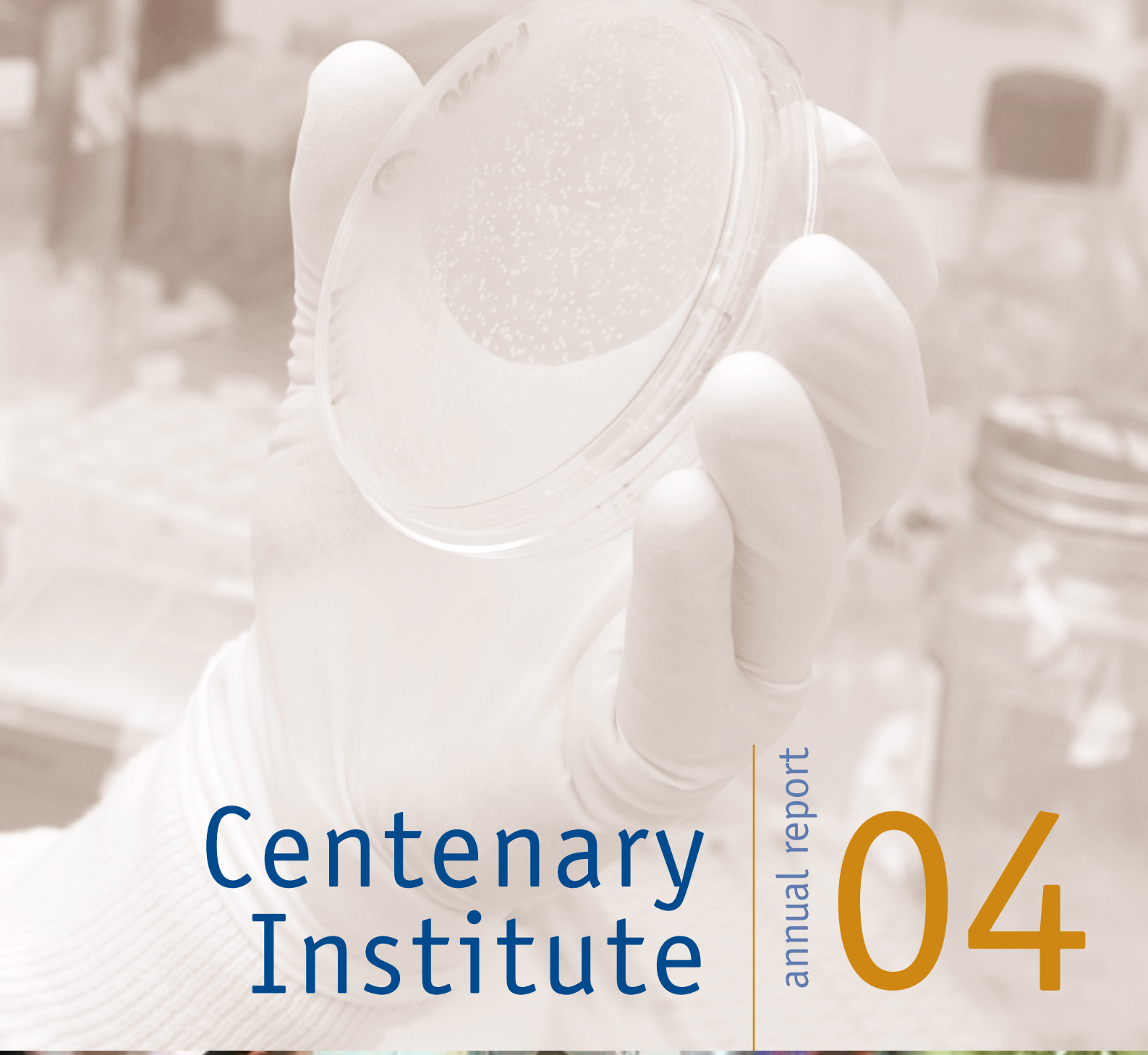


Centenary Institute

annual report 04

CENTENARY INSTITUTE

CANCER MEDICINE & CELL BIOLOGY

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 2004

Contents

2004 Highlights

NSW Young Tall Poppy

Associate Professor Chris Semsarian, head of Centenary's Agnes Ginges Centre for Molecular Cardiology, was honoured as a 2004 NSW Young Tall Poppy for his work on the genetic basis of sudden cardiac death in young people. The Tall Poppy Campaign was created in 1998 by the Australian Institute of Political Science to promote Australian intellectual excellence and endeavour. It is the second time a Centenary researcher has been recognised as a Young Tall Poppy, the other being Professor John Rasko in 2001.

RPA Foundation Prize

Professor Warwick Britton was awarded the 2004 Royal Prince Alfred Hospital Foundation prize worth $50,000. The award, in recognition of Prof Britton's outstanding contribution to the field of mycobacterial infection including tuberculosis and leprosy, was presented by Channel 9's Ms Jana Wendt, at a special ceremony in the Hospital's Kerry Packer Auditorium on November 5.

Centenary Medallists

The Centenary Institute is greatly honoured to count a number of Centenary Medallists among those associated with our governance including Professor Antony Basten, the Honourable John Brown and Dr Diana Horvath from the Institute Board of Governors, and Mr Tim Besley and Dr Ian Blackburne from the Cen*Tec* Board.

Major equipment upgrade

In June 2004 the Centenary Institute was awarded a 1.4 million dollar grant from the Federal government to upgrade and enhance the research capacity of our flow cytometry and transgenic facilities.

Australasian Autoimmunity Workshop

In May the Centenary Institute hosted the 9th Australasian Autoimmunity Workshop which brought together 75 delegates from across Australasia to share the latest research findings on autoimmune diseases such as diabetes and multiple sclerosis. The event was a great success.

Awards and Grants

Dr Chris Semsarian was appointed to a Clinical Associate Professorship and Dr Helen Briscoe was appointed Associate Professor at the University of Sydney.

The following grants were awarded to our researchers:

- NHMRC Practitioner Fellowship – Associate Professor Chris Semsarian
- NHMRC (RD Wright) Career Development Fellowship – Dr Stuart Tangye
- NHMRC Industry Fellowship – Dr Chris Jolly
- NHMRC CJ Martin Fellowship – Dr Umaimanthan Palendira
- NHMRC Project Grant (Tuberculosis) – Professor Warwick Britton, Dr Jamie Triccas and Associate Professor Helen Briscoe
- NHMRC Project Grant (HIV and mycobacterial infections) – Professor Warwick Britton
- NHMRC Project Grant (Roles of the dipeptidyl peptidase IV gene family in human liver disease) – Dr Mark Gorrell and Professor Geoff McCaughan
- NHMRC Project Grant (Basic mechanisms of spontaneous tolerance of liver allografts in a rat model) – Professor Geoff McCaughan, Dr Alex Bishop and Professor John Rasko
- NHMRC Equipment Grant (Recombinant Protein Facility) – Dr Mark Gorrell, Professor Geoff McCaughan and Dr Alex Bishop

- NHMRC Equipment Grant (Solid State Laser) –Professor Antony Basten, Professor Warwick Britton, Professor John Rasko, Associate Professor Barbara Fazekas de St.Groth, Dr Robert Brink, Dr Christopher Jolly, Dr Stuart Tangye, Dr Daniel Sze
- Sydney University Sesqui grant – Professor Warwick Britton
- Perpetual Trustees Grant – Professor Antony Basten
- Cecilia Kilkeary Foundation grants - Dr John Allen, Professor John Rasko and Dr Pablo Silveira
- Cellcept Australia Research Grant (Hepatitis C virus in transplanted livers) – Professor Geoff McCaughan
- Rebecca L Cooper Foundation grants – Associate Professor Chris Semsarian; Professor Warwick Britton; Professor John Rasko; Professor Geoff McCaughan, Dr Mark Gorrell and Dr Bernadette Saunders
- Ramaciotti Foundation equipment grants – Professor Antony Basten; Dr Pablo Silveira; Professor Geoff McCaughan. Dr Mark Gorrell and Dr Alex Bishop
- Cure Cancer Australia research grant – Professor John Rasko
- Community Health and Tuberculosis Australia (CHATA) research grant - Professor Warwick Britton and Dr Bernadette Saunders

University Medals & Student Awards

Ms Caroline Higgins from the T Cell Biology group and Ms Lan Nguyen from the Molecular Cardiology laboratory were awarded University of Sydney Medals for their Honours projects in 2003. Ms Higgins studied regulatory T cells in the mouse under the supervision of A/Prof Barbara Fazekas de St.Groth while Ms Nguyen investigated the effects of exercise on the heart under the supervision of A/Prof Chris Semsarian. In 2004 Ms Higgins commenced a Science/Law Degree at the University of Sydney and Ms Nguyen commenced her medical degree at Flinders Medical Centre, SA.

A/Prof Chris Semsarian and Ms Lan Nguyen at the graduation ceremony

Two undergraduate students Ms Amanda Cuss and Ms Korana Musicki will be awarded University of Sydney medals in 2005. Ms Cuss's Honours project performed under the supervision of Dr Stuart Tangye, involved identifying and characterising a population of transitional B cells, which represent immature B cells present in the peripheral circulation, in humans. Ms Musicki's project investigated the protective role of cell-bound Tumour Necrosis Factor against infection by the human pathogen Listeria under the supervision of Dr Bernadette Saunders. Ms Cuss will commence her PhD with Dr Tangye in 2005. Ms Musicki has been accepted into the University of Sydney's Graduate Medical Programme. The medals will be presented to the recipients during their graduation ceremony in March 2005.

Ms Cindy Ma of the Lymphocyte Differentiation group was a finalist in the New Investigator Awards at the 34th Annual Australasian Society for Immunology Conference held in Adelaide in December.

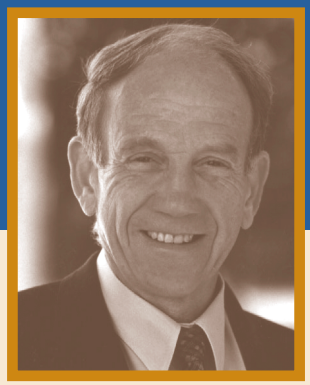
Scholarships

Ms Alexandra Spencer, a PhD student in the T Cell Biology group, was awarded a scholarship from the John Brown Sports and Tourism Youth Foundation to present her work at the 12th International Congress of Immunology in Montreal, Canada, in July 2004.

Dr Sandhya Limaye and Ms Katerina Ajami received NHMRC Postgraduate Scholarships. Mr Ben Roediger, Ms Alessandra Doolan, Ms Jennifer Randall and Mr Peter Tran were awarded Australian Postgraduate Award scholarships.

Publications

2004 was a very good year for the Centenary Institute with respect to publications in high impact journals such as Nature Genetics, Nature Immunology, Immunity, Journal of Clinical Investigation, Lancet, Blood, Molecular & Cellular Biology and Hepatology. Overall 12 papers were published in journals with an impact factor of 8 or more (ie the top 5% of all biomedical journals). In the Nature Genetics paper John Rasko's team reported their seminal discovery that Hartnup disorder is caused by mutations in the neutral amino acid transporter SLC6A19, while Stuart Tangye with collaborators from the Walter and Eliza Hall Institute was co-author on a Nature Immunology paper describing how antibody producing cells are regulated. The remaining 10 papers with high impact factors came from work done in the Director's group (4, including Brink, Tangye and Allen), the McCaughan group (3, including Bertolino), the Britton group (2) and the Fazekas group (1, Chklovskaia).



From the Director

I believe the key to developing any long-term strategic plan is to look to a role model from whom inspiration and guidance can be sought. In my case that model has been Dr Edward Jenner. In addition to his legendary discovery of smallpox vaccination, he was a truly rounded scientist who was elected to the Royal Society for his work on the habits of the cuckoo nestling and, who in his spare time, classified Sir Joseph Banks' botanical collection of Australian flora, collected during James Cook's second voyage to this land. What's more, he raised funds from the public and government to support his research and to set up vaccination clinics across the country – a true translational researcher. It is in the light of his achievements that we look at the Centenary Institute, 15 years after its creation. Over this period we have evolved in response to the external influences exerted by a tightening fiscal climate, what I have termed the 'epidemic of Institutes', and the 'biotechnology revolution', brought on by the sequencing of the human genome.

It is during times of financial constraint and changes in community perceptions of scientific research, that, more than ever before, we need to be perceived as having a significant contribution to make to the world of science. A central tenet of value is international competitiveness. In order to achieve this goal Centenary has a four-pronged strategy: to maintain its core of expertise in Immunology; to expand its base in molecular medicine; to enhance our collaborative network; and to commercialise our research.

Maintaining our core of expertise in immunology ensures that we can continue our high level of commitment to that discipline and its applications to infections, some forms of cancer, autoimmune disease, allergic disorders, immunotherapy and vaccination. By strengthening the molecular technology base in conjunction with existing expertise in immunology and cell biology, Centenary has ensured that it can be more competitive in the fields of gene therapy, carcinogenesis, genetic diseases and most recently stem cell science. Moreover, this technology base has enabled us to foster new collaborations with clinical colleagues on the local campus whose research is competitive and of mutual interest.

This network has included interactions with the Hospital's AW Morrow Centre for Gastroenterology and Liver Disease, the Institute of Haematology, the Sydney Cancer Centre, and the Department of Cardiology. Added to these local interactions are ongoing collaborations with over 20 national and 25 international research institutes, universities and hospitals in the USA, UK, and Europe.

The fourth prong of Centenary's research strategy has been the commercialisation of research projects at the proof of concept stage with a view to developing candidate molecules for diagnostic and clinical purposes. Two projects have Biotechnology Innovation Fund (BIF) support through our biotechnology company Cen*Tec* Ltd which is managed by a Board of leaders from industry and the corporate sector.

Collectively the various prongs of our strategy are designed to position Centenary at the centre of the 'biotechnology revolution'. In other words, they are aimed at securing adequate funds for our research programme through the appropriate balance between peer reviewed, commercial and community based sources - thus creating a niche for the Centenary network in the post-genomics era of biomedical research and realising the goal of being able to vaccinate, not just against infections but against autoimmune disease, allergy, and cancer. If we can emulate even to a modest extent, the achievements of Dr Edward Jenner, then Centenary is assured of a very bright future indeed.

This year we were joined by two new postdoctoral researchers. Dr Pablo Silveira who completed his PhD in the Centenary Institute in 2001 has returned after spending three years in the Jackson Laboratory in Maine, USA. Dr Silveira will continue his research into Type 1 Diabetes in the B Cell Biology Group within Centenary. Dr Didrik Paus has also joined the B Cell Biology Group to undertake research on memory B cells and plasma cell formation. Dr Paus completed his PhD in the Laboratory of Molecular Biology at Cambridge, England, under the supervision of the renowned antibody engineer, Dr Greg Winter, whose contributions were recently recognised by a knighthood.

The last year has been most successful for the Centenary Institute in terms of peer reviewed research funding, particularly from highly competitive sources like NHMRC. Moreover it was a good year with respect to our fundraising activities.

Awards & Grants

This year Associate Professor Chris Semsarian was among the recipients of a 2004 NSW Young Tall Poppy Award. The award was presented by the Minister for Science and Medical Research, the Honourable Frank Sartor MP, for his important work on the genetic basis of sudden death in young people. I would like to congratulate Chris on this remarkable achievement.

Congratulations also go to Professor Warwick Britton who

heads the Centenary Institute's Mycobacterial Research Group for being awarded the Royal Prince Alfred Foundation Medal for 2004. This is the third time in five years that a member of the Centenary's research team has won this $50,000 award. Warwick was presented with the award by Channel Nine's Sunday presenter Jana Wendt. The funds will be used to further his team's highly successful work on a new vaccine for TB.

This year four of our researchers took up NHMRC fellowships: Associate Professor Chris Semsarian received a five year NHMRC Practitioner Fellowship, Dr Stuart Tangye of the Lymphocyte Differentiation lab was awarded a NHMRC (RD Wright) Career Development Fellowship, Dr Chris Jolly of the B Cell Biology group received a NHMRC Industry Fellowship and Dr Umaimainthan Palendira who completed his PhD in the Mycobacterial Research group was awarded a NHMRC CJ Martin Training Fellowship. A number of other research and equipment grants were awarded to researchers at the Centenary Institute.

In addition, numerous grants were received by our researchers to present their work at various international and national conferences (see article on 12th International Congress of Immunology) and seven higher degree students were awarded scholarships to carry out PhDs in Centenary starting in 2005. This very pleasing result particularly in grant funding is underpinned by our research team's achievement in publishing 55 papers during the year.

Professor Jon Sprent, Fellow of the Royal Society, from The Scripps Research Institute will join Centenary's team in July 2005. Professor Sprent is the third researcher to receive the prestigious NHMRC Burnet Award which is designed to bring back the most distinguished expats to Australia after many years abroad. His decision to return to Centenary is a real feather in our cap and his presence will greatly enrich our research programmes.

Fundraising

Fundraising and in particular the generous ongoing donations made by members of the Research Society are vital to our research programme and it is a pleasure for me to take this opportunity to express my warm appreciation to all who have supported the Centenary both through the Research Society and appeals over the past year.

Through the generosity of those who supported our 2004 Christmas Library Appeal, we have raised $36,369 to help cover the purchase of journals for the library in 2005.

Centenary hosted its 11th Annual Raceday and Luncheon on Saturday, 9 October 2004 at Rosehill Gardens Racecourse. It was our most successful day yet and my thanks go to Board Deputy Chairman, Malcolm Noad and his Raceday Steering Committee for their hard work. The 2005 Raceday will once again be held at Rosehill Gardens Racecourse on 22nd October.

Professor Antony Basten
Executive Director

Board Governors

Mr Jim Longley FCPA FAICD was appointed Chairman of the Board in 2002. He has been a Governor since 1997 and served as Treasurer between 1999 and 2002. Formerly the State Member for Pittwater for almost 10 years, Mr Longley held various ministerial portfolios in the NSW Government between 1992-1995 and was the Chief Executive Officer of Anglican Retirement Villages, Diocese of Sydney between 1996-2000. Mr Longley is currently Head of Government Finance at the Commonwealth Bank of Australia.

Professor Tony Basten AO FAA FTSE was appointed Governor ex officio in 1989 at the time of his appointment as Founding Director of Centenary Institute. He holds the Chair of Immunology at the University of Sydney, is a consultant physician at Royal Prince Alfred Hospital and Chief Scientist of CenTec Limited.

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 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) 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.

Mr Paul Harris ASIA was appointed as a Governor in 1998. He has worked in the securities market in Australia for nearly 30 years holding a number of senior positions in merchant banks and stockbrokers. Mr Harris is a member of the Australian Stock Exchange and a Director of various companies including Ten Group Ltd, Gresham CEA Management Ltd and Stadium Australia Club Ltd.

Ms Jan Hogan MAPs was appointed as a Governor in 1998. She is a Psychologist and Family Therapist with an active practice. Ms Hogan holds directorships in several private companies and is a Trustee of the Centenary Institute Medical Research Foundation.

Dr Diana G Horvath AO appointed as a Governor in 1993 in her capacity as Chief Executive Officer of the former Central Sydney Area Health Service. Dr Horvath is currently CEO of the Sydney South West Area Health Service which is affiliated with the Centenary Institute.

Professor John Mathews AM was appointed as a Governor in 2000. He was the Founding Director of the Menzies School of Health Research in Darwin for 15 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 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.

Mr Malcolm Noad was appointed as a Governor in 1995. He held the position of Chairman between 1999-2002 and is currently Deputy Chairman. Mr Noad has an extensive background in newspaper publishing and was appointed to the News Ltd Board in 1992. Mr Noad is a former Chairman of the National Rugby League and is currently Chief Executive Officer of the 2004 Premiership NRL team, Mitsubishi Electric Canterbury – Bankstown Bulldogs. Mr Noad has been a Trustee of the Centenary Institute Medical Research Foundation since 1994.

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 1988 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.

Mr Michael Tidball BSW FAICD is the Chief Operating Officer of the Law Society of New South Wales. He has held the position of General Manager for the: Residential Aged Care Anglican Retirement Villages, Legalcare Group, and Corporate Strategy Group Technicatome. In addition he has held various Government positions such as General Manager for the Department of Business, the Arts, Sport and Tourism (ACT Government); National Manager for Government Business, Minet Australia; and State Policy Advisor, NSW Ministers for Health, Community Service and Ageing. He became Centenary's Treasurer in 2002.

Our History

The Centenary Institute was conceived in 1982 to commemorate the Centenaries of the University of Sydney Medical School and the Royal Prince Alfred Hospital. 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. Formal affiliations with the University and Hospital promote opportunities for students to become involved in research as well as the translation of basic discoveries into clinical practices. Centenary is located in the grounds of Royal Prince Alfred Hospital adjacent to the Medical School and University campus. It is housed in a purpose built facility capable of accommodating a research team of up to 150 career investigators, trainees and support staff. Facilities include a specific pathogen free grade animal house, mouse cardiac physiology and function facility, transgenic service, a state of the art flow cytometry facility, library with online capability and a lecture theatre.

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 680 articles in refereed journals and books, its staff have in excess of 950 presentations at international and national conferences since 1992, and it has attracted over $80 million dollars in grant funding to the campus.

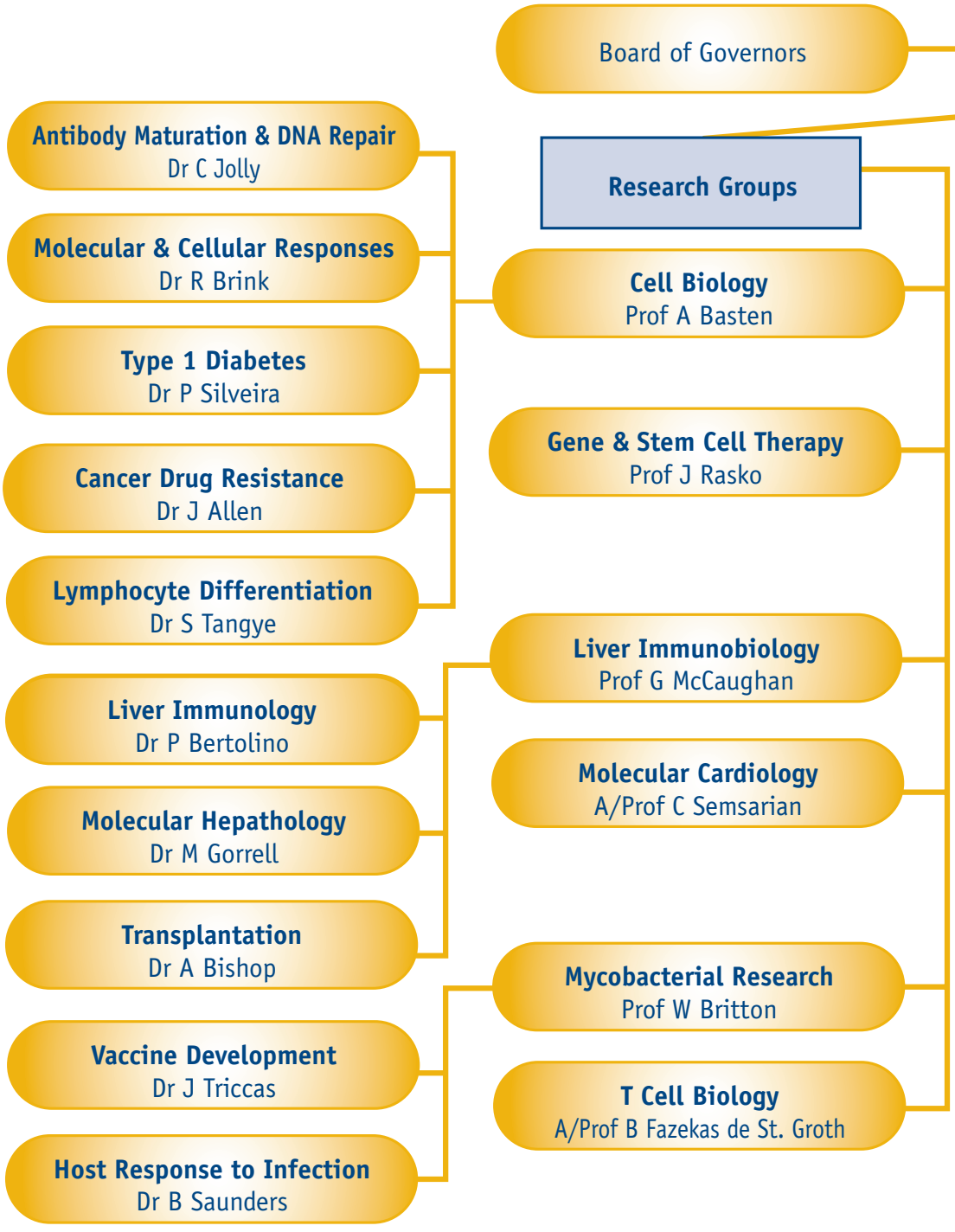
Centenary has a proud record of training PhD students. Since 1992 the Institute has produced 42 graduates. On completion of their PhDs students have gone on to successful post doctoral studies at many of the world's leading institutions.

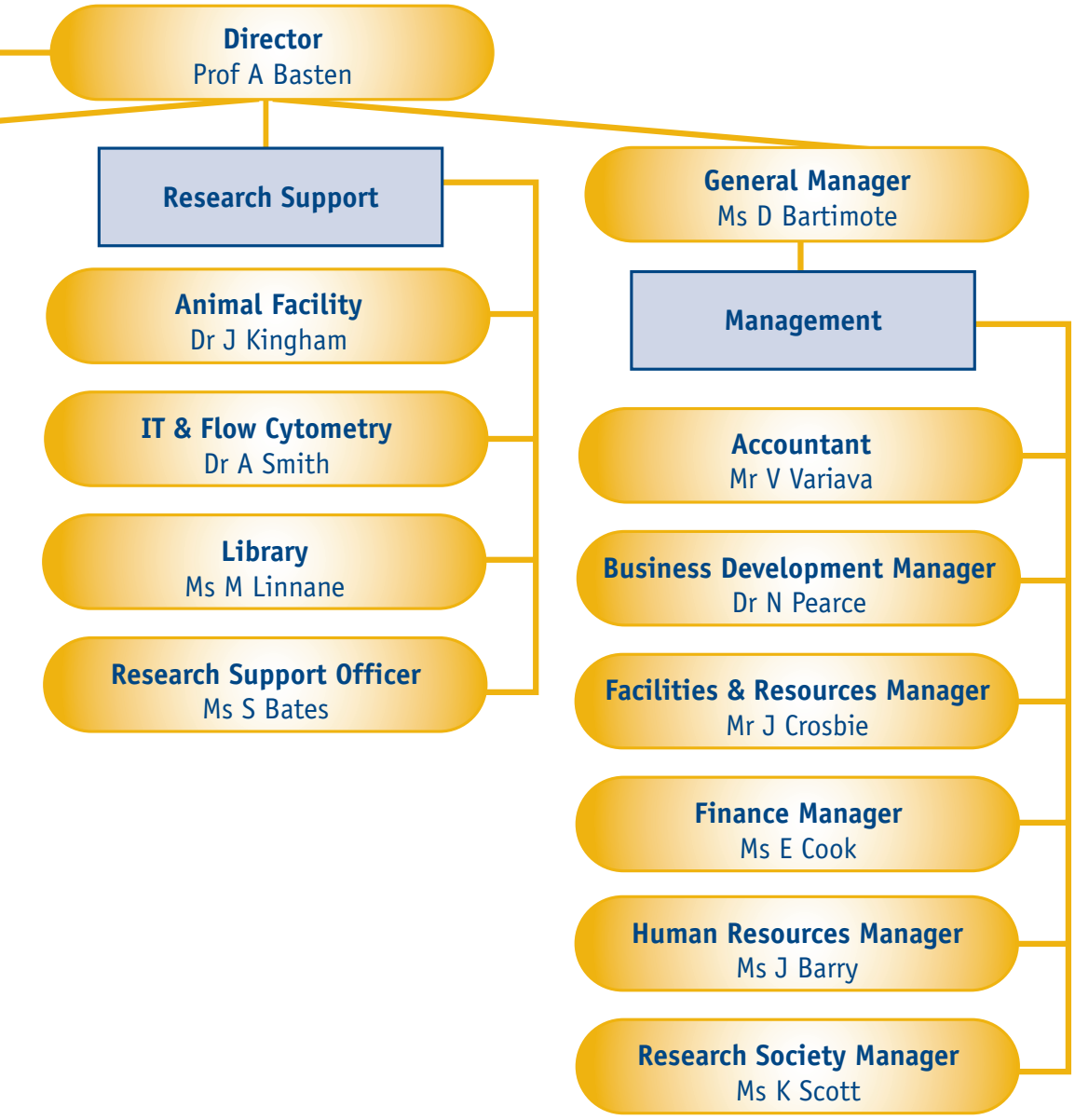
Centenary has a strong commitment to commercialising products of its research and has set up a biotechnology company, Cen*Tec* Ltd for this purpose. Two industry grants have been obtained to date by the company for developing a human antibody technology and a preventative vaccine for type 1 diabetes.

Defining milestones in the history of the Centenary Institute:

- Appointment of Professor Antony Basten as the Founding Director of the Centenary Institute.
- Commencement of the new $21.5 million building, which enabled Centenary to quadruple staff numbers to the current level of 120 and to diversify the research programme to encompass molecular medicine as well as immunology.
- Creation of Centenary's spin out company, Cen*Tec* Ltd, in 2001 for the purpose of developing projects with commercial potential. The company has been the recipient of two Federal Government Biotechnology Innovation Fund grants.
- Recruitment in 2005 of Professor Jonathon Sprent FRS who has received a highly prestigious Burnet Award from the NHMRC to bring him back to Australia after a brilliant 30 year research career in the USA and Europe. Prof Sprent is described by his referees as one of the two or three leading experts in the world on T cell biology.

Organisational Chart




Director
Prof A Basten
Research Support
Animal Facility
Dr J Kingham
IT & Flow Cytometry
Dr A Smith
Library
Ms M Linnane
Research Support Officer
Ms S Bates
General Manager
Ms D Bartimote
Management
Accountant
Mr V Variava
Business Development Manager
Dr N Pearce
Facilities & Resources Manager
Mr J Crosbie
Finance Manager
Ms E Cook
Human Resources Manager
Ms J Barry
Research Society Manager
Ms K Scott

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 within Centenary, namely B Cell Biology (the Director's lab), Cancer Drug Resistance, Gene and Stem Cell Therapy, Liver Immunobiology, Lymphocyte Differentiation, Molecular Cardiology, Mycobacterial Immunity, and T Cell Biology.

Cell Biology

Group Head: Professor Antony Basten

The research activities of the Director's group, also known as The Cell Biology Group encompass three different programmes managed by independent scientists with the overall support and leadership of the Director.

Dr Robert Brink from the Molecular and Cellular Responses lab investigates the signals inside cells, which are responsible for cell survival versus death. The Antibody Maturation & DNA Repair lab 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 Pablo Silveira's Type I Diabetes lab investigates the white cells responsible for destroying the insulin secreting apparatus in the pancreas of patients with diabetes.

The Lymphocyte Differentiation lab led by Dr Stuart Tangye investigates the regulation of the human immune system and how it responds to infection. 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.

Antibody Maturation and DNA Repair

Project Leader: Dr Chris Jolly

Antibodies form our first line of defence against most infections. Each antibody clone has the ability to specifically recognize (or "tag") a different 3D-shape on a molecular scale. As immune responses against infections mature, specific antibodies improve their tagging efficiency in a matter of only days. This improvement is achieved by the active point mutation (called "hypermutation") and rearrangement (called "class-switching") of antibody genes in cells responding to the infection. The goal of our research is to understand at the molecular level the mechanisms by which these "good" mutation processes occur, and understand how these mechanisms are different from "bad" mutation processes that cause cancer. We have developed unique methods and reagents that enable detailed investigation of antibody mutation. Using these methods we have, for instance, shown that an animal's antibody repertoire is increasingly dominated by mutated antibodies as the animal ages, thus demonstrating that antibody mutation adapts antibody repertoires in response to natural infections. We are also interested in how proteins that normally repair DNA damage and prevent mutation are involved in antibody mutation. We have shown that a key protein that normally protects against DNA damage (the DNA-dependent protein kinase, catalytic subunit, or DNA-PKcs) has a role in antibody gene mutation. So far, the only known enzymatic activity of DNA-PKcs is its "kinase" activity. That is, DNA-PKcs catalyses the addition of phosphate groups onto other DNA repair proteins, and thus activates them, when it is recruited to breaks in the DNA double helix. Surprisingly, we have found that the participation of DNA-PKcs in class-switching is largely independent of its kinase

activity, highlighting the multiple roles DNA-PKcs plays in DNA repair complexes.

In addition to the above projects, we are developing technologies that will allow us to isolate and produce human antibodies in the lab for end use as agents for the treatment of infections, venomous toxins, cancers and inflammatory diseases in humans. We are using chromosome engineering to produce B cell lines that will recapitulate B cell development in cell culture. The goal is to produce libraries of cells that express widely variant human antibodies constantly undergoing hypermutation from which we can quickly isolate human monoclonal antibodies with the desired binding properties and of the desired class against any protein of clinical interest.

Highlights:

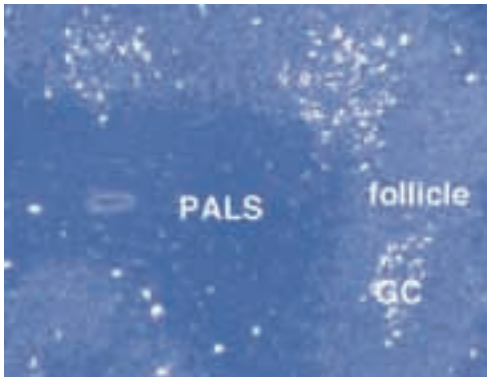
- Shown that a kinase-independent activity of the DNA-dependent protein kinase promotes antibody class switching.
- Proposed that the cleavage of opposing DNA strands, which produces DNA double strand breaks in antibody genes that are required for class-switching, occurs by two distinct mechanisms.
- Successful transfer of a human chromosome carrying a complete complement of Ig genes to a cultured B cell line.

Molecular and Cellular Responses

Project Leader: Dr Robert Brink

The B cells of the immune system are a subset of white blood cells that produce the antibodies that recognise and eliminate invading micro-organisms. Because of the destructive power of antibodies, their production is carefully regulated to ensure that autoantibodies which recognise the body itself are not produced. Our group studies the cells, molecules and genes that regulate antibody production and how they may malfunction to give rise to autoimmune disease, immunodeficiency or cancer. For this purpose a powerful mouse model (SWHEL mice) is used which allows us to follow antigen-specific B cell responses within immunised mice. These mice produce B cells that have a uniform high affinity for the well characterised protein antigen hen egg lysozyme (HEL).

A particular focus of our research is the role of the tumour necrosis factor receptor (TNFR) family and how these cell surface receptors transmit molecular signals into cells. Separate lines of genetically modified mice form the primary tools for our studies of how signalling through members of the TNFR superfamily are regulated in vivo. TNFR molecules are critical regulators of immune responses and many other physiological systems. The TNFR associated factors (TRAFs) are a family of intracellular proteins that transmit signals from TNFRs following ligand binding. To determine the precise functions of the different TRAF proteins, mice have been produced that carry specifically inactivated TRAF genes.



The fate of the anti-HEL B cells can be tracked *in vivo* by flow cytometry and immunohistology

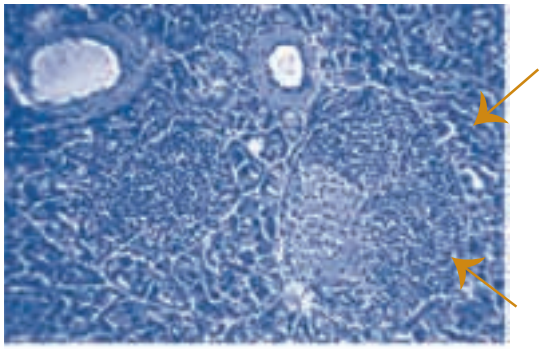
Highlights:

- Demonstrated that excess BAFF subverts B cell self tolerance.
- Discovered that TRAF2 differentially regulates the two major pathways of NF-kB activation.
- Identified the different responses of follicular and marginal zone B cells to T cell-dependent antigen.
- Produced a mouse conditionally deficient for the TRAF3 gene.

Type 1 Diabetes

Project Leader: Dr Pablo Silveira

Type 1 diabetes (T1D) is a disease that occurs when the body's own immune system mistakenly attacks and destroys the insulin producing beta cells of the pancreas. This is detrimental since insulin is an essential hormone used to regulate sugar levels in the blood. Currently, the disease affects more than 100,000 Australians and its incidence is increasing at an alarming rate in this country as well as in other developed nations. Using an animal model, our research has demonstrated that a class of immune cell, termed B cells, play an important role in the early stages of T1D. We are currently investigating the role of these dangerous B cells and why they are produced in diabetes-prone individuals. We hope this may eventually lead to the development of new therapies aimed at preventing the development of T1D.



Immune cell infiltrate destroying
B cells in the pancreas

The non-obese diabetic (NOD) mouse develops a form of Type 1 Diabetes (T1D) which closely resembles the human disease. As a model for the disease, it has led to many important discoveries about the immune basis of T1D. One important discovery revealed that a class of immune cell, termed T cells, are responsible for most of the damage to the insulin producing beta cells in patients who develop T1D.

Our research is attempting to identify the faulty immune mechanism/s responsible for the development of an aberrant population of B cells in NOD mice which are capable of taking up and presenting proteins from insulin secreting beta cells to T cells.

We are also interested in determining if some of the T1D susceptibility genes may be the same or similar to those conferring predisposition to other autoimmune diseases such as systemic lupus erythematosus or autoimmune gastritis.

By discovering the mechanisms that break down in order to produce self reactive B cells in NOD mice and identifying the genes and molecules that regulate the development and actions of this cell type, we hope to provide the basis for new therapies in humans designed to prevent immune mediated destruction of insulin producing beta cells in T1D susceptible individuals.

Highlights:

- In a paper published in the Journal of Immunology we compared the B cell controlling mechanisms in NOD mice to that of diabetes-resistant mouse strains.
- We have gained important insights into the mechanisms that break down in order for self reactive B cells to be produced in NOD mice.

Cancer Drug Resistance

Project Leader: Dr John Allen

The Cancer Drug Resistance Group aims to identify new mechanisms of resistance to anticancer drugs, to evaluate their clinical significance, and to identify and pursue ways of overcoming drug resistance. In pursuit of a better understanding of drug resistance we focus on resistance to new and promising anticancer drugs that are being applied to treating common, recalcitrant tumours, including breast cancer, prostate cancer, and melanoma.

In cases where cancer is disseminated throughout the body, as in leukaemia, or metastatic cancer, chemotherapy is the main treatment option and the long term survival rate is much poorer. An over-riding reason for this poor result is drug resistance.

Our comprehensive *in vitro* models allow identification of candidate cellular mechanisms relevant to drug resistance or related phenomena of drug pharmacokinetics and toxicity. Findings are followed up in preclinical mouse models and by analysis of molecular changes in patient tumour samples that are related to outcomes of treatments with particular drugs.

Interactions of new anticancer drugs with multidrug transporter proteins.

We are systematically evaluating the interactions of the new drugs with seven known multidrug transporter proteins. The project aims to determine whether one prominent source of drug resistance - multidrug transporter proteins - affects the efficacy and/or pharmacology of new anticancer drugs on trial at the Sydney Cancer Centre (including Glivec, Iressa, Flavopiridol, NV-06, Epothilone B and others). We collaborate in this work with the Sydney Cancer Centre, The Children's Cancer Institute Australia, several other research centres, and pharmaceutical companies.

Why does acquired drug-resistance emerge?

Unless a treatment is 100% effective, resistant tumour cells eventually grow back

Role of drug transport in the dose-limiting toxicity of irinotecan/CPT-11.

Irinotecan is a relatively new drug active against several types of cancer. Like most anticancer drugs, it has severe side effects that limit the tolerable dose. We are investigating the causes of these side effects in our lab, and several alternative ways of relieving them that are undergoing clinical trials at the Sydney Cancer Centre.

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 almost invariably fatal. In the coming year we will begin investigation of drug resistance in melanoma, focusing on the failure of melanoma cells to undergo apoptosis when damaged by anticancer drugs.

Drug resistance in haematological cancer

Myeloma is a cancer of the blood plasma cells, which are responsible for producing large quantities of antibodies, secreted into the blood. Although it often responds to chemotherapy initially, it is ultimately fatal. Plasma cells have a peculiar ability to cope with production of misfolded or damaged proteins and other internal stresses, known as the "unfolded protein response". We are investigating the possibility that this is what renders myeloma cells resistant to anticancer drugs.

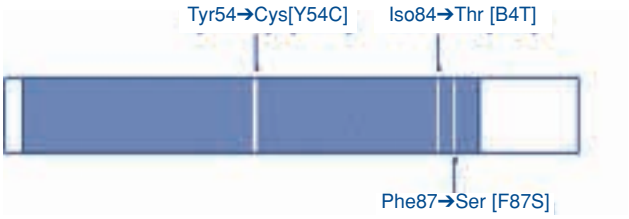
Highlights:

- The multidrug transporter MRP4 was identified as a source of resistance to the promising new drug Irinotecan and as a reliable marker of treatment outcome in childhood neuroblastomas. An important link has been established between this source of drug resistance and the frequent activation of MYC oncogenes in human cancers.
- John Allen was made a Fellow of the Cancer Institute NSW, an award which secured substantial NSW government funding for two of our major projects for the next three years.

Lymphocyte Differentiation

Project Leader: Dr Stuart Tangye

Research performed in our laboratory is focused on understanding the regulation of the human immune systems, both in normal individuals, as well as in individuals with defined diseases, such as immunodeficiencies; ie 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. The immunodeficiency that we study is called X-linked lymphoproliferative disease (XLP). XLP is a very rare disease, affecting ~ 1-2/106 males. It is caused by mutations in the SH2D1A gene which encodes the intracellular adaptor protein SAP. Through collaborations with labs in the USA and Italy, we have identified 15 patients from 10 different families affected by XLP, and have characterised the mutation in their SAP gene that is responsible for this disease.



SAP Mutations detected in different XLP patients

In 2004, there were two main focuses to our research. First was the analysis of different subsets of B cells present in human spleen – these include naïve B cells, memory B cells, and plasma cells, the latter of which are responsible for producing antibodies which protect us from invading pathogens. Second, we have investigated cellular defects in XLP in an attempt to understand how mutations in a single gene can result in a life-threatening illness.

Highlights:

- Characterised for the first time plasma cells present in human spleen.
- Completed gene profiling of B cell subsets (naïve, memory, plasma cells) present in human spleen.
- Identified a reduction in the number of memory B cells as well as a defect in the production of IL-10 by CD4+ T cells in patients with the immunodeficiency X-linked lymphoproliferative disease. This may explain the defects in B cell differentiation observed in this disease, and also offers new prospects for treatment.
- In collaboration with Dr Kim Nichols (Children's Hospital of Philadelphia), we determined that SAP, the gene defective in XLP, is required for the development of NK T cells in both humans and mice.

Gene & Stem Cell Therapy

Group Head: Professor John Rasko

The broad aims of the Gene & Stem Cell Therapy Group 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. Success in transferring genes into relevant animal models will represent a large step towards successful gene therapy in humans. 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. We have a well-established program studying haemopoietic stem cells (HSCs) and adult mesenchymal stem cells (MSCs). This is integrated with a model we have developed for autologous hemopoietic stem cell transfer in non-human primates.

Gene silencing and mechanisms of gene expression control

Another area of research in our lab is gene silencing and the mechanisms of gene expression control. We have developed a number of exciting molecular techniques for identifying and quantifying microRNA. We have demonstrated that microRNAs are intricately involved in the control of cell development and differentiation.

Aminoacidurias including Hartnup disease

Hartnup disease is an inborn error of renal and gastrointestinal neutral amino acid transport. The cloning and functional characterisation of a number of amino acid transporters has been performed by our laboratory to identify their potential role in the aminoacidurias.

Transcription factors in cancer biology

To explore mechanisms of gene expression we have studied aspects of the molecular and cellular biology of important transcription factors. Our studies show that the highly conserved zinc-finger transcription factor CTCF is of central importance in the regulation of proliferation-controlling genes. Our group also demonstrated for the first time that normal CTCF negatively regulates cell proliferation through unique effects on all phases of the cell cycle.

Highlights:

- Discovered the long-sought cause of Hartnup disease, SLC6A19, which we published in Nature Genetics.
- Developed a number of exciting molecular techniques for identifying and quantifying microRNA expression in normal and cancerous human cells.
- Established the only non-human primate model of adult stem cell function in Australia.
- Refined gene transfer technologies using adenovirus, adeno-associated virus, retrovirus and lentivirus vectors.

Liver Immunobiology

Group Head: Professor Geoffrey McCaughan

The Liver Immunology Group has three distinct research programmes. Dr Patrick Bertolino leads the Liver Immunology programme, Dr Mark Gorrell the Molecular Hepatology programme and Dr Alex Bishop the Transplantation programme.

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

Project Leader: Dr Patrick Bertolino

The liver has paradoxical and unique properties: it is the site of effective immune responses to different pathogens but under some circumstances it is also known to induce harmless immune responses. Poor responses can be beneficial in a transplantation setting. However this liver property can be exploited by some viruses, such as hepatitis B and C, to persist. Our research aims 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. We have demonstrated for the first time that unlike other solid organs, naïve T cells (cells that have never "seen" their antigen) can also be directly activated within the liver. Primary activation of T cells within a solid organ challenges the current dogma and implies that mechanisms of tolerance to liver antigens are more intricate than initially thought as the liver may compete with lymph nodes (LN) for recruitment/retention of antigen-reactive T cells. We are currently characterising the phenotype and function of naïve T cells activated within the liver compared to the phenotype of those activated LN. Using radiolabeling techniques and intravital microscopy in collaboration with Prof Alf Hamann (Berlin, Germany), we are also investigating adhesion molecules and chemokines that are important in early retention/activation within the liver. Our results indicate that ICAM-1/LFA-1 molecules are playing an essential role in these events. Finally in collaboration with David Lecouteur and Alessandra Warren (Concord Hospital, NSW), we are using electron microscopy to understand how lymphocytes can contact antigen-bearing hepatocytes, a type of interaction that might play an important role in hepatotropic viral infections in which hepatocytes represent the main APC. Our results are so far really exciting as they reveal that lymphocytes interact with hepatocytes through cytoplasmic extensions penetrating the fenestrae of the liver sinusoidal endothelial cells.

Model of competition for primary T cell activation between liver and lymph nodes

The research of our group also aims to understand and characterise parameters that allow liver diseases to become chronic. To address this question, we have set up multiple collaborations with different groups in Melbourne (Doug Hilton and Robyn Starr, Andreas Strasser and Phillipe Bouillet, Bill Heath, Thomas Kay and Mark Chong) and imported several gene-deficient mice that target different events, which could play a role in down-regulating the immune response (including cytokine production, cell survival and T cell help). We think that these experiments will give us important clues to understand parameters important for the balance between tolerance and immunity within the liver and how some autoimmune diseases become chronic.

Highlights:

- Demonstrated that the site of primary T cell activation determines the outcome of the immune response.
- Demonstrated that the liver can act as a site of primary T cell activation.
- Identified a novel mechanism of liver damage mediated by cytokines.

Molecular Hepatology

Project Leader: Dr Mark Gorrell

In our laboratory advanced technologies are applied to understanding the molecular pathogenesis of chronic liver injury and the biochemistry and biology of prolyl oligopeptidases.

Chronic liver diseases are increasingly common and include viral hepatitis, alcoholic hepatitis, cirrhosis, fatty liver and cancer. The increased incidences of obesity and hepatitis C virus infection are of great concern in our community and are the major causes of increased rates of liver disease. Our studies primarily use gene array, PCR and antibody stains of human liver samples to identify genes important in these processes.

Structure and function of DPIV and related proteins

DPIV (also known as CD26) is a large protein that is the prototypical member of the prolyl oligopeptidase gene family and is widely expressed in the human body by epithelial cells, blood vessel capillary cells and lymphocytes. DPIV is a target for new type 2 diabetes therapies that have entered advanced clinical trials. DPIV is potentially also a target for therapies related to blood vessel formation, anxiety, gut repair, obesity and insulin resistance.

DPIV has roles in the normal functioning of the liver, kidney, pancreas and digestive tract. DPIV and the closely related enzyme FAP (also called DP5) are implicated in various disease processes including liver disease and tumour growth. In addition to examining disease pathogenesis, we are investigating how DPIV can exert effects at the cellular level by dissecting out the enzymatic and extra-enzymatic functional activities of DPIV.

Highlights:

- Our gene expression analyses of human liver showed that high levels of a protein important for blood vessel formation, PLG3, are present in tumour-bearing liver.
- Our biochemical structure-function data mapped instructively onto the crystal structure of DPIV.
- The prolyl oligopeptidase gene family contains four peptidases that cleave X-Pro from the N-terminus of substrates: DPIV, FAP, DP8 and DP9.
- Several DPIV inhibitors cross-inhibit DP8 and DP9. This has caused pharmaceutical companies to ensure that their DPIV inhibitors are selective for DPIV.
- We were the first to clone cDNAs for DP8 and DP9 and show that their substrate specificities are close to that of DPIV. Based on expression data, DP8 and DP9 may be involved in inflammation, tumour growth and hematopoiesis.
- FAP expression correlates with liver fibrosis severity. We continue to obtain evidence that reinforces our view that inhibiting FAP enzyme activity will prove to be anti-fibrotic.
- We showed that some cellular functions, notably cell movement and death, are influenced by DPIV, FAP, DP8 and DP9 via extra-enzymatic functions of these proteins.

Transplantation

Project Leader: Dr Alex Bishop

The goal of the Liver Transplantation group is to identify natural treatments to prevent rejection of transplanted organs, thereby minimising use of the powerful but dangerous drugs that are used to treat transplant patients. We are assisted in this goal by an animal model where a transplanted liver is accepted without any requirement for drug treatment. We have previously found that liver transplant acceptance in this model is associated with rapid and paradoxical immune activation of the recipient's rejection response, which then exhausts itself. In collaboration with Dr Julie Jonsson and Dr Elizabeth Powell at Princess Alexandra Hospital in Brisbane, we have recently shown that a similar early immune activation occurs in liver transplant patients that show no evidence of liver rejection. This demonstrates the concordance between the clinical situation and the animal model and suggests that our findings regarding the mechanism of acceptance of transplanted livers in the model is likely to apply to human liver transplants. This is important as we have previously shown that one of the immunosuppressive drugs that is used to prevent rejection also inhibits liver transplant acceptance in the animal model.

We are also investigating the basic immune mechanism of this liver transplant model and in collaboration with Professor Bruce Hall we have found that IL-4 treatment breaks liver transplant tolerance. This is a novel finding as IL-4 was previously demonstrated to be responsible for some forms of transplant tolerance. It is, however, consistent with our previous findings that IL-4 is expressed at higher levels in transplanted livers that are undergoing rejection than in those that are accepted. We are also using novel molecular genetic approaches to identify the overall pattern of gene expression in transplant tolerance so that we can use gene therapy to reduce the requirement for drug therapy. These studies should also identify patterns of gene expression that can be used in clinical transplantation to diagnose rejection.

Highlights:

- The preliminary report of the ability of IL-4 to break rat liver transplant tolerance was selected in the top 200 abstracts of the International Transplant Congress, Vienna and an invited manuscript for the journal Transplantation.
- The work of the laboratory was selected for a keynote plenary address at the meeting of the Liver Transplantation Society in Kyoto, Japan.
- The link between clinical liver transplantation and our findings in animal models was established.

Molecular Cardiology

Group 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 group 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 and triggers of 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 commonest 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 compliment the studies in humans, our group has developed two unique transgenic models models of HCM, as well as cell culture models to evaluate the cellular effects of specific gene mutations.

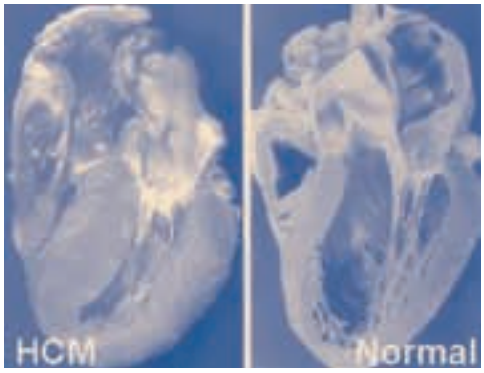


Figure 1

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 novel gene defects causing heart disease and sudden death in young people.
- Successful prevention of sudden death in young people using implantable cardioverter defibrillators.
- Development of genetic mouse models which replicate human disease.
- Ms Lan Nguyen, an Honours student in the laboratory, awarded the University of Sydney Medal for studying effects of exercise on the heart.
- A/Prof Chris Semsarian the recipient of both the 2004 NSW Young Tall Poppy Award, and a 5-year NHMRC Practitioner Fellowship.

Mycobacterial Research Group

Group Head: Professor Warwick Britton

The Mycobacterial Research Group studies various aspects of the immunological control of tuberculosis and leprosy. This includes the study of lymphocyte recruitment and cytokine production required to control pulmonary tuberculosis, and the development of subunit and live vaccines against pathogenic mycobacteria. More recently the group has studied the gene responses of macrophages to mycobacterial and HIV infection and genetic factors influencing the development of tuberculosis and leprosy.

Cellular and cytokine control of tuberculosis

Sub-unit vaccines against tuberculosis infection may be an effective way of boosting immunity induced by BCG. We have previously shown that DNA vaccines expressing secreted proteins are partially protective against tuberculosis infection. Teresa Wozniak is analysing a number of Th1 promoting cytokines as adjuvants for sub-unit vaccines. We have found that plasmids expressing IL-12 or IL-23 both increase T cell responses to mycobacterial antigens encoded by DNA vaccines and increase the protective effect of these vaccines against aerosol tuberculosis infection.

Previously, we have developed ScFvs to two surface molecules on dendritic cells, DEC-205 and CD11c and used these in DNA vaccines used to mycobacterial genes to enhance the immunogenicity of these vaccines. In studies with C Parish and J Altin at ANU, we have found that the anti-DEC-205scFV antibody fragments are effective for targeting liposome vaccines against experimental melanoma to dendritic cells. This improved the prophylactic and immunotherapeutic effect of these vaccines against melanoma.

Macrophages are the host cell for infection with *M.tuberculosis* and must be activated to kill the intracellular bacteria. To analyse the cellular gene response of macrophages to tuberculosis infection, Gabriella Ige has used micro arrays to find genes differentially regulated during infection. The cellular gene response is both rapid and broad and by 12 hours of infection, and 220 genes were differentiated regulated, including a number of previously unrecognised *M. tuberculosis* response genes. We are extending this study in collaboration with Professor Cunningham, to examine the effects of prior HIV infection and the macrophage response to *M. tuberculosis* infection.

We are continuing our collaboration with Professor Guy Marks to analyse the human T cell cytokine response to allergens. Allergy to house dust mite is strongly associated with asthma. As part of a large childhood asthma prevention study, which is examining the effects of house dust mite or changes in dietary fish oil on the effects of asthma in young children, we are analysing the effects of these interventions on T cell cytokine responses to house dust mite. We have now analysed data in 600 children aged 18-36 months and found that at 3 years the IL-5 and IL-13 T cell responses are associated with HPR 3 years.

Highlights:

- Plasmids expressing IL-12 and IL-23 are effective adjuvants for DNA vaccines against tuberculosis.
- Recombinant short chain antibody fragments targeting dendritic cells increase protective effect of experimental vaccines against melanoma.
- We have defined the broad cellular gene response of human macrophages to infection with *M. tuberculosis*.

Host Response to Infection

Project Leader: Dr Bernadette Saunders

We have continued our analysis of the role of TNF super family members in the control of *Mycobacterium tuberculosis* infection. Soluble and lymphotoxin alpha are both absolutely required to control experimental tuberculosis and *Listeria* infection. Dr Saunders has now demonstrated that transmembrane TNF, in the absence of soluble TNF, can control tuberculosis infection for a prolonged period of 4-5 months, however, eventually the granuloma structure containing infection breaks down and total disseminate tuberculosis develops. Both membrane and soluble TNF regulate chemokine expression and control of cellular influx at the site of infection. In addition, we have demonstrated that transmembrane TNF alone controls low dose *Listeria* infection, however, soluble TNF is required to control high dose *Listeria* infection.

Variations in macrophage genes may influence the capacity of macrophages to control *M. tuberculosis* infection. Suran Fernando has been examining the effects of polymorphisms in the gene for the P2X7 purinergic receptor on the surface of macrophages. Activation of this receptor with ATP induces a calcium channel leading to the activation of phospholipase D in the killing of mycobacteria. In collaboration with Professor J Wiley, Nepean Hospital, we have demonstrated that non-functioning polymorphisms in this gene block formation of calcium channels and prevent the activation of macrophages to kill intracellular mycobacteria. In 2004 we demonstrated that subjects, who are compound heterozygotes for different polymorphisms in the P2X7 gene, are unable to control BCG infection *in vitro*. The effects of these polymorphisms on susceptibility to tuberculosis are now being analysed.

Highlights:

- Transmembrane TNF is sufficient for the initial granuloma formation and control of *M. tuberculosis* infection.
- Polymorphisms in the gene encoding the P2X7 receptor are associated with failure to kill intracellular mycobacteria.

Vaccine Development and Mycobacterial Pathogenesis

Project Leader: Dr James Triccas

A major research focus of the unit aims to develop anti-tuberculosis strategies more effective than the current vaccine, *M. bovis* BCG. One approach under investigation is to over-express important *M. tuberculosis* antigens in BCG, either those lacking from the vaccine or those demonstrated to invoke protection. Work by Umamainthan Palendira has shown that recombinant BCG secreting two dominant *M. tuberculosis* antigens stimulated stronger protective immunity than BCG alone. This BCG strain is currently under evaluation as part of the NIH Tuberculosis Vaccine Testing Contract at the University of Colorado and other vaccines developed within the laboratory are being prepared for pre-clinical testing. BCG is also being engineered to produce mammalian molecules important in the host immune response, such as cytokines and chemokines, which may enhance the effectiveness of BCG-based vaccines and therapeutic agents. Studies with

Professor Mike O'Donnell from the University of Iowa have shown that the secretion of interleukin 18 by BCG markedly improves the immunogenicity of the vaccine. The protective effect of these BCG strains is currently under evaluation. We are also investigating the suitability of attenuated *M. tuberculosis* strain as vaccine candidates. Rachel Pinto has demonstrated that a strain of *M.tuberculosis* deficient in the transporter for the phthiocerol dimycoserate cell wall molecule is attenuated for growth in mice. This strain induced stronger and more sustained T cell responses to mycobacterial antigens than the current BCG vaccine and six months following immunization induced stronger protective immunity against experimental tuberculosis.

A macrophage infected with Mycobaterium tuberculosis

In order to elucidate strategies employed by pathogenic mycobacteria to promote virulence, we have used genetic screens to identify *M. tuberculosis* genes preferentially expressed within host cells. These studies have identified metabolic pathways that may be required for bacterial survival within the host, and we have focused our efforts on the sulphate-activation pathway (SAP) of *M.tuberculosis*. In collaboration with Professor Thomas Leyh at the Albert Einstein College of Medicine we have determined that the *M. tuberculosis* cysDNC genes form a stress-induced operon that encodes a tri-functional sulfate-activating complex. Detailed biochemical analysis of the components of the *M. tuberculosis* SAP is being used to build a picture of sulphur metabolism in prokaryotes.

Highlights:

- Developed the first attenuated strain of *M.tuberculosis* that is more protective than the current BCG vaccine.
- Determined that recombinant BCG over-expressing fusion protein of Ag85-ESAT6 is more effective than BCG in protecting against experimental tuberculosis infection.
- Identified components of the *M. tuberculosis* sulfate-activation pathway as stress-induced proteins that may play a role in mycobacterial virulence.
- Demonstrated that the BCG vaccine secreting the cytokine IL-18 is a potent activator of cell-mediated immunity.

T Cell Biology

Group Head: Associate Professor Barbara Fazekas de St.Groth

The T cell Biology Group has two main areas of research. The first relates to questions of basic immunology, such as how dendritic cells activate T cells to different programmes of differentiation, and how T cells compete with each other for access to antigen and other factors. Our second area of interest is the environmental and immunological factors responsible for susceptibility to autoimmune and allergic diseases. Such diseases include juvenile diabetes, MS and rheumatoid arthritis, inflammatory bowel disease and asthma.

Recent work within the group has highlighted the importance of a particular subset of T cells in preventing diseases such as juvenile diabetes, MS and rheumatoid arthritis, inflammatory bowel disease and asthma, providing new lines of inquiry into their cause. These "regulatory" T cells have potent ability to suppress the activity of dendritic cells, the cells that first stimulate T cells to make an immune response. When too few of these regulatory T cells are active, dendritic cells can cause T cells to respond to substances that would normally be ignored, such as normal bowel bacteria, in the case of inflammatory bowel disease, and inhaled house dust mite particles, in the case of asthma.

Highlights:

- Identified deficits in regulatory T cells in patients with inflammatory bowel disease.
- Established a new method for accurately identifying regulatory T cells in human blood.
- Demonstrated that cells primed to foreign antigens are vital in the early stages of graft rejection.
- Demonstrated transfer of peptide-MHC II complexes between dendritic cells in vivo, providing a mechanism for rapidly screening the T cell repertoire.
- Established techniques for selective reconstitution of dendritic cells *in vivo*, without disturbing the T cell compartment.

Core Facilities

Flow Cytometry Facility

Flow cytometry and cell sorting are key technologies that are used extensively by most of the groups at Centenary. Centenary's facility is very well equipped with two cell sorters - a Becton Dickinson (BD) FACSVantageDiVa (equipped with 3 lasers, and capable of simultaneous measurement of 10 parameters and sorting cells at up to 30,000 per second) and a BD FACStarPlus (2 lasers, 7 parameters). In addition the facility houses 2 flow analysers - a BD FACSCalibur (2 lasers, 6 parameters) and a BD FACScan, (1 laser, 5 parameters). There are plans to considerably expand the facility in 2005 with the addition of 3 new instruments and a confocal microscope.

Microinjection Facility

The use and development of the latest transgenic (overexpression of a single gene) and knock out (deletion of a single gene) technology has for many years been a high priority for the 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 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 Programme

An objective of the Centenary Institute is development of the next generation of research leaders through our student programme.

This year the student body at Centenary comprised 28 PhD and 7 Honours students. Two Centenary Honours students were awarded University Medals as a result of their outstanding research in 2004.

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 (approximately 18 months for full-time students). 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 venue for constructive suggestions for both candidates and supervisors.

We would like to congratulate all of the candidates enrolled through the Centenary (Department of Experimental Medicine) who successfully completed their Midpoint Reviews, submitted their Thesis or were awarded their Doctorates in 2004.

Midpoint Reviews

PhD Student	Supervisor(s)	Group
Ms Vanessa Bryant	Dr Stuart Tangye/Prof Antony Basten	Lmphocyte Differentiation
Ms Keefe Chng	Prof John Rasko	Gene & Stern Cell Therapy
Mr Adam Cook	Dr Chris Jolly/Prof Antony Basten	B Cell Biology
Ms Alessandra Doolan	A/Prof Chris Semsarian/Prof Antony Basten	Molecular Cardiology
Dr Suran Fernando	Prof Warwick Britton/Dr Bernadette Saunders	Mycobacterial Research
Ms Kim Good	Dr Stuart Tangye/Prof Antony Basten	Lymphocyte Differentiation
Dr David Gracey	A/Prof Barbara Fazekas de St Groth	T Cell Biology
Mr Ben Roediger	A/Prof Barbara Fazekas de St Groth /Prof Antony Basten	T Cell Biology
Mr Anthony Ryan	Prof Warwick Britton/Dr Jamie Triccas	Mycobacterial Research
Ms Sioh Yang-Tan	A/Prof Barbera Fazekas de St Groth /Prof Antony Basten	T Cell Biology
Ms Teresa Wozniak	Prof Warwick Britton	Mycobacterial Research

PhD Submissions

Student	Supervisor(s)	Thesis Title
Dr Tri Giang Phan	Dr Robert Brink	Cellular and molecular aspects of B Cell responses
Ms Rachel Pinto	Prof Warwick Britton/Dr Jamie Triccas	Genetic approaches to vaccines designed against tuberculosis
Ms Gabriella Ige (nee Scandurra)	Prof Warwick Britton/Dr Jamie Triccas	Regulation of gene expression by mycobacterial infection

PhDs Awarded

Student	Supervisor	Thesis Title
Ms Elissa Deenick	Dr Phil Hodgkin	Quantitative analysis of T and B lymphocyte behaviour
Mr Umaimainthan Palendira	Prof Warwick Britton	Dendrite cell based vaccine designed against tuberculosis

Centenary hosts Postgraduate Seminars as part of its student programme, providing students with a broader exposure to immunology than the area of their studies. These seminars are held between May and November each year and are presented by Centenary researchers as well as invited national and international scientists. Students are encouraged to fully participate in the discussions during these and other Centenary presentations. The 2004 Postgraduate Research Workshops were sponsored by ASI NSW.

2004 Postgraduate Research Workshop Programme

Speaker	Title	Date
Dr Chris Jolly B Cell Biology, Centenary Institute	Who wants to be a millionaire?	3rd June
A/Prof Barbara Fazekas de St Groth T Cell Biology, Centenary Institute	Immulogical controversies past and present	17th June
Dr Tim Dobbins School of Public Health, University of Sydney	A crash course in biostatistics	29th July
Prof Warwick Britton Mycobacterial Research, Centenary Institute	From clinical curiosity to immunological insight	12th August
Dr Robert Brink B Cell Biology, Centenary Institute	For whom the bugs toll	26th August
Dr Stuart Tangye Lymphocyte Differentiation, Centenary Institute	Making the most of your host	23rd September
A/Prof Nicholas King Dept of Pathology, University of Sydney	The nature of the evidence	7th October
Dr Adrian Grech B Cell Biology, Centenary Institute	CSI: Criminal Scientific Investigations	21st October
Professor Antony Basten B Cell Biology, Centenary Institute	Ten scientific discoveries that changed the world	4th November

2004 Seminar Series

Centenary Institute Seminars are an opportunity for scientists to gather and discuss recent scientific work, and to share ideas and results. Presentations are given by Centenary staff, as well as visiting local and international researchers.

Centenary hosts seminars every Tuesday at 1pm in the Level 6 Lecture Theatre.

We would like to thank our organisers Dr Pablo Silveira and Dr Adrian Grech, the sponsors for their generous support, and all the presenters for sharing their knowledge and research findings, making this a most successful 2004 Seminar Series.

Speaker	Title	Date
A/Prof Angelo Izzo Colorado State University, USA	Matrix metalloproteinases in tuberculosis granulomas	12th January
Prof Tom Gordon Flinders University, SA, Australia	A physiological approach to identify functional autoantibodies in Sjögren's syndrome and type 1 diabetes	3rd February
Mr Umaimainthan Palendira Centenary Institute, NSW, Australia	Improving vaccines against tuberculosis	10th February
Dr Georges Grau Universite de la Mediterranee, Marseille, France	Cytokines and immunopathology of cerebral malaria	12th February
Dr Andrew Brown University of New South Wales, NSW, Australia	Towards an understanding of cellular cholesterol homeostasis	17th February
Dr Nicholas West Centenary Institute, NSW, Australia	The role of lipopolysaccharide during gastrointestinal colonisation of *Shigella flexneri*	24th February
Dr Cecile King Scripps Institute, CA, USA	T cell homeostasis in autoimmune disease	2nd March
Dr Ruth Haites University of Melbourne, VIC, Australia	The function of phosphatidylinositol in mycobacteria	5th March
Dr Christopher Siatskas Ontario Cancer Institute, Canada	Gene therapy approaches for the treatment of Fabry disease	8th March
Prof Andrew Coats University of Sydney, NSW, Australia	Causes of symptom generation in chronic heart failure: Potential new therapeutic targets	9th March
Prof Mauro Sandrin Austin Research Institute, Victoria *Sponsored by Miltenyi Biotec*	Structure/function studies of the alpha(1,3)Gal/GalNAc family of glycosyltransferases	16th March
Dr Sarah Russell Peter MacCallum Institute Victoria, Australia *Sponsored by Roche Applied Science*	The regulation of T cell polarity: Implications for immune function	23rd March
Dr Margaret Cooley University of New South Wales, NSW, Australia	Immunosuppression by a bacterial quorum sensing molecule	30th March
Dr Allison Abendroth Westmead Millenium Institute	Varicella zoster virus pathogenesis and immune evasion	6th April

Prof Christopher Parish John Curtin School of Medical Research, ACT, Australia *Sponsored by Becton Dickinson*	New approaches to cancer immunotherapy	13th April
Prof Alan Rickinson University of Birmingham, UK	T cell control of Epstein-Barr virus infection	19th April
Richard Christopherson University of Sydney, NSW, Australia	New technology for identifying leukaemias	20th April
Dr Nikolai Petrovsky John Curtin School of Medical Research, ACT, Australia *Sponsored by Crown Scientific*	Apoptosis pathways in type 1 diabetes	27th April
Dr Peter Estibeiro ExpressOn BioSystems, Midlothian, UK	Application of ACCESSarray® 4000™ to gene knockdown research and drug discovery applications	3rd May
Dr Jesse Jun John Curtin School of Medical Research, ACT, Australia	Identifying the MAGUK protein Carma1 as a central regulator of humoral immune responses by genome-wide ENU	4th May
Dr David Serreze The Jackson Laboratory, Maine, USA *Sponsored by ASI*	Promiscuity of a diabetogenic TCR: playing fast and loose with the MHC	10th May
Dr Mark Smythe Peter MacCallum Institute, Victoria, Australia *Sponsored by QIAGEN*	Innate effectors and regulators of immunity	11th May
Dr David Izon Telethon Institute for Child Health Research, WA, Australia	T cell development in a post-Notch world	13th May
Dr Steve Turner University of Melbourne, Victoria, Australia *Sponsored by Medos*	Functional and structural dissection of Influenza-specific CD8+ T cell responses	18th May
Dr Allan Jones University of Sydney, NSW, Australia	X-Ray Microtomography - 3D microscopy & analysis	8th June
Dr Andreas Strasser Walter and Elisa Hall Institute, Victoria, Australia *Sponsored by Sigma-Aldrich*	Cell death control in the normal immune system and in immunopathology	15th June
Dr Carola Vinueza John Curtin School of Medical Research, ACT, Australia *Sponsored by Perkin Elmer*	Roqin: a novel T cell regulator required to prevent systemic and organ-specific autoimmunity	6th July
Prof Charles Mackay The Garvan Institute, NSW, Australia	Concepts for lymphocyte migration, and new prospects for therapeutic intervention for inflammatory diseases	15th July
Dr Graham Jones Westmead Millenium Institute, NSW, Australia	Genetic association studies of early childhood atopic dermatitis	27th July
Dr Tri Phan Centenary Institute, NSW, Australia	To HEL with my PhD!	3rd August

Dr Katherine Belov Australian Museum, NSW, Australia	Antigen receptor diversity: lessons from marsupials and monotremes	10th August
Dr Jose Villadangos Walter and Elisa Hall Institute, Victoria, Australia	Control of MHC II antigen presentation and MHC I cross presentation in dendritic cells	17th August
Prof Jonathon Sprent Scripps Research Institute, CA, USA	Stimulating naive CD8+ cells	26th August
Dr David Booth Westmead Millenium Institute, NSW, Australia	Gene expression in multiple sclerosis: expect the unexpected	31st August
Dr Jean-Laurent Casanova Hospital Necker, Paris, France *Sponsored by ASI*	The human model: a genetic dissection of immunity to infection in natural conditions	15th September
Dr Michael Rolph The Garvan Institute, NSW, Australia	Th2 immunity and lipid homeostasis: discovery of a bi-directional regulatory link	21st September
Dr Andrew Collins University of New South Wales, NSW, Australia the study of	Understanding the allergic response from normal IgE immunoglobulin gene sequences	5th October
Dr Lynn Corcoran Walter and Elisa Hall Institute, VIC, Australia	Contribution of octamer binding trascription factors to antibody secreting cell differentiation	12th October
Dr Chris Engwerda Queensland Institute of Medical Research, Queensland, Australia	The role of TNF family members in murine malaria and leishmaniasis	18th October
Dr Sharon McKracken Kolling Institute of Medical Research, NSW, Australia	The role of NFkB in the regulation of maternal immunity	19th October
Dr Phil Hodgkin Walter and Elisa Hall Institute, Victoria, Australia *Sponsored by Chemicon*	The Cyton: The lymphocyte calculator of costimulation, tolerance and memory	26th October
Dr Suresh Mahalingam University of Wollongong, NSW, Australia	Immunopathology of human metapneumovirus infection	2nd November
Dr Shane Grey The Garvan Institute, NSW, Australia	Searching for gene therapy candidate for the cure of Type 1 Diabetes	9th November
Prof David Hume University of Queensland, Queensland, Australia *Sponsored by Millipore*	Transcriptional regulation in macrophages	23rd November
Dr Dirk Busch Technische University Munich, Munich, Germany	*In vivo* differentiation of antigen-specific T cells	21st December

2004 Publications

1. Ajami K, Abbott CA, McCaughan GW, Gorrell MD (2004) Dipeptidyl peptidase 9 is cytoplasmic and has two forms, a broad tissue distribution, cytoplasmic localization and DPIV - like peptidase activity. BBA - Gene Struct Expression, 1679(1):18-28.
2. Bowen D, Zen M, Holz L, Davis T, McCaughan G, Bertolino P (2004) The site of primary T cell activation is a determinant of the balance between intrahepatic tolerance and immunity. J Clin Invest, 114:701-712.
3. Britton WJ (2004) Leprosy. In Infectious Diseases, 2nd ed Cohen J, Powderley WG 2nd Ed. (Mosby, London) p. 1507-1513.
4. Britton WJ (2004) Neonatal BCG vaccination against tuberculosis. Expert Rev Vaccines, 3:25-29.
5. Britton WJ, Lockwood DNJ (2004) Leprosy. Lancet, 363:1209-1219.
6. Bröer A, Klingel K, Sonja Kowalczuk, Rasko JEJ, Cavanaugh J, Bröer S (2004) Molecular cloning of mouse amino acid transport system B0, a neutral amino acid transporter related to Hartnup disorder. J Biol Chem, 279:24467-24476.
7. Chklovskaia E, Nowbakht P, Nissen C, Gratwohl A, Bargetzi M, Wodnar-Filipowicz A (2004) Reconstitution of dendritic and natural killer-cell subsets after allogeneic stem cell transplantation: effects of endogenous flt3 ligand. Blood, 103:3860-3868.
8. Chtanova T, Tangye SG, Newton R, Frank N, Hodge MR, Rolph MS, Mackay CR (2004) T follicular helper cells express a distinctive transcriptional profile, reflecting their role as non-th1/th2 effector cells that provide help for B cells. J Immunol, 173:68-78.
9. Crawford DH, Fletcher LM, Hubscher SG, Stuart KA, Gane E, Angus PW. Jeffrey GP, McCaughan GW, Kerlin P, Powell LW, Elias E.E. (2004) Patient and graft survival after liver transplantation for hereditary hemochromatosis: Implications for pathogenesis. Hepatology, 39(6):1655-1662.
10. Cummings J, Zelcer N, Allen JD, Yao D, Boyd G, Maliepaard M, Friedberg TH, Smyth JF, Jodrell DI (2004) Glucuronidation as a mechanism of intrinsic drug resistance in colon cancer cells: contribution of drug transport proteins. Biochemical Pharmacology, 67:31-9.
11. Dahlke MH, Larsen SR, Rasko JEJ, Schlitt HJ (2004) The biology of CD45 and its use as a therapeutic target. Leukemia Lymphoma 45:229-236
12. Dahlke MH, Popp FC, Larsen S, Schlitt HJ, Rasko JEJ (2004) Stem cell therapy of the liver - fusion or fiction? Liver Transplantation 10(4):471-479.
13. Den Dulk M, Wang C, Li J, Clark DA, Hibberd AD, Terpstra OT, McCaughan GW, Bishop GA. (2004) Synergism between donor leucocyte administration and immunosuppressive drug treatment for survival of rat heart allografts. Transplant Immunology, 13:177-184.
14. Doolan A, Langlois N, Semsarian C (2004) Causes of sudden cardiac death in young Australians. MJA, 180:110-112.
15. Doolan G, Nguyen L, Chung J, Ingles J, Semsarian C (2004) Progression of left ventricular hypertrophy and the angiotensin-converting enzyme gene polymorphism in hypertrophic cardiomyopathy. Int J Cardiol, 96:157-163.
16. Doolan A, Nguyen L, Semsarian C (2004) Hypertrophic Cardiomyopathy: from “heart tumour” to a complex molecular genetic disorder. Heart Lung Circ, 13:15-25.
17. Ellyard JI, Avery DT, Phan TG, Hare NJ, Hodgkin PD, Tangye SG (2004) Antigen-selected, immunoglobulin-secreting cells persist in human spleen and bone marrow. Blood, 103:3805-3812.
18. Fazekas de St Groth B, Smith AL, Higgins CA (2004) T cell activation: in vivo veritas. Immunol Cell Biol 82:260-268.
19. Gilbertson B, Germano S, Steele P, Turner S, Fazekas de St Groth B, Cheers C (2004) Bystander activation of CD8+ T lymphocytes during experimental mycobacterial infection. Infect Immun, 72:6884-6891.
20. Grech AP, Amesbury M, Chan T, Gardam S, Basten A, Brink R (2004) TRAF2 differentially regulates the canonical and non-canonical pathways of NF-kB activation in mature B cells. Immunity, 21:629-642.
21. Green BJ, Soon Lee C, Rasko JEJ (2004) Biodistribution of the RD114/mammalian type D retrovirus receptor, RDR. J Gene Med, 6:249-259.
22. Haber PS, Apte MV, Moran C, Applegate TL, Pirola RC, Korsten MA, McCaughan GW, Wilson JS. Non-oxidative metabolism of ethanol by rat pancreatic acini. Pancreatology, 2004;4:82-89
23. Hasbold J, Corcoran LM, Tarlinton DM, Tangye SG, Hodgkin PD (2004) Evidence from the generation of immunoglobulin G-secreting cells that stochastic mechanisms regulate lymphocyte differention. Nature Immunology, 5:55-63.
24. Ho PJ, Gibson J, Joshua D (2004) The treatment of multiple myeloma: current management and new approaches. American Journal of Cancer, 3:47-66.

25. Jayatilleke I, Doolan A, Ingles J, McGuire M, Booth V, Richmond DR, Semsarian C (2004) Long-term follow-up of implantable cardioverter defribrillator therapy for hypertrophic cardiomyopathy. Am J Cardiol, 93:1192-1194.

26. Jonsson JR, Gu W, Vanags DM, Bishop GA, McCaughan GW, Fawcett J, Lynch SV, Balderson GA, Powell EE, Clouston AD (2004) Increased mononuclear cell activation and apoptosis early after human liver transplantation is associated with a reduced frequency of acute rejection. Liver Transplant, 10:397-403.

27. Limaye S, Steele RH, Quin J (2004) HIV and TB co-infection in South Western Sydney: Experience from a case series. Internal Medicine Journal, 34(4):203-6.

28. Luo Y, Yamada H, Chen X, Ryan AA, Evanoff DP, Triccas JA, O'Donnell MA (2004) Recombinant Mycobacterium bovis bacillus Calmette-Guerin (BCG) expressing mouse IL-18 augments Th1 immunity and macrophage cytoxicity. Clin Exp Immunol, 137:24-34.

29. Ma CS, Hodgkin PD, Tangye SG (2004) Automatic generation of lymphocyte heterogeneity: Division-dependent changes in the expression of CD27, CCR7 and CD45 by activated human naive CD4+ T cells are independently regulated. Immunol Cell Biol, 82:67-74.

30. Mackay F, Tangye SG (2004) The role of the BAFF/APRIL system in B cell homeostasis and lymphoid cancers. Current Opin Pharmacol, 4:347-354.

31. McCaughan GW (2004) Molecular approaches to the side effects of immunosuppressive drugs. Transplantation, 78:1114-1115.

32. McCaughan GW (2004) Immunosuppression for HCV post liver transplant: Enough is just enough. Transplantation, 78:1326.

33. McCaughan GW, George J (2004) Fibrosis progression in chronic hepatitis C virus infection. Gut 53:312-321

34. McCaughan GW, Zekry A (2004) Mechanisms of HCV reinfection and allograft damage after liver transplantation. J Hepatol, 40:368-374.

35. Mikkers H, Nawijn M, Allen J, Brouwers C, Verhoeven E, Jonkers J, Berns A (2004) Mice deficient for all PIM kinases display reduced body size and impaired responses to hematopoietic growth factors. Molec Cell Biol, 24:6104-6115.

36. Mithieux SM, Rasko JEJ, Weiss AS (2004) Synthetic elastin hydrogels derived from massive elastic assemblies of self-organized human protein monomers. Biomaterials, 25:4921-4927.

37. Ng LG, Sutherland APR, Newton R, Qian F, Cachero TG, Scott ML, Thompson JS, Wheway J, Chtanova T, Groom J, Sutton IJ, Xin C, Tangye SG, Kalled SL, Mackay F, Mackay CR (2004) B Cell-activating factor belonging to the TNF family (BAFF)-R is the principal BAFF receptor facilitating BAFF costimulation of circulating T and B cells. J Immunol, 173:807-817.

38. Ng WS, Gallagher J, McCaughan GW (2004) "Pinworm" infection of the liver: Unusual CT appearance leading to hepatic resection. Digestive Diseases & Sciences, 49:466-468

39. Pinto R, Saunders B M, Camacho L R, Britton W J, Gicquel B, Triccas JA (2004) Mycobacterium tuberculosis defective in phthiocerol dimycocerosate translocation provides greater protective pmmunity against tuberculosis than the existing bacille Calmette-Guérin vaccine. Journal of Infectious Diseases, 189:105-112.

40. Pinto R, Tang Quing Xui, Britton WJ, Leyh TS, Triccas JA (2004) The Mycobacterium tuberculosis cysD and cysNC genes form a stress-induced operon that encodes a tri-functional sulfate-activating complex. Microbiology, 150:1681-1686.

41. Riminton DS, Kandasamy R, Dravec D, Basten A, Baxter AG (2004) Dermal enhancement: bacterial products on intact skin induce and augment organ-specific autoimmune disease. J Immunol, 172:302-309.

42. Riminton DS, Limaye S (2004) Primary immunodeficiency diseases in adulthood. Internal Medicine Journal, 34(6):348-54.

43. Saunders B, Briscoe H, Britton WJ. (2004) T cell-derived TNF is essential but not sufficient for protection against Mycobacterium tuberculosis infection. Clin Exp Immunol, 137:279-287.

44. Semsarian C, Seidman CE (2004) Cardiovascular genetics. Principles of Molecular Cardiology. 1st Ed. Patterson and Runge, The Humana Press Inc.

45. Semsarian C, Seidman CE (2004) Molecular genetics of inherited cardiomyopathies. Braunwald Companion – Molecular Cardiology, 2nd Ed. W.B. Saunders Co.

46. Seow HF, Broer S, Broer A, Bailey CG, Potter SJ, Cavanaugh JA, Rasko JEJ (2004) Hartnup disorder is caused by mutations in the gene encoding the neutral amino acid transporter SLC6A19. Nature Genetics, 36:1003-1007.

47. Silveira PA, Dombrowski J, Johnson E, Chapman HD, Nemazee D and Serreze DV (2004) Defects in B cell

selection underlie the diabetogenic antigen presenting cells in NOD mice. J Immunol, 172:5086-5094.

48. Stam RW, Van den Heuvel-Eibrink, den Boer ML, Ebus MEG, Janka-Schaub GE, Allen JD, Pieters R (2004) Multidrug resistance genes in infant acute lymphoblastic leukemia: Ara-C is not a substrate for the breast cancer resistance protein. Leukemia, 18:78-83.

49. Stefninaos C, Parish C, Demangel C, Britton WJ, Altin JG. (2004) Targeting dendritic cells with antigen-containing liposomes: a highly effective procedure for induction of anti-tumor immunity and for tumor immunotherapy. Cancer Research, 64:4357-4365.

50. Sud A, Hui JM, Farrell GC, Bandara P, Kench JG, Fung C, Lin R, Samarasinghe D, Liddle C, McCaughan GW, George J (2004) Fibrosis prediction in chronic hepatitis C: utility of a fibrosing probability index incorporating measures of insulin resistance. Hepatology, 39:1239-1247.

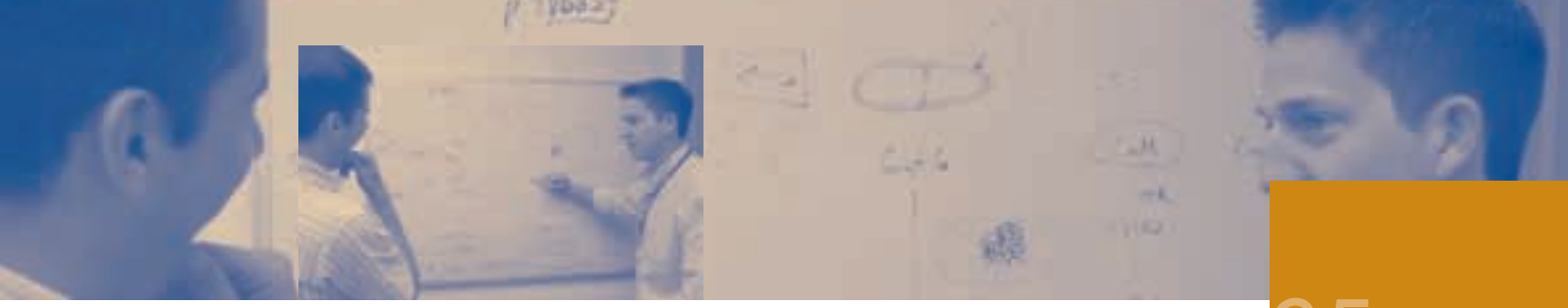
51. Tangye SG, Hodgkin PD (2004) Divide and conquer: the importance of cell division in regulating B-cell responses. Immunology, 112:509-520.

52. Thien M, Phan TG, Gardam S, Amesbury M, Basten A, Mackay F, Brink R (2004) Excess BAFF rescues self-reactive B cells from peripheral deletion and allows them to enter forbidden follicular and marginal zone niches. Immunity, 20:785-798.

53. Van Maurik A, Fazekas de St Groth B, Wood KJ, Jones ND (2004) Dependency of direct pathway CD4+ T cells on CD40-CD154 costimulation is determined by the nature and micro-environment of primary contact with alloantigen. J Immunol, 172:2163-2170.

54. Zekry A, Gleeson M, Guney S, McCaughan GW (2004). A prospective cross-over study comparing the effect of mycophenolate versus azathioprine on allograft with recurrent chronic HCV infection. Liver Transplantation, 10:1.

55. Zhang R, Burke LJ, Rasko JEJ (2004) Dynamic association of the mammalian insulator protein CTCF with centrosomes and the midbody. Exp Cell Res, 294:86-93.



2004 Presentations

International

Invited presentations

1. Basten A (2004) The cellular and molecular basis of humoral immunity. AntibOZ 2, Heron Island.
2. Bertolino P (2004) Activation and control of T cells in the liver. European Association for the Study of the Liver (EASL) "Immune-mediated liver injury: from basic science to future therapies" Freiburg, Germany.
3. Bertolino P (2004) Hepatocytes as targets of autoreactivity. Falk-Liver-Week 2004. Freiburg, Germany.
4. Bertolino P (2004) Immune responses within the liver: sevelar players for singular immunological outcomes. 12th International Congress of Immunology 2004 (ICI-FOCIS 2004), Montreal, Canada.
5. Bishop GA (2004) (Keynote Plenary Address) Tolerance induction in clinical liver transplantation. 10th Annual Congress of the Liver Transplantation Society, Kyoto, Japan.
6. Britton WJ (2004) Invited participant workshop on Leprosy Diagnostics organized by the IDEAL initiative. Addis Ababa, Ethiopia.
7. Britton WJ (2004) Leprosy research. The Leprosy Mission, Technical Reference Panel, Chennai, India.
8. Britton WJ (2004) New Approaches to vaccine development for tuberculosis and leprosy. Indian Australian Biotechnology Conference, Bangalore, India.
9. Britton WJ (2004) Novel single nucleotide polymorphisms in the P2X7 gene reduces ATP-mediated killing of mycobacteria. 12th International Congress of Immunology and 4th Annual Conference of FOCIS, Montreal, Canada.
10. Fazekas de St.Groth B (2004) Dendritic cell exchange of intact peptide MHC II complexes in vivo' and 'in vivo T cell activation and competition between regulatory T cells'. 12th International Congress of Immunology, Montreal, Canada.
11. Haber P, Seth D, Gorrell MD, McCaughan GW (2004) Molecular pathogenesis of alcoholic liver disease. International Society for Biomedical Research on Alcoholism, Heidelberg, Germany.
12. Ho J (2004) Gene expression analysis in beta thalassemia Community Genetics in Asia Conference, Pasteur Institute and World Health Organisation, Shenzhen, China.
13. McCaughan GW (2004) The hepatic transcriptone in human liver disease. Hong Kong – Shanghai International Liver Congress. Hong Kong.
14. McCaughan GW (2004) Use of HBV core Ab donors. Meet the Professors Breakfast Session, ATC, Boston, USA.
15. McCaughan GW (2004) Optimal use of HB1G in liver transplantation. ILTA meeting, Kobe, Japan.
16. McCaughan GW (2004) Pre-emptive therapy for HCV recurrence post liver transplant. 3rd International Congress on Immunosuppression, San Diego, USA.
17. McCaughan GW (2004) Prevention and treatment for HBV infection post liver transplantation. APASL, Delhi, India.
18. McCaughan GW (2004) Immunopathogenesis of hepatitis B and C under immunosuppression. APASL, Delhi, India.
19. McCaughan GW (2004) Gene array and proteomics for liver disease analysis. APASL, Delhi, India.
20. Rasko JEJ (2004) Plenary Speaker, 15th International Symposium on Molecular Biology of Hematopoiesis Hemato-Oncology in Post-Genomic Era, and 10th Annual Meeting of Japan Society of Gene Therapy, Tokyo, Japan.
21. Saunders BM (2004) Genetic control of mycobacterial infection, functional significance of polymorphisms in the P2X7 Receptor. Hansens Research Centre Louisiana State University, Baton Rouge, Louisiana, USA.
22. Saunders BM (2004) Membrane-bound TNF controls granuloma formation and acute but not chronic resistance to M. tuberculosis infection. Department of Microbiology, Immunology and Pathology, Colorado State University Fort Collins Colorado, USA.
23. Saunders BM (2004) Membrane-bound TNF controls granuloma formation and acute but not chronic resistance to M. tuberculosis infection. Department of Veterinary Medicine, Cornell University, Ithaca, New York, USA.
24. Saunders BM (2004) Membrane-bound TNF in induction and sustained resistance to M. tuberculosis. Trudeau Research Institute, Saranac Lake, New York, USA.
25. Tangye SG (2004) Altered human lymphocyte development and differentiation resulting from mutations in SH2D1A/SAP. Institute of Biochemistry, University of Lausanne, Lausanne, Switzerland.
26. Tangye SG (2004) Impaired lymphocyte activation and differentiation resulting from mutations in

SH2D1A/SAP in X-linked lymphoproliferative disease. National Institute of Health (NIH), Bethesda, Maryland, USA.

27. Tangye SG (2004) Molecular and cellular defects resulting from mutations in SH2D1A/SAP in X-linked lymphoproliferative disease. DNAX Research Institute of Molecular and Cellular Biology, Palo Alto, California, USA.

28. Tangye SG (2004) Molecular and cellular defects resulting from mutations in SH2D1A/SAP in X-linked lymphoproliferative disease. Institut de recherches cliniques de Montreal (IRCM), Montreal, Canada.

29. Tangye SG (2004) The role of SAP-associating receptors in X-linked lymphoproliferative disease. University of California San Francisco, San Francisco, California, USA.

Abstracts, oral and poster presentations

30. Allen J, Norris MD, Smith J, Tanabe K, Tobin T, Scheffer G, Borst P, Marshall GM, Haber M (2004) Expression of multidrug transporter MRP4 is a marker of poor prognosis in neuroblastoma and confers resistance to irinotecan in vitro. AACR 95th Annual meeting, Orlando, Florida, USA.

31. Avery DT, Ellyard JI, Hodgkin PD, Tangye SG (2004) Increased expression of CD27 on in vitro-activated memory B cells precedes acquisition of CD38 and correlates with commitment to the plasma cell lineage. 12th International Congress of Immunology. Montreal, Canada.

32. Bertolino P (2004) The liver: an immunological oddity. Children's Research Institute, Columbus Ohio, USA.

33. Bishop GA (2004) Post-transplant IL-4 treatment converts rat liver allograft tolerance to rejection. Twentieth International Congress of the Transplantation Society, Vienna.

34. Bowen DG, Davis T, McCaughan GW and Bertolino P (2004) Competition between liver and lymph nodes for primary activation of CD8+ T cells determines cytotoxic T cell response and the development of hepatitis. International Congress of Immunology. Montreal, Canada.

35. Britton WJ, Marks GB, Cristafulli D, Mirrshahi, Peat J (2004) T cell cytokine responses to house dust mite (HDM) at ages 18 months and 3 years: Relation to HDM Allergy at 3 years.

36. Bröer S, Seow HF, Bröer A, Kowalczuk S, Bailey CG, Potter SJ, Cavanaugh JA, Rasko JEJ (2004) Neutral amino acid transport by system B0 and its relation to Hartnup disorder, Transporters 2004 Conference, Selwyn College, Cambridge UK.

37. Cavanaugh JA, Seow HF, Broer S, Potter SJ, Rodgers HJ, Bailey CG, Rasko JEJ (2004) The Hartnup gene displays allelic heterogeneity and incomplete penetrance. AM Soc Hum Genet, Toronto, USA.

38. Cook A, Oganesian L, Harumal P, Basten A, Brink R, Jolly C (2004) The SCID defect reduces switching to all immunoglobulin isotypes, without blocking switching to any: an indication of kinase independent roles for DNA-PKcs in DNA repair? ICI, Montreal.

39. Dahlke MH, Popp FC, Piso P, Schlitt HJ and Bertolino P. Immune-mediated hepatitis drives bone marrow to hepatocyte plasticity. 2nd Annual meeting ISSCR, Boston, USA.

40. Dupre L, G Andolfi, SG Tangye, Roncarolo HF (2004) Abnormal cytotoxic activity of SAP-deficient CD8+ T lymphocytes from XLP and HLH patients. 12th International Congress of Immunology, Montreal, Canada.

41. Grech AP, Amesbury M, Chan T, Gardam S, Basten A, Brink R (2004) TRAF2 controls B cell survival, NF-?B2 processing and marginal zone B cell development through negative regulation of BAFF signalling. Keystone Symposium Lymphocyte Activation and Signaling, Steamboat Springs, CO, USA.

42. Grech AP, Amesbury M, Chan T, Gardam S, Basten A, Brink R (2004) TRAF2 controls B cell survival, NF-?B2 processing and marginal zone B cell development through negative regulation of BAFF signalling.12th International Congress of Immunology, Montreal, Quebec, Canada.

43. Haber P, Seth D, Gorrell MD, McCaughan GW (2004). The novel intrahepatic gene expression in the human alcoholic hepatitis. 55th Annual Meeting of The American Association for the Study of Liver Diseases, Boston, USA.

44. High K, Manno C, Sabatino D, Hutchison S, Dake M, Razavi M, Kaye R, Aruda V, Herzog R, Rustagi P, Rasko JEJ, Hoots K, Blatt P, Sommer J, Ragni M, Ozelo M, Konkle B, Lessard R, Luk A, Glader B, Pierce G, Couto L, Kay M (2004) Immune Responses to AAV and to Factor IX in a Phase I Study of AAV-Mediated, Liver-Directed Gene Transfer for Hemophilia B American Society of Gene Therapy, Minneapolis, USA.

45. Hodgkin, PD, Deenick EK, Hasbold J, Hawkins ED, Todd HF, Corcoran LM, Tarlinton DM, Tangye SG (2004) Signal Integration by Lymphocytes: The Cellular Calculus. 12th International Congress of Immunology. Montreal, Canada.

46. Huang XX, Gorrell MD, Williams RB, Seth D, Shackel NA, McCaughan GW (2004). The hepatic transcriptome in hepatitis C virus (HCV) associated cirrhosis with hepatocellular cancer (HCC): Is there a premalignant profile? 54th Annual Meeting of the American Association for the Study of Liver Diseases, Boston, USA.

47. Jolly CJ, Cook A, Harumal P (2004) Altered somatic mutation of recombined S regions in SCID B cells suggests that the template strand of S regions may be nicked independently of AID. ICI, Montreal, Canada.

48. Kong A, Horan K, Sriratana A, Nandurkar H, Collyer L, Shisheva A, Bailey C, Rasko JEJ, Rowe T, Mitchell C (2004) The 72 kDa inositol polyphosphate 5-phosphatase promotes translocation of GLUT4 to the plasma membrane independent of insulin stimulation. ASBMB Conference, Boston, USA.

49. Ma CS, Hare NJ, Adelstein S, Nichols KE, Tangye SG (2004) Impaired B-cell differentiation in vivo in X-linked lymphoproliferative disease (XLP) is associated with reduced effector function of CD4+ T cells. 12th International Congress of Immunology. Montreal, Canada.

50. Norris MD, Smith J, Tanabe K, Tobin P, Flemming C, Scheffer GL, Wielinga P, Cohn SL, London WB, Marshall GM, Allen J, Haber M (2004) Expression of multidrug transporter MRP4/ABCC4 is a marker of poor prognosis in neuroblastoma and confers resistance to irinotecan in vitro. Advances in Neuroblastoma Research, Genoa, Italy.

51. Nichols KE, Hom J, Koretzky G, Ma CS, Tangye SG, Ganguly A, Cannons J, Schwartzberg P, Stein P. (2004) Regulation of NKT cell development by SAP, the adaptor mutated in X-linked lymphoproliferative disease (XLP). 12th International Congress of Immunology. Montreal, Canada.

52. Phan TG, Gardam S, Basten A, Brink R (2004) Comparative analysis of T cell-dependent immune responses by follicular versus marginal zone B cells. 12th International Congress of Immunology. Montreal, Quebec, Canada.

53. Riminton S, Britton WJ (2004) The Design and Implementation of a Comprehensive, Interactive, Web-based Register of Primary Immunodeficiency Diseases for Australia and New Zealand.

54. Saunders BM, Briscoe H, Britton WJ (2004) Membrane-bound TNF mediates T cell migration and protective immunity against M. tuberculosis. Keystone Symposia. Host: Pathogen Standoff, Taos, New Mexico, USA.

55. Seow HF, Ong HT, Khor TO, Bailey C, Potter S, Broer S, Cavanaugh J, Rasko JEJ (2004) Detection of SLC6A19 transcripts by real time quantitative PCR. 5th Princess Chulabhorn Intl. Science Congress, Bangkok, Thailand.

56. Tangye SG (2004) Missense mutations in SH2D1A identified in patients with X-linked lymphoproliferative disease differentially affect the expression and function of SAP in human lymphocytes. 12th International Congress of Immunology, Montreal, Canada.

57. Thien M, Phan TG, Gardam S, Mackay F, Basten A, Brink R (2004) A subset of follicular self-reactive B cells is rescued from clonal deletion and anergy in autoimmune-prone BAFF-transgenic mice. 12th International Congress of Immunology. Montreal, Quebec, Canada.

58. Wang C, Shaun C, Jian L , Bertolino P, McCaughan GW, Allen R, Bishop GA (2004) Studies of allograft tolerance and rejection in mouse heart and kidney transplant models. Twentieth International Congress of the Transplantation Society, Vienna.

59. Wang XM, Yu DMT, McCaughan GW, Gorrell MD (2004). Fibroblast activation protein (FAP) overexpression inhibits cell adhesion and migration on collagen and fibronection. 55th Annual Meeting of the American Association of the Study of Liver Diseases, Boston, USA.

60. Warren A, Bertolino P, Fraser R, Bowen D, McCaughan GW and LeCouteur DG (2004) Model of interaction between naïve T lymphocytes and hepatocytes. 12th International Symposium On Cells Of The Hepatic Sinusoid, Bilbao, Spain, E.U.

National

Invited presentations

1. Allen J (2004) Drug resistance in haematological cancers. Pathology Update, Darling Harbour, Sydney.

2. Allen J (2004) Drug delivery to tumours. Australasian Pharmaceutical Science Association (APSA) Annual Conference, Melbourne.

3. Basten A (2004) Centenary Institute and its research. Probus Club of Grandviews Inc, Peakhurst.
4. Basten A (2004) Dinner Address. Australian Academy of Technological Sciences and Engineering, Sydney.
5. Basten A (2004) Invited speaker. Inaugural Chair of Allergic Disease, Westmead Children's Hospital, Sydney.
6. Basten A (2004) Dinner Speaker and Student Award Presentation. ANZCCART 2004 Conference Animal Ethics: New Frontiers, New Opportunities, Novotel Hotel, Brighton Beach, Sydney.
7. Basten A (2004) Judge and speaker. St. Vincent's and Mater Health Research Symposium, Sydney.
8. Bertolino P (2004) Competition between liver and lymph nodes for primary CD8+ T cell activation is a determinant of the balance between tolerance and immunity. 9th Autoimmunity Workshop, Sydney.
9. Bertolino P (2004) Activation of naive CD8+ T lymphocytes within the liver: role in tolerance and immune-mediated hepatitis. TSANZ annual scientific meeting, Canberra.
10. Bishop GA (2004) Laboratory techniques in transplantation research. TSANZ Postgraduate Training Course, Canberra.
11. Bishop GA (2004) Transplant tolerance induction. TSANZ Postgraduate Training Course, Canberra.
12. Brink R (2004) Differential regulation of B cell development, responsiveness and NF-?B activation pathways by TRAF2. 34th Annual Conference of the Australasian Society for Immunology, Adelaide.
13. Britton WJ (2004) Containing or eradicating Mycobacterium tuberculosis: the role of TNF superfamily members and P2X7 receptors. Australian Society of Clinical Immunology & Allergy, Gold Coast.
14. Britton WJ (2004) Containing or eradicating Mycobacterium tuberculosis: the role of TNF superfamily members and P2X7 receptors. Australian Society of Microbiology, Sydney.
15. Britton WJ (2004) Drugs for Immunosuppression. Speaker, Immunology Nursing Program, Bone & Joint and Neurosciences, CSAHS, RPAH, Sydney.
16. Britton WJ (2004) T cell cytokine responses to house dust mite (HDM) stimulation in vitro at ages 18 months and 3 years: Relation to HDM allergy. From Cell to Society 2004 Research Conference – College of Health Sciences, University of Sydney, Leura, Blue Mountains.
17. Britton WJ (2004) TNF-alpha: Its role in controlling TB. Prince of Wales Hospital TB Group, Randwick.
18. Britton WJ (2004) Tuberculosis. Community Health and Tuberculosis Association, Darlington Centre, University of Sydney, Sydney.
19. Britton WJ (2004) Tuberculosis. Symposium for Sirius Naraqi, College of Health Sciences, Western Clinical School, Nepean Hospital, Sydney.
20. Britton WJ (2004) Vaccines for other neonatal infections. Festschrift in honour of Professor Margaret Burgess, Royal Alexandra Hospital for Children, Sydney.
21. Fazekas de St.Groth B (2004) In vivo activation and competition between regulatory T cells. 9th Australasian Autoimmunity Workshop, Sydney.
22. Fazekas de St.Groth B (2004) Regulatory deficiencies and immune-mediated pathology. Australian Society for Rheumatology Annual Meeting, Palm Cove.
23. Fazekas de St.Groth B (2004) Dendritic cell stimulatory capacity: the command centre of the immune response. Brisbane Immunology Group Annual Meeting, Sunshine Coast.
24. Fazekas de St.Groth B (2004) Tcells/DCs/Proliferation. 7th FIMSA/Australasian Society for Immunology Advanced Training Course in Immunology, Adelaide.
25. Ho J (2004) Iron chelation – where are we going? Pathology Update Conference 2004. Royal College of Pathologists of Australasia, Sydney.
26. Ho J (2004) Molecular pathogenesis of myeloma. South Australian State Meeting of Haematology Society of Australia and New Zealand, Adelaide.
27. Ho J (2004) New therapeutic agents in myeloma. South Australian State Meeting of Haematology Society of Australia and New Zealand, Adelaide.
28. Ho J (2004) Novel insights into the pathogenesis of myeloma. Haematology Society of Australia and New Zealand Annual Scientific Meeting, Melbourne.
29. Ho J (2004) Phenotype prediction in beta-thalassemia – a mechanistic approach. Genetics and Population Health Conference, Australian Public Health Genetics Consortium, Fremantle.
30. McCaughan GW (2004) HLA matching and liver transplantation. International Asia Pacific Tissue Typing meeting Sydney, Australia.
31. Rasko JEJ (2004) Chair, World Congress of Bioethics Symposia: Towards a Consensus on Cloning and Stem Cell Research: Ethics, Law and Public Policy; Civil

Society and Responsible Global Governance of the New Human Genetic Technologies: New Voices, New Perspectives; Implications of International Genetic Research for Public Health, UNSW.

32. Rasko JEJ (2004) Plenary Speaker, 2nd Annual Australian National Stem Cell Centre National Conference, Sydney.
33. Saunders BM (2004) Importance of Membrane-bound TNF in regulating granuloma formation and control of Mycobacterium tuberculosis infection. The John Curtin School of Medical Research, Australian National University.
34. Semsarian C (2004) Molecular Basis of Hypertrophic Cardiomyopathy. 2nd Australian Health and Medical Research Congress, Darling Harbour, Sydney.
35. Semsarian C (2004) Frontiers in Cardiology: Cardiovascular Genetics. Rural Physicians Update. RPAH, Sydney.
36. Semsarian C (2004) Utility of Mouse Models in Hypertrophic Cardiomyopathy. IBR Symposium, University of Sydney, Sydney.
37. Semsarian C (2004) Cardiomyopathies. RPAH FRACP Trainees. RPAH, Sydney.
38. Semsarian C (2004) Molecular Cardiology: Hypertrophic Cardiomyopathy Leading The Way. Cardiology Grand Rounds, QE II Hospital, Adelaide.
39. Semsarian C (2004) Molecular Genetic Advances in Understanding the Athero-Inflammatory Process. Keynote Speaker. 52nd Cardiac Society of Australia and New Zealand Scientific Meeting, Brisbane.
40. Semsarian C (2004) Genetic Testing: Current Status and Future Directions. Physicians Update Meeting. Port Douglas, Queensland.
41. Semsarian C (2004) Hypertrophic Cardiomyopathy: From Heart Tumour to Complex Genetic Disorder. Physicians Update Meeting, Port Douglas.
42. Semsarian C (2004) Getting to the Heart of Sudden Death. Cardiology Grand Rounds, Flinders Medical Centre, Adelaide.
43. Semsarian C (2004) Hypertrophic Cardiomyopathy: From Heart Tumour to Complex Genetic Disorder. Cardiomyopathy Association Meeting, Royal North Shore Hospital, Sydney.
44. Tangye SG (2004) Using human knockouts to identify key regulators of the immune system. Walter and Eliza Hall Institute for Medical Research, Parkville.
45. Triccas J (2004) Tuberculosis: virulence and vaccines. School of Biotechnology and Biomolecular Sciences, University of New South Wales, Sydney.
46. Triccas J (2004) Building better BCG vaccines to combat tuberculosis. Australian Society for Microbiology annual meeting, Sydney.
47. Triccas J (2004) Building better BCG vaccines to combat tuberculosis. Australian Society of Microbiology annual meeting, Sydney. Invited speaker for the Canberra 2005 meeting.
48. Wozniak TM, Britton W (2004) Adjuvant effects of pIL-23 and pIL-27 in enhancing the immune response to DNA vaccines. Australasian Society for Immunology, NSW Branch Conference, Wiseman's Ferry.
49. Wozniak TM, Britton W (2004) Plasmid IL-23 but not pIL-27, enhances and promotes a Th1-like T cell response to DNA immunisation against Mycobacterium tuberculosis infection. Australasian Society for Immunology, Adelaide.

Abstracts, oral and poster presentations

50. Allen J (2004) MRP4 – new twists. Dept of Pharmacology, University of Sydney, Sydney.
51. Allen J (2004) MRP4 as a prognostic marker in cancer and its regulation by MYC family proteins. Sydney Cancer Centre Research Seminar, Sydney.
52. Allen J (2004) Multidrug transporters and new anticancer drugs. ABC Transporter Symposium, University of NSW, Sydney.
53. Allen J (2004) The MRP4 multidrug transporter – new twists. School of Pharmacy, University of Sydney.
54. Bertolino P (2004) Naïve CD8+T cell-hepatic interactions: outcomes and consequences.Garvan Institute, Sydney.
55. Bowen DG, Zen M, Holz L, Davis T, McCaughan GW and Bertolino P (2004) Competition between liver and lymph nodes for primary CD8+ T cell activation is a determinant of the balance between tolerance and immunity. 9th Autoimmunity Workshop, Sydney.
56. Bryant V, Hodgkin PD, Tangye SG (2004) Investigating the differentiation potential of human IgM memory B cells. 34th Annual Meeting of the Australasian Society for Immunology, Adelaide.
57. Bryant V, Hodgkin PD, Tangye, SG (2004) Human Splenic IgM-memory B cells differentiate more readily into isotype switched and ISCs than naïve B cells. 2nd Australian B-Cell Dialogue, Walter and Eliza Hall Institute, Melbourne.

58. Chiu C, Ingles J, Semsarian C (20040) Gender differences in patients with hypertrophic cardiomyopathy. 2nd Australian Health and Medical Research Congress, Sydney.

59. Cordoba S, Wang C, Williams R, Sharland A, McCaughan G, Bishop AG (2004) Microarray analysis of spontaneously tolerant and rejecting allografts in rodent models. Transplantation Society Of Australia And New Zealand, Canberra.

60. Doolan A, Ingles J, Chiu C, Tebo M, Richmond DR, Seidman JG, Seidman C, Semsarian C (2004) Genetic basis of sudden cardiac death in hypertrophic cardiomyopathy. 2nd Australian Health and Medical Research Congress, Sydney.

61. Doolan A, Tebo M, Ingles J, Richmond DR, Seidman JG, Seidman C, Semsarian C (2004) Genetic analysis of families with hypertrophic cardiomyopathy and a history of sudden cardiac death. 52nd CSANZ Annual Scientific Meeting, Brisbane.

62. Grech AP, Amesbury M, Chan T, Gardam S, Basten A, Brink R (2004) TRAF2 differentially regulates the canonical and non-canonical pathways of NF-?B activation in mature B cells. 2nd Australian B Cell Dialogue, Walter and Eliza Hall Institute for Medical Research, Melbourne.

63. Kanatani T, Lanzetta M, Owen E, McCaughan GW, Matsumoto T, Bishop GA (2004) Donor leukocytes combined with immunosupressive drug theray to induce long-term acceptance of limb allografts. Transplantation Society of Australia and New Zealand, Canberra.

64. Li J, Wang C, McCaughan GW, Bishop AG (2004) Donor-recipient cell interactions in rat kidney transplant tolerance. Transplantation Society Of Australia And New Zealand, Canberra.

65. Limaye S, Grech A, Basten A, Brink R (2004) Regulation of T-dependent B cell responses by TRAF2. 34th Annual Conference of the Australasian Society for Immunology, Adelaide.

66. Lin MW, Kershaw GW, Rasko JEJ, Britton WJ (2004) Acquired hypoprothrombinaemia in SLE and catastrophic anti-phospholipid antibody syndrome Australasian Society of Allergy and Clinical Immunology, Gold Coast.

67. Lucas KM, Tanabe KM, Galettis P, Allen JD (2004) Influence of flavonoids on the activity of P-glycoprotein. Australian Health and Medical Research Congress 21-26 November, Darling Harbour NSW.

68. Mitchell CA, Kristie H, Huysmans RD, Tan A, Sriratana A, Wiradjaja F, Dyson J, Ooms, Gurung R, Bailey C, Rasko JEJ, Kong A (2004) Regulation Of Phagocytosis By Inositol Polyphosphate 5-Phosphatases, Haematology Society of Australia and New Zealand Annual Meeting, Melbourne.

69. Musicki K, Briscoe H, Britton WJ, Saunders BM (2004) Transmembrane and soluble TNF contribute to immunity to acute intracellular bacterial infection. NSW Australasian Society of Immunology Branch Meeting, Weismanns Ferry.

70. Nguyen L, Tsoutsman T, Chung C, Semsarian C (2004) Cardiac response to exercise in mice with hypertrophic cardiomyopathy. 52nd CSANZ Annual Scientific Meeting, Brisbane.

71. Park J, Ajami K, Gorrell MD (2004) Characterization of human dipeptidyl peptidase 8 and DPIV produced in a baculovirus expression system. Combined Biosciences Annual Conference, Perth.

72. Park J, Ajami K, Gorrell MD (2004) Human dipeptidyl peptidase (DP) 8 and the prospective type 2 diabetes therapeutic target DPIV: Enzymology of proteins produced in insect cells using engineered baculovirus. The Australian health and Medical Research Congress, Sydney.

73. Rasko JEJ (2004) The Australasian Hartnup Consortium The last transporter. Australasian Genemappers Workshop.

74. Saunders BM (2004) Importance of Membrane-bound TNF in regulating inflammation and control of intracellular pathogens. Retirement Symposium for Assoc Professor Christina Cheers. Melbourne University, Melbourne.

75. Saunders BM, Fernando S, Sluyter R, Skarratt K, Wiley J and Britton WJ (2004) Novel single nucleotide polymorphisms in the P2X7 gene reduces ATP-mediated killing of mycobacteria. Oral Presentation, ASI NSW Annual Conference ,Wisemanns Ferry.

76. Saunders BM, Fernando S, R Sluyter, K Skarratt, Wiley J and Britton WJ (2004) Novel single nucleotide polymorphisms in the P2X7 gene reduces ATP-mediated killing of mycobacteria. Oral Presentation, Sydney University Colleges of Health Sciences Research Conference, Leura.

77. Seow HF, Bröer A, Kowalcuk S, Bailey CG, Potter SJ, Cavanaugh JA, Rasko JEJ Bröer S (2004) Epithelial transport of neutral amino acids and its role in Hartnup disorder ComBio, Sydney.

78. Tanabe KM, Millward M, Allen JD (2004) Interactions of patupilone (epothilone B) with multidrug transporter proteins. Australian Health and Medical Research Congress, Darling Harbour, Sydney.

79. Tangye SG (2004) Increased expression of CD27 on in vitro-activated memory B cells precedes acquisition of CD38 and correlates with commitment to the plasma cell lineage. The 2nd Australian B-cell Dialogue, Melbourne.

80. Tangye, SG (2004) Increased expression of CD27 on in vitro-activated memory B cells precedes acquisition of CD38 and correlates with commitment to the plasma cell lineage. Australasian Society of Immunology 34th Annual Scientific Meeting, Adelaide.

81. Tran P, Lee JH, Waneck G, Bishop AG, Sharland AF (2004) HLA-E is not expressed on LCL13271 cells unless other HLA class-1 molecules are present. Transplantation Society Of Australia And New Zealand, Canberra.

82. Triccas J (2004) Tuberculosis: virulence and vaccines. School of Biotechnology and Biomolecular Sciences, University of New South Wales, Sydney.

83. Triccas J (2004) Expanding the antigenic repertoire of BCG improves protective efficacy against aerosol Mycobacterium tuberculosis infection in mice. College of Health Sciences 4th Biennial Research Conference, Lorne.

84. Tsoutsman T, Chung C, Nguyen L, Semsarian C (2004) Effect of aging on the conducting system (ECG) in normal mice. 52nd CSANZ Annual Scientific Meeting, Brisbane.

85. Wang C, Cordoba S, Li J, Bertolino P, McCaughan GW, Allen R, Bishop GA (2004) Comparison of kidney allograft tolerance and heart allograft rejection in a mouse transplant model. Transplantation Society of Australia And New Zealand, Canberra.

86. Wang XM, Yu D, Kable E, Cox G, McCaughan G, Gorrell M (2004) Fibroblast Activation Protein (FAP) Overexpression Reduces Cell Adhesion and Migration on Collagen and Fibronectin. Congress Of The International Society On Fibrinolysis And Proteolysis (ISFP2004), Melbourne.

87. Wang XM, Yu DMT, McCaughan GW, Gorrell MD (2004) Fibroblast activation protein (FAP) overexpression inhibits cell adhesion and migration on fibronectin and type I collagen. Combined Biosciences Annual Conference, Perth.

88. Wang XM, Yu DMT, McCaughan GW, Gorrell MD (2004) Human fibroblast activation protein (FAP) overexpression is associated with reduced cell adhesion and migration on fibronection and type I collagen. 2nd Australian Health and Medical Research Congress, Sydney.

Centenary Committees 2004

Board Committees

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Ms Judith Barry

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Ms Mary Linnane

Research Society Manager
Ms Kate Scott

Research Support Officer
Ms Sonja Bates

Personal Assistant to the Director
Ms Gabriella O'Neil
Ms Clare Hill (temp)

Personal Assistant to the General Manager
Ms Lilia Robinson (temp)

Reception
Ms Maisie Aguilar
Ms Dinah Utian

Website Project
Dr Pearly Harumal (from October)

Research Facilities and IT

Research Facilities & IT Manager
Dr Adrian Smith

Officer In Charge of Flow Cytometry
Mr Joseph Webster

Network Manager
Mr Brian Bulliman

IT & Network System Support
Mr Robert Middleton (from August)

Research Assistants – FACS
Ms Tara McDonald
Ms Vivienne Moore (from May)

Laboratory Assistant
Mr Hai Nguyen

Animal Facility

Veterinarian
Dr Jenny Kingham

Technical Officer
Ms Marisa Mourelle

Technical Assistants
Mr Bradley Harper
Ms Rachel Nowell

Animal Attendants
Ms Artika Autar
Mr Andy Hall
Ms Tamara Lancaster
Mr Brendan Lee
Mr Dane Millanta
Mr Kamil Rezk
Ms Karen Ridgeway
Mr Joel Robertson
Ms Catherine Sorokine

Research Groups

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Dr Chris Jolly BSc(Hons) PhD
Dr Pablo Silveira BMedSci PhD

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Dr Adrian Grech
Dr Pearly Harumal
Dr Didrik Paus
Dr Mu Yao (Cen*Tec*)

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Ms Tyani Chan
Ms Sandra Gardam
Ms Kamila Nejedly
Ms Joanna Raftery
Mr Chris Seet (from Sept)

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Mr Tom Davis (CenTec)

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Mr Adam Cook
Dr Lye Lin Ho
Dr Sandhya Limaye
Dr Tri Phan
Ms Marilyn Thien

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Mr Andrew Jessup

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Mr Peter Tobin

Honours Student
Ms Keryn Lucas

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Ms Vanessa Gysbers

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Mr Kenneth Mackun

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Dr Rosetta Martiniello-Wilks

Liver Immunobiology

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Dr Mark Gorrell
Dr Patrick Bertolino

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Dr Devanshi Seth

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Dr Nick Shackel (North Carolina until Dec)

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Ms Jian Li (from April)
Dr Chuanmin Wang

Visiting Scholar
Dr Shigang Tang

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Mr Shaun Cordoba
Ms XiaoXuan Huang
Mr Joohong Park
Ms Sunmi Song
Mr Peter Tran
Ms Maggie Wang
Ms Denise Yu

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Ms Danielle Priestley

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Ms Kim Good
Ms Cindy Ma

Honours Student
Ms Amanda Cuss

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A/Prof Christopher Semsarian MBBS PhD FRACP

Research Officer
Dr Tatiana Tsoutsman

Cardiovascular Genetics Co-ordinator
Ms Jodie Ingles

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Ms Jessica Chung
Ms Lan Nguyen
Ms Molly Tebo

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Honours Student
Ms Lien Lam

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PhD MBBS BScMed FRACP FRCP FRCPA DTM&H

Honours Co-ordinator
A/Prof Helen Briscoe

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Dr Jamie Triccas BSc(Hons) PhD

CJ Martin Fellow
Dr Umaimainthan Palendira
(UK until 2006)

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Dr Nick West

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Mr Stephen Tran

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Ms Rachel Pinto
Mr Anthony Ryan
Ms Teresa Wozniak

Honours Student

Ms Korana Musicki

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Ms Cindy Zhu

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Mr Ben Roediger
Ms Alex Spencer
Ms Sioh-Yang Tan

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Mr Martin McGrane

Haematology Group

Group Head

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Dr Daniel Sze (RPAH)

Research Associate

Dr Joy Ho (RPAH)

Research Assistants

Ms Melinda Jeffels (RPAH)
Ms Shi-Hong Yang (RPAH)

2005 - The Year Ahead

Burnet Award

Professor Jonathon Sprent FRS will take up a position in the Centenary Institute in June 2005 after being granted a prestigious Burnet Award from the National Health and Medical Research Council. The award worth $2 million over five years is used to bring distinguished researchers back to Australia. Prof Sprent is currently at the world renowned Scripps Research Institute in San Diego. One of the previous recipients of this award was Nobel Laureate Professor Peter Doherty.

NHMRC grants commencing 2005

Program Grants

Professor Geoff McCaughan was successful in obtaining a prestigious Program Grant entitled “Molecular and cellular pathogenesis of liver disease”, in conjunction with colleagues at the Westmead Millennium Institute valued at $4.6 million over 5 years.

Project Grants

Professor John Rasko was awarded grant funding for his project entitled "RNA interference in normal and neoplastic myelopoiesis".

Associate Professor Chris Semsarian was awarded grant funding for his project entitled "Genetic basis of sudden cardiac death in the young".

Professor Warwick Britton and Dr Bernadette Saunders are chief investigators on a project grant awarded to Professor James Wiley of the University of Sydney.

Dr John Allen is a chief investigator on a project grant awarded to Professor Peter Hersey of the University of Newcastle.

Other grants commencing 2005

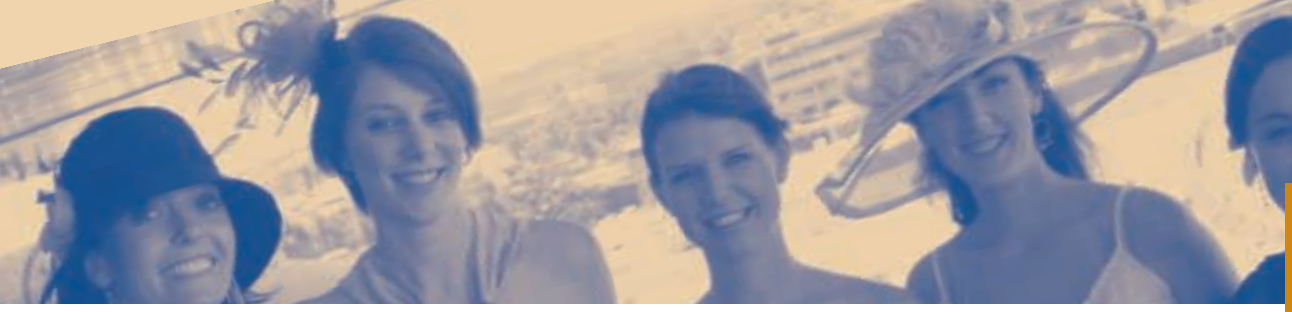
- Australian Research Council (ARC)
  - Professor John Rasko
- Leukemia Foundation research in aid grant
  - Professor John Rasko
- NSW Cancer Council research grant
  - Dr Stuart Tangye
- Heart Foundation grant
  - Associate Professor Chris Semsarian
- Perpetual Trustees equipment grant
  - Professor Tony Basten
- University of Sydney equipment grant
  - Professor Warwick Britton
- Perpetual Trustees equipment grant
  - Professor Warwick Britton
- Rebecca L Cooper Foundation equipment grant
  - Professor Warwick Britton
- Rebecca L Cooper Foundation equipment grant
  - Professor John Rasko

Scholarships commencing 2005

Ms Sandra Gardam was awarded the inaugural NHMRC John Shaw scholarship. Ms Lauren Holz was awarded a NHMRC Dora Lush scholarship and Dr Silvia Ling an Anthony Rothe Foundation scholarship. Ms Amanda Cuss, Ms Keryn Lucas, Ms Lien Lam and Mr Lewis Cox were awarded Australian Postgraduate Award scholarships.

Research Fellowships

A/Prof Barbara Fazekas, head of the T cell Research group was again awarded a NHMRC Principal Fellowship, valued at $600,000 over the next five years. Dr John Allen of the Cancer Drug Resistance group was successful in obtaining one of the inaugural Cancer Institute NSW Career Development and Support Fellowships valued at $590,000 over three years commencing in 2005.



Fundraising

11th Annual Race Day and Luncheon

Centenary held its 11th Annual Raceday at Rosehill Gardens on Saturday October 9, 2004. The perfect spring day set the scene for our most successful Raceday raising over $160,000 through the generosity of sponsors and luncheon guests. This year's event focused on raising funds to purchase a BD 'Diva' the latest equipment used in flow cytometry, a cellular analysis technology designed to acquire information on the body's cells and assist with researching a wide range of immune diseases, such as cancer and diabetes.

Our sincere thanks and appreciation go to the Raceday Steering Committee chaired by Centenary Board Governor Malcolm Noad and to all those who, by their presence, contributed to a very special and most successful Raceday.

Young Winemaker of the Year Awards

The Wine Society's Young Wine Maker of the Year Awards was held on Saturday November 27th at a Gala Dinner at the Four Seasons Hotel. Hosted by Australian Rugby Legend Phil Kearns, the dinner provided guests with the opportunity to taste 20 wines produced by the 10 Finalist young wine makers. Our congratulations go to Matthew Gant from St Hallet who was awarded the 2004 Young Wine Maker of the Year.

Over $13,000 was raised through a raffle, mystery envelopes and a silent auction. The funds will be used to support Centenary research carried out by Dr John Allen and his colleagues in the Cancer Drug Resistance Group. Centenary is most grateful to the Wine Society for their ongoing support for our research.

End of Tax Year Appeal

The generosity of those who supported our most recent special initiative fundraising activity is particularly appreciated. This year's End of Tax Year Appeal raised over $70,000 towards providing a research assistant to work with Dr Pablo Silveira of the B Cell Biology Laboratory. His ground breaking research has the potential to help patients not only with Type I childhood diabetes but certain types of cancer as well.

We would be delighted if you would consider supporting us.

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

Centenary Institute Annual Report 2004

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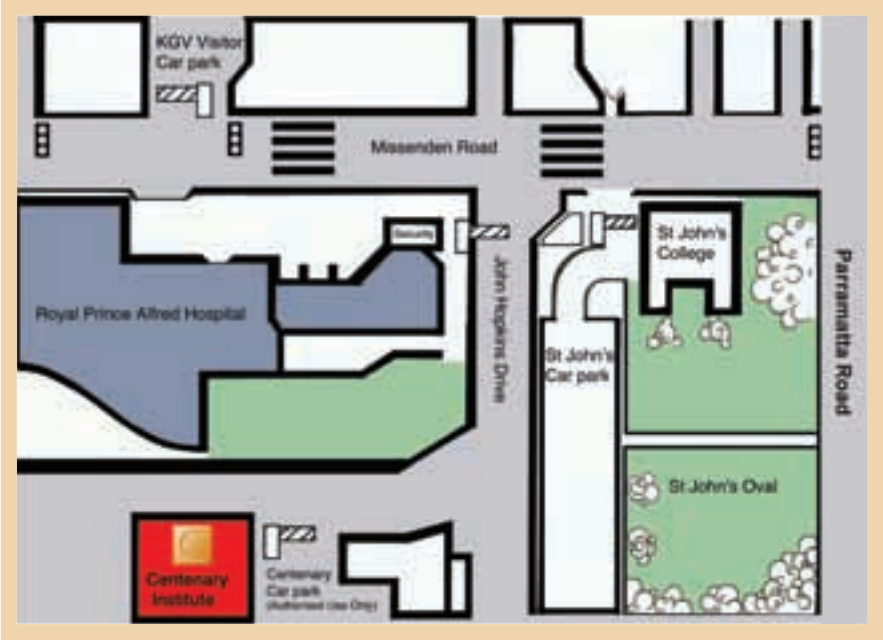

To City

If you would like more information please browse our website at www.centenary.org.au or call us on +61 2 9565 6156 or email enquiries@cenint.org

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