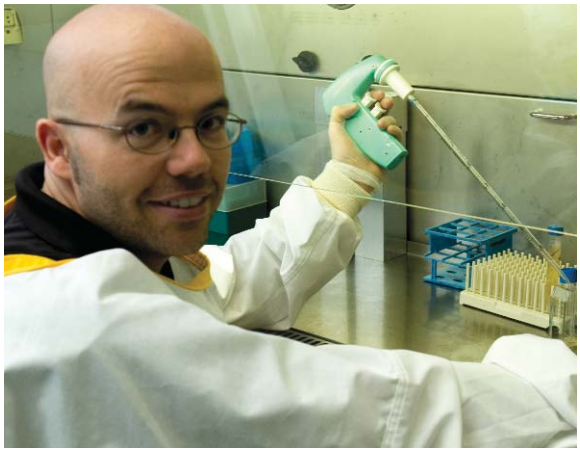
Multiple myeloma is an incurable cancer of the plasma cells, cells that produce antibodies to fight infection. These cells have a revved-up mechanism for dealing with errors of protein folding during the production of large amounts of antibodies for secretion, a quality control and garbage disposal system known as the Unfolded Protein Response. We suspect that this is what makes myelomas resistant to many drugs but, conversely, susceptible to a new class of drugs, the proteasome inhibitors. Initial results indicate that a simple marker of the unfolded protein response can predict the sensitivity of myelomas to the proteasome inhibitor Bortezomib. If it pans out, it will enable haematologists to determine beforehand which patients are likely to benefit from proteasome inhibitors and thus expedite their treatment while avoiding the delay, discomfort and disappointment and expense entailed in trying to treat patients who are unlikely to respond to the drugs. Preliminary data suggest that this technique might also predict responsiveness to the drugs in other types of human cancers, including lymphomas, breast cancer or prostate cancer. We are pleased to collaborate in this work with our neighbours at the Haematology Institute, RPAH.

Highlights:

- Identification of a molecular marker for responsiveness to proteasome inhibitors in multiple myeloma.
- Establishment of a mouse melanoma model for investigating the contribution of defective apoiptosis pathways to drug resistance.
- A multidrug resistance gene, *MRP4*, is directly upregulated by oncogenes of the *MYC* family, which are frequently over-active in common cancers.
- A side effect of daily use of the new drug for chronic myeloid leukaemia (CML), Imatinib, is that it could promote photosensitivity and other toxicities as a result of abnormal retention of porphyrin metabolites.

Lymphocyte Differentiation

Project Leader: Dr Stuart Tangye



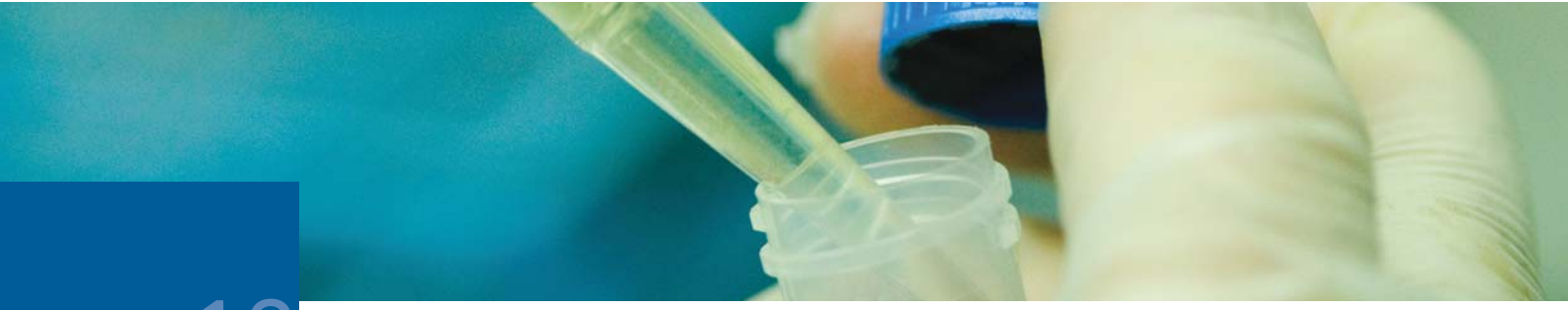
Research performed in our laboratory is focused on understanding the regulation of the human immune system, both in normal individuals, as well as in patients with defined diseases, such as immunodeficiencies (individuals who have defects in their ability to mount a sufficient immune response, and are thus susceptible to infection with specific pathogens, such as viruses). We are particularly interested in understanding the mechanism by which the immune system responds following infections or vaccinations, thereby providing us with a "memory" of the initial response so that following subsequent exposure to the same infection, our immune systems will respond more rapidly.

Areas of Research

- Intrinsic differences in the biological behaviour between naïve B cells (that have not seen antigen) and memory B cells (those that have previously responded to antigen)
- The signals required to generate effector B cells from populations of naïve and memory B cells
- The development of memory and other effector B cells in vivo
- The regulation of effector function of subsets of CD4+ T cells
- The human immunodeficiency X-linked lymphoproliferative disease

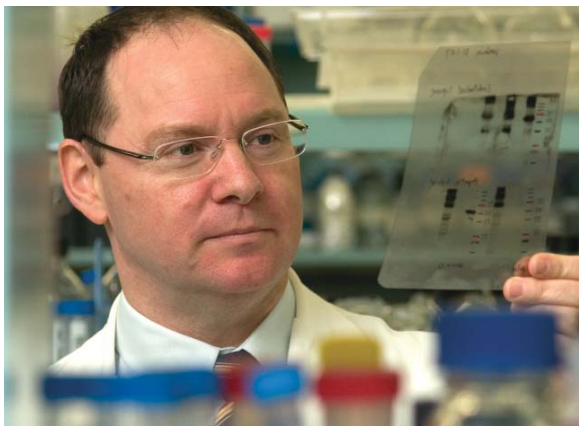
Highlights:

- identifying human transitional B cells, and their potential contribution to human immunodeficiencies (published in the Journal of Immunology, Feb 2006)
- characterising B-cell development and differentiation in the human immunodeficiency X-linked lymphoproliferative disease (published in the Journal of Clinical Investigation, Jan 2006)



Gene and Stem Cell Therapy Program

Program Head: Professor John Rasko



The broad aims of the Gene & Stem Cell Therapy Program are to overcome the barriers to successful human gene therapy, develop models to understand the biology of adult stem cells and shed light on disease mechanisms including cancer and genetic disorders. The group undertakes research in five areas, namely gene therapy, stem cell biology, gene silencing, genetic disorders and cancer biology. 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 overall focus of our 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. 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. Haemopoietic stem cells have the capacity to divide to produce billions of progeny cells throughout a lifetime and it is these progeny that form the basis of our immune system. We have a well-established program studying HSCs and adult mesenchymal stem cells that are also present in the bone marrow. This is integrated with a model we have developed for autologous haemopoietic stem cell transfer in non-human primates.

Models of systemic and stem cell gene delivery

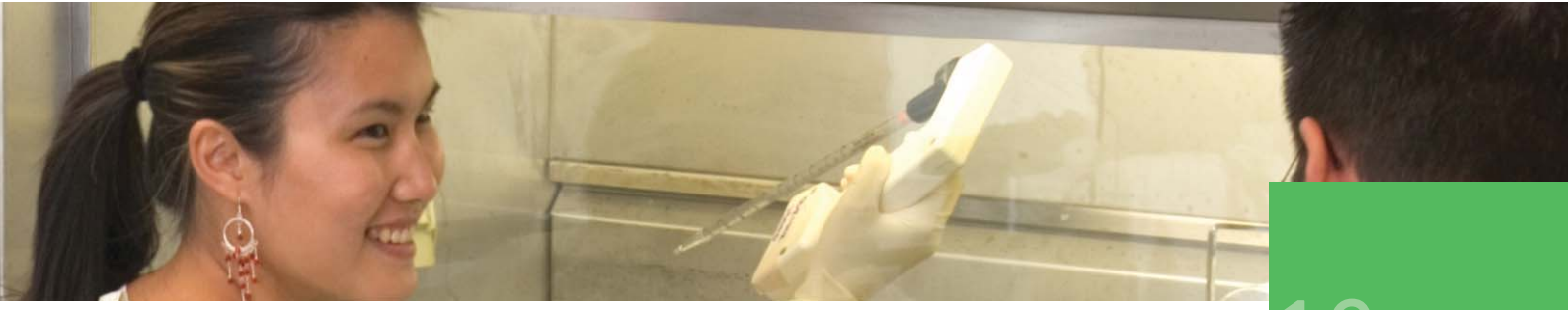
We have established mouse and nonhuman primate models to test novel agents for their ability to mobilise haemopoietic progenitors and stem cells. Using this model we can investigate means to improve the mobilisation of HSCs and other stem cell populations into the peripheral blood. We have established the SCID-repopulating cell (SRC) assay using NOD/SCID mice to evaluate different mobilisation regimens and to investigate the long-term repopulating 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.

Gene silencing and mechanisms of gene expression control

An understanding of the way haemopoiesis is regulated in the body has widespread relevance to diseases like leukaemia and the way they are treated. MicroRNAs recently identified in the phenomenon of gene silencing are found to be intricately involved in the control of cell development and differentiation. The role of microRNAs in normal and malignant haemopoiesis is only now being revealed. We are studying the importance of this new class of regulatory molecules in order to discover their previously hidden functions in normal blood cells and leukaemia in humans. Already we have developed a number of exciting molecular techniques for identifying and quantifying microRNA expression in cells. Ultimately this project may lead to novel treatments involving gene therapy and bone marrow transplantation.

Aminoacidurias

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 two groups from Canberra and its importance has been recognised by successful peer reviewed grants from both the NHMRC and ARC. During 2005 we further dissected the various mutations involved in Hartnup disease and reported the results of further functional studies in several publications. The mutations found in SLC6A19 were shown either to completely abolish or impair amino acid transport. During 2006 we have embarked on a wider analysis of other diseases affecting aminoacid transport including imminoglycinuria to provide a clearer understanding of these intriguing inborn errors of metabolism.



Cancer Biology

Since 2001 we have collaborated with the group of Victor Lobanenkov at the NIH in Washington DC, USA, examining the role of the tumour suppressor gene CTCF, and its related cancer/testis gene BORIS. BORIS is a putative oncogene, which is normally expressed in the testis, however becomes overexpressed in many different types of tumors. During 2006 we have shown that BORIS acts an oncogene when over expressed in cell lines, suggesting that its expression in tumours may be an early event in their transformation. This study will be supported over the next 3 years by the Cancer Institute of NSW in the form of an Early Career Development Fellowship for Dr Jeff Holst.

Highlights:

- With international collaborators, in a world first, achieved safe and successful short-term gene therapy for the bleeding disorder haemophilia, published in Nature Medicine.
- Optimised and characterised adult stem cell collection technologies and their therapeutic use in diseases of the blood and muscle.
- Consolidated gene transfer technologies using adenovirus, adeno-associated virus, retrovirus and lentivirus vectors.
- Refined techniques to study transcription factors and a new set of molecular control molecules (microRNAs) present in normal and cancerous human cells.
- Showed that a special type of stem cell that forms the support structure of bone marrow can be coaxed out of its niche – paving the way for their easy collection prior to therapeutic transplantation.

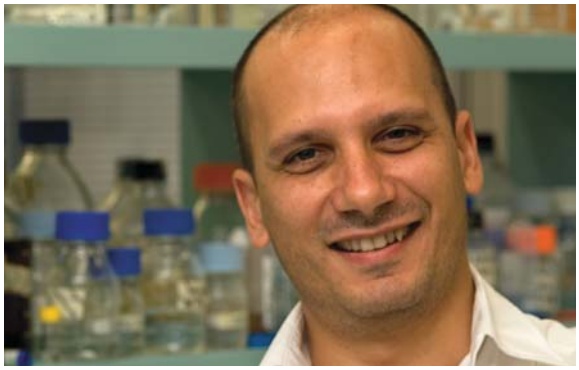
Liver Immunobiology

Program Head: Professor Geoffrey McCaughan

The Liver Immunobiology Group has a number of distinct research programs. Dr Patrick Bertolino leads the Liver Immunology program, Dr Mark Gorrell the Molecular Hepatology program, Dr Devanshi Seth the Alcoholic liver disease program, Dr Nick Shackel the Liver Cell Biology program and Dr Fiona Warner the Angiotensin converting enzyme and liver disease program. Transgenic, genomic and post-genomic advanced technologies are applied to understanding the molecular pathogenesis of liver injury, the biochemistry and biology of prolyl oligopeptidase in liver diseases, and the cellular basis of liver immune responses and non-responsiveness in infection and transplantation.

Liver Immunology

Dr Patrick Bertolino

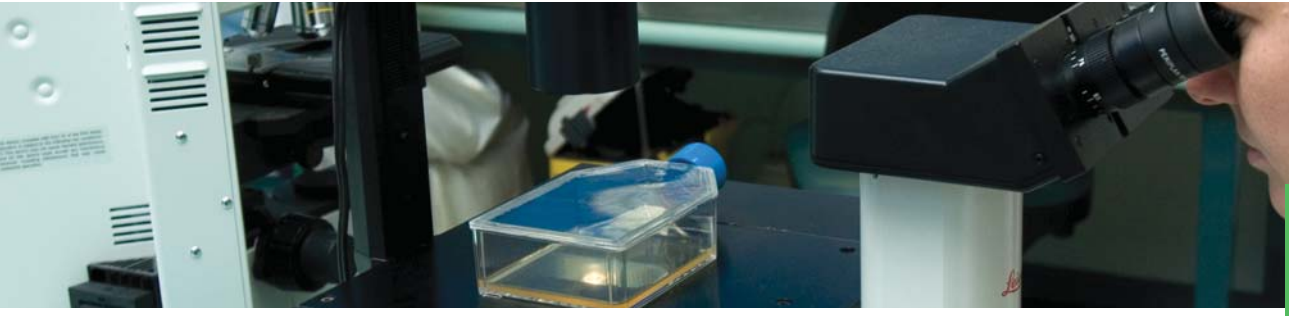


Our research is particularly focused on the liver, an organ with unique tolerogenic properties. In many species, liver transplants are spontaneously accepted across a complete MHC mismatch. The tolergenic properties of the liver may be exploited by viruses (ie Hepatitis C) that persist as chronic infections. The broad aims of our group are to understand the interactions between T lymphocytes and hepatic cells, the parameters that determine the balance between tolerance and immunity in the liver as well as those leading to chronic hepatitis.

We are particularly interested in dissecting complex mechanisms of liver-induced tolerance of CD8+ T cells, which are responsible for graft rejection and virus clearance. 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 generally accepted view that primary T cell responses can only be initiated in lymphoid tissues (lymph nodes and spleen). 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.

Last year we dissected and identified the adhesion molecules involved in this retention. Continuing this work we have identified for the first time how lymphocytes circulating in the blood interact with hepatocytes despite an endothelial barrier. Understanding how this type of interaction occurs is very important as the process might play an important role in hepatotropic viral infections in which hepatocytes represent the main APC.

In collaboration with Prof David Le Couteur and Ms Alessandra Warren (Concord Hospital, NSW) who are world-leading experts in studying liver endothelial cell fenestrations, we have used electron microscopy technology to show that intrahepatic lymphocytes interact with hepatocytes through cytoplasmic extensions penetrating the fenestrae of the liver sinusoidal endothelial cells. This is the first demonstration of direct contact between parenchymal cells and circulating T lymphocytes. This work, recently published by Hepatology, was the subject of an editorial review and appeared on the front cover. It has also been selected as a research highlight by EarthOrbit and the Sydney Morning Herald (9th November 2006). In a follow-up study published in the Journal of Hepatology, we demonstrated that following injury (hepatitis), the liver protects itself from further damage and contact with T cells by closing the pores present in blood vessel cells. Our study suggests that regulating the size and number of these pores might be used as a strategy to prevent chronic liver disease or regulate liver damage by the immune system.



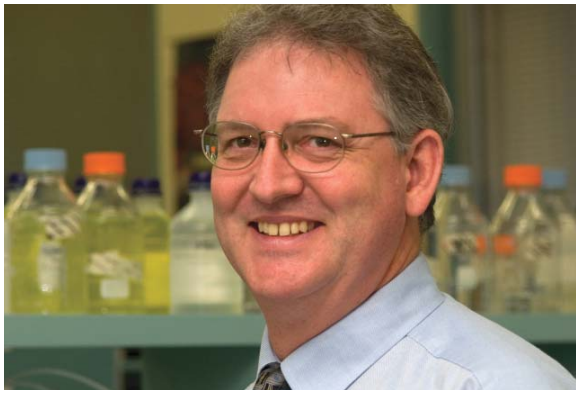
We are also characterising the phenotype, function and fate of T cells activated in the liver and compare these parameters to those of T cells activated in the LN. We think that these studies will provide important clues to understanding mechanisms associated with the "liver tolerance effect".

Highlights:

- We have proposed a new model to explain the mechanisms regulating intahepatic immunity that might play an important role in establishing chronic hepatitis C infection.
- We have demonstrated for the first time that early antigen-specific T cell retention and primary T cell activation in the liver is predominantly ICAM-1/LFA-1 dependent.
- We have identified a new type of interaction between T cells and hepatocytes through liver sinusoidal endothelial cell fenestrations.

Molecular Hepatology

Mark Gorrell



The research led by Mark Gorrell is focused upon understanding the biological roles and biochemistry of enzymes of the dipeptidyl peptidase IV [DPIV] gene family and harnessing that knowledge to improve human health, particularly liver diseases and disorders. We also study the role of an unrelated gene, discoidin domain receptor 1 [DDR1], in liver biology and in 2006 we manufactured the liver/brain enzyme Kynurenine Aminotransferase 1 [KAT-1] to use in basic pharmacological research.

Our Molecular Hepatology research has four aspects:

1. Contributions of the DPIV family to liver fibrosis.
2. The biochemical and enzymological characterisation of new DPIV family members DP8 and DP9.
3. Roles of DP8 and DP9 in cell biology and mammalian biology.
4. Roles of DDR1 in liver biology.

The DPIV family.

The DPIV family of enzymes consists of DPIV, DP8, DP9 and fibroblast activation protein (FAP).

We previously found that FAP levels increase in human liver in proportion to the extent of scarring. We are examining the role of FAP in two ways: In cell culture and in a mouse strain that is genetically unable to make FAP. We found that FAP deficient mice and DPIV deficient mice exhibit less liver scarring and inflammation than normal mice. We found that this reduced scarring relates to the presence of fewer B lymphocytes. We made and purified FAP protein and used that protein to find that none of the existing DPIV inhibitors were very effective against this enzyme.

We were first to clone DP8 and DP9. DP8 and DP9 are used to ensure that DPIV inhibitors are DPIV selective. The major use for DPIV inhibitors under development is as a novel therapy for type 2 diabetes. Merck has United States FDA approval to market their DPIV inhibitor under the brand name Januvia. Their data indicates that DPIV inhibition improves pancreatic beta cell function and stalls the worsening control of glucose metabolism. Type 2 diabetes and insulin resistance are part of the metabolic syndrome that often involves fatty liver, which is a condition affecting about 20% of Australian adults.

Biochemistry and functions of DP8 and DP9.

We found that liver levels of DP8 and DP9 vary greatly between patients, suggesting roles for these enzymes in liver function. We developed a method of identifying which cell types in human tissue samples express the DP8 and DP9 genes and showed that DP8 and DP9 are made by injured hepatocytes.

In the last few years we developed methods of producing and purifying DPIV, FAP, DP8 and DP9 in quantity. Large quantities of pure enzyme are needed to make antibodies and perform full biochemical analyses and enzymological profiling. Using the skills and equipment assembled for this work we also made the unrelated enzyme KAT-1 for inhibitor development in collaboration with the Faculty of Pharmacy and made other proteins for a collaborative project with Transplant Surgery.

We published our cloning of DP10 [DPL2] in 2006. DP10 is similar to DPIV but lacks enzyme activity. This completes the cloning of the DPIV gene family.

Roles of DP8 and DP9 in cell biology and mammalian biology.

A major post-genomic challenge is discovering functions of the many recently discovered genes. The long term relevance of DP8 and DP9 research depends upon discovering their biological roles, which we are addressing both in vivo and in vitro.

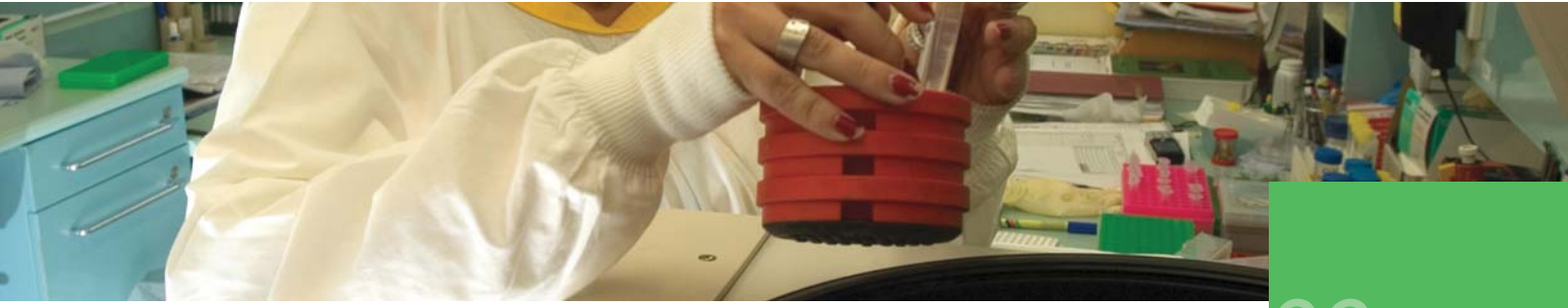
The best in vitro approach is to force cells to make a protein in cell culture in such a way as to identify which cells make the protein and quantify the altered behaviour of that cell. We have done that by tagging each peptidase with green fluorescence. Using flow cytometry and fluorescence imaging the behaviours of thousands of peptidase-expressing cells were rapidly assessed in each experiment. We have found that cells that make FAP or DP9 are less adherent and slower than control cells and that these functions are additional to the enzyme activities. Cell adhesion and movement are crucial in organ development, inflammation, tumour growth and wound healing.

Roles of DDR1 in liver biology.

DDR1 is a cell surface protein activated by collagen, which is the major component of the liver scarring which results 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 are studying mechanisms of DDR1 action in liver cells using the in vitro systems developed to study the DPIV family.

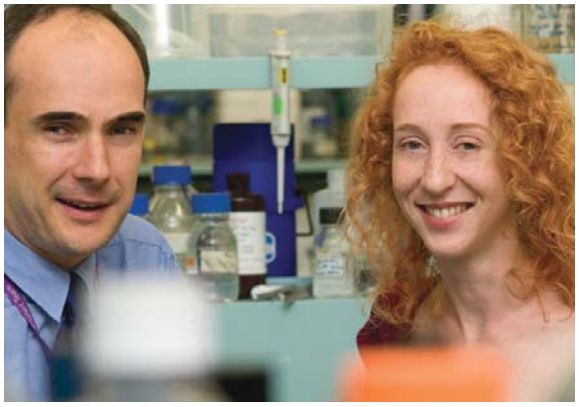
Highlights:

- Discovered that reduced mouse liver scarring due to DPIV or FAP deficiency correlates with the presence of fewer B lymphocytes.
- Completed publishing our cloning of the DPIV gene family.
- Discovered FAP, DP8 and DP9 extra-enzymatic functions in cell behaviour.
- Visualised DP8 and DP9 in lymphocytes and hepatocytes.
- Made and purified five proteins.



Liver Cell Biology

Dr Nick Shackel and Dr Fiona Warner



Liver Remodelling

Liver fibrosis results from injury from many diverse causes including viruses, alcohol, autoimmune disease and metabolic disorders and is characterised by loss of liver structure and development of dense fibrous bands of tissue in what is known pathologically as cirrhosis. The consequences of cirrhosis include liver failure and liver cancer. In Australia the health burden from liver disease is significant and increasing with options for effective treatment being limited. The health burden from Hepatitis C highlights the need for a better understanding of fibrogenesis pathogenesis as in excess of 830 000 Australians are likely to be infected by 2020. Hepatitis C is now the leading indication for liver transplantation within Australia. Therefore, a better understanding of the development of fibrogenesis in disease such as hepatitis C is essential.

The research led by Dr Shackel in 2006 focused on a novel molecule, CD147, which is abundantly expressed in the liver and a known potent inducer of matrix metalloproteinases, which are involved in the development of fibrosis. Our results are the only description of CD147 expression in fibrotic liver disease and indicate that this is an abundant protein within the liver which is capable of regulating fibrosis. Further, we continued genomic studies aim at identifying novel molecules not previously recognised as being involved in fibrosis and hepatitis C development using CD antibody arrays. This work was presented internationally and it is the first description of a CD antigen profile of hepatitis C liver injury and human liver cirrhosis.

Highlights:

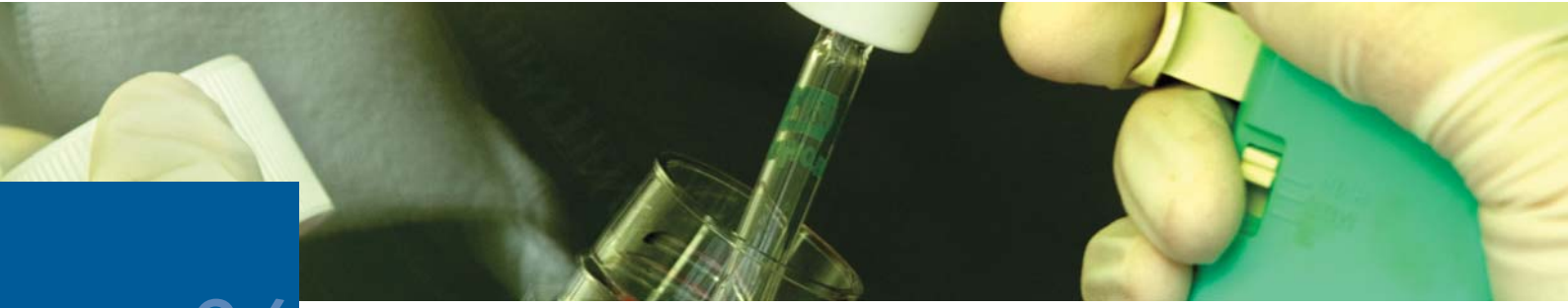
- Awarded an Immunovirology Research Network grant to study: "Gene Expression in Peripheral Blood Mononuclear Cells (PBMC) in Acute Hepatitis C (HCV) Infection."
- Dr Shackel appointment as both a Research Officer within the Centenary Institute and a Physician within the Australian National Liver Transplantation Unit and AW Morrow Gastroenterology and Liver Centre located at RPAH

Angiotensin converting enzyme and liver disease

Proteinases play a key role in many aspects of cell regulation - from fertilisation and embryogenesis to death. The main focus of our research is to understand the molecular and cell biology of critical metalloproteinase targets in the liver. A primary focus involves the angiotensin converting enzyme (ACE) family. Recent studies have not only changed the way we think about the role of the peptide, angiotensin, and angiotensin converting enzyme (ACE) in regulating vascular tone but more importantly, have shown that the system is far more complex than first thought. This new research has uncovered new players in the system such as the ACE homologue ACE2. ACE2 has been implicated in cardiac and renal function, as well as being identified as a receptor to the severe acute respiratory syndrome (SARS) coronavirus. We have shown that expression of ACE2 is increased following myocardial infarction and liver failure (hepatitis and cirrhosis). We have a number of projects aimed at trying to understand the physiological role of ACE2 in health and disease, characterising the mechanisms by which ACE2 is trafficked to the cell surface and the cellular mechanism regulating it protein expression and contribution to the progression fibrosis in diseased liver.

Highlights:

- Awarded NHMRC funding as a New Investigator to study 'The regulation of ACE2 expression and its role in liver injury
- Dr Warner was awarded a Rolf Edgar Lake Fellow from the Faculty of Medicine, University of Sydney for 3 years



Alcoholic Liver Disease

Devanshi Seth

Alcohol-induced liver disease (ALD) remains a major problem in Australia and there is no widely accepted treatment. ALD is a multi-step disease that includes alcoholic steatosis, alcoholic hepatitis and cirrhosis. The genetic and molecular factors that underlie progression to alcoholic hepatitis and cirrhosis are not well understood. It involves continuing liver injury with prominent inflammation and fibrosis from chronic alcohol abuse. The hepatic transcriptome in ALD was profiled by studying thousands of expressed genes. These studies defined a broad range of differentially expressed genes within the liver of humans with varying stages of ALD and in the baboon model of ALD. Through these studies, novel molecules such as osteopontin, CD209, TNF receptors, claudins, connexins, annexin A2, p11, plasminogen, PAI-1 and tPA and processes such as fibrinolysis and fibrogenesis have been highlighted. To define the mechanisms of injury and therapeutic potential of molecules defined in this study, further studies will employ in vivo acute and chronic alcohol mouse models and *in vitro* hepatic cell culture models.

Osteopontin (Opn) is a Th1 cytokine that may contribute to the progression of ALD through cell signalling via integrin binding. Three Opn isoforms (cloned by collaborator Dr M Beard, University of Adelaide) are involved in cell growth, adhesion, migration and tumour development and we are studying their roles in ALD. Annexin A2 (Ax2) and p11 form heterotetramers on the cell surface of several cell types, including hepatocytes. We have shown that alcohol induced Ax2/p11 complexes on hepatocyte and stellate cell surfaces result in increased plasmin activity and fibrinolysis. This may have a role in regulating fibrogenic responses.

Highlights:

- We are the first to describe and compare hepatic transcriptomes in progressive stages of human ALD (Seth et al Journal of Hepatology 2006). Our overexpression of osteopontin data was on the front cover of the August 2006 issue Journal of Hepatology.
- We have recently established a C57BL6 mouse model of acute alcoholic steatosis that is a very useful model to study early effects of alcohol.
- This work has received international recognition, collaborations in India and USA and two invited presentations by Dr Seth on the roles of osteopontin and fibrinolysis in ALD at the International Society of Biomedical Research on Alcohol (ISBRA) 2006, held in Sydney

Molecular Cardiology

Program Head: Associate Professor Chris Semsarian

The Agnes Ginges Centre for Molecular Cardiology is focused on the integration of basic laboratory research in heart disease and clinical cardiology. While there are several lines of integrated research within the laboratory, the unifying main 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.

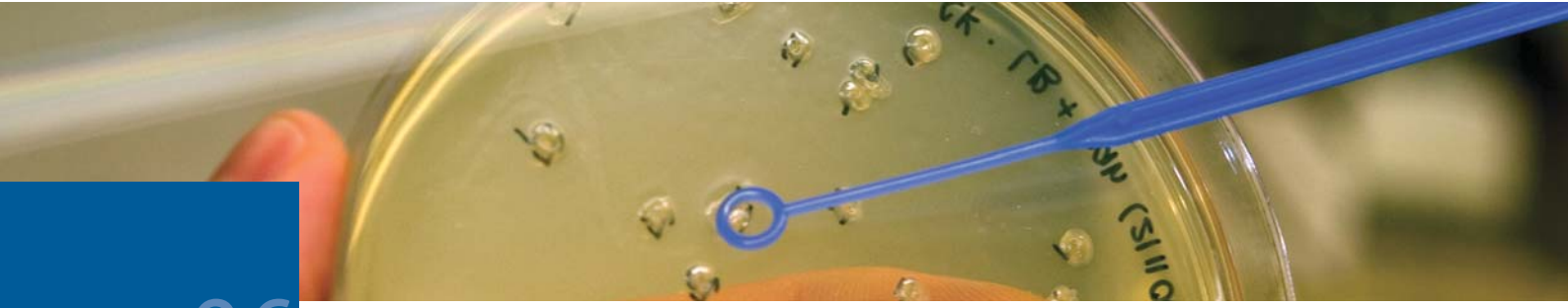
The aims of this laboratory are to understand the molecular basis of how gene mutations lead to cardiac disease and how these pathogenic mechanisms are influenced by modifying factors. These aims are being addressed in an integrated research program utilising three concurrent sets of studies; in isolated cells, in genetically-modified mice, and in humans with inherited cardiovascular disorders attending the Genetic Heart Disease Clinic at RPAH. Two particular areas of interest are understanding the genetic basis of and triggers for sudden cardiac death in the young, with a specific focus on the most common structural cause of sudden death, Hypertrophic Cardiomyopathy (HCM, Figure 1).

HCM is characterised by marked thickening of the heart muscle and occurs in approximately 1 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 300 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.

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 boundaries are limitless. Integration of molecular biology, genetic technologies and clinical medicine will ultimately reduce human heart diseases and prolong life. It is the focus of our research to realise these goals in the coming years.

Highlights:

- Identification of key gene defects involved in the causation of inherited cardiomyopathies and sudden death.
- Clinical and genetic evaluation of hundreds of Australian families with genetic heart diseases, including sudden death.
- Investigation of the biology of cardiac troponin I as a key molecule in both normal cardiac physiology and in genetic cardiomyopathies.
- Development of a novel murine model of severe cardiomyopathy caused by double gene defects, for which Mr Matthew Kelly (honours student) received the University of Sydney medal, and Dr Tatiana Tsoutsman (research officer) was a finalist in the prestigious Ralph Reader Basic Science Research Prize at the CSANZ Scientific meeting in Canberra.
- Ms Emily Tu, a research assistant in the laboratory, awarded a prestigious National Heart Foundation of Australia 3-year scholarship to commence her PhD studies in 2007 investigating sudden death in young patients with type 1 diabetes



Mycobacterial

Program Head: Professor Warwick Britton

Vaccines Against Tuberculosis

We continue to study a variety of vaccines against tuberculosis infection, including sub-unit vaccines based on a small number of protein antigens from the tuberculous bacillus, recombinant BCG vaccines, and attenuated strains of *M. tuberculosis*. In 2006 we published our findings that demonstrate improved the effectiveness of DNA vaccines against tuberculosis by delivering them with the plasmid cytokines IL-12 or IL-23. These cytokines, which share a common p40 chain, were as equally effective as adjuvants with a DNA vaccine expressing the immunodominant antigen 85B from *M. tuberculosis*. We have used mice deficient in the common IL-12 p40 chain to examine the relative capacity of IL-12 and IL-23, to promote immunity against tuberculosis. IL-23 was as effective as IL-12 in increasing the T cell Interferon-? responses to a DNA-85B. In addition, both plasmid IL-12 and IL-23 complemented the deficiency of IL-12 p40 for protective immunity against tuberculosis infection. We also discovered that BCG immunization of IL-12 p40 deficient mice stimulated a novel population of IL-17 secreting T cells. In the absence of IFN-? these T cells conferred a small, but significant protective effect against tuberculosis infection. Teresa Wozniak purified and expanded these BCG specific IL-17 producing T cells, and demonstrated that they conferred protective immunity against tuberculosis infection in RAG-1 deficient mice which lack T cells. This demonstrates that the IL-17-producing T cells can develop in the absence of IL-23 and, in addition to their inflammatory effects, can confer partial protection against tuberculosis infection.

Dr Nick West has expressed members of the family of secreted cutinase-like proteins of *M. tuberculosis*, a novel family of mycobacterial enzymes. He has demonstrated diversity in the functional activity of these enzymes as service esterases or lipases. In addition, we have developed DNA vaccines expressing each of the seven members of this family and shown that four of them confer partial protection against experimental tuberculosis infection. We are now examining the effects of combinations of these proteins with plasmid vaccines against tuberculosis.

In collaboration with Professor Ian Ramshaw at John Curtin School of Medical Research, we are developing novel anti-tuberculosis subunit vaccines which express fusion constructs of mycobacterial proteins. We have found a particular combination of these proteins which was very effective in protecting against tuberculosis infection. We are now developing new ways to deliver this effective vaccine construct. The most effective vaccine contains components of antigen 85B. Through a collaboration with Professor Joel Ernst at MYU, we have obtained TCR transgenic mice which recognise the dominant CD4 T cell epitope in this antigen. These T cells recognise *M. tuberculosis* infected dendritic cells and will be used to characterise the different capacity of novel vaccines to stimulate protective CD4 immunity against tuberculosis infection.

Dr James Triccas is continuing his studies on recombinant BCG strains expressing chemokine molecule MCP3 and the cytokine gene GM-CSF. Anthony Ryan has shown that BCG expressing MCP3 stimulated increased T cells responses to BCG and attenuated the virulence of the vaccine in immunodeficient mice whilst maintaining protective immunity against *M. tuberculosis* infection. He has also shown that recombinant BCG expressing the cytokine GM-CSF stimulates increased T cell immunity against the vaccine and reduced dissemination of tuberculosis infection. This effect is associated with the early effects on the dendritic cell population. Dr Triccas and Jonathan Nambiar has have further investigated the effects of delivering BCG-GMCSF directly into the lungs. This resulted in a marked increase of the anti-mycobacterial T cell response within the lung and its draining lymph nodes. Moreover, the RBCGrBCG-GMCSF induced increased protective immunity against early exposure to virulent *M. tuberculosis*. We are now testing the late protective effects of this method of delivery of this new vaccine strain.

Some strains of BCG lack important antigens or enzymes present in *M. tuberculosis*. For example, BCG lacks functional alanine dehydrogenases and Gabriella Scandurra, in our group, prepared recombinant BCG expressing alanine dehydrogenase and demonstrated its effects on the persistence and protective efficacy induced by BCG vaccine.

Highlights:

- Demonstrating that the cytokines IL-12 and IL-23 were equally effective as adjuvants with DNA vaccines against *Mycobacterium tuberculosis;* and for complementing the deficiency of IL-12 in the control of tuberculosis infection.
- The discovery of the protective effects of members of the family of secreted cutinase-like proteins of *M. tuberculosis* against experimental tuberculosis infection, and the definition of the functional activity of this new class of mycobacterial enzymes.
- The definition of the protective effects of novel anti-tuberculosis subunit vaccines expressing fusion constructs of mycobacterial proteins.
- The definition of the immunological and protective effects of recombinant BCG strains expressing the chemokine MCP3 and cytokine GMCSF against experimental tuberculosis infection.

Host Response to Tuberculosis

Group Head : Bernadette Saunders

Our group is investigating how protective immunity to tuberculosis is generated and maintained and genetic factors that influence this response. The risk of developing clinical tuberculosis is influenced by a number of environmental and genetic factors. One of the major aims of our group is to understand the genetic factors that influence immunity to TB. For several years now our group has been examining the mechanism of action and importance of the P2X7 receptor in immunity to tuberculosis infection. Stimulation of the P2X7 receptor with ATP activates a number of cellular processes, within the macrophage that lead to mycobacterial killing. In 2006, Dr Suran Fernando, completed his PhD examining the function of the P2X7 receptor and the effect of loss-of-function single nucleotide polymorphisms on gene expression and function. In particular we have demonstrated that a single nucleotide polymorphism in the P2X7 gene, 1513A-C, significantly reduces ATP mediated mycobacterial killing. Further, in collaboration with Professor James Wiley at Nepean Hospital and Dr Guy Marks at the Woolcock Institute we have recently published our findings showing that, in two independent studies, the presence of the 1513A-C SNP was associated with a significantly increased risk of developing extrapulmonary tuberculosis.

In collaboration with colleagues in Nepal we have also examined the involvement of polymorphisms in the P2X7 gene with the development of leprosy, which is caused by another member of the mycobacterium family *Mycobacterium Leprae*. Our studies of over 400 leprosy patients and controls indicates that, while this gene is important in control of tuberculosis infection, it is not associated with increased susceptibility to developing leprosy. A second leprosy project that we have been participating in with colleagues in the USA has however, generated exciting results demonstrating novel functions for the cytokines TNF and lymphotoxin alpha in generating and maintaining immunity to *M. leprae* infection.

We have also commenced an exciting collaborative project with Professor John Rasko (Gene and Stem Cell laboratory) to test new therapies for increasing immunity to tuberculosis infection. During 2006 we have generated a number of viral vectors which overexpress proteins involved in protective immunity to tuberculosis. In 2007 we shall begin testing these vectors to determine if we can enhance the immunity to tuberculosis and thereby reduce the severity of disease in our animal model. It is hoped that these approaches may lead to alternative therapies for treating tuberculosis disease.

2006 has also seen the expansion of projects analysing the involvement of the macrophage effector molecules IDO and LRG-47 in control of mycobacterial infection. An honours

student working in the laboratory, Lara Walker, demonstrated that human macrophages infected with mycobacteria produce large amounts of both IDO and LRG-47. Studies are progressing to examine how overexpression of these proteins, or blocking the function of either of these proteins, influences development and maintenance of protective immunity to tuberculosis infection. Again it is hoped that this research may lead to the discovery of alternative therapies to treat tuberculosis infection.

Highlights:

- Publication of our findings demonstrating how a single nucleotide polymorphism in the gene encoding the P2X7 receptor is associated with increased susceptibility to extrapulmonary tuberculosis.
- Development of a number of lenti-viral vectors overexpressing macrophage effector molecules as a mechanism to boost natural immunity to tuberculosis infection.

T Cell Biology

Program Head: Associate Professor Barbara Fazekas de St.Groth

The goal of the T Cell Biology Research Program is to develop new therapies for immunological disease based on a better understanding of how the immune response is controlled. Our primary focus is on CD4 T cells, which serve as dominant regulators of other lymphocytes such as CD8 T cells and B cells. In turn, the behaviour of CD4 T cells reflects their interactions with dendritic cells. It is likely that abnormal interactions between CD4 T cells and dendritic cells are the starting point for the allergic, autoimmune and immunoinflammatory diseases that are becoming increasingly common in Western communities and now affect at least 20% of the population. One of our goals is to understand how dendritic cells and CD4 T cells interact with the environment to increase our susceptibility to such diseases. Targeted modification of these environmental factors could then be used for prevention or treatment of immunological disease.

Interactions between CD4 T cells and dendritic cells

We need to understand how different types of dendritic cells control CD4 T cell behaviour, in order to find the source of the abnormalities causing allergic, autoimmune and immunoinflammatory disease. Unfortunately, in vitro cultures are not yet complex enough to accurately reflect the range of CD4 T cell responses seen in vivo. We are therefore using a range of cellular and molecular techniques to dissect the function of different dendritic cells in mouse models. The dendritic cell research team, led by Dr Elena Shklovskaya, has established novel methods for restricting antigen presentation in vivo to particular dendritic cell subsets. Her studies have shown that some dendritic cells, such as those derived from the epidermis, are not capable of supporting memory T cell differentiation and survival, despite the provision of optimal levels of antigen and adjuvant. Molecular analysis of these dendritic cells will allow us to pinpoint the signals required by CD4 T cells for differentiation to a memory phenotype.

We have previously shown that dendritic cells can exchange pre-formed antigen-MHC complexes in vivo. Ben Roediger, a PhD student, has now used bone marrow chimeras to show that such exchange occurs under steady state physiological conditions. This mechanism displays incoming antigen-MHC to all the T cells in the lymph node, rather than restricting access to the small number of T cells that actually contact migrating dendritic cells. We believe that this mechanism is used to increase the speed with which the T cell repertoire can be scanned for high affinity cells of appropriate specificity.

Regulatory T cells

$CD4^+CD25^+FoxP3^+$ regulatory T cells are an essential component of a normal immune system. In their absence, susceptibility to autoimmune and immunoinflammatory conditions is greatly increased. However the role of more subtle regulatory deficits in human autoimmune and immunoinflammatory disease remains controversial. We are studying mouse and human regulatory T cells with the aim of using interspecies comparisons to highlight the fundamental aspects of regulatory T cell biology.

Our murine studies, performed by PhD student Sioh-Yang Tan, have established novel assays that distinguish between regulatory deficits that are intrinsic to conventional T cells versus those that result from deficits in regulatory networks. These studies have underlined the importance of CTLA-4 for normal function of regulatory T cells, providing an intriguing link with our finding that regulatory T cells can control dendritic cell expression of CTLA-4 ligands, the costimulatory molecules CD80 and CD86.

Past studies of human regulatory T cells have been hampered by problems in identification and isolation of pure populations. In collaboration with colleagues at the Centre for Immunology, St Vincent's Hospital, we have shown that downregulation of CD127, the alpha chain of the IL-7 receptor, is characteristic of $CD25^+$ regulatory T cells but not $CD25^+$ effector/memory T cells. Unlike FoxP3, CD127 is expressed on the cell surface, and is therefore ideal as for use in flow cytometric sorting. We have patented this technique and are currently negotiating with commercial partners to licence the technology, which has been received with great interest internationally.

Our clinical studies using the new technique have focussed on two conditions: inflammatory bowel disease (IBD) and

HIV infection. IBD is common in mice with regulatory T cell deficiencies, and we are testing whether the similar deficiencies are seen in IBD patients. We have measured the number of regulatory T cells in blood, mesenteric lymph nodes and bowel mucosa, and found a selective deficit in naïve regulatory T cells in patients under the age of 35, irrespective of IBD type, activity or therapy. This age range corresponds to the peak disease onset, strongly suggesting that regulatory T cell deficiency serves as a susceptibility factor for inflammatory bowel disease. In contrast, regulatory T cells are selectively increased in patients with HIV infection, particularly in the bowel. This is consistent with the recent finding by our collaborators at the Centre for Immmunology that regulatory T cells are relatively spared by HIV infection. The imbalance between regulatory and effector T cells in HIV infection may account for the observation that the onset of immunodeficiency often precedes significant loss of CD4 T cells.

Tolerance under lymphopaenic conditions

The occurrence of lymphopaenia in HIV infection, bone marrow transplantation and cancer chemotherapy has major consequences for the ability of the immune system to maintain normal regulatory mechanisms. In a study of tolerance induction in lymphopaenic mice, Dr Elena Shklovskaya has shown that abnormal expression of the survival receptor CD127 is implicated in survival of cells that should be deleted after responding to tolerogenic antigen. This may, at least in part, explain the observation of increased autoimmune disease and allergy in lymphopaenic patients.

Competition between CD4 T cells in vivo

Studies undertaken by Alex Spencer as part of her PhD have shown that the transition of CD4 T cells to central versus effector memory phenotypes is differentially affected by competition for antigen-MHC complexes. The generation of central memory cells appears to require only a small amount of antigen, and the repertoire of the central memory population reflects the wide range of receptor affinities present early in the response. Effector memory cells, on the other hand, undergo continuous selection for antigen affinity, generating a highly focussed repertoire.

CD4 T cells in graft rejection

Dr David Gracey's PhD studies have shown for the first time that memory cells are essential for skin graft rejection. This finding underlines the need for new therapeutic approaches to induction of graft tolerance in human transplantation, since virtually all transplant recipients have a significant number of memory cells that cross-react with transplantation antigens. Many of the novel therapies currently under trial target naïve rather than memory cells.

Highlights:

- Received international recognition of their new technique for identification and isolation of human regulatory T cells after the publication of 2 papers in the Journal of Experimental Medicine. The discovery was highlighted in Commentaries in Nature Reviews Immunology, Trends in Immunology, and Immunology in the News.
- Filed a PCT application for a new regulatory T cell technique in July, 2006.
- PhD student Ben Roediger was selected to give a presentation in a plenary session at the 9th International Conference on Dendritic Cells in Edinburgh. Ben's work, performed in collaboration with Senior Research Officer Elena Shklovskaya, demonstrated that transfer of preformed peptide-MHC complexes between dendritic cells occurs under physiological conditions in vivo.
- Identified involvement of the IL-7 receptor in the abnormal resistance of CD4 T cells to deletion under lymphopaenic conditions.
- Demonstrated that the dominant defect in CTLA-4-deficient mice is in regulatory T cell function rather than intrinsic T cell hyperreactivity.
- Associate Professor Barbara Fazekas de St.Groth is part of a team awarded a prestigious NHMRC Program Grant for 2007-11, totalling $15.55M.

Core Facilities

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 groups at Centenary. Following the expansion of the facility in 2005 we are clearly among the top handful of cytometry facilities in Australia, offering 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. In 2006, we continued to enhance the facility with the addition of a new solid state laser and instrumentation for making finely time-resolved measurements of samples in flow.

The Centenary's facility is well equipped with three cell sorters - the BD FACSAria (equipped with 3 lasers and capable of measuring 13 different parameters for analysis and sorting of up to 25,000 cells/second at purities of over 99%), a BD FACSVantageDiVa (equipped with 3 lasers, 10 parameters, sorting cells at up to 20,000 per second) and a BD FACStarPlus (2 lasers, 7 parameters). In addition the facility houses four flow analysers - a BD LSR-II (4 lasers, 15 parameters), a BD FACSCanto (2 lasers, 8 parameters), BD FACSCalibur (2 lasers, 6 parameters) and a BD FACScan, (1 laser, 5 parameters).

Other highlights in 2006 included the attendance of the facility manager at local and international cytometry conferences and advanced training in the US for the facility's technical officer.

In Vivo Imaging

In July 2006, the Centenary Institute completed the installation and commissioning of a XenogenIVIS-100 *in-vivo* bioluminescent imaging system with advanced fluorescent detection. This system is capable of providing images in real-time to monitor and record cellular and genetic activity within a living organism. The equipment features a central digital camera which is cooled to less than -1000C to minimise electronic background noise and maximise sensitivity.

Light emitted from cells inside a living tissue or mouse can be detected by the system, offering unique opportunities for diverse applications in molecular research such as monitoring the mechanisms of drug action, the roles of certain genes in disease and the measurement of tumour growth in a mouse.

Microscopy

In 2007 there are plans to continue expanding the facility with the addition of confocal and multiphoton microscopes. The multiphoton microscope is particularly exciting due to its ability to image within intact tissues or animals. The new instruments will provide a direct complement to high level flow cytometry and small animal imaging resources already in use. The technologies each provide unique, but partial, information about the disease process under investigation. Combining them will significantly increase the total value of the research that can be carried out at the Centenary Institute.

Microinjection Facility

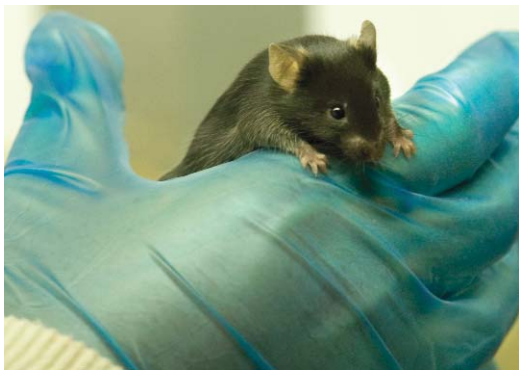
The use and development of the latest transgenic (overexpression of a single gene) and knockout (deletion of a single gene) technology has for many years been a high priority for Centenary. The first transgenic mice at Centenary were created in the mid 1980s, the first knockout mice in the mid 1990s and the facility continues to produce new strains every year. Centenary's transgenic and knockout mice are the subject of hundreds of scientific publications. Mouse sperm freezing techniques are also performed at the facility, enabling the storage of mouse strains in liquid nitrogen for future use without the ongoing costs of maintaining a mouse colony.

Mouse Cardiac Physiology and Function Facility

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

- Blood pressure measurement (tail-cuff)
- Electrocardiography (ECG)
- Electrophysiological stimulation studies
- 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

Centenary houses a PC3 containment facility that allows work on level 3 pathogens such as *Mycobacterium 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.

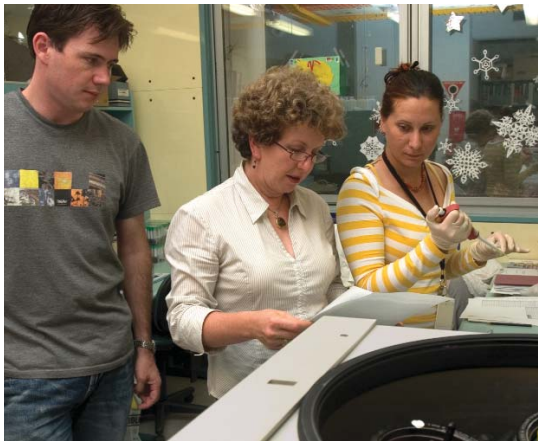
Postgraduate Training Program

An objective of Centenary is the development of the next generation of research leaders through our student programme. The Centenary Institute is closely affiliated with the University of Sydney and RPAH. Conveniently located on the grounds of the hospital adjacent to the University's main campus, we provide students with access to facilities, support and opportunities available at both of these organisations.

Our student body is made up of a group of students from diverse ethnic and academic backgrounds with the common goal of achieving excellence. This year the student body at Centenary comprised of 31 PhD, 2 Masters and 9 Honours students.

Centenary's Student Affairs Subcommittee oversees the activities of PhD students at Centenary. Every year the committee assesses the progress of PhD students who are half way through their candidature. For their Midpoint Review, candidates must submit a report on their work to the committee and are subsequently interviewed on the contents of their report. The purpose of the interview is to examine the overall strategy of the project, data obtained to date and future directions. In this way any problems, which have arisen or are likely to arise can be identified and discussed. Thus the interview acts as a medium for constructive suggestions for both candidates and supervisors.

Our thanks go to Centenary's Postgraduate Co-ordinator Associate Professor Chris Semsarian for his hard work. We would like to congratulate all of the candidates who successfully completed their Midpoint Reviews, submitted their thesis or were awarded their doctorates in 2006.



PhDs Awarded

Student	Supervisor	Thesis Title
Suran Fernando	Professor Warwick Britton/ Dr Bernadette Saunders	The role of the purinergic receptor P2X7 in mycobacterial disease in humans
Gabriella Scandurra	Professor Warwick Britton/ Dr Jamie Triccas	Macrophage Gene Responses to *Mycobacterium tuberculosis* and HIV and Genetic Approaches to Vaccine Development
Cindy Ma	Dr Stuart Tangye/ Professor Antony Basten	Elucidating the cellular defects in X-linked Lymphoproliferative disease resulting from mutations in SH2D1A
Joohong Park	Dr Mark Gorrell	Expression, purification and characterisation of dipeptidyl peptidase 8 and DPIV.
Alexandra Spencer	Associate Professor Barbara Fazekas	A transgenic mouse model approach to investigate the interactions between T cells during the course of an immune response

Masters Awarded

Student	Supervisor	Thesis Title
Vanessa Gysbers	Prof John Rasko	Homology-mediated silencing of retroviral vectors in mammalian stem cells

Midpoint Reviews

PhD Student	Project Title	Supervisor(s)	Group
Lien Lam	Proteomic analysis of normal and cardiomyopathic mice.	A/Prof Chris Semsarian / Dr Jonathon Arthur	Molecular Cardiology
Dr Silvia Ling	Drug resistance in multiple myeloma and other haematological cancers	Prof Douglas Joshua / Dr John Allen	Cancer Drug Resistance
Keryn Lucas	The significance of defective apoptosis for drug resistance in mouse models of melanoma	A/ Prof Barbara Fazekas/ Dr John Allen	Cancer Drug Resistance
Lauren Holz	Investigating the phenotype of CD8+ Transgenic T Cells activated within the Liver	Prof McCaughan/ Dr Patrick Bertolino	Liver Immunobiology

2006 Seminars and Visiting Speakers

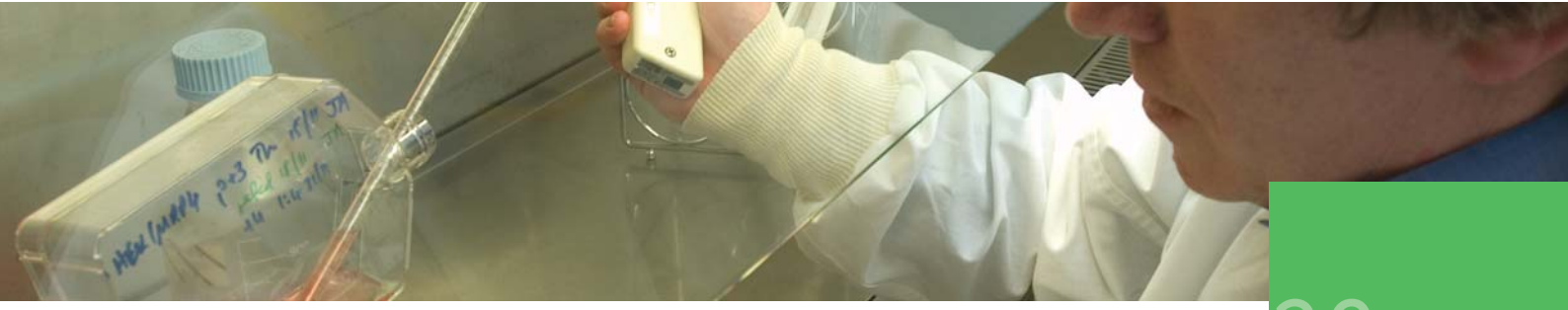
Speaker	Title	Date
Mr Paul Field *Biolink, NSW, Australia*	Partner Early: The Biolink model for commercialisation of pre-clinical research.	7th February
Dr Nick Pearce *Centenary Institute, Sydney, NSW, Australia*	IP: What, why and where is the money?	7th February
Professor Carlo Croce *Human Cancer Genetics Program Ohio State University, Ohio, USA*	MicroRNAs miR15 and 16 in chronic lymphocytic leukaemias	8th February
Dr Leona Samon *Professor of Biological Engineering and Toxicology Massachusetts Institute of Technology, MA, USA*	Complex Cellular Responses to DNA Damaging Agents	21 February
Professor Douglas Young *Fleming Professor, Centre for Molecular Microbiology and Infection Division of Investigative Sciences.Imperial College, London*	The Global Plan to Stop TB	16 March
Professor Angus Thomson *Professor of Surgery, BiochemistrySchool of MedicineUniversity of Pittsburgh, USA*	Dendritic leukocytes: adversaries and allies	23 March
Professor Richard Pestell *Director, Kimmel Cancer Centre, Thomas Jefferson University, Philadelphia, PA, USA*	Nuclear Receptors and Cyclins in Hormone Signalling	30 March
Dr Daniel Christ *MRC Laboratory of Molecular Biology, University of Cambridge, UK*	Modular Approaches to Proteomics and Protein Engineering: From Antibodies to Novel Proteins	4 April
Dr Fiona Warner *Liver Immunobiology, Centenary Institute of Cancer Medicine and Cell Biology, Sydney, NSW, Australia*	A new fACE in the angiotensin-renin system	11 April
Dr Suran Fernando *Mycobacterial Research, Centenary Institute of Cancer Medicine and Cell Biology, Sydney, NSW, Australia*	The P2X7 purinergic receptor and mycobacterial infections in humans	2 May
Associate Professor Greg Dore *Head of Viral Hepatitis Clinical Research Program, National Centre in HIV Epidemiology and Clinical Research, UNSW, Sydney, NSW, Australia*	Advancing therapeutic strategies in viral hepatitis	9 May
Associate Professor Alison Kesson *Discipline of Paediatrics and Child Health, University of Sydney, Sydney, NSW, Australia*	Regulation of immune recognition molecules MHC-I and ICAM-1, by flaviviruse	18 May
Associate Professor Peter McMinn *Head of Division of Virology, Princess Margaret Hospital, Perth, WA*	Counteracting viral encephalitis in Southeast Asia by vaccine development and technology transfer to enhance laboratory surveillance	25 May

Speaker	Title	Date
Dr Tony Roscioli *Sydney South West Integrated Genetics Service (SWIGS) Prince of Wales Hospital, Randwick, NSW*	Mutations in the gene encoding the PML nuclear body protein Sp110 are associated with immunodeficiency and hepatic veno-occlusive disease" (subtitle: White cells, acid-fast bacilli and hepatic sinusoids: do they all converge on nuclear bodies?)	20 June
Ms Alessandra Doolan *Molecular Cardiology Research Program, Centenary Institute, Sydney, NSW*	Clinical and Molecular Aspects of Sudden Cardiac Death in the Young	27 June
Dr Jeremy S Chrisp *CEO, Medsaic &* *Dr Nick Shackel* *Centenary Institute*	New technology for protein characterisation using a cell capture antibody microarray	18 July
Professor Michael Neuberger *Protein and Nucleic Acid Chemistry Division Medical Research Council Library of Molecular Biology Cambridge University, UK*	Immunity through DNA deamination	20 July
Dr Phil Kearney *Director of External Research Santaris Pharma, Copenhagen*	Antisense as a Therapeutic. New chemistries come of age	25 July
Associate Professor Ygal Haupt *The Lautenberg Center for General and Tumor Immunology*	The Hebrew University, Israel p53 regulation through meeting points and cascades	27 July
Professor Margaret Morris *Professor of Pharmacology School of Medical Sciences University of New South Wales, Sydney, NSW, Australia*	Neuropeptide Y – role in obesity and epilepsy	2 August
Professor Phillip D Greenberg *Fred Hutchinson Cancer Center, Seattle & Division of Oncology, University of Washington, Washington DC, USA*	Cellular and Molecular engineering of T cell responses for the treatment of malignancies and chronic viral infections	4 August
Professors Tony Burgess and Peter Colman *Ludwig Institute of Cancer Research, and The Walter and Eliza Hall Institute of Medical Research, Melbourne, VIC, Australia*	Synchrotron Light and the next decade of medical research	23 August
Dr Miles Davenport *Sylvia and Charles Viertel Senior Medical Research Fellow* *Center for Vascular Research, UNSW, Sydney, NSW, Australia*	Understanding the molecular basis of 'public' T cell responses	29 August
A/Prof Paul Jackson *Oncology Research Centre* *Prince of Wales Hospital, Sydney, NSW, Australia*	Understanding the basis of downregulation of KAI1 in urological cancers	12 September
Dr Peter Papathanasiou *Stanford University, California, USA*	Mutants, stem cells & epigenetics	17 October

Speaker	Title	Date
Prof Graham Pawelec *University of Tubingen,* *Center for Medical Research Germany*	Immunosenescence, immunosuppression and tumour escape	27 October
Dr David Huang *Molecular Genetics of Cancer Division,* *Walter and Eliza Hall Institute of Medical Research,* *Melbourne, VIC, Australia*	Overcoming survival mechanisms for cancer therapy	31 October
Dr John Allen *Senior Research Fellow of the Cancer Institute and Head of the Cancer Drug Resistance Group,* *Centenary Institute, Sydney, NSW, Australia*	Imatinib and porphyrin toxicity, et al, from the Cancer Drug Resistance Group.	6 November
Dr Phillipe Bouillet *Molecular Genetics of Cancer Divsion* *The Walter and Eliza Hall Institute of Medical Research, Melbourne, VIC, Australia*	Genetic models to dissect the regulation of the BH3-only proteins.	7 November
Dr Jean-Pierre Levesque *Mater Medical Research Institute, Brisbane, QLD, Australia*	The mobilisation of haematopoietic stem cells: when innate immunity assails the cells that make blood and bone.	14 November
Professor Rudolf Jaenisch *Professor of Biology* *The Whitehead Institute & Department of Biology, MIT, Massachusetts, USA*	Nuclear Cloning, Embryonic Stem Cells and Cell Therapy: Promises, Problems and Reality.	21 November
Thomas Blankenstein *ASI Visiting Speaker* *Max-Dalbruck Center for Molecular Medicine, Berlin, Germany*	Transgenic mice with sporadic immunogenic tumours.	27 November

2006 Publications

1. Brink R (2006) Regulation of B cell self-tolerance by BAFF. *Semin Immunol* 18:276-283
2. Britton WJ. (2006) Hypersensitivity (Type IV), in Immunology, 7th ed, Male, D, Brostoff J, Roth DB, Roitt I. (Mosby, London) p 477-491.
3. Bröer A, Cavanaugh JA, Rasko JEJ, Bröer S (2006) The molecular basis of neutral aminoacidurias. *Pflügers Arch* 451:511-517
4. Chen T, Ajami K, McCaughan GW, Gai WP, Gorrell MD, Abbott CA (2006) Molecular characterization of a novel dipeptidyl peptidase like 2 short form (DPL2-s) that is highly expressed in the brain and lacks dipeptidyl peptidase activity. *Biochim Biophys Acta* 1764:33-43
5. Chiu C, Ingles J, Lind JM, Semsarian C (2006) Mutationa analysis of the natriuretic peptide precursor B (NPPB) gene in patients with hypertrophic cardiomyopathy. *DNA Sequence* 17:392-395
6. Chklovskaia E, Fazekas de St Groth B (2006) Balancing tolerance and immunity: the role of dendritic cells and T cell subsets. In: Immunological Tolerance edited by Paul J Fairchild, Human Press
7. Cordoba S, Wang C, Williams R, Li J, Smit L, Sharland A, Allen R, McCaughan G, Bishop GA (2006) Gene array analysis of a rat model of liver transplant tolerance identifies increased complement c3. *Liver Transpl* 12:636-643
8. Crawford BA, Cabio ED, Strasser SI, McCaughan G (2006) Vitamin D replacement for cirrhosis-related bone disease. *Nat Clin Pract Gastroenterol Hepatol* 3:689-699
9. Crawford BA, Kam C, Pavlovic J, Handelsman DJ, Angus PW, McCaughan GW (2006) Zoledronic acid prevents bone loss after liver transplantation: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 144:239-248
10. Cuss AK, Avery DT, Cannons JL, Yu LJ, Nichols KE, Shaw PJ, Tangye SG (2006) Expansion of functionally immature transitional B cells is associated with human-immunodeficient states characterized by impaired humoral immunity. *J Immunol* 176:1506-1516
11. Dahlke MH, Loi R, Warren A, Holz L, Popp FC, Weiss DJ, Piso P, Bowen DG, McCaughan GW, Schlitt HJ, Bertolino P (2006) Immune-mediated hepatitis drives low-level fusion between hepatocytes and adult bone marrow cells. *J Hepatol* 44:334-341
12. Fernando Sl, Britton WJ (2006) Genetic susceptibility to mycobacterial disease in humans. *Immunol Cell Biol* 84:125-137
13. Fernando SL, Britton WJ (2006) Genetics of tuberculosis and leprosy. *Immunol Cell Biol* 4:125-137
14. Gaus K, Chklovskaia E, Fazekas de St Groth B, Jessup W, Harder T (2006) Condensation of the plasma membrane at the site of T lymphocyte activation. *J Cell Biol* 171:121-131
15. Good KL, Bryant VL, Tangye SG (2006) Kinetics of human B cell behavior and amplification of proliferative responses following stimulation with IL-21. *J Immunol* 177:5236-5247
16. Gorrell MD, Wang XM, Park J, Ajami K, Yu DM, Knott H, Seth D, McCaughan GW (2006) Structure and function in dipeptidyl peptidase IV and related proteins. *Adv Exp Med Biol* 575:45-54
17. Hare NJ, Ma CS, Alvara F, Nichols KE, Tangye SG (2006) Missense mutations in SH2D1A identified in patients with X-linked lymphoproliferative disease differentially affect the expression and function of SAP. *Int Immunol* 18:1055-1065
18. Heyman JK, Whitfield CJ, Brock KE, McCaughan GW, Donaghy AJ (2006) Dietary protein intakes in patients with hepatic encephalopathy and cirrhosis: current practice in NSW and ACT. *Med J Aust* 185:542-543
19. Holland ML, Panett JA, Hoskins JM, Bebawy M, Roufogalis BD, Allen JD, Arnold JC (2006) The effects of cannabinoids on P-glycoprotein transport and expression in multidrug resistant cells. *Biochem Pharmacol* 71:1146-1154
20. Holst J, Rasko JE (2006) The use of retroviral vectors for gene transfer intho hematopoietic stem cells. *Methods Enzymol* 420:82-100
21. Iyengar L, Patkunathan B, Lynch OT, McAvoy JW, Rasko JEJ, Lovicu FJ (2006) Aqueous humour and growth factor-induced lens cell proliferation is dependent on MAPK/ERK1/2 and Akt/PI3-K signalling. *Exp Eye Res* 83:667-678
22. Kelly M, Chick J, Gribble R, Gleeson M, Holton M, Winstanley, McCaughan GW, Haber PS (2006) Predictors of relapse to harmful alcohol after orthotopic liver transplantation. *Alcohol Alcohol* 41:278-283



23. Kong AM, Horan KA, Sriratana A, Bailey CG, Collyer LJ, Nandurkar H, Shisheva A, Layton M, Rasko JE, Rowe T, Mitchell CA (2006) Phosphatidylinositol(3)phosphate is generated at the plasma membrane by inositol polyphosphate 5-phosphatase hydrolysisphosphatidylinositol(3,5)-bisphosphate. *Molec Cell Biol* 26:6065-6081

24. Lam L, Lind J, Semsarian C (2006) Application of proteomics in cardiovascular medicine. *Int J Cardiol* 108:12-19

25. Larsen SR, Kingham JA, Hayward MD, Rasko JEJ (2006) Damage to incisors arfter nonmyeloablative total body irradiation may complicate NOD/SCID models of hemopoietic stem cell transplantation. *Comp Med* 56:209-214

26. Lind JM, Chiu C, Semsarian C (2006) Genetic basis of hypertrophic cardiomyopathy. *Expert Rev Cardiovasc* Ther 4:927-934

27. Liu W, Putnam AL, Xu-yu Z, Szot GL, Lee MR, Zhu S, Gottlieb PA, Kapranov P, Gingeras TR, Fazekas de St Groth B, Clayberger C, Soper D, Ziegler S, Bluestone JA (2006) CD127 expression inversely correlates with FoxP3 and suppressive function of human $CD4^+$ T reg cells. *J Exp Med* 203:1701-1711

28. Loss M, Ng WS, Karim RZ, Strasser SI, Koorey DJ, Gallagher PJ, Verran DJ, McCaughan GW (2006) Hereditary lysozyme amyloidosis: spontaneous hepatic rupture (15 years apart) in mother and daughter. role of emergency liver transplantation. *Liver Transpl* 112:1152-1155

29. Ma CS, Pittaluga S, Avery DT, Hare NJ, Maric I, Klion AD, Nichols KE, Tangye SG (2006) Selective generation of functional somatically mutated IgM^+CD27^+, but not Ig isotype-switched, memory B cells in X-linked lymphoproliferative disease. *J Clin Invest* 116:322-333

30. Maekawa A, Schmidt B, Fazekas de St Groth B, Sanejouand Y-H, Hogg PJ (2006) Evidence for a domain-swapped CD4 dimer as the co-receptor for binding to class II MHC. *J Immunol* 176:6873-6878

31. Manno CS, Pierce GF, Glader B, Arruda VR, Ragni M, Rasko J, Ozelo MC, Hoots K, Blatt P, Konkle B, Dake M, Kaye R, Razavi M, Zajko A, Zehnder J, Nakai H, Chew A, Leonard D, Fraser Wright J, Lessard RR, Sommer JM, Tigges M, Sabatino D, Luk A, Jiang H, Mingozzi F, Couto L, Ertl HC, High KA, Kay MA (2006) Successful transduction of liver in hemophilia by AAV-Factor IX and limitations imposed by the host immune response. (Letter) *Nat Med* 12:342-347

32. Musicki K, Briscoe H, Tran S, Britton WJ, Saunders BM (2006) Differential requirements for soluble and transmembrane tumor necrosis factor in the immunological control of primary and secondary Listeria monocytogenes infection. *Infect Immun* 74:3180-3189

33. Nguyen L, Chung J, Lam L, Tsoutsman T, Semsarian C (2006) Abnormal cardiac response to exercise in a muring model of familial hypertrophic cardiomyopathy. Int J Cardio 119:245-248

34. Park J, Ajami K, Gorrell MD (2006) Dipeptidyl peptidase 8 has post-proline dipeptidyl aminopeptidase and prolyl endopeptidase activities. Adv Exp Med Biol 575:93-102

35. Paus D, Phan TG, Chan TD, Gardam S, Basten A, Brink R (2006) Antigen recognition strength regulates the choice between extrafollicular plasma cell and germinal center B cell differentiation. *J Exp Med* 203:1081-1091

36. Phan TG, Paus D, Chan TD, Turner ML, Nutt SL, Basten A, Brink R (2006) High affinity germinal center B cells are actively selected into the plasma cell compartment. *J Exp Med* 203:2419-2424

37. Prakoso E, Strasser SI, Koorey DJ, Verran D, McCaughan GW (2006) Long-term lamivudine monotherapy prevents development of hepatitis B virus infection in hepatitis B surface-antigen negative liver transplant recipients from hepatitis B core-antibody-positive donors. *Clin Transplant* 20:369-373

38. Rasko JE (2006) Bill to ban reproduction of inmates with cancer proposed in New South Wales. *Med J Aust* 185:575-576

39. Rasko J, O'Sullivan G, Ankeny R (editors) The ethics of inheritable genetic modification; a dividing line? Cambridge University Press 2006

40. Scandurra GM, Ryan AR, Pinto R, Britton WJ, Triccas JA (2006) Contribution of L-alanine dehydrogenase to in vivo persistence and protective efficacy of the BCG vaccine. *Microbiol Immunol* 50:805-810

41. Seddiki N, Santner-Nanan B, Martinson J, Zaunders J, Sasson S, Landlay A, Solomon M, Selby W, Alexander SI, Nanan R, Keller A, Fazekas de St Groth B (2006) Expression of interleukin (IL)-2 and IL-7 receptors discriminates between human regulatory and activated T cells. *J Exp Med* 203:1693-1700

42. Seddiki N, Santner-Nanan B, Tangye SG, Alexander SI, Solomon M, Lee S, Nanan R, Fazekas de St Groth B (2006) Persistence of naïve CD45RA$^+$ regulatory T cells in adult life. *Blood* 107:2830-2838

43. Seth D, Gorrell MD, Cordoba S, McCaughan GW, Haber PS (2006) Intrahepatic gene expression in human alcoholic hepatitis. *J Hepatol* 45:306-320

44. Shackel NA, McCaughan GW (2006) Liver biopsy: is it still relevant? *Intern Med* J 36: 689

45. Shackel NA, Seth D, Haber PS, Gorrell MD, McCaughan GW (2006) The hepatic transcriptome in human liver disease. *Comp Hepatol* 5:6

46. Shemon A N, Sluyter R, Fernando S L, Clarke A L, Dao-Ung LP, Skarratt KK, Saunders BM, Tan KS, Gu B J, Fuller SJ, Britton W.J, Petrou S, Wiley JS (2006) A Thr357 to Ser polymorphism in homozygous and compound heterozygous subjects causes absent or reduced P2X7 function and impairs ATP-induced mycobacterial killing by macrophages. *J Biol Chem* 281: 2079-2086.

47. Shklovskaya E, Fazekas de St Groth B (2006) Severely impaired clonal deletion of CD4+ T cells in low-dose irradiated mice: role of T cell antigen receptor and IL-7 receptor signals. *J Immunol* 177:8320-8330

48. Tangye SG, Bryant VL, Cuss AK, Good KL (2006) BAFF, APRIL and human B cell disorders. *Semin Immunol* 18:305-317

49. Tsoustsman T, Chung J, Doolan A, Nguyen L, Williams I, Tu E, Lam L, Bailey CG, Rasko JEJ, Allen DG, Semsarian C (2006) Molecular insights from a novel cardiac troponin I mouse model of familial hypertrophic cardiomyopathy. *J Molec Cell Cardiol* 41:623-632

50. Tsoutsman T, Lam L, Semsarian C (2006) Genes, calcium and modifying factors in hypertropic cardiomyopathy. *Clin Exp Pharmacol Physiol* 36:139-145

51. Wang XM, Yu DM, McCaughan GW, Gorrell MD (2006) Extra-enzymatic roles of DPIV and FAP in cell adhesion and migration on collagen and fibronectin. *Adv Exp Med Biol* 575:213-222

52. Warren A, Lc Couteur D, Fraser R, Bowen D, McCaughan G, Bertolino P (2006) T Lymphocytes interact with heptocytes through fenestrations in murine liver sinusiodal endothelial cells. *Hepatology* 44:1182-90

53. Wozniak TM, Ryan AA, Britton WJ (2006) Interleukin-23 restores immunity to Mycobacterium tuberculosis infection in IL-12p40 deficient mice and is not required for the development of IL-17-secreting T cell responses. *J Immunol* 177:8684-8692

54. Wozniak TM, Ryan AA, Triccas JA, Britton WJ (2006) Plasmid interleukin-23 (IL-23) but not plasmid IL-27, enhances the protective efficacy of a DNA vaccine against Mycobacterium tuberculosis infection. *Infect Immun* 74:557-565

55. Yu DM, Wang XM, Ajami K, McCaughan GW, Gorrell MD (2006) DP8 and DP9 have extra-enzymatic roles in cell adhesion, migration and apoptosis. *Adv Exp Med Biol* 575:63-72

56. Yu DM, Wang XM, McCaughan GW, Gorrell MD (2006) Extra-enzymatic functions of the dipeptidyl peptidase (DP) IV related proteins DP8 and DP9 in cell adhesion, migration and apoptosis. FEBS J 273:2447-2460

57. Zaunders JJ, Ip S, Munier ML, Kaufmann DE, Suzuki K, Brereton C, Sasson SC, Seddiki N, Koelsch K, Landay A, Grey P, Finlayson R, Kaldor J, Rosenberg ES, Walker BD, Fazekas de St Groth B, Cooper DA, Kelleher AD (2006) Infection of CD127+ (Interleukin-7 receptor+) CD4+ cells and overexpression of CTLA-4 are linked to loss of antigen-specific CD4 T cells during primary human immunodeficiency virus type 1 infection. *J Virol* 80:10162-10172

2006 Presentations

International

Invited presentations

Britton WJ (2006) American Leprosy Mission Scientific meeting, Infectious Diseases Research Institute, Fort Collins, Colorado, USA.

Britton WJ (2006) Complementation of IL-12P40 deficiency with IL-23 generates activated T cells and provides partial protection against Mycobacterium tuberculosis infection. Australasian Society for Immunology Annual Scientific Conference, Auckland, New Zealand.

Britton WJ (2006) Control of Mycobacterium tuberculosis infection by human macrophages: The role of purinergic receptor P2X7. Annual Scientific Conference; Infectious Disease Institute, Makerere University, Kampala, Uganda.

Britton WJ (2006) Control of Tuberculosis Infection: Roles of membrane TNF and purinergic receptors. Laboratory of Parasitic Disease, NIAID, NIH, Bethesda, Maryland, USA.

Britton WJ (2006) Immunopathology of Tuberculosis. Annual Scientific Meeting, Gates Grand Challenge, Tuberculosis and HIV Infection in Africa. Kampala, Uganda.

Britton WJ (2006) The role of purinergic receptors in the control of tuberculosis infection.
Tuberculosis Research Centre, Chennai, India.

Britton WJ (2006) Workshop of the Initiative for Diagnostic and Epidemiological
Assays for Leprosy (IDEAL), Rio de Janeiro, Brazil.

McCaughan G (2006) Gene arrays and Liver disease. American Association for the Study of the Liver San Francisco, USA.

McCaughan G (2006) Mechanisms of HCV Reinfection and allograft damage post Liver Transplantation. European Association for the Study of the Liver Single Topic Symposium: Liver Transplantation for Viral Hepatitis. Paris, France.

McCaughan G (2006) The Molecular Pathogenesis of HCV Disease Recurrence.
European Liver Transplant Society/European Association for The Study of the Liver Joint Meeting. Vienna, Austria.

McCaughan G (2006) The Natural History of HCV Infection in Liver Transplant Recipients and Relationship with Altered Immune Response. 41st Annual Meeting of European Association for the Study of the Liver Study post graduate Course on Immunological Phenomena in HCV in and outside the Liver. Vienna, Austria.

McCaughan G (2006) Mechanisms of Coagulopathy in Chronic Liver Disease. 16th Conference of the Asian Pacific Association for the Study of the Liver: Manila, Philippines.

McCaughan G (2006) Fibroblast Activation Protein- A novel cell surface protease on Human Stellate Cells. Shanghai – Hong Kong International Liver Congress Shanghai, China.

McCaughan G (2006) Key Note Lecture Mechanisms of HCV Recurrence post Liver Transplant. Shanghai – Hong Kong International Liver Congress Shanghai, China.

McCaughan G (2006) Symposium Lecture. Prevention of Liver Fibrosis in HCV infection post Liver Transplant. Shanghai – Hong Kong International Liver Congress Shanghai, China.

McCaughan G (2006) Optimising Immunosuppression in Viral Hepatits patients post Liver Transplant. 3rd National Organ Transplant meeting. Kunming, China.

McCaughan G (2006) The Challenge of HCV Infection following Liver Transplantation. Asian Pacific Digestive Diseases Week. Cebu, Philippines.

McCaughan G (2006) Post Liver Transplant Cholangiopathy. Asian Pacific Digestive Diseases Week. Symposium Lecture. Cebu, Philippines.

Gorrell MD (2006) The Prolyl Oligopeptidase family. Institut Researches Servier, Paris, France.

Rasko JEJ (2006) The Hartnup Disorder: Awry Aminoacid Transport. The Wellcome Trust Sanger Institute, Cambridge, UK.

Rasko JEJ (2006) The Hartnup Disorder: Awry Aminoacid Transport. Santaris Pharma A/S Copenhagen, Denmark.

Rasko JEJ (2006) Micro RNAs: a role in biology and ripe for PMO targeting?, AVI BioPharma, Corvallis, Oregon, USA.

Ryan A, Chklovskaia E, Wozniak T, Luo Y, O'Donnell M, Britton WJ, Triccas JA.

Determinants of Host Resistance, Susceptibility or Immunopathology to Pathogens: Targeting Antigen presenting cells as a strategy to improve protective immunity against tuberculosis Keystone Symposia, Keystone, Colorado, USA.

Saunders BM, Fernando SL, Pong A, Sluyter R, J. Wiley J, Britton WJ. Upregulating expression of the P2X7 Receptor enhances resistance to mycobacterial infection. Symposium Presentation 36th Annual Meeting of the Australasian Society of Immunology, Auckland, New Zealand.

Wozniak TM, Ryan A, Britton WJ. Complementation of IL-12p40 deficiency with IL-23 generates activated T cells and provides partial protection against Mycobacterium tuberculosis infection Keystone Symposia, Keystone, Colorado, USA.

Abstracts, oral and poster presentations

Aung HT, Flamant S, Lu DP, Read RL, Humphreys DT, Tan SA, Rajasekhar M, Martin DIK and Rasko JEJ (2006) A refined RT-PCR based quantitative technique to identify and characterize new micro RNAs. RNAi and Related Pathways Keystone Meeting, Vancouver, Canada.

Combettes MM, Harley E, Lonchampt M, Lambeir A-M, Meester ID, Gorrell M, Benoist A, Nanteuil GD, Ktorza A (2006) S 40755, a selective, long acting Dipetidyl-Peptidase-IV (DPP-IV) inhibitor, improves glucose tolerance in Zucker fatty (fa/fa) rats. American Diabetes Association 66th Annual Scientific Meeting, Washington DC, USA.

Cua IH, George J, Bandara P, Sud A, Farrell GC, Kench JG, McCaughan GW, Morahan G (2006) Association of IL12B promoter polymorphisms with severity of liver injury in chronic hepatitis. American Association for the Study of Liver Diseases, Boston, USA.

Fazekas de St. Groth F, Roediger R, Shklovskaya E, Boes M, and Ploegh H (2006), Langerhans Cells Transfer MHC Class II Molecules to Lymph Node Resident Dendritic Cells In Vivo. Australasian Society for Immunology 36th Annual Scientific Meeting, Auckland, New Zealand.

Fazekas de St Groth B, Seddiki N, Santner-Nanan B, Martinson J, Zaunders J, Sasson S, Landay A, Nanan R and Kelleher A (2006) "Novel regulatory T cell subsets in humans - relevance to HIV. NIH/OAR workshop on Regulatory T cells and HIV/AIDS, Cincinnati, Ohio, USA.

Fazekas de St. Groth B (2006) Novel T-reg markers, International Society for Neuroimmunology and Immunology of Diabetes Society Satellite Symposium. San Francisco, California, USA.

Fazekas de St Groth B, Seddiki N, Santner-Nanan B, Martinson J, Zaunders J, Sasson S, Landay A, Nanan R and Kellehe A (2006) Expression of IL-2 and IL-7 receptors discriminates between human regulatory and activated T-cells within CD45RA and CD45RO compartments. FOCIS 6th Annual Meeting, San Francisco, California, USA.

Dilda PJ, Don AS, Tanabe KM, Higgins VJ, Allen JD, Dawes IW and Hogg PJ (2006) Mechanism of selectivity of an angiogenesis inhibitor from screening a genome-wide set of *Saccharomyces cerevisiae* deletion strains. American Association of Cancer Research 97th Annual Meeting, Washington DC, USA.

Haber M, Smith J, Flemming C, Ho LL, Allen D, Cohn SL, London WB, Buxton A, Marshall GM, Norris MD (2006) Expression of Multidrug Transporter MRP4/ABCC4 Is a Powerful Marker of Poor Prognosis in Neuroblastoma. Advances in Neuroblastoma Research 2006, Los Angeles, California, USA.

Hing A, Hicks M, Gao L, Faddy S, Tran P, Kwan J, Kesteven S, Sharland A, Stewart G, Macdonald P (2006) Hormone resuscitation of brain dead donor and its effect on transplantable organs. World Transplantation Congress, Boston, Massachusetts, USA.

Holz L, O'Reilly L, Benseler V, McCaughan GW, Bertolino P (2006) Hepatocyte-activated CD8+ T cells are programmed to die and do not recirculate in lymph nodes. Annual Scientific meeting of the Australasian Society for Immunology, Auckland, New Zealand.

Larsen SR, Chng K, Battah F, Armstrong M, Hayward M, Leung L, Thomson S, Hennessy A and Rasko JEJ (2006) Cytokine-induced In vivo Expansion and Mobilization of Marrow Mesenchymal Stem Cells in Nonhuman Primates. BMT Tandem Meetings, Honolulu, Hawaii, USA.

Larsen SR, Chng K, Zhou S, Wright J, Armstrong M, Thompson S, Hennessy A, Martiniello-Wilks R, Gibson J, Joshua DE and Rasko JEJ (2006) Optimizing Mobilization, Augmentation, and Gene Transfer of Multipotent Mesenchymal Stromal Cells (MSCs). American Society of Hematology, Orlando, Florida, USA.

Lucas K, Davis T, Zhang XD, Hersey P, Huang D, Allen J (2006) Resistance to apoptosis *versus* other drug resistance mechanisms in melanoma. Perspectives in

Melanoma X and the Third International Melanoma Research Congress, Noordwijk, The Netherlands.

Mignozzi F, Maus MV, Sabatino DE, Hui DJ, Rasko JEJ, Ragni MV, Manno CS, Ertl HCJ and High KA (2006) AAV-2 Capsid-specific $CD8^+$ T Cells Limit the Duration of Gene Therapy in Humans and Cross-React with AAV-8 Capsid. American Society of Hematology, Orlando, Florida, USA.

Rahman WH, Huang P, Bevlov L, Sharland A, Jamias JD, Chrisp J, McCaughan GW, Shackel NA (2006) Immunophenotyping of human liver disease using a cluster of differentiation (CD) antibody microarray. American Association for the Study of Liver Diseases, Boston, Massachusetts, USA.

Roediger B, Shklovskaya E, Boes M, Ploegh H and Fazekas de St. Groth B (2006) Langerhans Cells Transfer MHC Class II Molecules to Lymph Node Resident Dendritic Cells *In Vivo*. 9th International Conference on Dendritic Cells, Edinburgh, Scotland.

Shklovskaya E, Roediger B and Fazekas de St.Groth B (2006) Antigen presentation by epidermal-derived dendritic cells results in CD4 clonal deletion and lack of memory. 9th International Conference on Dendritic Cells, Edinburgh, Scotland.

Spencer A and Fazekas de St Groth B (2006), Differential effects of antigen-specific and non-specific competition in the primary and memory responses of $CD4^+$ T cells, Keystone symposium on "Determinants of Host Resistance, Susceptibility or Immunopathology to Pathogens", Steamboat Springs, Colorado, USA.

Tan S (2006) Spontaneous lymphoproliferation in CTLA-4 deficient mice is due solely to a defect in regulatory T cells. Keystone Symposium on Tolerance, Autoimmunity and Immune Regulation, Breckenridge, Colorado, USA.

Tran P, Hing A, Hicks M, Gao L, Faddy S, Kesteven S, Stewart G, MacDonald P, Sharland A (2006) Expression of NKG2D ligands following brain-death. World Transplantation Congress, Boston, USA.

Wang XM, Yu DMT, McCaughan GW, Gorrell MD (2006). Fibroblast activation protein and dipeptidyl peptidase IV influence cell adhesion, migration and apoptosis. Asia Pacific Organisation for Cell Biology, Beijing, China.

Wang XM, Yu DMT, Cordoba S, Marguet D, Rettig W, Schnapp A, McCaughan GW and Gorrell MD (2006) The Role of Fibroblast Activation Protein (FAP) in Cell Adhesion, Migration and Liver Fibrosis. Liver Fibrosis workshop, Washington DC, USA.

National

Invited presentations

Allen J (2006) Cancer Drug Resistance: Myeloma, Melanoma and MYC. September 6, Oncology Research Centre, Prince of Wales Hospital, Randwick.

Allen J (2006) Cancer drug resistance: transporters, MYC, myeloma and melanoma. September 11, Department of Pathology and Centre for Vascular Research, University of NSW, Randwick.

Allen J (2006) Imatinib and porphyrin toxicity, et al., from the Cancer Drug Resistance Group. November 6, Sydney Cancer Centre Seminar, Centenary Institute, Sydney.

Allen J (2006) Cancer drug resistance: transporters, MYC, myeloma and melanoma. September 11, Department of Pathology and Centre for Vascular Research, University of NSW, Sydney.

Bertolino, P (2006) The liver as an immune organ, Innate Immunity Workshop, Melbourne.

Britton WJ (2006) Control of Tuberculosis Infection: Roles of membrane TNF and purinergic receptors. University of Technology, Sydney.

Britton WJ (2006) Genetic control of susceptibility to Mycobacterium tuberculosis.
Novartis Foundation Symposium, ANU, Canberra.

Britton WJ (2006) Macrophages, Genetics and Tuberculosis. Department of Immunology and Infectious Diseases seminar, St George Hospital, Kogarah.

Britton WJ (2006) Tuberculosis: Progress towards a new vaccine. Infectious Diseases, Immunization and Allergy Symposium 150th Anniversary, Faculty of Medicine, University of Sydney, Sydney.

McCaughan G (2006) Hepatitis C infection: From Blood Donor to Allograft Failure. 13th International Meeting on Hepatitis C and Related Viruses. Plenary Lecture. Cairns.

McCaughan G (2006) Pathogenesis of HCV Infection Frank Dudley Festchrift Alfred Hospital, Melbourne.

McCaughan G (2006) What happens to the HCV Post Liver Transplant? Yyonne Cossart Festchrift, Sydney.

McCaughan G (2006) Pathogenesis of Hepatitis virus associated Hepatocellular Cancer. Australian Liver Foundation Single topic Conference on Liver Cancer, Melbourne.

Rasko JEJ (2006) Serendipity and Sluice: Inherited Disorders of Aminoacid Transport, Lorne Genome Conference, Lorne.

Rasko JEJ (2006) Gene Therapy Works! Well, sometimes. The Prince of Wales Hospital, Randwick.

Rasko JEJ (2006) Stem Cells Seen Loitering Near the Clinic, Sydney Cancer Centre Grand Rounds, Sydney.

Rasko JE (2006) Adult Stem Cells: Marrow to Manufacture, Inaugural Cancer Research Network, University of Sydney, Sydney.

Rasko JEJ (2006) Micro RNAs: Could tiny RNA molecules be involved in hematologic malignancies? NSW Bone Marrow Transplant Network, Sydney.

Rasko JEJ (2006) Stem Cells and Gene Therapy: Future Applications in Cancer. Sydney Cancer Centre – 10th Anniversary Cancer Symposium, Sydney.

Rasko JEJ (2006) Stem Cells for Muscle Repair, RPAH Medical Officers Association 72nd Annual Reunion, Sydney.

Rasko JEJ (2006) Two steps forward, one step back: Gene Medicine's Progress. Combined Grand Rounds, RNS/UTS/USYD/Kolling 22nd Annual Scientific Research Meeting, Sydney.

Semsarian C (2006) Clinical trials overview: the role of genes. Asia Pacific Interventional Advances Meeting, Darling Harbour, Sydney.

Semsarian C (2006) Genes in cardiovascular disease. FRACP Trainees Course, RPAH, Sydney.

Semsarian C (2006) Genes and heart disease. Heart Health Forum – NHF, Easts Leagues Club, Sydney.

Semsarian C (2006) Genetic basis of cardiovascular disease. RPAH Nurses Forum, RPAH, Sydney.

Semsarian C (2006) Molecular Cardiology. Chairman's Luncheon, Observatory Hotel, Sydney.

Semsarian C (2006) Managing the "genotype positive-phenotype negative" patient.
54th CSANZ Scientific Meeting, Canberra.

Semsarian C (2006) Gene-gender interactions in hypertrophic cardiomyopathy.
54th CSANZ Scientific Meeting, Canberra.

Semsarian C (2006) Case presentation: sudden cardiac death in the young.
54th CSANZ Scientific Meeting, Canberra.

Semsarian C (2006) An update on genetic research in hypertrophic cardiomyopathy. Cardiomyopathy Association of Australia Annual Meeting, Royal North Shore Hospital, Sydney.

Semsarian C (2006) Translational Research at the Centenary Institute. 72nd RPAH Medical Officers Association Reunion Meeting, RPAH, Sydney.

Semsarian C (2006) Surgical aspects in hypertrophic cardiomyopathy. Cardiothoracic Surgery Department Meeting, RPAH, Sydney.

Semsarian C (2006) Sudden cardiac death in the young: an indigenous health perspective. West Kempsey Community "Know Your Heart" Meeting, Crescent Head.

Semsarian C (2006) Genes in cardiovascular disease: are we there yet? Scientific Meeting of the National Heart Foundation of Australia, Darling Harbour, Sydney.

Semsarian C (2006) Double trouble: bad genes in heart disease. Medical Grand Rounds, RPAH, Sydney.

Seth D (2006) Osteopontin: An early marker for alcoholic liver injury? International Society of Biomedical Research on Alcohol, Sydney.

Seth D(2006) Identification of novel therapeutic targets for alcoholic liver disease. International Society of Biomedical Research on Alcohol, Sydney.

Shackel N (2006) State of the Art Lecture: Molecular Markers of Disease Behavior: "*Liver Biopsy Strikes Back*", Australian Gastroenterology Week 2006, Adelaide.

Shacekl N (2006) Hepatic fibrogenesis: New twist to an old tale, Annual Melbourne Liver Group Meeting, Melbourne.

Shackel N, (2006) Fishing for HCV. Annual Melbourne Liver Group Meeting, Melbourne.

Abstracts, oral and poster presentations

Banavara M, Kable EPW, Braet F, Wang XM, Gorrell MD, Cox G (2006). Detection of Collagen by Second Harmonic Microscopy as a Diagnostic Tool for Liver Fibrosis. The University of Sydney 5th Health Research Conference, Leura.

Benseler V, Holz L, Schlitt H, Brinkmann V, McCaughan GW, Bertolino P (2006) FTY720 treatment leads to sequestration but not accumulation of antigen- specific CD8+ T cells activated in lymph nodes. Transplantation Society of Australia & Zealand 24th Annual Scientific Meeting, Canberra.

Benseler V, Warren A, Holz L, Bowen D, Schlitt H, Couteur DL, McCaughan GW, Bertolino P (2006) The liver promotes antigen-specific clearance of naïve CD8+ T cells activated in situ. Transplantation Society of Australia & Zealand 24th Annual Scientific Meeting, Canberra.

Chiu C, Lind JM, Ingle J, Arthur JW, Semsarian C (2006) Leu39ter mutation identified in the phospholamban gene in a family with hypertrophic cardiomyopathy. 54th CSANZ Annual Scientific Meeting, Canberra 2006 & World Congress of Human Genetics, Brisbane.

Cochrane N, Ingles J, Lind JM, Chiu C, Weintraub R, Semsarian C (2006) Clinical and genetic studies in families with left ventricular noncompaction. 54th CSANZ Annual Scientific Meeting, Canberra.

Doolan A, Langlois N, Chiu C, Ingles J, Lind JM, Semsarian C (2006) Postmortem molecular analysis of sudden unexplained death in young Australians. 54th CSANZ Annual Scientific Meeting, Canberra.

Evans KA, Wang XM, McCaughan GW, Gorrell MD (2006). Dipeptidyl peptidase IV and fibroblast activation protein in liver fibrosis. The University of Sydney 5th Health Research Conference, Leura.

Flamant S, Aung HT, Lu DP, Read RL, Humphreys DT, Tan SA, Rajasekhar M, Martin DIK and Rasko JEJ (2006) Refined quantitative RT-PCR to identify and characterise predicted micro-RNAs. New Directions in Leukaemia Research, Sunshine Coast.

Gellert L, Heyman J, Strasser S, McCaughan GW, Donaghy AJ (2006) A randomised controlled trial of oral zinc therapy in liver cirrhosis. Australian Gastroenterology Week, Adelaide.

Gellert L, Heyman J, Strasser SI, McCaughan GW, Donaghy AJ (2006) Nutritional substrates: biochemical and endocrine response in liver cirrhosis. Australian Gastroenterology Week, Adelaide.

Gellert L, Strasser SI, McCaughan GW, Donaghy AJ (2006) The prevalence of serum zinc and insulin-like growth factor-I (IGF-I) deficiency patients with advanced cirrhosis. Australian Gastroenterology Week, Adelaide.

Hing A, Hicks M, Gao L, Faddy S, Tran P, Kwan J, Kesteven S, Sharland A, Stewart G, Macdonald P (2006) Hormone resuscitation of brain dead donor and its effect on transplantable organs. Transplantation Society of Australia & Zealand 24th Annual Scientific Meeting, Canberra.

Kable EPW, Braet F, Cox GC, Banavara M, Wang XM, Gorrell MD (2006). Detection of Collagen by Second Harmonic Microscopy as a Diagnostic Tool for Liver Fibrosis. Australian Microscopy on Microscopy and Microanalysis, Sydney.

Kowalczuk S, Azmanov DN, Bailey B, Rasko JEJ, Cavanaugh JA and Bröer S (2006) Functional analysis of novel mutations associated with Hartnup disorder, ComBio2006, Brisbane.

Larsen S, Chng K, Armstrong M, Hayward M, Thomson S, Hennessy A, Gibson J, Joshua D and Rasko JEJ (2006) Mesenchymal Stromal Cells Can Be Mobilised and Augmented in the Bone Marrow following Cytokine Administration, HSANZ, Hobart.

Lee B, Larsen SR, Kingham JA, Hayward MD and Rasko JEJ (2006) The Care of NOD/SCID Mice Receiving Total Body Irradiation. Australian and New Zealand Society for Laboratory Animal Science (ANZSLAS) Conference, Canberra. Best Scientific Poster Award

Lind JM, Chiu C, Ingles J, Heather AK, Semsarian C (2006) Association of the androgen receptor gene repeat region and severity of left ventricular hypertrophy in males with hypertrophic cardiomyopathy. 54th CSANZ Annual Scientific Meeting, Canberra 2006 & World Congress of Human Genetics, Brisbane.

Lind JM, Kwok T, Tu E, Ingles J, Semsarian C (2006) Association of the Y chromosome and risk factors for sudden cardiac death in males with hypertrophic cardiomyopathy. 54th CSANZ Annual Scientific Meeting, Canberra.

Lind JM, Chiu C, Ingles J, Semsarian C (2006) Gene-gender interactions in patients with hypertrophic cardiomyopathy.Heart Foundation Scientific Meeting, Sydney.

Ling S, Catalano A, Iland H, Ho PJ, Joshua D and Allen J (2006) Predicting response of multiple myelomas to proteasome inhibitors. Haematology Society of Australia and New Zealand, ANZSBT, ASTH Joint Annual Scientific Meeting, Hobart.

Osborne B, Wang XM, Park J, Yu DMT, Gorrell MD (2006). Recombinant human fibroblast activation protein: Expression and purification for enzymology and inhibitor development. The University of Sydney 5th Health Research Conference, Leura.

Park J, Knott HM, Wang XM, Yu DMT, Nadvi NA, Collyer CA, Church WB, Gorrell MD (2006) Expression of functionally active epitope-tagged recombinant human enzymes using baculovirus. 3rd Australian Health and Medical Research Congress, Melbourne and The University of Sydney 5th Health Research Conference, Leura.

Rahman WH, Huang P, Belov L, Sharland A, Jamias J, Chrisp J, McCaughan GW, Shackel NA (2006) Immunophenotyping of human liver disease using a cluster of differentiation (CD) antibody microarray. Australian Gastroenterology Week, Adelaide.

Richardson S, McCaughan GW, Warner FJ, Gorrell MD, Shackel NA (2006) CD147 is a novel mediator of hepatocyte extracellular matrix interactions. Australian Gastroenterology Week, Adelaide.

Shackel NA, Jamias J, Rahman W, Strasser SI, Koorey D, McGuinness PH, Guney S, McCaughan GW (2006) A study of hepatitis C viral load and calcineurin immunosuppression post liver transplantation. Australian Gastroenterology Week, Adelaide.

Seth D, Beard MR, Gorrell MD, McCaughan GW, Haber PS (2006) Osteopontin: An early marker for alcoholic liver injury? International Society of Biomedical Research on Alcohol (ISBRA), Sydney.

Seth D, Hogg P, Gorrell MD, McCaughan GW, Haber PS (2006) Identification of novel therapeutic targets for alcoholic liver disease. International Society of Biomedical Research on Alcohol (ISBRA), Sydney.

St.George A, Johnston A, Bauman A, Iverson D, Tapsell L, McCaughan GW, Strasser SI, McGrath L, Green J, Farrell GC, George J (2006) Lifestyle intervention in early liver disease: metabolic changes at 3 months. Australian Gastroenterology Week, Adelaide.

Tran P, Hing A, Hicks M, Gao L, Faddy S, Kesteven S, Stewart G, MacDonald P, Sharland A (2006) Expression of NKG2D ligands following brain-death. Transplantation Society of Australia & Zealand 24th Annual Scientific Meeting, Canberra.

Tsoutsman T, Chung J, Doolan A, Nguyen L, Williams IA, Tu E, Lam L, Bailey C, Rasko J, Allen DG and Semsarian C (2006) Mouse cardiac troponin I model of hypertrophic cardiomyopathy: phenotype associated with abnormal calcium handling. International Society for Heart Research Annual Scientific Meeting, Canberra.

Tsoutsman T, Chung J, Doolan A, Nguyen L, Williams IA, Tu E, Lam L, Bailey CG, Rasko JEJ, Allen DG and Semsarian C (2006) Mouse Cardiac Troponin I Model Of Hypertrophic Cardiomyopathy: Phenotype Associated With Abnormal Calcium Handling. 30th Annual Scientific Meeting of the International Society for Heart Research, Canberra.

Tsoutsman T, Tu E, Chung J, Lam L, Seidman J, Seidman C, Semsarian C (2006) Double mutations in hypertrophic cardiomyopathy: development of a novel mouse model with a severe phenotype. 54th CSANZ Annual Scientific Meeting, Canberra.

Williams RBH., Lau ACH, Cowley MJ, Shackel NA, Ajami K, Seth D, Gorrell M., McCaughan G (2006) Finding disease related molecular machines in human liver transcriptomes. Bioinformatics Australia Conference, Sydney.

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2007 - The Year Ahead

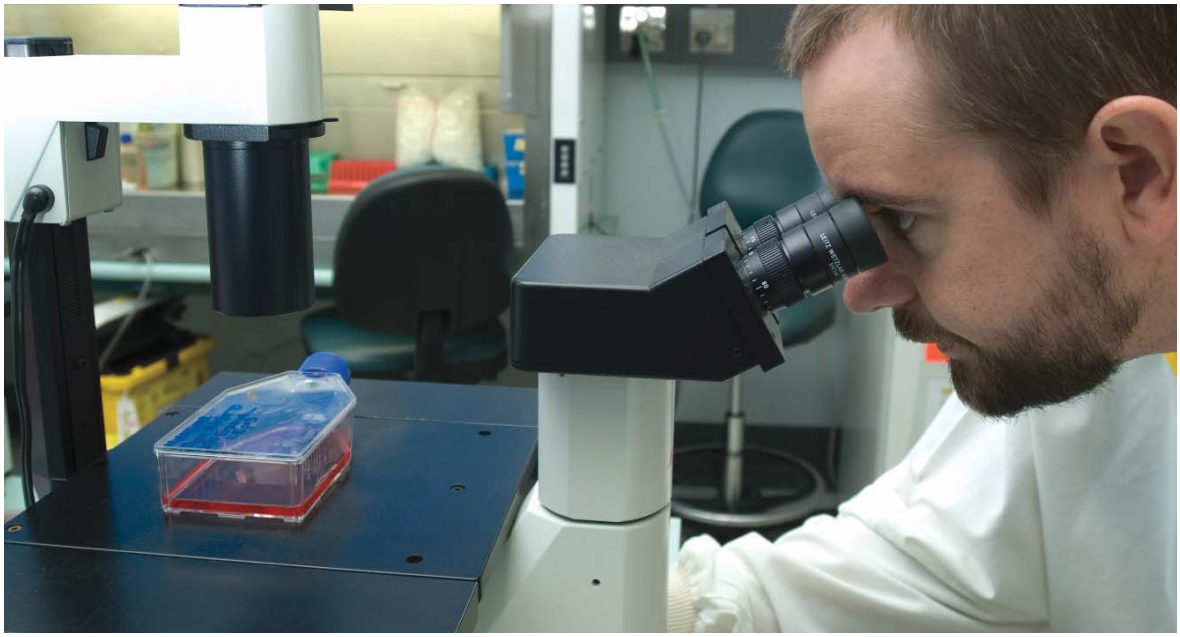
2007 promises to be an exciting year for Centenary with the recruitment of Professors Mathew Vadas, Jennifer Gamble and Wolfgang Weninger and Drs Ryuichi Aikawa and Pu Xia. Professors Vadas and Gamble and Dr Xia have relocated from the Institute of Medical and Veterinary Science, Adelaide. Within the scientific community, Professor Vadas has an internationally established reputation in the fields of inflammation and cancer and is one of Australia's most highly cited scientists. He is one of Australia's Inaugural ISI-Thompson Citation Laureates and current list of ISI Thompson "Highly Cited" scientists. His scientific research embodies a multi-disciplinary approach to the discovery of new molecules or pathways leading to novel therapeutics. Professor Gamble has a major interest in angiogenesis, the formation of new blood vessels, is now one of the best known vascular biologists in Australia. Associate Professor Xia is a medical graduate from China who specialised in endocrinology before going to Harvard and working at the prestigious Joslin Center for Diabetes Research. After joining Professors Vadas and Gamble in Adelaide, he made a major discovery about the wiring of endothelial (and indeed cancer) cells. This discovery led to 10 years of intensive research and a growth from a few people to as many as 30 interested in the fine details of this wiring process, the central player of which is an enzyme called sphingosine kinase.

Professor Wolfgang Weninger joins Centenary in June from the prestigious Wistar Institute in Philadelphia USA. He received his medical training from the University of Vienna. Wolfgang will be leading research into how white blood cells are able to invade and destroy cancers. By using the latest techniques in microscopy Wolfgang aims to pinpoint how white blood cells that travel from the blood stream into cancers are able to destroy cancer cells some of the time, but fail all too often.

Dr Ryuichi Aikawa currently at Tufts University, Boston Massachusetts USA, will join Centenary in the second half of 2007. Ryuichi's research will be using gene therapy to treat heart disease. He received his medical training in Cardiology at the University of Tokyo and has spent the last six years researching heart disease in Boston.

NHMRC Grants Commencing 2007

- NHMRC Program Grant – Associate Professor Barbara Fazekas de St. Groth, is a co-recipient of a 15.5 million grant with collaborators from the Garvan Institute and ANU entitled "Molecular and cellular studies of the adaptive immune response in health and disease"
- NHMRC Project Grant - Dr Patrick Bertolino and Dr Alex Bishop from the University of Sydney were awarded funding for their project entitled "Effective clearance of antigen-specific T cells in the liver: role in tolerance".
- NHMRC Project Grant - Dr Nick West was awarded funding for his project entitled "Genome wide investigations of Mycobacterium tuberculosis to reveal processes of pathogenesis"
- NHMRC Project Grant - Triccas J, Britton WJ, "Manipulating immunity to Mycobacterium tuberculosis with novel vaccines and immunotherapeutics"

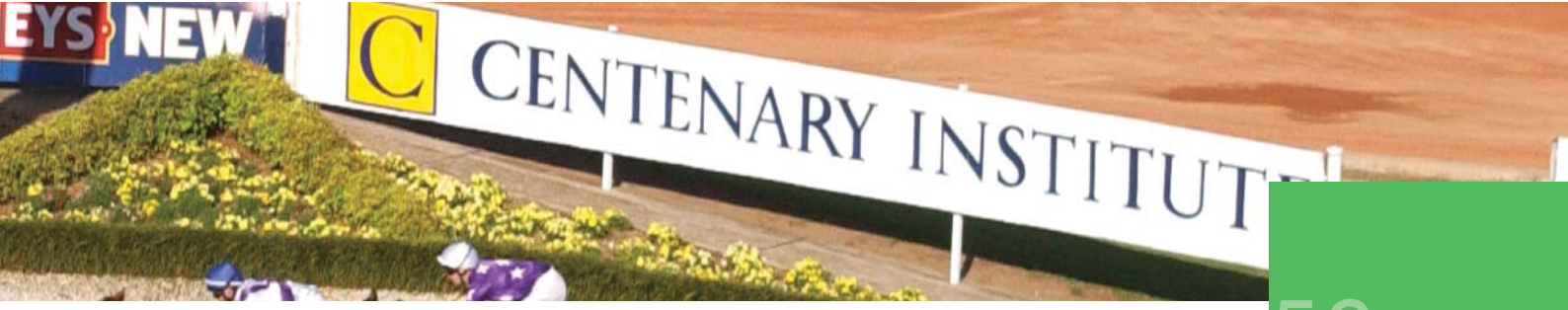


Other grants commencing 2007

- Professor Warwick Britton was the co recipient of a grant from the Wellcome Trust with collaborators from ANU.
- Dr Siliva Ling was awarded funding from the International Myeloma for her project entitled "The role of XBP-1 in the drug resistance of multiple myeloma".
- Dr Jeff Holst was awarded a Cancer Institute NSW early career development fellowship entitled "Dissecting the role of cancer/testis antigen transcription factors in neoplasia".
- Professors Jennifer Gamble and Mathew Vadas were awarded funding from the National Heart Foundation for their project entitled "Sphingosine kinase as a Key Regulator of Endothelial Cell Permeability".
- Associate Professor Chris Semsarian was awarded funding from the National Heart Foundation for his project entitled "Sudden death in young people with diabetes".
- Dr Nick Shackel and Professor Geoff McCaughan were co-recipients of a grant from the Australian centre for HIV and Hepatitis Virology Research entitled "The role of the Chemokine CXCL-10 in intrahepatic fibrogenesis".
- Dr Fiona Warner was awarded a University of Sydney Research & Development grant for her project entitled "The role of biliary epithelial to mesenchymal transition (EMT) in liver fibrosis".
- Dr Stephen Larsen was awarded a career establishment grant from the Leukemia Foundation entitled "Optimisation of treatment refractory GVHD using mesenchymal stromal cells".
- Equipment grants were awarded to Centenary from Perpetual Trustees, the Clive and Vera Ramaciotti Foundation, Rebecca L Cooper Medical Research Foundation, Cancer Institute NSW, NHMRC and the University of Sydney

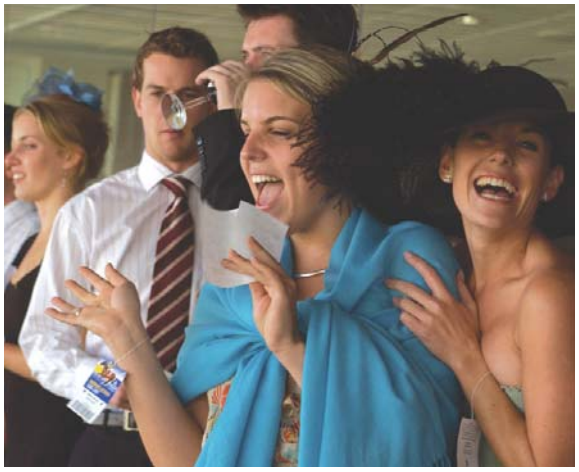
Postgraduate Scholarships

Ms Emily Tu, Ms Keryn Lucas, Dr Lye Lin Ho, and Ms Jessamy Tiffen received scholarships from the National Heart Foundation, Cancer Institute NSW, The Royal Australasian College of Physicians and Australian Rotary Health Research Fund, respectively.



Fundraising

13th Annual Raceday and Luncheon



The Centenary Institute celebrated its 13th Annual Race Day on Saturday, 28 October, 2006 at Rosehill Gardens Racecourse.

Master of Ceremonies A/Prof Chris Semsarian (Molecular Cardiology Group) did a superb job at entertaining guests and raising awareness of heart disease and cancer research at Centenary.

A healthy person drops dead for no obvious reason; the heart stops beating without any warning - it's known as sudden cardiac death. The disease is caused by mistakes in patients' genes. It affects 50,000 Australians each year and is the focus of Chris' research. Guest speaker Liz Jones (a patient of Chris') shared her touching story of how sudden cardiac death robbed her family of a loving brother and how through Chris' research she was given a second chance at life. She has a defibrillator implanted. It restarts her heart if it stops beating properly. Liz recounted the episode of when the machine restarted her heart. "It was an incredible feeling to have that kind of back up. I was in the office alone. Without the machine the attack could have been fatal".

Chris' research is working on what triggers the heart to malfunction and how to prevent the disease developing in people with the defective genes.

Special thanks to our corporate sponsors

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- Regional Radioworks
- The Wine Society

Thank you to the organisers, volunteers, and guests who by their presence contributed to a very special and memorable day. The event raised more than $160,000 for medical research.

Arrangements are well underway for the 14th Annual Raceday and Luncheon, to be held at the Sydney Turf Club on Saturday, October 27, 2007 at Rosehill Gardens.

Young Winemaker of the Year Awards

Ms Emma Wood (Seppelt Great Western) with Wine Society CEO John Winstanley.

The Wine Society celebrated its 60th birthday with its 6th Annual Young Wine Maker of the Year Award Dinner at the Westin Hotel on 25 November, 2006. Centenary was the nominated 'charity of choice' for the 5th year. We'd like to extend our sincere thanks and gratitude to the organisers and supporters, with the event raising close to $8,000 for the Centenary Institute.

The evening was a great success with fabulous food accompanied by superb wine from some of Australia's best young wine makers. During the evening, attendees were entertained by MC Simone Thurtell from the ABC's Grandstand program, the SCEGGS String Ensemble, the Wine Society's own James Roser and Australian Idol Finalist Bobby Flynn.

Congratulations to the Young Wine Maker of the Year Emma Wood of Seppelt Great Western (pictured below) and the Members' Choice winner Justin Coates of Step Rd.

End of Tax Year Appeal

Thank you to all of you who generously donated to our 2006 End of Tax Year Appeal.

A total of $73,375 was raised towards Dr Chris Jolly's research aimed at investigating the use of antibodies to treat diseases including cancer and rheumatoid arthritis.

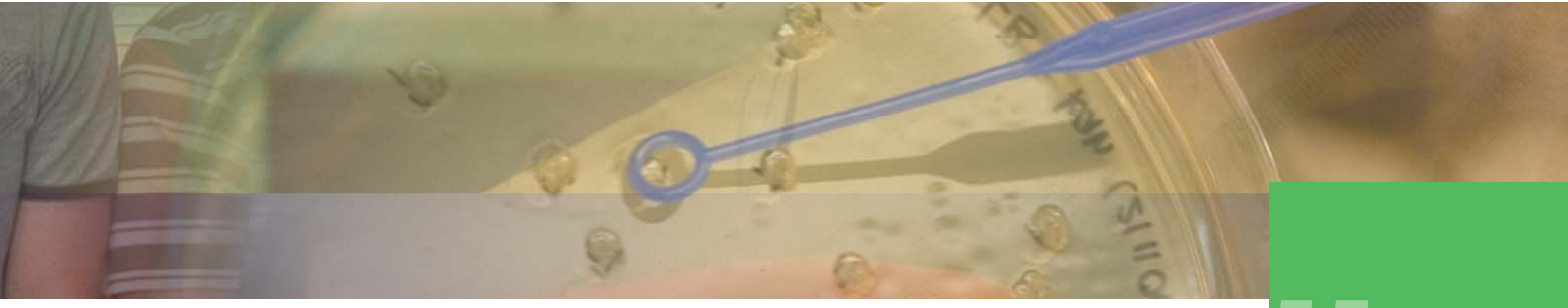
2006 Christmas Appeal

We gratefully acknowledge the generous contributions by supporters to our 2006 Christmas Appeal. A total of $21,970 was raised for the *Centenary Young Researcher Prizes*, supporting the work of some of our students and junior Postdoctoral Scientists.

We would be delighted if you would consider supporting us.

There are many ways in which you can support the Centenary Institute's research programme depending on your own particular interests. All donations of $2.00 or more are tax deductible and acknowledged in the Centenary News, published twice a year.

For information on making a donation, please visit www.centenary.org.au or call (toll-free) 1800 677 977.



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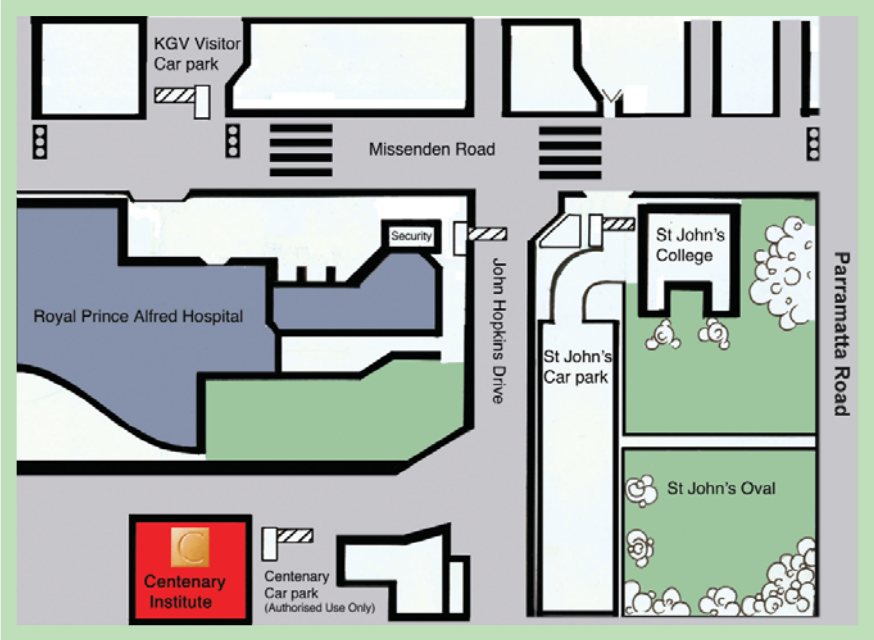

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Acknowledgements

Editorial: Nick Pearce (Acting General Manager)
Editorial Support: Centenary Editorial Committee
Photography: Gary Jones
Graphic Design: Penguin Graphics
Printing: MMB Print Management


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