Centenary Institute
research for life

Annual Report **2008**

The Centenary Institute, located between Royal Prince Alfred Hospital and the University of Sydney, is a world class medical research facility focusing on cancer, cardiovascular and infectious diseases. It forms a critical point of contact and intellectual engagement between the Hospital and the University.

The Institute is in an exciting growth phase, having grown from 100 to 170 staff in the past two years.

Our history

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

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CHAIRMAN'S REPORT

2008 has been an excellent year for Centenary, both within the Institute and in reaching out to our colleagues, stakeholders and patients.

Within Centenary there has been an acceleration of activity: by the end of the year our staff numbers grew by another 40 people to reach 170 and our research income increased to almost $13 million. A lot of the energy of the Institute comes from its students: we had 46 in Centenary enrolled for Honours or PhD degrees. Students seem enthralled by the combination of science and clinical utility that many of the projects offer in the Centenary.

In reaching out to our stakeholders, the ever energetic Board Member Neil Lawrence led our Foundation to a wonderful formal start with a function at Government House. Our Guest of Honour The Hon Julia Gillard spoke with passion and knowledge about the importance of medical research not only for the health of our nation but also for the training of our young and enquiring minds.

Our Annual General Meeting had as its Guest of Honour the Nobel Laureate Professor Peter Doherty, who commented on the excellence of research at the Centenary Institute and also emphasised the importance of co-location for the optimal synergistic interaction of institutes and universities.

Indeed, we feel privileged to be situated near the two great institutions of the University of Sydney and Royal Prince Alfred Hospital. We were very pleased to welcome the new Vice Chancellor, Dr Michael Spence, to our AGM and plan together to continue our close working relationship the University. We also welcomed Di Gill and have continued to develop with her future plans for the Centenary including expanding our research space in a manner that synergises with the hospital.

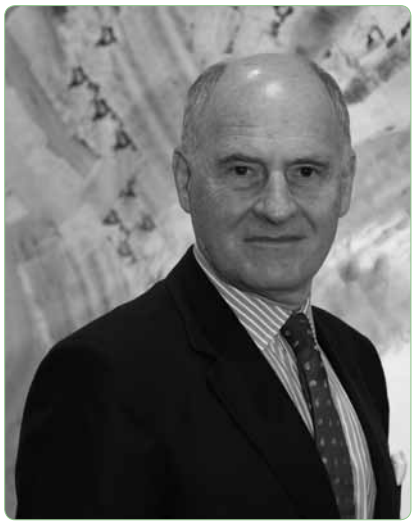
Our activities to see the campus become an internationally recognised cancer precinct have also accelerated. We support the University Cancer Network, have formed an agreement with the Peter MacCallum Cancer Centre to develop joint programs, and our partnership with the Sydney Cancer Centre to build an Integrated Cancer Research facility has also progressed with the commissioning of a business plan and acceleration/approval of the clinical building, now named RPA LifeHouse.

The Centenary Institute is an enthusiastic partner in Sydney Institutes of Health and Medical Research (SIHMR), an umbrella organisation that will develop to maximise our resources and for consortia amongst institutes to develop large programs, beyond the capabilities of individual members.

Finally an important aspect of Centenary Institute's activities has been translational research, and several programs, including one of Professor Semsarian on Aboriginal cardiovascular health and of Professor Britton on tuberculosis within Australia, Vietnam and in India, have continued to expand and make major inroads to these very real problems.

The Hon Michael Egan

EXECUTIVE DIRECTOR'S REPORT



The last year has brought about a number of exciting developments at the Centenary Institute, all of which have strengthened our Institute and allowed an intensification of our focus to improve the health of all Australians.

Our new system of having two Assistant Directors on rolling appointments has been a success. We congratulate Professor Wolfgang Weninger who joins Professor Geoff McCaughan as Assistant Director. Our Assistant Directors have helped formulate policy, ensure adequate communication and have been a source of wise and mature advice.

Cohesion and collaboration are essential for achievement. To this end we have continued our annual retreats with senior staff where we refine our identity and order our priorities for the coming years. We have introduced Director's morning teas, where I address the whole Institute and provide opportunities for questions and discussion. Furthermore, we have undertaken an Institute-wide survey into our internal communication. The information and positive feedback were the basis of improvements including the launch of a new intranet site.

Collaboration with University of Sydney, and SIHMR, led to a successful application to the Federal Government's Higher Education Endowment Fund for $95m toward construction the first stage of the ARC building adjacent to the Centenary Institute; a 'Centre for Obesity, Diabetes and Cardiovascular Diseases', and we look forward to expanding our work into this building, scheduled for completion in 2013.

We also worked with the Sydney Cancer Centre to establish a Comprehensive Cancer Centre consisting of research and clinical buildings. Finally, we have signed an agreement with Peter MacCallum Cancer Institute to enhance the research and academic exchanges between the two organisations

Our Fundraising and Marketing team, under the direction of Sally Castle, has kicked into a new gear. I am sure you will agree our newsletters have become easier to read and more informative, our achievements are better covered in the media, and our wonderful advertisements have been well received both on television and in the press.

I want to thank our Board Member, Neil Lawrence, for being a guiding hand in developing the advertisements and Singleton Ogilvy Mather, especially its CEO Stuart O'Brien who ensured the project was given priority by his highly talented team. The placement was aided by Geoff Dixon and Zenith Optimedia.

It has been wonderful to see the Foundation become established and begin to grow, and have an enthusiastic group involved in various aspects of the Institutes activities. We have welcomed over 3500 new supporters in 2008 and with their help plan to take the Centenary forward in leaps and bounds in 2009.

The operations of the Institute continue to improve and expand under the guidance of our Chief Operating Officer Nick Pearce. Our imaging capacity was expanded with the

purchase of a multi-laser spectral confocal microscope for imaging cells and tissues. This microscope allows researchers to investigate dynamic cellular processes over time via high resolution 3D images and videos. Also, we will expand our multi-photon capabilities with the purchase of an additional laser and a second microscope in 2009.

The Centenary Institute was part of successful ARC LIEF grant application with the Universities of Sydney and NSW that will lead to acquisition of two new high-end flow cytometry instruments in 2009. Finally, the purchase of individually ventilated mouse cages and a rack washer, expand the capacity of our animal facility.

Ultimately, however it is our science and the difference we make to health that defines our success. The Centenary's income has increased from $10.3 million (2007) to $12.9 million (2008). Peer reviewed income increased from $5.9 million to $8.1 million, with 41% of our NHMRC project applications being successful. We have further improved this rate in 2009 to 50% against a national average of 26%.

Our output had an excellent year with approximately 80 publications, including journals of the highest impact, such as *New England Journal of Medicine, Nature Immunology, Nature Cell Biology, Immunity, Journal of Experimental Medicine, Journal of Clinical Investigation, Annals Internal Medicine, Circulation, Nature Structure, Hepatology* and *Blood*. Almost half our journal publications (37/80) were in journals with impact factors over five and just more than 20% in journals with impact factors over 10. What is especially pleasing is that our work is also being cited, with one of the highest citation rates over the last five years amongst the research institutes.

Some of the innovations last year, have now become fixtures. For example, our Director's lunches have continued to be well received. We had the pleasure of hosting The Hon John Fahey, who is now Head of the World Anti-Doping Agency and Professor Alan Trounson, President of the California Institute for Regenerative Medicine. They addressed areas that ranged from 'technology and sociology of drug use in sport' to 'Energisation of California Stem Cell Research Program'.

Our Colloquia entitled "Opportunities" have also continued energetically with two being held. One, in January concerning one of the most exciting class of molecules, MicroRNAs. We were pleased to welcome Professor Gunter Meister from the Max Planck Institute in Martinsreaid, Germany and Dr Bharat Chowrira from Merck and Co USA. In June on stem cell research, we welcomed Professor Don Metcalf from the Walter and Eliza Hall Institute as guest of honour. Both colloquia were fully subscribed and enhanced the reputation of the Centenary. I thank the Centenary Institute scientists who organised the colloquia for their contributions and congratulate them on the success of these events

The Seminar Program run by Professors Gamble and Rasko, have also become a focus for scientific exchange around the campus, with an increasing number of colleagues from nearby Institutes attending.

Finally, I congratulate Jeff Holst, who was the inaugural winner of Research Australia's inaugural Discovery Award for his research into the immune system.

Professor Mathew Vadas

BOARD OF GOVERNORS

The Honourable Michael Egan (Chair)

Re-appointed Chair in October 2008. Nominated by Michael Spence, Vice Chancellor of the University of Sydney

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

Mr John Samaha (Deputy Chair)

Appointed Governor in 2003

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

Dr Teresa Anderson

Appointed Governor in 2007

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

The Honourable John Brown AO FAMI

Appointed Governor in 2001

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

Mr Alastair Davidson MICA (Scot)

Appointed Governor in 2004

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

Mr Geoff Dixon

Appointed Governor in 2007

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

Ms Di Gill

Appointed Governor in 2006

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

Professor John Horvath AO

Appointed Governor in 2007

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

Mr Graham Kelly

Appointed Governor in 2006

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

Mr Neil Lawrence

Appointed Governor in 2006

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

Associate Professor Kelly-Anne Phillips

Appointed Governor in 2007

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

Professor Bruce Robinson

Appointed Governor in 2007

Professor Robinson is Dean of the Faculty of Medicine, University of Sydney and Head of the Cancer Genetic Laboratory at the Kolling Institute. In 2003, he was awarded the Daiichi Prize by the Asia and Oceania Thyroid Association for this work on the pathogenesis of thyroid cancer. Professor Robinson is the Founding Chairman of Hoc Mai, the Australia Vietnam Medical Foundation, which sponsors and supports medical nursing, allied health and scientific exchanges between Australia and Vietnam. He is a Fellow of the Australian Institute of Company Directors.

Professor Mathew Vadas

Appointed Governor in 2007

Professor Vadas trained in medicine at the University of Sydney and as a physician at the Royal Prince Alfred Hospital before completing a doctorate at the Walter and Eliza Hall Institute in Melbourne. After postdoctoral work at Harvard, he returned to Australia and built a significant research enterprise in Adelaide. He was a chief initiator and inaugural Director of the Hanson Centre for Cancer Research (now Hanson Institute). Professor Vadas has also contributed strongly to the Australian biotechnology sector, being involved in the establishment of two ASX listed biotechnology companies. He served as Chair of the Medical Research Advisory Committee of the Australian Cancer Research Foundation for five years, stepping down in 2007. He currently serves on the Board of Governors of the SMILE Foundation and Arts & Health Foundation. His research embodies a multidisciplinary approach to discover new molecules or pathways that may uncover fundamental phenomena of nature and/or lead to novel therapeutics. Using techniques of cell biology, molecular biology, biochemistry, bioinformatics and genomics, he has primarily focused on endothelial and leucocyte biology with special emphasis on cytokines or growth factors and pathways of cellular signalling.

In 2008, the Board of Governors underwent several changes:

- The Hon Michael Egan was re-appointed Chairman for another three year term.
- Associate Professor Kelly-Anne Phillips, Mr Geoff Dixon and Ms Di Gill resigned.

The Centenary Institute extends sincere thanks to the outgoing Governors for their contribution to the Institute throughout their appointments.

RESEARCH PERSPECTIVE

The Centenary Institute is dedicated to helping all Australians live longer, healthier lives. Our researchers work across a diverse spectrum of scientific investigation focused in three areas – cancer, cardiovascular disease and infectious diseases.

CANCER

With one in two men and one in three women in Australia diagnosed with cancer before the age of 85, it is no surprise that cancer is the biggest disease concern of Australians.

While cancer survival rates have certainly improved through screening, early detection and better treatment, there is still a long way to go.

To overcome the immense challenges presented by cancer, the Centenary Institute is working hard to answer four fundamental research questions:

- What causes cancer?
- Why does cancer spread?
- Why does cancer regress?
- How can we improve cancer treatment?

CARDIOVASCULAR DISEASE

Cardiovascular disease accounts for over a third of all deaths in Australia. More than 45,000 Australians lose their lives to a form of the disease each year.

Death rates have declined in the past decade but more than three million Australians are still affected by cardiovascular disease annually.

To reduce the impact of cardiovascular disease on Australian families, the Centenary Institute is seeking answers to crucial questions:

- What are the genetic causes of heart disease?
- How do signals that communicate between and within cells go awry leading to disease?
- How does blood vessel development proliferate unnecessarily causing cardiovascular disease?

INFECTIOUS DISEASES

Tuberculosis (TB) is a worldwide pandemic – more than two billion people are infected and 1.6 million die from the disease each year.

Chronic liver damage affects up to 20% of our population. It has many causes including infections (Hepatitis B and C). Liver cancer is often caused by chronic liver damage and is one of the fastest growing cancers in our community.

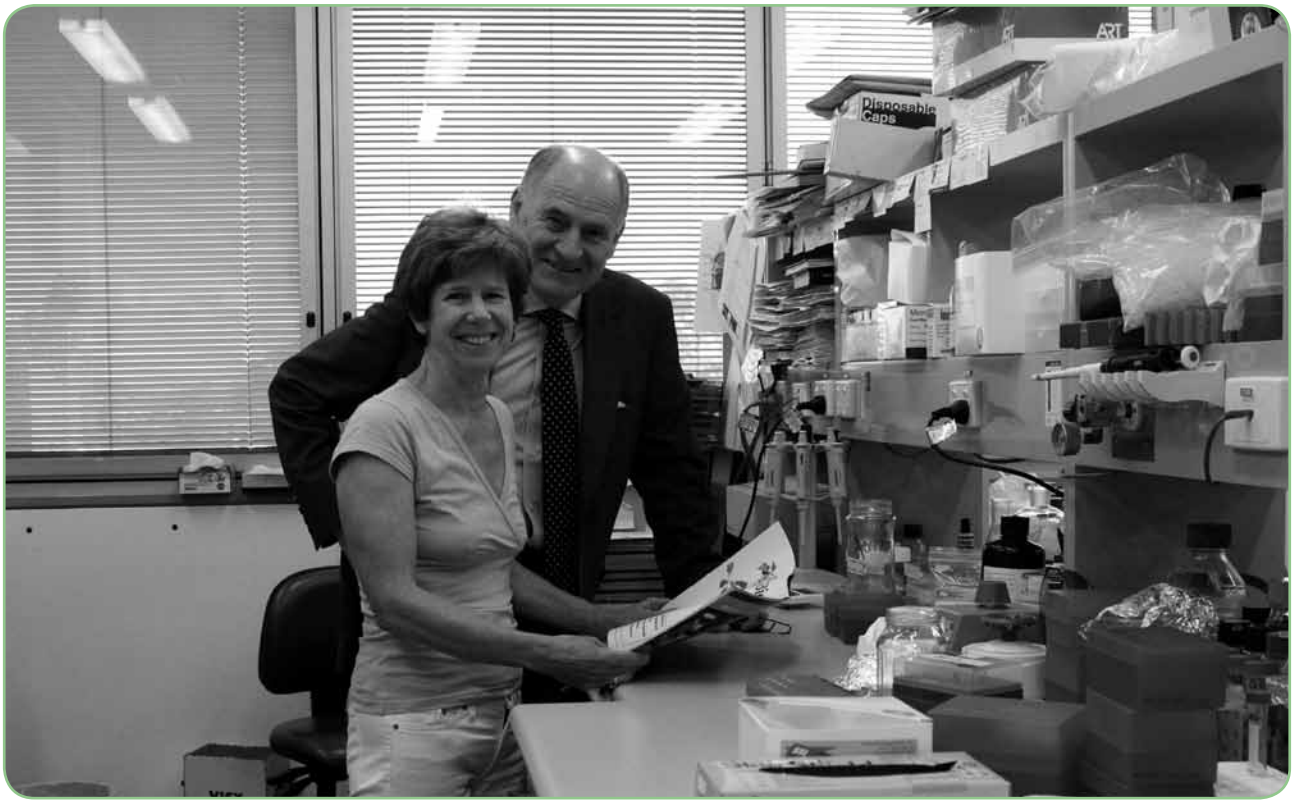
The Centenary Institute is hoping to decrease the impact on infectious diseases within the community by answering these questions:

- Why do latent TB infections progress to active diseases?
- How can we improve the vaccines for tuberculosis?
- How does liver damage cause liver failure or liver cancer?
- What properties in the liver result in successful organ transplantation?

VASCULAR BIOLOGY

Professors Jennifer Gamble and Mathew Vadas

Our blood vessels play an essential role in keeping us healthy. In some cases, however, the growth of new blood vessels can exacerbate diseases such as cancer and cardiovascular disease.



Professor Jennifer Gamble and Professor Mathew Vadas

The principle cell of the blood vessel is the endothelial cell (EC), which in most vessels forms a continuous lining, regulating the passage of nutrients and cells from the blood into the tissues. In adults, blood vessels normally do not proliferate except during the female reproductive cycle. However, in pathologies such as solid tumour growth and cardiovascular diseases, uncontrolled blood vessel growth and dysfunctional endothelial cells are a hallmark of these diseases.

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

Highlights of 2008

- Endothelial progenitor cells (EPC) contribute to vascular repair and are proposed as a source of cells to revascularise grafts. EPCs can be isolated from the bone marrow, the vascular wall and from the peripheral circulation. However, what defines each of these EPC populations, whether they are involved in distinct functions and what regulates their differentiation to mature functional endothelial cells is not understood.

The lipid kinase, sphingosine kinase-1 (SphK-1) is essential for the survival of mature EC and the function is mediated through both an intracellular and extracellular action of its biologically active metabolite sphingosine 1-phosphate. Recently we have shown that SphK-1 is also a key regulator of the rate of differentiation of EPC to mature EC. We propose that regulation of the level of SphK-1 activity may be a useful tool in the production of mature, functional EC. Further work is directed to understanding the mechanism whereby SphK controls the differentiation process.

How will this research impact community health?

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

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

Major projects

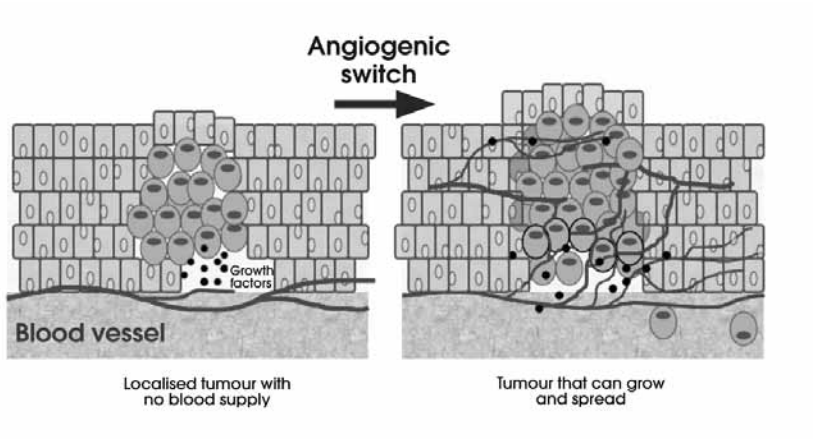
Blood vessels age

One of the critical features of ageing is the increased incidence of cardiovascular disease and cancer. Indeed age is the most significant risk in cardiovascular disease development. We have discovered a gene *senex* (Latin for old age or old man) that causes endothelial cells to age undergoing a process known as senescence.

Expression of senex is essential for EC survival, thus suggesting that senex is a major fulcrum for dictating EC function. We have started a program of research to characterise how this gene is induced (for example, by oxidative stress), how it effects cellular functions (for example on vascular permeability) and the mechanism underlying its regulation.

Role of senescence in tumour growth

Senex is also expressed in epithelial cells and when over-expressed induces senescence similar to that seen in EC. However, senex does not appear to be essential for epithelial cell survival and the mechanism of regulation displays differences to that seen for EC. Dr Matthew Grimshaw has initiated work to delineate the role of senex in breast development and in breast cancer progression.



Blood vessel formation

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

miRNAs are involved in developmental timing, apoptosis, metabolism and cell differentiation. Recently, abnormal patterns of miRNA expression have been found in disease states, including cancer. We have identified a group of miRNAs which are regulated during blood vessel formation and which control two different but major signalling pathways known to be essential for endothelial cell function.

Further work is directed to understanding the impact of these specific miRNAs in normal and tumour associated angiogenesis, particularly in progression from chronic liver cirrhosis to hepatocellular carcinomas.

Differentiation of Endothelial Progenitor Cells (EPC)

Since the maturation of EPCs to EC is a major differentiation process we predict that miRNAs will also serve central regulatory roles. We have initiated a project to identify the suite of miRNAs which control EPC differentiation and to determine whether these are common to the differentiation of EC from the three classes of EPC (bone marrow, peripheral blood and vascular wall).

T CELL BIOLOGY

Professor Barbara Fazekas de St Groth

The immune system is involved in many common chronic illnesses such as cancer, cardiovascular disease, infections, allergies and autoimmune diseases. Our approach is aimed at understanding the role of the immune system in chronic disease and, in particular, how immune imbalances can cause or exacerbate disease. We are particularly interested in how increasingly rapid changes in the environment have increased the negative effects of the immune system on human health.

The T Cell Biology Group aims to understand how different parts of the immune system – CD4 T cells, dendritic cells and regulatory T cells – come together to determine whether an immune response will be beneficial or detrimental.

Beneficial responses include defence against infection, particularly after vaccination, and long term control of cancer. Detrimental responses lead to the chronic inflammation present in cardiovascular and inflammatory bowel disease, asthma, type 1 diabetes, rheumatoid arthritis and multiple sclerosis. These inflammatory diseases are on the increase, and are believed to be due to lifestyle changes that have made the environment too "hygienic" to allow the immune system to function normally.

We are researching how interactions between the environment and the immune system can affect immune function. By comparing our results in mouse models and human studies, we hope to identify the environmental factors that interfere with normal immune function and lead to inflammatory disease. We are also researching methods to enhance long-term immune control of cancer.

Dr Elena Shlovskaya and Professor Barbara Fazekas de St Groth

Highlights of 2008

- Setting up pancreatic islet grafting in a transgenic mouse model and showing that naïve major histocompatibility complex (MHC) II allo-reactive T cells cannot reject MHC mismatched islet grafts without assistance from pre-primed cross-reactive T cells.
- Showing that regulatory T cell fluctuations in patients undergoing chemotherapy for cancer are significantly reduced by co-administration of microtubule inhibitors such as taxanes and vinorelbine.
- Publishing our findings on how subsets of epidermal and dermal dendritic cells migrate in response to adjuvant and showing that epidermal Langerhans cells and dermal dendritic cells induce different responses in the CD4 T cell compartment.
- Using interleukin (IL) 2/anti-IL2 complexes to support expansion of functional regulatory T cells in the spleen of immunodeficient recipients, leading to a reduction in expression of costimulatory molecules by splenic dendritic cells.

How will this research impact community health?

Detrimental immune responses are a major health problem in both the developed and developing world, and are predicted to increase as world standards of living rise. Our research has the potential to arrest this increase by identifying and re-establishing the environmental factors required for normal immune function.

In cancer, our aim is to enhance the ability of the immune system to control tumour growth and spread. Together with advances in cancer drugs, our research has the potential to significantly reduce the death rate from cancer.

Major projects

Human regulatory T cells

Following our landmark identification of CD127 as a key marker to distinguish between human activated versus regulatory T cells (*Journal of Experimental Medicine* 2006 vol 203 pp1693-1700 and 1701-11, together cited over 500 times since publication), we are now using this method to study human regulatory T cells in a number of conditions.

This year we completed a study of patients undergoing chemotherapy for cancer at the Sydney Cancer Centre. In contrast to previous studies of early responses to chemotherapy, we showed that regulatory T cells are not selectively reduced over the course of multiple chemotherapy cycles.

In association with collaborators at Nepean Hospital, we have been defining the immune changes associated with pregnancy and have shown that the balance between regulatory T cells and pro-inflammatory T helper 17 cells is disturbed in pre-eclampsia, the most common serious complication in pregnancy.

We have recently collaborated with the Sydney Childhood Asthma Prevention Study to measure regulatory T cells in blood samples from a cohort of 150 eight-year-olds and to correlate our findings with clinical markers of allergic disease.

Dendritic cell function in mouse models

The interaction between dendritic cells and CD4 T cells is fundamental in setting the course of the immune response. We are using mouse models to identify the functions of individual subtypes of dendritic cells, using the in vivo response of T cell receptor transgenic T cells as a readout. To date we have shown that epidermal Langerhans cells cannot support the generation of effector and memory CD4 T cells. This finding is important for understanding how dendritic cells at epithelial surfaces maintain tolerance to commensal organisms that pose no threat to the animal.

We have previously shown that dendritic cells over-express costimulatory molecules in immunodeficient animals. To test whether the absence of regulatory T cells is specifically responsible for this phenotype, we are transferring purified regulatory T cells into immunodeficient mice, together with a source of IL2 to support their proliferation and function. Our preliminary data indicate that regulatory T cells, but not conventional T cells, are able to reduce costimulatory molecule expression to normal levels.

We have also defined how T cells and dendritic cells interact to cause rejection of foreign grafts. Building on previous work showing that rejection of fully mismatched skin grafts is initiated within the graft itself and is not dependent on migration of dendritic cells from the graft to the host draining lymph node, we have now shown that rejection of pancreatic islet grafts also begins when cross-reactive primed T cells enter directly into the graft, liberating graft-derived antigen that recruits naïve T cells in the draining node, independent of dendritic cell migration.

In our asthma model, we are defining how regulatory T cells control the allergic response. We are currently testing whether regulatory T cell activation in vitro will enhance their ability to suppress lung inflammation in sensitised mice.

STRUCTURAL BIOLOGY

Dr Mika Jormakka

Membrane proteins are a critical target for effective drug design. Drugs work by targeting membrane proteins in specific cells. A helpful analogy is to think of the membrane protein as a multi-dimensional lock and the drug the key to its activation. If you do not know what the inside of the lock looks like, designing a key that fits is a matter of complex trial and error. This very new and exciting area of science is mapping the structure of the 'locks' and has the potential to dramatically reduce the time taken to design new therapies.

The Structural Biology program is focused on structural studies of membrane proteins involved in cellular respiration and transport. Of particular interest are transporters involved in cellular drug extrusion, the proteins that 'pump' drugs out from the cell and therefore reduce the efficiency of cancer chemotherapy and antibiotics.

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

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

Highlights of 2008

- The Structural Biology Group solved the 3D structure of a large membrane protein complex involved in cellular respiration, providing molecular insight to generation of a proton gradient across bacterial and mitochondrial membranes, which is subsequently used to generate cellular energy currency in the form of adenosine triphosphate (ATP).
- We obtained structural information on quinone inhibitor-enzyme complexes, which enables us to understand the generation of reactive oxygen species (causing cellular damage and cancer).
- We determined the structure of the G protein domain (GTPase) of a bacterial metal transporter critical for virulence in many pathogenic organisms. This provided information on G protein coupled membrane processes in general, and the transport mechanism of this protein.

How will this research impact community health?

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

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

Dr Mika Jormakka and Dr Megan Maher

Major projects

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

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

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

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

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

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

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

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

SIGNAL TRANSDUCTION

Associate Professor Pu Xia

It is now believed that most of, if not all, human diseases including cancer, diabetes and heart attack, are attributed to defects in communication between and within the cells of our bodies. By understanding the process of cell communication, (called signal transduction), diseases can be treated in a more effective and safe way.

Signal transduction is a means for cells to perceive and correctly respond to their microenvironment. It is a complex system of communication that governs basic cellular activities and coordinates cell actions enabling our bodies to function properly.

The process of signal transduction often involves multiple ordered sequences of biochemical reactions and forms the communication networks inside the cell. Research in the Signal Transduction program aims to understand how cells utilise specific proteins and lipids as unique languages to communicate between and/or within cells and how the communication is jammed, leading to diseases such as cancer and diabetes. By understanding the molecular basis of diseases, we seek to develop new therapeutic strategies for prevention and treatment of diseases that account for more than a third of all deaths in Australia.

Dr Eileen McGowan and Associate Professor Pu Xia

Highlights of 2008

- Breast cancer remains one of the most common causes of cancer-related death in Australian women. The onset of drug resistance is a major obstacle for successful treatment of this malignant disease. However, the biological basis for the resistance is still poorly understood.

  In 2008, we completed a National Health and Medical Research Council-funded project designed to examine the role of sphingosine kinase (SphK) in drug resistance. We found that breast cancer cells that have high levels of this protein had a poor response to the anti-cancer drug tamoxifen. Remarkably, inhibition of this enzyme dramatically restored the drug sensitivity leading to cancer cell death. Our work suggests that inhibition of SphK may offer a new strategy to overcome drug resistance and improve the outcomes of breast cancer treatment.

- Due to the current and growing trends of obesity and type 2 diabetes throughout the community, insulin resistance represents a key metabolic determinant underlying the development of cardiovascular diseases, such as heart attack and stroke.

  In 2008, we initiated a new project seeking to identify the molecular mechanisms underlying insulin resistance in blood vessel walls. We aim to specifically examine the cell signal communications under insulin resistant status, and find new ways to prevent and treat cardiovascular diseases.

Major projects

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

Our current research projects include:

- Since our first report demonstrating a tumourigenic effect of SphK, its study has been of greater interest in cancer research. A growing body of evidence suggests that SphK plays a critical role in the development of various human cancers, such as breast, lung and prostate. We have recently found that SphK is able to promote cell growth in breast cancer, helping the cells escape from death after treatment with anti-cancer drugs. We now seek to further understand the mechanisms of how cancer cells use SphK for communication to escape death and whether blocking this signalling pathway could induce killing of cancer cells.

- Atherosclerotic cardiovascular diseases including diabetic complications are now recognised as inflammatory diseases. This recognition highlights a critical role for the endothelium which normally forms a non-thrombogenic surface and selective permeability barrier for the maintenance of normal homeostasis, in particular, the so-called anti-inflammatory phenotype of the vessel wall. In various disease states (e.g. diabetes), multiple or individual risk factors damage this phenotype resulting in dramatic changes in the functional characteristics of the endothelium, rendering it adhesive and inflamed. We have found that this process of damage is mediated by the SphK signalling pathway. We are investigating how SphK mediates vascular inflammation, especially under obese, insulin resistant and diabetic pathologies. At the completion of this project, we hope to provide a potential drug target for intervention to halt or slow down the progression of obesity or diabetes-associated cardiovascular diseases.

- Diabetes is now a serious global health problem. Currently, more than one million Australians suffer from diabetes and this number is expected to double by 2015. Dysfunction or destruction of pancreatic beta-cells caused by apoptosis, programmed cell death (cell suicide), is a common pathogenic factor for both type 1 and type 2 diabetes. Thus, attempting to protect beta-cells against death and rescue their insulin secretory function is emerging as a strategy for the management of diabetes. We aim to examine how pancreatic beta-cells communicate for their survival especially under cellular stress, such as high levels of blood sugar. We also seek to understand the interrelationship between molecular mechanisms underlying defects in beta-cell survival and insulin secretion. This study will not only reveal a novel signalling pathway in the regulation of beta-cell function and survival, but may also provide a new drug target for treatment of diabetes.

How will this research impact community health?

Currently most therapeutics, especially for cancer, are often restricted by either serious side effects or development of resistance to the drugs.

More recently, a new class of more effective drugs have emerged that target key sites of cellular communication networks, namely signal transduction inhibitors. Such drugs have exhibited potent efficiency in treatment of cancer without damages on normal cells.

Our recent work has uncovered a new protein, sphingosine kinase, that plays a pivotal role in cell signal transduction and contributes to the development of cancer. We aim to identify whether this protein could serve as an ideal drug target for novel signal transduction inhibitors on the treatment of cancer. This translational research work from basic science to drug development will help to provide a more effective and safe way for cancer treatment and prevention.

MYCOBACTERIAL

Professor Warwick Britton

Tuberculosis (TB) represents a global health burden of staggering proportions. More than two billion people, or one third of the world's population, are infected with the bacteria responsible.

Dr Nicholas West, Dr Bernadette Saunders and Professor Warwick Britton

A number of major obstacles exist toward controlling TB. The current vaccine Bacille Calmette-Guerin (BCG), developed almost 90 years ago, is ineffective and does not control the spread of the disease.

Another challenge is the rapid emergence of *M. tuberculosis* strains resistant to many of the antibiotics used to treat TB. Alarmingly some strains are resistant to all known treatments.

The Mycobacterial Group aims to contribute to the control of TB through the development of more effective vaccines and the identification of possible targets for new drugs against *M. tuberculosis* infection.

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

Highlights of 2008

The Mycobacterial Group had many highlights throughout 2008, including:

- The initiation of the TB component of the Infection and Immunity Genetic Consortium with the screening of genetically modified mice for resistance to *M. tuberculosis* and the establishment of one new line of susceptible mice.
- The discovery that rBCG expressing the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) is much more protective against pulmonary TB when given intranasally rather than subcutaneously. This was associated with a sustained increase in T cell responses. We are collaborating on the development of a vaccine based on this principle for use in humans.

- We expanded our studies on a special group of T cells secreting the cytokine, IL 17, which are induced by BCG immunisation of mice lacking the cytokine IL12 or interferon-gamma, and showed these could protect against TB infection.
- Anthony Ryan and Jonathan Nambiar found that the BCG vaccine can induce CD8 T cells which are protective against TB, but BCG is less efficient than natural *M. tuberculosis* infection because less antigen is delivered by BCG to the draining lymph nodes.
- In a new collaboration with Professor D Cook and Dr A Dinoram, University of Sydney, we have found that a cell wall component of virulent *M. tuberculosis* can regulate electrolyte and fluid transport across respiratory epithelial cells. Jason Han received the University Medal in Physiology for these studies.
- Anthony Ryan and Teresa Wozniak completed PhDs in Immunology and Sultan Mahmuda was awarded MSc (Med) for her work on the MPT83 lipoprotein.
- Frank Kao has constructed a new viral vaccine and cytokine adjuvant to test for their protective effects against tuberculosis. Frank received the GlaxoSmithKline award for a postgraduate student to support his studies in 2009.
- Dr Jamie Triccas and Professor Britton received National Health and Medical Research Council (NHMRC) funding to continue their work on memory T cell responses to new anti-tuberculosis vaccines.
- Professor Britton visited the National Tuberculosis Control Program in Hanoi, Vietnam, to participate in an International Workshop to review the National Prevalence Survey of Tuberculosis in Vietnam, and to establish an ongoing collaborative research program with the National Tuberculosis Program of Vietnam.
- Professor Britton was invited to speak about the work of the Mycobacterial Program at four international meetings.

How will this research impact community health?

Eight million new cases of tuberculosis are diagnosed each year. The ultimate goal of our research is to eliminate TB as a human disease.

With the emergence of new drug resistant strains and the increased spread of HIV, we need both a more protective vaccine and new therapies to aid eradication of existing infections.

Our research is directed at understanding the inflammatory response generated to TB infection, the cytokines that direct this response and the genes that are essential to control this infection. Understanding how the inflammatory response to TB infection is generated and maintained will hopefully lead to new therapies to modulate treatment against TB infection and potentially against other inflammatory diseases such as arthritis and Crohns disease.

A large number of tuberculosis cases result from "reactivation" of the bacterium from a "dormant" state, usually when the individual's immune system, for some reason, is suppressed.

We need to develop a more effective vaccine to protect uninfected individuals but also new, effective and affordable drugs to kill the bacteria in its dormant phase before it can reactivate.

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

Major projects

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

We are also exploring how the bacterium responds to infection in the host by changing the genes it expresses after it invades host cells, and the function of selected proteins from *M. tuberculosis* and *M. leprae*.

In addition, we are studying how *Mycobacterium leprae*, the cause of leprosy in humans, changes cellular gene expression in Schwann cells, the host cell which coats peripheral nerves. Leprosy is one of the most common causes of peripheral nerve damage.

HOST RESPONSE TO TUBERCULOSIS

Dr Bernadette Saunders

Our own immune response to TB disease causes damaging inflammation in the lungs. Understanding how this process is regulated is essential for the development of new therapies to treat the infection and moderate inflammation. Our group is examining the factors that control protective immunity to TB and genetic aspects that influence this response.

We are working to uncover new genes that regulate resistance or susceptibility to TB infection and determine how these genes regulate these processes. We are also working to understand the chemical messengers (called cytokines) that are important in controlling inflammation. We are determining the pattern of cytokine expression and how this controls subsequent inflammation. We hope that by expressing defined cytokines that we can increase resistance to TB infection.

Highlights of 2008

- We established the TB screen for the Infection and Immunity Genetic Consortium by screening 85 pedigrees of N-ethyl-N-nitrosourea-modified mice, identifying eight pedigrees with changes in susceptibility to TB, many of which we are pursuing, and breeding one line of highly susceptible mice for genetic mapping.
- As a part of our longstanding collaboration with the National Hansen's Disease program at Baton Rouge, USA, we have proven that the cytokines Lymphotoxin-α and tumour necrosis factor (TNF) have essential but distinct roles in the cellular control of experimental leprosy infection.
- Dr Saunders and Professor Britton received NHMRC funding to continue their work on the role of TNF in controlling TB infection.

Major projects

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

Macrophages are the primary cell in which TB infection resides. These are also the cells responsible for killing the bacteria. We are using a number of gene deficient mice to examine the role of the macrophage in control of TB infection. We are doing this by over-expressing macrophage effector molecules to try to enhance their killing capabilities. Further, we are using macrophages with specific genes deleted to determine the function of these genes in resistance to TB infection. It is hoped that this research may lead to the discovery of alternative therapies to treat TB infection.

At a genetic level, we are identifying host genes that influence resistance and susceptibility to TB. We are screening mutant mice for novel genes that control immunity to TB as part of a Wellcome Trust-funded project with collaborators at Australian National University (ANU) in Canberra, Oxford and Paris. It is hoped that this exciting project will uncover new factors that regulate resistance and susceptibility to TB.

VACCINE DEVELOPMENT AND PATHOGENESIS

Dr Nicholas West

Ultimately we hope to prevent the spread of TB through vaccination and to improve the outcome for those already infected.

To achieve these two goals we must first understand the microbe and how it causes disease. This is why research within the group is aimed at identifying the genetic repertoire possessed by the bacterium, which is essential for its replication within the host and causation of disease. Additionally, we are concerned how the bacterium is able to survive within the host for the life of the host, usually without causing any symptoms at all.

With this information we will be better placed to make informed decisions regarding drug development to treat both acute and chronic infections. Furthermore, knowing what pathways are essential to the bacterium may also provide new vaccine candidates.

Highlights of 2008

- Importantly, an *M. tuberculosis* mutant library has been established, comprising of thousands of individual, single gene mutants. This library is a fantastic resource and a prerequisite for projects of genetic discovery.
- We have defined the different enzyme functions of members of the *M. tuberculosis* cutinase-like protein (Clp) family, and identified the active site of one of these enzymes which is shared with *M. leprae*. Further, we have constructed fusion proteins with some Clp proteins and discovered that they are protective against TB infection.
- On the personnel front the group was strengthened by the addition of another PhD student, a further Research Assistant and an international Research Officer.

Major projects

Our focus is to investigate processes of pathogenesis with the outcome being improved vaccines and treatments for tuberculosis. We are searching for and identifying potential vaccine candidate proteins of *M. tuberculosis*. With these newly identified candidate vaccine components we are investigating novel ways to deliver them to the host.

Another active research project includes the characterisation of a family of *M. tuberculosis* enzymes which are secreted from the bacterium. At least one of these proteins is believed to be essential to the survival of the organism.

In addition to our vaccine work we are committed to understanding the disease process, from a bacterial prospective. We endeavour to identify the gene set required to: 1. Colonise the lung, 2. Spread to distant organs, and 3. Establish a life-long chronic infection. Research staff and students are actively pursuing programs in each of these broad topic areas.

DNA REPAIR

Dr Chris Jolly

Each year, more than 100,000 Australians are diagnosed with cancer. A break down in DNA repair can lead to cancer developing. An understanding of DNA repair pathways is essential to a complete understanding of the causes of cancer, with the potential to prevent early stage cancer from progressing.

Dr Chris Jolly and PhD scholar George Sharbeen

How will your research impact community health?

Comprehension of DNA repair pathways will underpin a full understanding of the causes of cancer, because damage to DNA contributes to most cancers. In the future it may be possible to prevent early stage cancers from progressing by identifying the DNA repair defect that has initiated the cancer in the first place.

New tissue growth and tissue replacement involves controlled cell division and proliferation. As an essential part of cell division, DNA inside the nucleus has to be replicated perfectly. This is because nuclear DNA encodes information essential for cell function. However, genes in the DNA are continuously damaged by irradiation, chemicals and even replication mistakes.

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

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

Highlights of 2008

- We developed a new "fast-track" experimental model that allows us to silence or otherwise manipulate DNA repair pathways in normal proliferating cells in vivo. This model reduces experimental time from years to a few months.
- We were invited by the world-leading *Journal of Experimental Medicine* to write a review on the relationship between antibody mutation and cancer.

Major projects

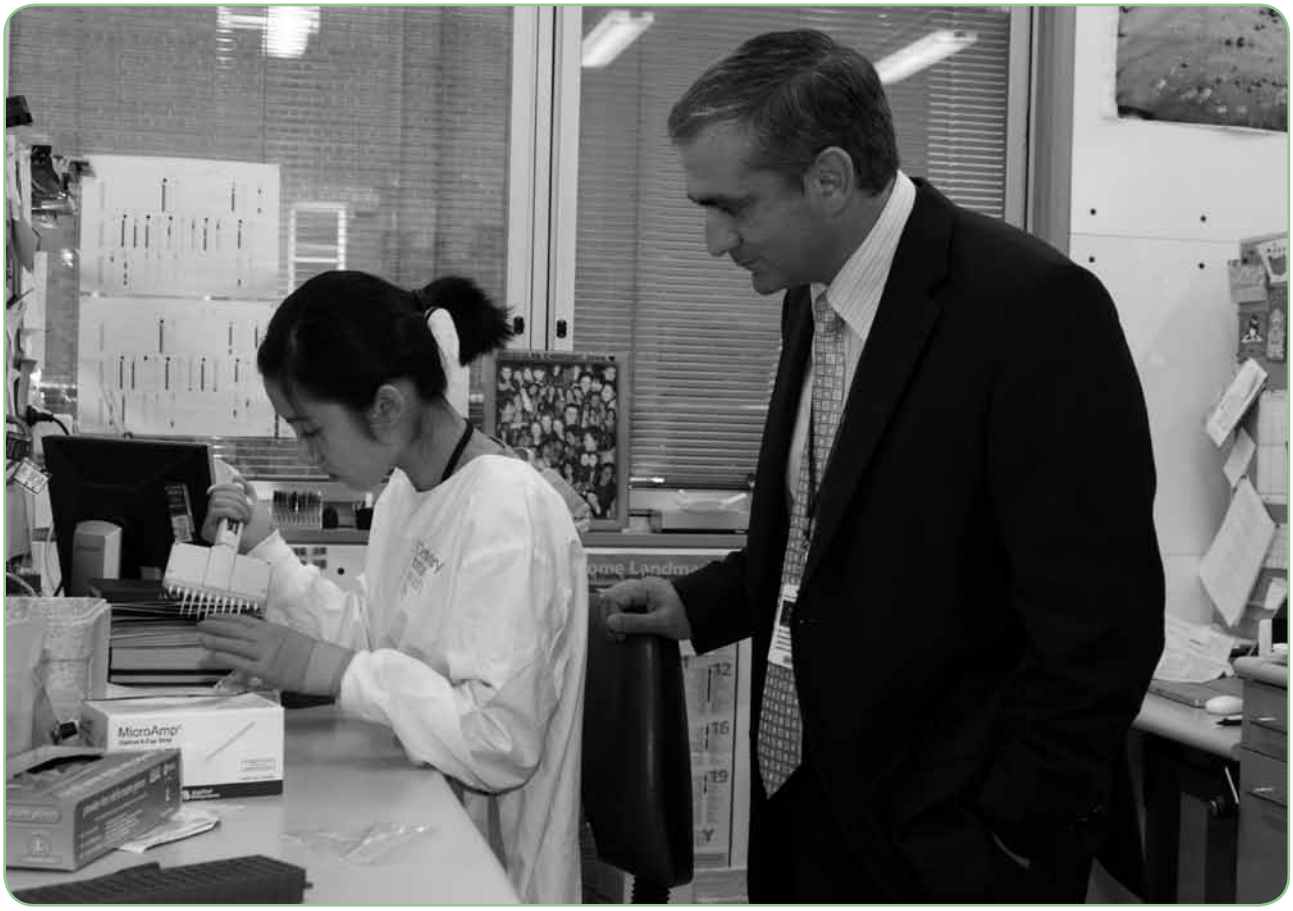
The DNA Repair Group use the mutation of antibody genes in B cells (white blood cells that secrete antibodies) as a physiologically-relevant model of DNA damage. Antibody gene mutation is a natural process of extremely accelerated gene mutation (i.e. hypermutation) that occurs in lymph nodes during immune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

MOLECULAR CARDIOLOGY

Professor Christopher Semsarian

One of the great benefits of identifying potentially fatal genetic diseases in families is the opportunity for that finding to save lives for generations into the future.

Cardiovascular disease affects one in five Australians and one out of two families. However, many of the genetic causes of heart disease remain unknown.



PhD scholar Christine Chiu with Professor Christopher Semsarian

Understanding the basic biology of heart muscle function and defining new ways to treat heart muscle disorders may lead to significant therapeutic benefits for cardiovascular disorders such as cardiomyopathies, heart rhythm disorders and coronary artery disease.

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

Highlights of 2008

- A major breakthrough in understanding the role of multiple gene faults in patients with cardiomyopathy and heart failure was made. A novel animal model of disease was established and insights into how heart failure develops were gained. This research was published in the highest ranking cardiovascular journal in the world, *Circulation*.
- A National Genetic Heart Disease Registry in Australia was established

in 2008. This is truly a world first, and will enable families from around Australia to be enrolled in this registry. The registry will be invaluable in understanding the prevalence of genetic heart diseases in our community, improving patient education, and will facilitate research studies to be conducted in key patient groups.

- Expansion of our research both into remote areas, such as our research into inherited heart disease in an Indigenous population in Kempsey NSW, as well as initial links to understanding the clinical and genetic basis of sudden death in South East Asia, specifically in Hanoi, Vietnam.

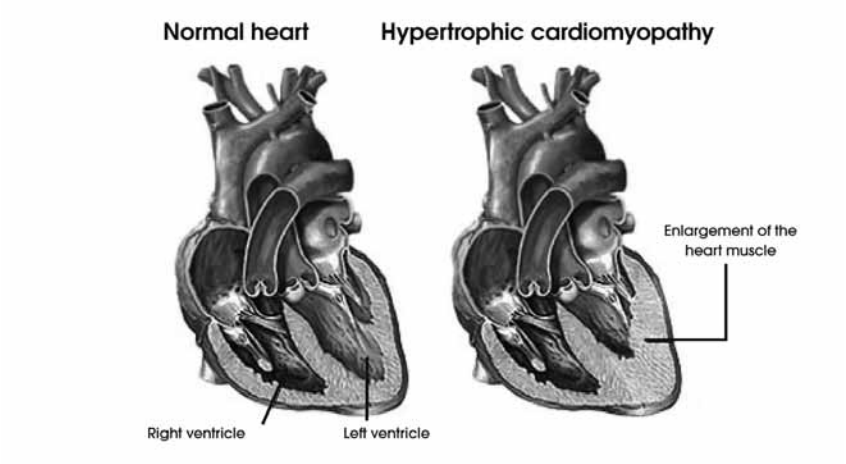
Major projects

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

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

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

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



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

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

Hypertrophic cardiomyopathy is characterised by marked thickening of the heart muscle and occurs in approximately one in 500 people, making it the most common genetic heart disorder known. Our research program has seen and collected clinical information and DNA in over 400 hypertrophic cardiomyopathy families to enable genetic studies to be performed. To complement the studies in humans, our laboratory has developed a number of unique transgenic models of hypertrophic cardiomyopathy, as well as cell culture models to evaluate the cellular effects of specific gene mutations. These models will likely provide the keys to unlock the mysteries of genetic heart diseases and their complications, including heart failure and sudden death.

How will this research impact community health?

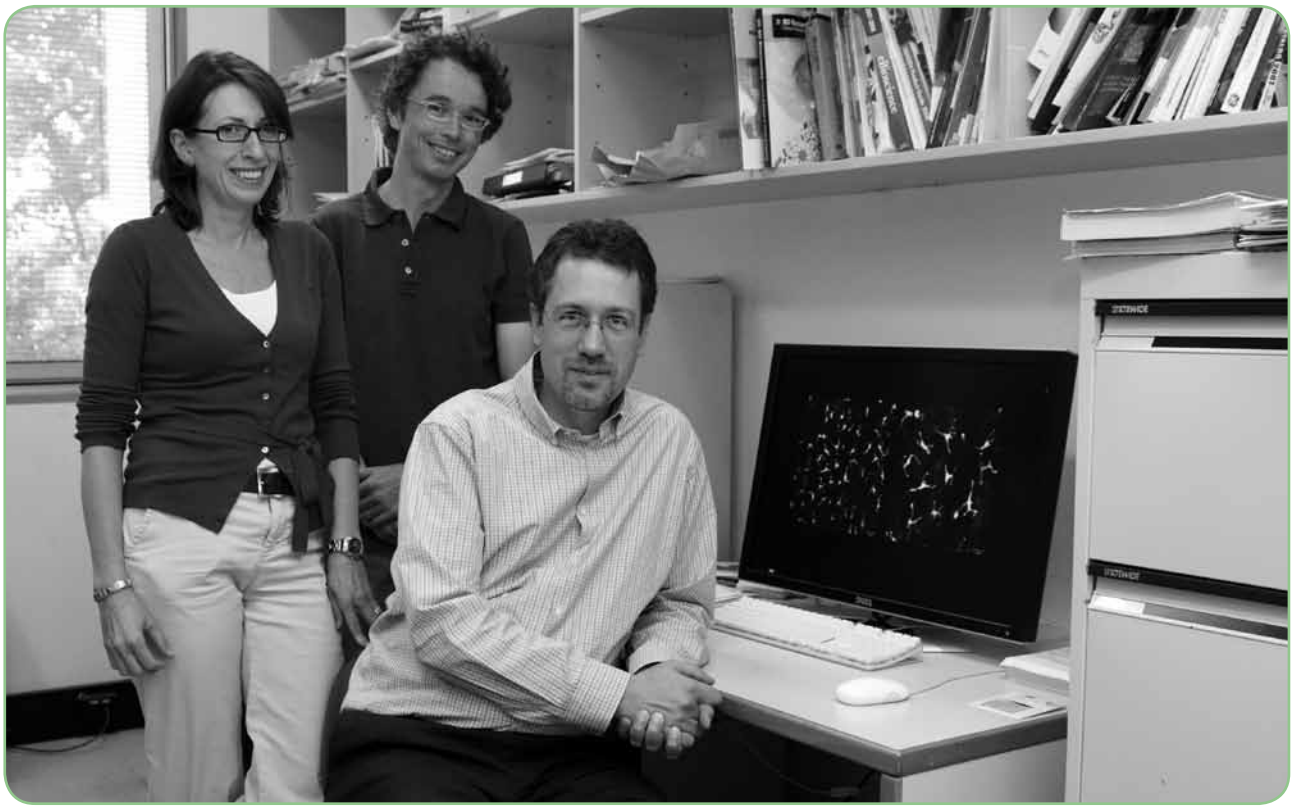
Over the next five years, our research will lead to improved diagnosis of patients with genetic heart disease. Since diagnoses will be based on detection of abnormal genes, this can be done earlier in life, providing a greater therapeutic window for initiation of treatment and prevention strategies.

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

IMMUNE IMAGING

Professor Wolfgang Weninger

The Immune Imaging program studies basic questions related to cancer and infectious diseases. We are using cutting-edge microscopy techniques to determine how the immune system fights tumours and microbes. We are further interested in determining the role of cancer stem cells in the development of melanoma and the effects of targeted therapies on these cells in vivo.



Dr Lois Cavanagh, Dr Nikolas Haass and Professor Wolfgang Weninger

The principle approach of the Immune Imaging program is the use of a state-of-the-art imaging technique called multi-photon microscopy. This technology allows for visualisation of fluorescently-tagged cells and molecules within the context of living tissues. We can now study the dynamics of cell movements and interactions at a level of resolution that has not been reached before. Using this approach, the laboratory is investigating fundamental questions related to skin and pulmonary infections as well as cutaneous tumours.

One interest is the visualisation of white blood cell (leukocyte) behaviour within living tissues. Leukocytes are responsible for the recognition and destruction of invading microbes, such as viruses, bacteria and parasites, as well as tumour cells. Multi-photon microscopy enables us to study how microbes and tumour cells are detected and destroyed by leukocytes in real time in the context of intact tissues.

A second interest relates to the pathogenesis of melanoma, the most aggressive and often therapy-resistant form of skin cancer with a particularly high incidence in Australia. The resistance of metastatic melanoma to conventional chemotherapy may be explained by the existence of a recently discovered multi-drug resistant population of cells, called melanoma stem cells (MSC). Our aim is to use multi-photon microscopy in order to characterise the biology of MSC both in three-dimensional melanoma models in vitro as well as in mouse models in vivo.

Highlights of 2008

- We have visualised, for the first time, how an innate immune cell subset responds to an encounter with a pathogen in real time in the context of intact tissues in vivo. This study demonstrates that migratory skin dendritic cells act as rapid sensors of Leishmania parasites through the elaboration of highly motile cellular processes capable of tracking and capturing parasites (Ng et al., *PLoS Path*, 2008).
- We have defined a novel immunologic checkpoint in the anti-tumour immune responses. Thus, we have found that CD44, a receptor for extracellular matrix proteins, is a critical regulator of intratumoural T cell migration. In its absence, T cells are inhibited in interstitial navigation resulting in impaired anti-tumour immunity (Mrass et al., *Immunity,* 2008).
- A ground-breaking paper on targeted therapy for metastatic melanoma was published (Haass et al., *Clin Cancer Res,* 2008). This paper is the basis for randomised phase II trials for patients suffering from metastatic melanoma.

Major projects

Role of dendritic cells in skin infections

Dendritic cells, including those in the skin, act as sentinels for intruding pathogens. We have recently developed an intravital multi-photon microscopy model that allows us to directly visualise these cells in intact skin. Using a Leishmania parasite and a Herpes simplex virus model, we are investigating how dendritic cells behave during the early phase of immune responses, and how pathogens are recognised and transported from the skin to draining lymph nodes. These studies have implications for the development of vaccines against infections.

Interplay of innate and adaptive immune cells during influenza virus infection

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

We are making use of intravital multi-photon microscopy to study how innate immune cell subsets induce the activation of antigen specific T cells in draining lymph nodes of the lung during infection. In-depth insight into this process is not only important for increasing our knowledge of regulatory pathways of anti-viral immunity, but may, in the long-term, lead to the development of improved vaccine strategies against this important disease.

Mechanisms of T cell migration and interactions in tumours

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

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

Our experiments will provide mechanistic insights into the events leading to tumour cell destruction or tumour immune evasion. Therefore, these studies have important implications for the optimisation of immuno-therapeutic strategies that aim to target cancer.

Role of melanoma stem cells in melanomagenesis

We are testing the hypothesis that melanomas recur after chemotherapy because MSC are chemo-resistant and can reinitiate tumour growth.

The central idea of our current work is that both MSC and melanoma tumour cells need to be targeted simultaneously to achieve complete remission of melanoma. We have developed three-dimensional melanoma culture models, which recreate the correct interactions of the melanoma with its tumour microenvironment and thus can predict the effects of drugs on the tumour in a much better way than conventional two-dimensional cell culture. These models are used in combination with in vivo mouse models and multi-photon microscopy to study the interactions of MSC and melanoma cells with their microenvironment.

We are further assessing the effects of chemotherapeutic drugs on these cells. From these experiments we hope to develop novel therapeutic concepts for this devastating disease.

How will this research impact community health?

Cancer and infectious diseases are the leading causes of death in the industrialised world and in developing countries. We still have an incomplete understanding of the host response against these diseases. In addition, there is great need for innovative therapeutic and vaccination approaches against these diseases.

Our novel imaging approach will provide a new angle for studying basic questions related to the interactions of the immune system with microbes and cancer cells. We will further be able to test the effects of targeted therapies directly within tissues. This will give us insight about their mode of action, and will allow for optimising therapeutic strategies.

GENE AND STEM CELL THERAPY

Professor John Rasko

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

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

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

Highlights of 2008

The major highlight of 2008 has been the publication of the genetic cause of the amino acid transport disease, iminoglycinuria, in the prestigious *Journal of Clinical Investigation.* This complex disease is caused by a combination of genes and the results are the culmination of three years work by the Gene and Stem Cell Therapy laboratory, in collaboration with researchers at the Australian National University.

Other highlights include:

- Publication of the history of regenerative medicine from Greek myth to modern science in *Annals of Internal Medicine.*
- Determining the optimal cytokine combinations involved in mobilisation of hemopoietic progenitor cells from bone marrow, which was published in *Stem Cells.*

How will this research impact community health?

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

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

Prostate cancer is the most prevalent cancer in Australian males, affecting 13,000 men each year. The current treatments are not generally curative and new alternatives are needed. We will examine the role of protein pumps that control the amount of nutrients taken into and out of cancer cells. One particular protein pump is dramatically increased in prostate cancer and may be responsible for increasing nutrients and enhancing survival of the cancer cells. Understanding its role may provide clues for dietary or drug therapy design to 'starve the cancer' that are entirely novel.

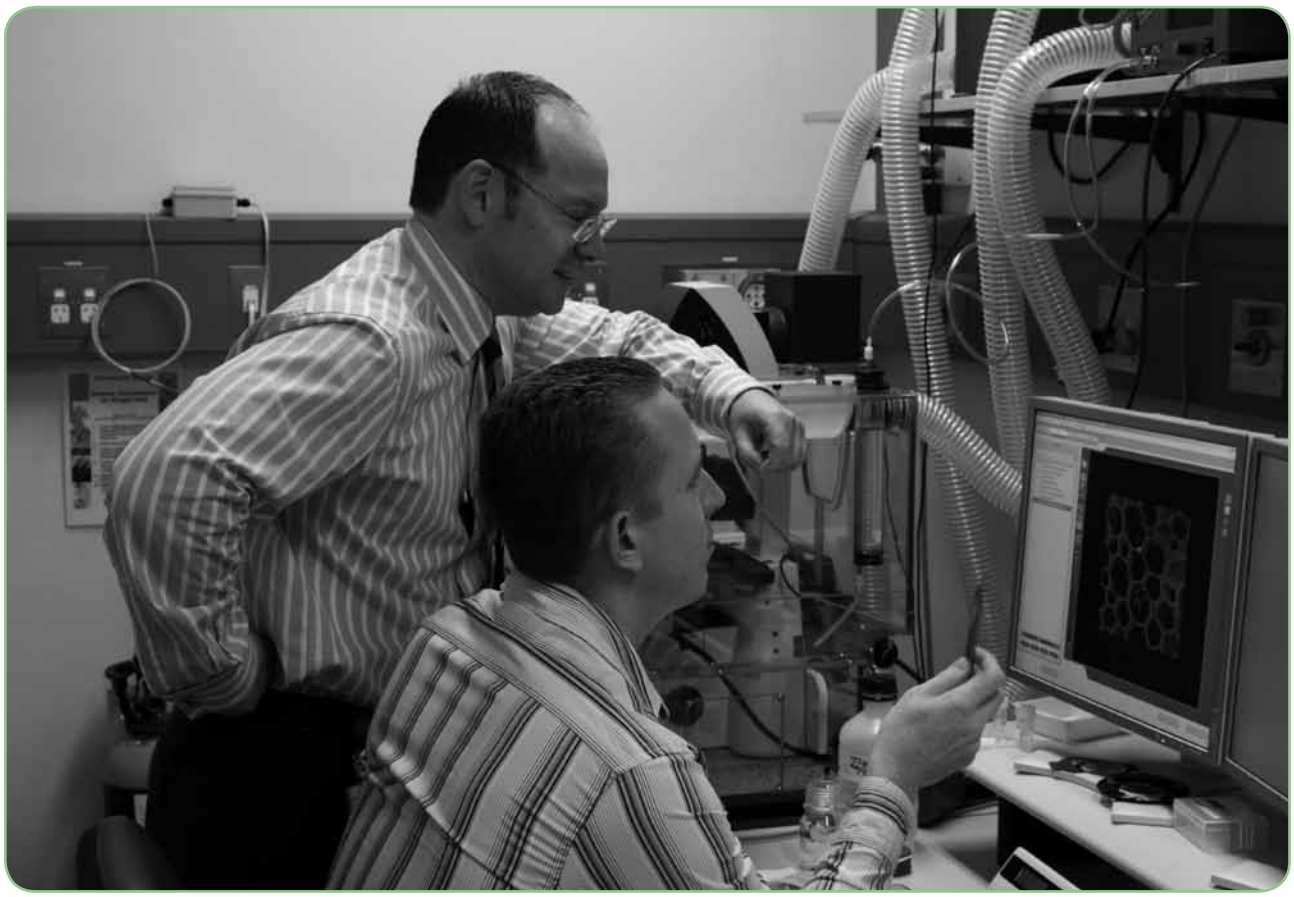
Major projects

Stem cells and gene delivery

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

HSCs have the capacity to divide to produce countless billions of progeny cells throughout a lifetime and it is these progeny that form the basis of our immune system. We have established the severe combined immunodeficiency (SCID) repopulating cell (SRC) assay using nonobese diabetic(NOD)/SCID mice to evaluate different mobilisation regimens and to investigate the long-term re-populating ability of different HSC subsets, including HSCs purified by the Hoescht side population method.

We have developed protocols for differentiating non-human primate mesenchymal progenitors into cells



Professor John Rasko and Dr Jeff Holst

of adipogenic, chondrocytic and osteogenic origin.

In both HSCs and mesenchymal progenitors we are working to optimise gene transfer using retroviral and adeno-associated vectors. We have achieved the successful introduction of gene modified cells into small animal models to study therapies for diseases of blood and muscle.

Mechanisms of genetic disease

For the past decade, the group has collaborated with the group of Victor Lobanenkov at the National Institutes of Health (Washington DC, USA), examining the role of the tumour suppressor gene CTCF and its related cancer/testis gene brother of regulator imprinted sites (BORIS). BORIS is normally only expressed in the testis, however it is over-expressed in many different types of tumours. During the last two years, we have shown that CTCF and BORIS share a number of protein interactors, whilst also having unique binding proteins. We have also shown for the first time that BORIS, which was initially thought to be an oncogene, is actually a tumour suppressor gene.

Hartnup disorder is an inborn error of renal and gastrointestinal neutral aminoacid transport. In 2004, we described a breakthrough in this field by cloning and characterising the gene responsible for Hartnup disease, SLC6A19. During the last three years we have studied the genetic cause of other aminoacid transport diseases including imminoglycinuria, hyperglycinuria and dicarboxylic aminoaciduria, resulting in the *Journal of Clinical Investigation* paper in 2008.

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

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

ORIGINS OF CANCER

Dr Jeff Holst

The importance of lifestyle and environmental factors on development of disease has long been a focus of biomedical research and media attention. Diet in particular is implicated in many different diseases, however measuring the effects of nutrition on disease has been limited. It is known that the expression of specific amino acid transporters is increased in many primary cancers, and indeed there is growing literature that obesity can be linked with diabetes, cardiovascular disease and cancer.

Tumours require a constant supply of nutrients in order to maintain their growth advantage and it has been shown that cancer cells consume more nutrients than normal cells. Scientists are now discussing the "tumour metabolome", the characterisation of which will provide increased understanding of how the metabolic requirements of tumours may lead to new treatments for cancer.

Over the last decade, drugs designed to block blood vessel formation have provided an entirely new string to the cancer treatment bow. There are over 350 different nutrient transporters, which can transport a variety of substrates, including amino acids. In this project we propose an exciting and novel extension derived from these observations: just like anti-angiogenic therapies, a new approach to anticancer therapeutics may include nutrient uptake inhibitors.

Highlights of 2008

- The Prostate Cancer Foundation of Australia awarded a four year $475,000 grant to investigate the role of amino acid transplant in prostate cancer. This has enabled Dr Kevin Wang, a post doctoral scientist in the laboratory, to begin work on this project in 2008.
- Showing the link between phosphatase and tensin homolog (PTEN) mutation/deletion and amino acid transport in prostate cancer cell lines.
- A personal invitation to Dr Holst to attend the PacRim Breast and Prostate Cancer Conference in Whistler Canada, August 2008.
- Dr Jeff Holst was awarded the prestigious Research Australia Discovery Award in November 2008.

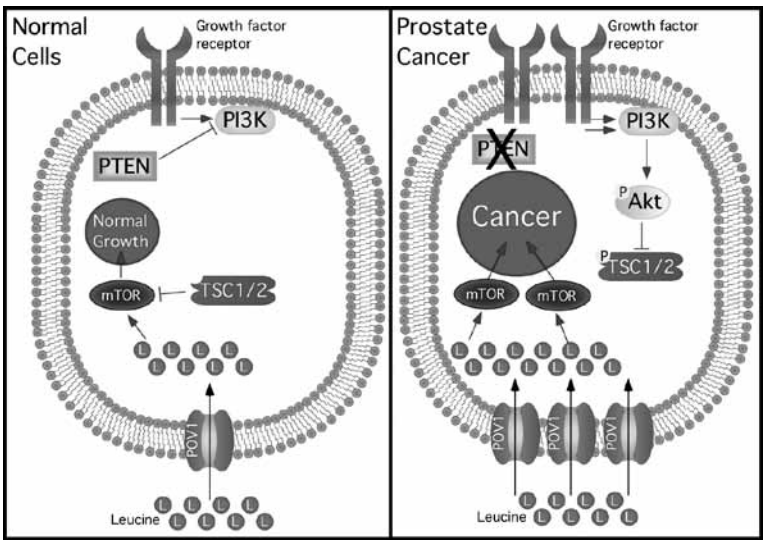
Major projects

The role of amino acid transport in prostate cancer

The 1-phosphatidylinositol 3-kinase (PI3K), PTEN, V-akt murine thymoma viral oncogene homolog (Akt) pathway is frequently altered in prostate cancer. Up and down-regulation of many members of this pathway, including mammalian target of rapamycin (mTOR), neutral endopeptidase and PTEN, together or separately, are found in most prostate cancers.

Amino acids such as leucine have been shown to activate mTOR, thereby contributing to uncontrolled proliferation of prostate cancer cells. The host laboratory's international track record in amino acid regulation will be applied to dissect how transporters including leucine transporters, may promote prostate cancer.

This will be studied using prostate cancer cell lines and a prostate cancer mouse model crossed with a new knockout mouse model. Analysis of the genes involved in the onset and progression of prostate cancer will be determined in these models. POV1 transporter is a potential target for therapeutic intervention, and understanding this complex network may provide new insights into the effect of diet (particularly red meats and dairy which are high in leucine) on the development and progression of prostate cancer.



Schematic showing how the transport of nutrients into cells may contribute to the signalling pathways involved in prostate cancer.

LIVER IMMUNOBIOLOGY

Professor Geoffrey McCaughan

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

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

The understanding of how inflammatory, immunological and fibrosis pathways contribute and interact in causing liver damage and cancer is the overall common theme to the program.

The primary liver cell, the hepatocyte, is the major target in liver disease. The molecular and cellular mechanisms surrounding the response of this cell is common across our work. How this cell interacts with immune cells and fibrotic pathways are of particular interest and focus.

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

The distinct research groups are:

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

Associate Professor Mark Gorrell, Dr Fiona Warner, Dr Patrick Bertolino, Professor Geoffrey McCaughan, Dr Nicholas Shackel and Dr David Bowen.

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

Alcoholic liver disease (ALD) is a multi-stage and multi-factorial disease that is established on long term alcohol misuse. Of more than 60 types of diseases and injury associated with alcohol, ALD remains the most prominent, second only to alcohol dependence. It is a major health concern contributing 50% to the total liver disease burden.

Despite the recognition of alcohol as an important cause of liver disease, treatment remains unsatisfactory. Once established, there is currently no specific treatment for ALD that consistently improves the course of this disease, therefore new therapies are needed.

The current collaboration revolves around two main areas - molecular targets in alcohol induced liver injury and genetic risk factors for ALD. Molecular targets include Osteopontin (Opn) and the plasmin/fibrinolytic pathway. We have shown that Osteopontin isoforms are involved in cell growth, migration and tumour development.

Current studies are investigating mechanisms of Opn action by using Opn knockouts, Opn si RNA, Opn-mediated signalling and interaction with receptors (FRET) in collaboration with colleagues at the University of Sydney (F Braet), University of Adelaide (M Beard) and National Centre for Cell Science, India (G Kundu).

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

The second main area has been driven by Dr Seth who has recently established an international consortium to establish a genome wide association study for alcoholic liver disease. This group plans to identify genetic risk factors for ALD in a genome wide association study. This is to be the first study of its kind in ALD and has attracted well known alcohol researchers from USA, UK, Germany, France, Switzerland and Australia.

Dr Seth and Professor Haber have been successful in obtaining funding from the Alcohol and Health Research Grants Scheme for a pilot project as the Australian arm of the large consortium study. This feasibility study focuses on establishing a clinically characterised Australian cohort of patients with alcohol dependence with and without alcoholic cirrhosis.

How will this research impact community health?

In animal models, liver transplants are spontaneously accepted. Understanding why liver transplants are not rejected like other solid organ transplants would help us to design new strategies to prevent rejection of liver transplants in the clinic and significantly improve the outcome of liver transplantation.

Additionally, this may shed light on possible ways to use this property of the liver to induce acceptance of other solid organs that are normally rejected.

Our focus on understanding the pathogenesis of liver injury will enable us to develop therapeutic strategies to stop the progression of liver injury and the development of liver cancer (the fourth most common human malignancy).

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

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

Furthermore, we wish to increase understanding of liver fibrosis progression and the biological functions of the six enzymes of the prolyl oligopeptidase gene family. This has the potential to improve therapy for chronic liver disease sufferers, whether their illness is hepatitis B or C, autoimmune disease or fatty liver disease. These molecules also are likely to play a role in the pathogenesis of diabetes and are already therapeutic targets in this disease.

LIVER IMMUNOLOGY

Dr Patrick Bertolino and Dr David Bowen

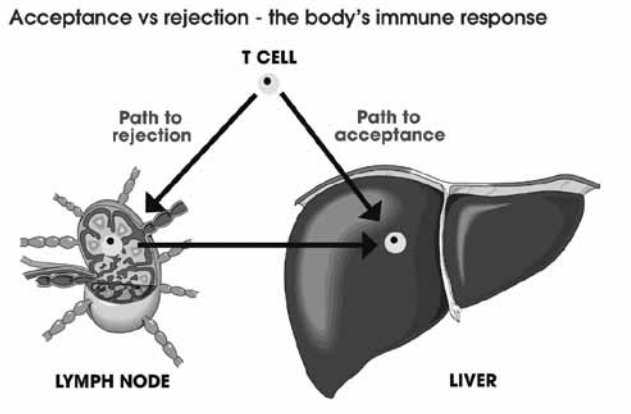
The research of the Liver Immunology Group aims to understand how intrahepatic immunity is regulated, and why immune responses within the liver are biased towards the induction of tolerance.

Understanding the mechanisms of intrahepatic immunity is critical in two important clinical areas: transplantation and infection by viruses that predominantly infect the liver, such as the hepatitis B (HBV) and hepatitis C (HCV) viruses. Preventing immunity in the liver would improve the outcome of liver and other solid organ transplantation: in contrast to other solid organs, liver transplants are spontaneously accepted through unknown mechanisms.

Understanding how this tolerance is established would help us to develop new strategies to prevent rejection of other solid organs. In contrast, chronic infection with HBV and HCV are associated with complications that are extremely costly to the community. Enhancing immunity to these viruses would allow clearance of these infections.

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

Our results have demonstrated that due to its unique structure, the liver can retain and activate naïve cytotoxic (CD8+) T cells, therefore acting as a site of primary activation. This finding contradicts the generally accepted view that primary T cell responses can only be initiated in lymph nodes (LN). These results suggest that the site of initial activation of T cells is a critical determinant of the outcome of immune responses, with activation within the liver and LN programming T cells towards different fates: unlike T cells activated in LN, which become effective cytotoxic T lymphocytes, most liver-activated T cells become poor effectors and die rapidly, leading to tolerance. It is the first demonstration that a non-lymphoid organ can be the site of primary activation, a seminal finding with important implications for liver transplantation and HCV research.



In addition to our work in transgenic mouse models, we are undertaking human studies in individuals undergoing liver transplantation for diseases related to HCV infection. Liver transplantation for HCV infection is associated with universal re-infection of the transplanted organ, with variable outcomes. However, our understanding of what determines the course of HCV-related liver disease post-liver transplantation remains relatively limited. By studying the immune response to HCV in those individuals with this infection who receive a liver transplant, we aim to gain important insights into the factors that underlie the variation in outcomes observed in this population.

Highlights of 2008

- Published a study in the prestigious journal *Gastroenterology* (top journal in this discipline), which demonstrated that T cells activated in the liver by hepatocytes display different markers than those activated in lymphoid tissues. We have characterised the molecular pathway leading to the death of the T cells and have identified Bim as a key regulator of this cell death.
- Identified a new dominant mechanism by which T cells activated in the liver are inhibited and killed in the liver. This mechanism might play a very important role in purging the repertoire of antigen-specific T cells during HCV as well as transplantation.
- Awarded a very competitive international grant by the Roche Organ Transplantation Research Foundation to investigate the mechanisms leading to the acceptance of mouse liver transplants. A microsurgery facility funded by a successful University of Sydney equipment NHMRC grant has been set up to investigate this question.
- Award of a Sylvia and Charles Viertel Clinical Investigatorship to further enable our study of HCV immunology.

Major projects

Our studies are currently focused on four main aspects:

- Altering the fate of T cells activated by hepatocytes by using mice deficient for genes important for regulating cell death or effector function.
- Investigating the mechanisms responsible for the clearance of recently activated T cells by hepatocytes.
- Developing solid organ transplantation in mice to understand the mechanisms of spontaneous liver graft acceptance and use of this knowledge to improve the acceptance of other solid organ transplants.
- Understanding immune responses to the HCV in individuals undergoing liver transplantation for HCV-related liver disease, and how these responses influence the clinical outcome of liver transplantation in this population.

MOLECULAR HEPATOLOGY

Associate Professor Mark Gorrell

Liver fibrosis often leads to severe scarring (cirrhosis) and cancer of the liver. We seek to determine the molecular basis of liver fibrosis and inflammation in order to improve therapy and prevention of chronic liver injury and thus of cirrhosis and cancer. HCV infection and fatty liver associated with obesity are the major and increasing causes of chronic liver injury.

We have discovered that in the injured liver the genes fibroblast activation protein (FAP), dipeptidyl peptidase (DP) IV, DP8, DP9 and DDR1 exhibit heightened expression by liver cells and are involved in cell movement and proliferation, and for some genes glucose homeostasis and tumour growth. DPIV is also interesting because it is the target of a new diabetes therapy. Our discoveries on DPIV and related genes significantly assisted the drug development process for this new type 2 diabetes therapy.

Highlights of 2008

- PhD thesis completions by students Katerina Ajami and Sunmi Song.
- Completion and publication of work done with transplantation (Dr A Sharland) and cystic fibrosis (Dr J Manos, Dr B Rose) researchers at the Faculty of Medicine, University of Sydney.
- We discovered that:
  - DP8 and DP9 are made in all parts of the body.
  - Liver scarring in the absence of DPIV or FAP has altered lymphocyte types in mouse.
  - DP8 inactivates some molecules called chemokines that are important in cell movement.
  - DP8 and DP9 are more active in conditions similar to those in healthy cells than stressed cells, so DP8 and DP9 might be like coal mine canaries by signalling that a cell is unhealthy.

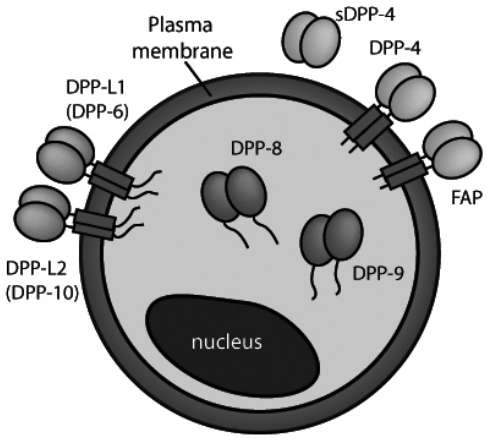
Major projects

The DPIV (DPP4) family of enzymes consists of DPIV, DP8, DP9 and FAP. We have obtained evidence that these enzymes have or may have roles in liver scarring. We are now increasing our understanding of these roles. We are studying fibrosis, immune systems and obesity in mouse strains that lack individual genes of the DPIV gene family. Co-workers include Associate Professor S Twigg and Dr S McLennan of the Faculty of Medicine, University of Sydney.

We cloned and patented DP8 and DP9 in the late 1990s. The value of these genes primarily relates to using DP8 and DP9 to reduce risks of drug side effects by ensuring that new DPIV inhibitory drugs are DPIV selective. The major use for these DPIV inhibitors, such as sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin, is as a new therapy for type 2 diabetes. We have worked with pharmaceutical companies to evaluate DPIV inhibitor selectivity.

Discoidin domain receptor (DDR) 1 is a cell surface protein activated by collagen, which is the major component of the liver scarring resulting from long-term liver injury. We have derived various evidence that DDR1 has important roles in responses to chronic human liver injury.

Collaborative work with Dr WB Church, Faculty of Pharmacy, University of Sydney, on the liver/brain enzyme Kynurenine Aminotransferase 1 (KAT-1) has developed very effective methods of making this protein. The research is directed towards discovering a compound that will control KAT-1 in the brain of Alzheimer's sufferers and thereby alleviate their illness.



The DPP4 gene family: DPP4, FAP, DPP6 and DPP10 are attached to the cell surface. DPP8 and DPP9 are inside cells. DPP4 also has a soluble form, sDPP4, that is released from the cell.

LIVER CELL BIOLOGY

Dr Nicholas Shackel and Dr Fiona Warner

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

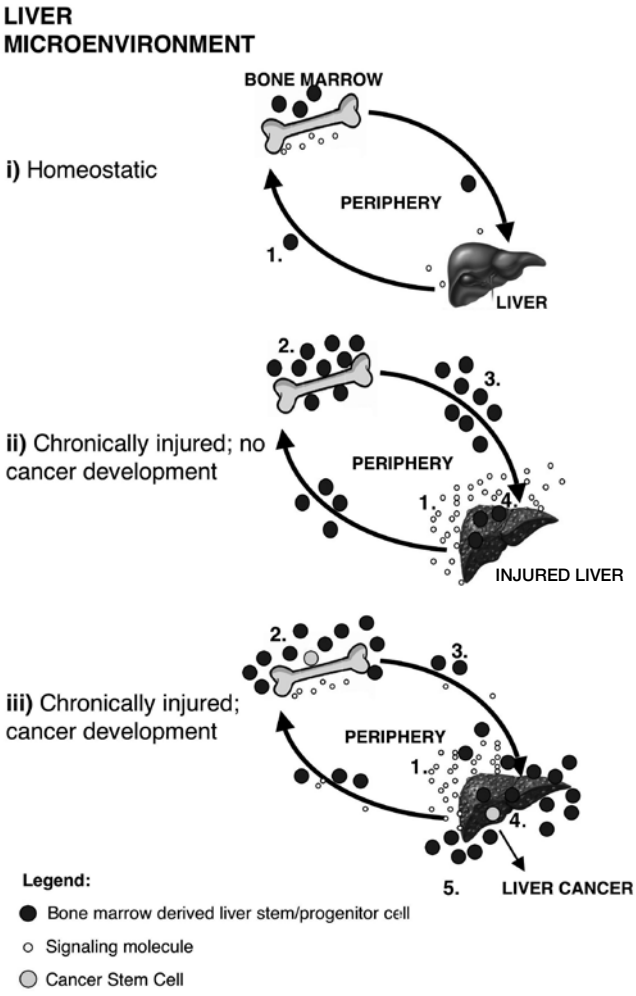
Highlights of 2008

- Dr Shackel was awarded Pillar and CellCept Australia Research Award grants from Roche for research into predicting HCV treatment responses to interferon treatment.
- Honours Student Melanie Eckersley-Maslin accepted a scholarship in the PhD program at Watson School of Biological Sciences at the Cold Spring Harbor Laboratory, New York State.
- William d'Avidgor was awarded a PhD Scholarship to study novel gene expression in progressive liver injury and hepatocellular carcinoma by the Rebecca L Cooper Medical Research Foundation.
- Second year PhD student, Sarah Richardson, was named the 2008 recipient of the June Halliday Young Investigator Award for Basic Research by the Gastroenterology Society of Australia for her presentation entitled *Functional studies in primary hepatocytes: The relationship between CD147 expression and metalloproteinase activity.*
- Our work has been accepted and presented during 2008 at the Asia Pacific Association for the Study of Liver Disease in Seoul, Korea, the American Society for the Study of Liver Disease Annual Meeting in San Francisco USA, and Australian Gastroenterology Week in Brisbane.

Major projects

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

- Analysis of liver disease using a functional genomics approach.
- The role of molecule extracellular matrix metalloproteinase inducer (EMMPRIN) and the hepatocyte in extracellular matrix interactions in liver fibrogenesis.
- Investigation of novel hormonal/signalling pathways (renin-angiotensin system and Hedgehog Pathway) and their role in liver injury and cancer.
- Stem cell contribution to liver injury and cancer.



Bone Marrow Contribution to Liver Fibrosis and Liver Cancer Development

The bone marrow is capable of contributing to intrahepatic cell populations. Bone marrow stem cell populations capable of migrating to and engrafting in the liver. i) In liver homeostasis, stem cells that are capable of giving rise to liver cells, reside within the bone marrow. The bone marrow secretes low levels of signalling molecules. A small proportion of these cells circulate in the periphery (1). ii) When the liver is chronically injured, the liver environment is altered, and various signalling molecules are produced. In response, stem cell populations in the bone marrow are activated, proliferate (2), migrate to the periphery (3), home to the injured liver and engraft (4). iii) In certain cases, oncogene/s may be activated in the bone marrow stem cells, generating a cancer stem cell. These cells are also capable of homing to and engrafting in the liver, resulting in the development of liver cancer (5).

CANCER DRUG RESISTANCE

Dr John Allen

As anyone who has ever undergone chemotherapy will agree, it is a gruelling form of treatment. The goal is to kill the cancer cells without killing the patient.

Unfortunately chemotherapy does not always succeed, but we know that if we can get the treatment right the first time it gives the patient the best chance of survival.

If we understand the key differences between cancers that respond to drugs and those that don't, then perhaps something can be done about them.

The Cancer Drug Resistance Group take special interest in understanding resistance to new anticancer drugs employed to treat common, recalcitrant cancers, such as melanoma (a particular scourge in Australia) and multiple myeloma.

We are working towards a personalised medicine approach to chemotherapy by seeking to identify molecular markers that indicate whether an individual is likely to develop a resistance to specific drugs

Highlights of 2008

- Dr Lye Lin Ho and Ms Keryn Lucas submitted their PhD theses.
- Dr Ho's work showed that the multidrug resistance gene MRP4 is responsive to the MYC oncoproteins. The work predicts that particular types of drug resistance, mediated by MRP4, will be associated with overactivity of the MYC genes, which is very common in many types of cancer. The finding will influence the choice of drugs used to treat cancers where MYC genes are known to be active.
- Ms Lucas's work helped clarify the contribution of different cellular mechanisms to drug resistance in melanoma, which hardly responds to chemotherapy. Australia has the highest incidence of melanoma in the world. Ms Lucas's work suggested that the protein NOXA plays a critical role in the growth and progression of melanoma, as well as affecting its resistance to drugs. This exciting development is being followed up by her successor.

Dr Ammira Hadi Al-Shabeeb and Dr John Allen

Major projects

Drug resistance in melanoma

Australia holds the dubious honour of having the highest melanoma rate in the world. Melanoma is one of the cancers most resistant to chemotherapy. Unless caught early, melanoma is almost invariably fatal.

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

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

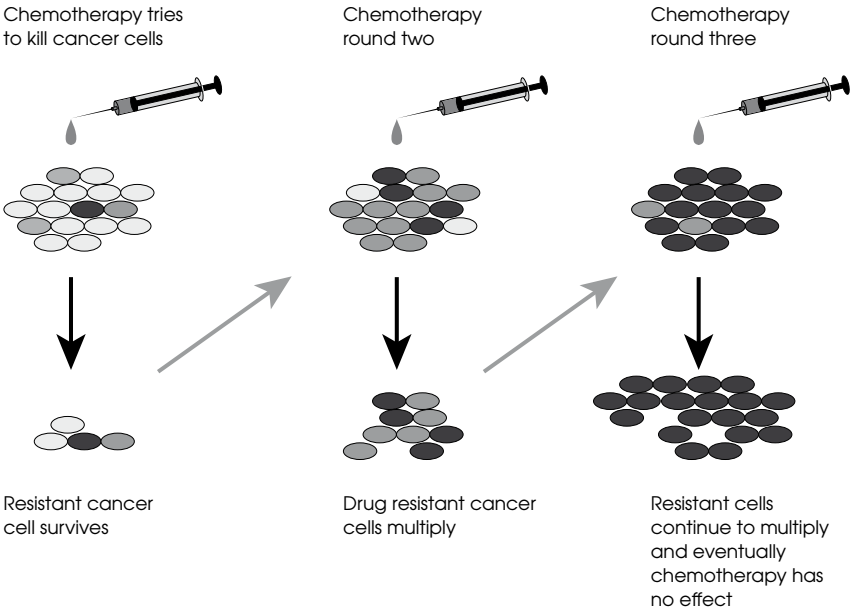
Drug resistance in multiple myeloma

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

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

We believe that dependence on this system is what makes myelomas resistant to many drugs but, conversely susceptible to a new class of new drugs, the proteasome inhibitors. Initial results indicate that markers of the UPR can predict the sensitivity of myelomas to the proteasome inhibitor Velcade both in vitro and in myeloma patients.

How drug resistance works



How will this research impact community health?

Research into cancer drug resistance will lead to improved cancer treatment and better outcomes for cancer patients. Cancer is now the leading cause of death in the developed world and this trend will continue as the population ages and other causes of death, such as heart disease, decline.

Cancer is extremely expensive to treat and with the high numbers of patients it is a key issue for the Australian healthcare system. There is enormous opportunity to improve patient outcomes and to reduce the cost of cancer treatment. Centenary's results in this field of research are often rapidly translate into clinical practice. Specific benefits include:

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

CORE FACILITIES

Cytometry and Imaging

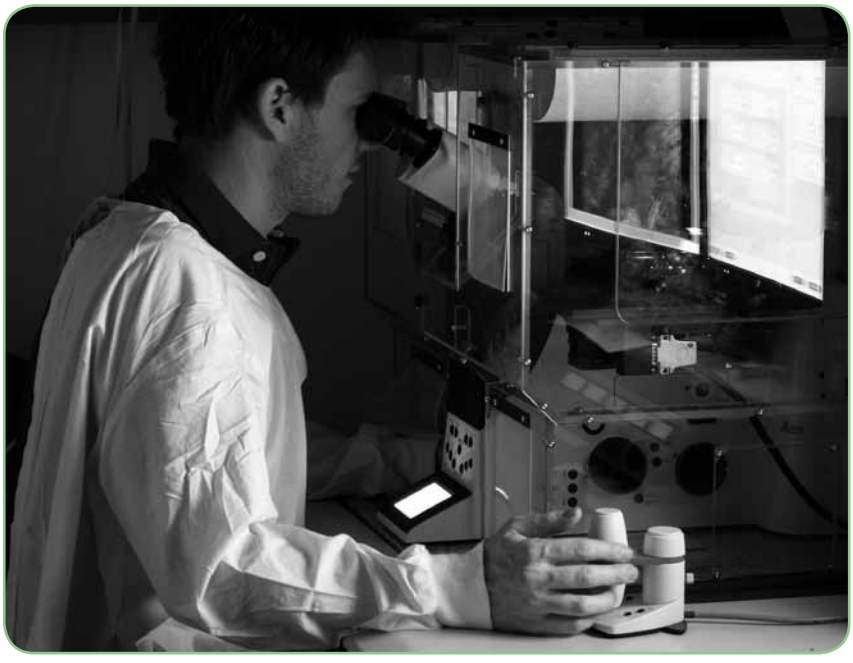
Flow cytometry

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

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

Highlights of 2008

- Flow cytometry highlights in 2008 included the attendance by Dr Adrian Smith at the major international cytometry congress (held in Budapest, Hungary) representing a continued commitment to best practice research techniques at the Centenary Institute. This year also saw closer collaboration with the flow cytometry resources on the University of Sydney campus, resulting in Centenary hosting a number of workshops for researchers from across Sydney. This collaboration (along with researchers from UNSW) was also involved in a successful Australian Research Council LIEF grant application that will lead to acquisition of two new high-end cytometry instruments for the Centenary/University campus in 2009.



PhD scholar Ben Roediger using Centenary's new confocal microscope

Imaging

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

LaVision Biotec TriMscope

This cutting edge multi-photon microscope enables researchers unprecedented access to the secret workings of living tissues at the cellular and molecular level. The multi-photon microscope at the Centenary Institute has two unique features, its imaging mode and laser. The unique imaging mode uses multiple laser beams.

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

Funding was obtained late in 2008 to extend the multi-photon facility with an additional laser and a second microscope. These additions will add flexibility to our imaging of living tissues and will keep the facility on the cutting-edge of multi-photon imaging.

Confocal microscope

In 2008, the Centenary Institute welcomed a new multi-laser spectral confocal microscope for imaging cells and tissues. This microscope allows researchers to investigate dynamic cellular processes over time via high resolution 3D images and videos.

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

Microinjection Facility

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

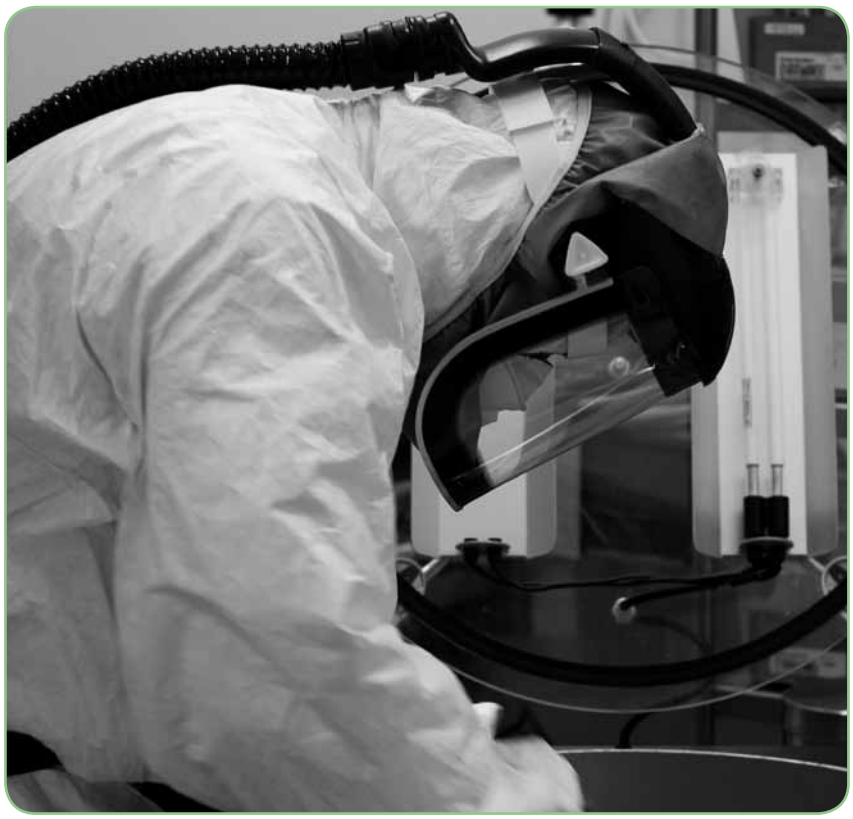
The Centenary Institute, with funding from the Cancer Institute NSW, employs an expert microinjection technician who has made a large number of genetically modified mouse strains. This enables the generation of new genetically modified animals to directly capitalise on the investments made in multi-photon microscopy, small animal imaging and flow cytometry.

Genomics Facility

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

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

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



Professor Warwick Britton in the PC3 facility

Mouse Cardiac Physiology and Function Facility

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

- Blood pressure measurement (tail-cuff);
- Electrocardiography (ECG);
- Electrophysiological stimulation studies; and
- Echocardiography.

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

PC3 Laboratory

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

The facility contains equipment permitting cell culture, genetic manipulation of bacteria and aerosol exposure system for animal infection models. In 2008, expansion work on the PC3 laboratory commenced.

Animal Facility

Genetically modified mouse lines are bred under Level 2 Specific Pathogen Free conditions in the Centenary Institute Animal Facility. IVC caging, 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.

CENTENARY INSTITUTE FOUNDATION REPORT

Foundation Chairman, Mr Neil Lawrence, Centenary Institute Executive Director Professor Mathew Vadas, Deputy Prime Minster, The Hon Julia Gillard MP, and Centenary Chairman, The Hon Michael Egan launch the Foundation

2008 was a year of great energy at Centenary Institute. As our research capacity grew, so did our need to raise funds from the community.

In 2008 the Foundation focused on three key activities: the acquisition of new supporters, building of our Friends of the Foundation group and improving communication with the public.

I was pleased to welcome 2,600 new donors to the Centenary Institute in 2008. I'd also like to thank all of our existing supporters for their continuing contributions to medical research. Your ongoing support is vital if we are to achieve of our ambitious plans to accelerate the pace of research into cancer, cardiovascular and infectious diseases.

Sincere thanks need to go to our major donors who all made very generous gifts in 2008, and to all members of the Research Society whose long term support has been crucial to our success over the years.

The Centenary Foundation was launched at Government House on 28 October. The Hon Julia Gillard MP, Deputy Prime Minister was guest of honour. She spoke movingly about the vital role that medical research plays in the health of Australia and encouraged those present to support the Centenary Institute.

The Foundation is chaired by Neil Lawrence of STW Group. Neil is ably assisted by our Trustees & Friends whose vision, personal contributions and advice have created a solid platform for the Foundation to grow in 2009.

Thanks also to our corporate partners Inghams, The Wine Society, Swiss Re, Lifestyle Financial, O'Halloran's Lawyers, Fossil Group, The Prospect Shop & MMB for your generous contributions.

Centenary was very fortunate to have the support of STW Group, Yello Brands and Singleton Ogilvy & Mather who combined forces to deliver a compelling new brand and advertising campaign to help Centenary share our vision of *Research for Life* with the community. The production of the advertising campaign was kindly supported by Plush Films, the Tait Gallery, Bean Colour, Song Zu, Pulse Foods & Health and St Ignatius College.

The ad campaign was generously supported by a who's who of Australian media. Our thanks go to Channel 7, Channel 9, Channel 10, Fairfax, MCN (the Multi Channel Network), News Limited, My Doctor and Popular Science. This extraordinary level of support would not have been achieved without the help of Geoff Dixon and Zenith Optimedia who arranged for the pro bono placement of our ads.

2008 was a tumultuous year for the Australian media, however, luckily for us many stellar journalists with a solid understanding of medical research are still hard at work. I would like to thank all in the media who covered our work in 2008 for their assistance in communicating the excitement and potential of medical research to the broader community.

Finally, the Foundation runs on a small staff that achieves results beyond its size. Congratulations and thanks to Erin Sharp, Dianne Missiris and Sonny Liang for their contributions. Thanks also to our volunteer Duncan Cruise. Your dedication and support are most sincerely appreciated.

Sally Castle
Fundraising & Marketing Manager

Professor Warwick Britton and the team from ABC's Catalyst program

2008 SEMINAR SERIES AND VISITING SPEAKERS

Speaker	Seminar title
Nick Shackel Centenary Institute	Going fishing: Application of array technology to disease pathogenesis
Golo Ahlenstiel National Institutes of Health, USA	KIR/HLA genotypes determine antiviral response kinetics of natural killer cells
Emma Whitelaw Queensland Institute of Medical Research	Epigenetics in health and disease
Gavin Recchia Davies Collison Cave	Patents: Who is an inventor and who owns the invention?
Alpha Yap Institute for Molecular Bioscience, The University of Queensland	Making contacts: Cadherin-actin cooperativity in cell-cell interactions
David Bowen Centenary Institute	Mechanisms of hepatitis C virus persistence: Virus and host
Chris Semsarian Centenary Institute	Genes and heart disease: From heartbreak to heartthrob
Lois Cavanagh Centenary Institute	An introduction to 2-photon intravital microscopy
Shaun Jackson Australian Centre for Blood Diseases, Monash University	Therapeutic targeting of PI 3-kinase signalling pathways in cardiovascular disease
Barbara Fazekas de St Groth Centenary Institute	How to write a successful animal ethics application
Jenny Gamble Centenary Institute	Regulation of vascular permeability
Eileen McGowan Centenary Institute	Endocrine resistance in breast cancer
Kim O'Connell Mallesons Stephen Jaques	Options for commercialising IP: Unlocking the jargon
Warren Alexander Walter and Eliza Hall Institute	Genetic dissection of haematopoiesis
Ryuichi Aikawa Centenary Institute	Cardiac gene therapy by AAV vectors
Merlin Crossley The University of Sydney	The mammalian Kruppel-line factor (KLF) family and gene control
Bernadette Saunders Centenary Institute	Macrophage signalling and the control of tuberculosis
Richard Boyd Monash University	Aging and regeneration of the immune system: the highs and lows of sex and drugs
John Allen Centenary Institute	Understanding response and resistance of myeloma to proteasome inhibitors
Lorraine Robb Walter and Eliza Hall Institute	The Mixl 1 homobox gene: Roles in development and leukaemia
Mikaela Rapp Centenary Institute	The ins and outs of membrane proteins
Rob Parton Institute for Molecular Bioscience	New insights into the formation and function of caveolae
Liz Jazwinska Johnson & Johnson Research	Licensing in the pharmaceutical industry
Chris Mitchell Monash University	Regulation of PI3-kinase signalling by lipid phosphatases
John Allen, Chris Semsarian and Barbara Fazekas de St Groth Centenary Institute	Presenting science to a non-scientific audience

Speaker	Seminar title
Claude Bernard Monash University	Multiple sclerosis: Novel approaches to control the battle between destruction and repair
Derek Baigent Mallesons Stephen Jaques	IP commercialisation vehicles
Tim Hla University of Connecticut Health Centre, USA	Sphingosine 1-phosphate signalling in the vasculature
Paul Kubes University of Calgary, Canada	Organ specific leukocyte recruitment
Guy Heathers Cancer Therapeutics CRC	Cancer therapeutics: From research to the patient, drug discovery from your cancer research
Martin Alexander Schwartz University of Virginia, USA	Integrin signalling and cancer
Grant McArthur Peter MacCallum Cancer Centre	Identifying therapeutic targets for cancer from lab to clinic practice
Nick West Centenary Institute	TB, or not TB: The difference could be a single gene
Elena Shklovskaya Centenary Institute	Role of dendritic cells in immunity and tolerance
Anne Kelso WHO Collaborating Centre for Reference and Research on Influenza	Of birds and men: the challenge of influenza
Martin Ashdown ImmunAid Pty Ltd	Effective immunotherapy for cancer …it's more common than you think!
Tony Weiss University of Sydney	Human elastin: Flexing proteins, quantized assembly and elastic tissue repair
Nital Sumaria Centenary Institute	The relevance of specific molecular and cellular effectors during murine cytomegalovirus infection
Prue Hart Telethon Institute for Child Health Research	Sunlight (ultraviolet rays) and asthma: links and immunological mechanisms
Gavin Recchia Davies Collison Cave and Jens Tampe, Bio-link	Patent and commercialisation essentials I: What is needed for a patent attorney to write a patent and for Bio-link to commercialise your invention?
Robert Graham Victor Chang Cardiac Research Institute	The enigma of cardiac regeneration
Michelle O'Han Centenary Institute	Analysis of insulin-like growth factor binding protein function in breast cancer using RNA interference
Stephen MacMahon The George Institute for International Health	Cardiovascular disease: A global perspective
Lai Guan Ng Centenary Institute	Visualising dendritic cell responses in the skin
Edna Hardeman University of NSW	Functional specialisation of the actin cytoskeleton by tropomyosins
Jane Visvader Walter and Eliza Hall Institute	Getting abreast of mammary development and cancer
Jens Tampe, Bio-link and Gavin Recchia, Davies Collison Cave	Patent and commercialisation essentials II: how to read a patent specification and the patent space – sometimes more than PubMed
Perry Bartlett The Queensland Brain Institute, University of Queensland	Activating neurogenesis in the adult hippocampus
Antal Rot Novartis Institutes for BioMedical Research, Austria	Chemokine interceptors: Bringing order into chemokine chaos
Andrew Baker University of Glasgow, UK	Genetic manipulation in the cardiovascular system: Application to basic science and to the development of novel therapies
Tanya Mayadas Harvard Medical School & Brigham and Women's Hospital, USA	Mechanisms of neutrophil recruitment and tissue injury in antibody-mediated diseases
Tony Burgess Ludwig Institute	Targeting a locally misfolded region of tumour associated EGFRs

Speaker	Seminar title
William Ritchie and Stephane Flamant Centenary Institute	Using conservation and expression data to discover microRNA targets
Carolyn Deacon The Panum Institute, Denmark	Efficacy of DPP-4 inhibitors as a novel treatment of type 2 diabetes
Devanshi Seth Centenary Institute	Novel mechanisms in pathogenesis of alcoholic liver disease
John Rasko Centenary Institute	Mendelian inheritance in man: disorders of aminoacid transport
Paul Foster University of Newcastle	Identification of a critical link between TRAIL and CCL20 for the activation of TH2 cells and the expression of allergic asthma
Ygal Haupt Peter MacCallum Cancer Centre	Regulation of p53 by c-Abl
So Iwata Imperial College London, UK	Structural studies on membrane proteins – production, crystallisation and crystallography
Werner Kühlbrandt Max Planck Institute for Biophysics, Germany	Electron microscopy and X-ray crystallography as complementary methods to study membrane protein structure and function
Danilo Perrotti The Ohio State University Medical Center, USA	MicroRNAs control leukemic cell differentiation by affecting RNA binding protein function: the BCR/ABL–MAPK –HnRNP2-miR328-CEBPa Network
Barbara Fazekas de St Groth Centenary Institute	Women in science: Recent trends
Geoff McCaughan Centenary Institute	Molecular and cellular aspects of Hepatitis C: From acute hepatitis to allograft failure
Stephen Locarnini Victorian Infectious Diseases Reference Laboratory	Molecular Pathogenesis of Chronic Hepatitis B: Role of the HBeAG/ PrecoreProtein
Antje Blumenthal Cornell University, USA	An unexpected role for RP105 in macrophage activation by mycobacterium tuberculosis
Rob Sutherland Garvan Institute	Oestrogen, the cell cycle & breast cancer
Alan Trounson California Institute for Regenerative Medicine	Driving stem cell research: The Californian model
Nadia Rosenthal Monash University	Enhancing mammalian regeneration
David Jans Monash University	Nuclear targeting of chromatin remodelling factors: Developmental switches in the mammalian testis
Mark Gorrell Centenary Institute	The cut and thrust of proteases in liver and diabetes: the dipeptidyl peptidase 4 gene family
Wayne M Yokoyama Howard Hughes Medical Institute, Washington University, USA	What poxviruses teach us about immunology
Charles Bailey Centenary Institute	Solving a 50 year old puzzle: Iminoglycinuria – a simple or complex Mendelian disorder?
Peter Leedman West Australian Institute for Medical Research	Exploring the functional role of miroRNAs and cancer
Sally Castle and Erin Sharp Centenary Institute	Communicating science to a lay audience
Sarah Russell Peter MacCallum Cancer Centre and Swinburne University of Technology	T cell polarity and the regulation of T cell fate
Marc Feldmann Imperial College London, UK	Anti-cytokine therapy: anti-TNF and the future
Amittha Wickrema University of Chicago, USA	The role of osteopontin in erythropoiesis and red cell physiology
Maria Wynne Centenary Institute	Murine infectious diseases: Would your research by compromised?
Dario Vignali St Jude Children's Research Hospital, USA	Molecular control of T cell development and regulatory T cell function

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Zebol JR, Hewitt NM, Moretti PAB, Lynn HE, Lake JA, Li P, **Vadas MA**, Wattenberg BW, Pitson S. The CCT/TriC chaperonin is required for maturation of sphingosine kinase 1. **Int. J of Biochemistry & Cell Biology**. 2008 Aug 14. (Epub ahead of print).

2008 INVITED PRESENTATIONS

International

Bertolino P. T cell activation inside versus outside the liver. Hepatic Inflammation and Immunity; 2008; Jan 25- 27; Galveston, USA.

Bertolino P. Role of T cells in transplantation . XXII International Congress for The Transplantation Society; 2008 Aug 10-14; Sydney, Australia.

Bertolino P. The unique microenvironment of the liver. 15th International Symposium on Hepatitis C and Hepatitis C and related viruses; 2008 Oct 5-9; San Antonio, Texas.

Bertolino P. T cell tolerance in the liver: a new insight into an old question. 1st International Meeting on Mesenchymal Stem Cells in Solid Organ Transplantation; 2008 Nov 24; Regensburg, Germany.

Bertolino P. Hepatocytes as antigen presenting cells. Immune Mediated Liver Injury; 2008 Dec 4-6; Hamburg, Germany.

Bertolino P. T cell tolerance in the liver: new insight into an old question. Institute for Immunology, LMU ; 2008 Nov; Munich, Germany.

Bertolino P. T cell tolerance in the liver: new insight into an old question. Dt. Rheumaforschungszentrum; 2008 Nov; Berlin, Germany.

Bertolino P. T cell tolerance in the liver: new insight into an old question. Institute of Molecular Medicine and Experimental Immunology; 2008 De; Bonn, Germany.

Bertolino P. T cell tolerance in the liver: new insight into an old question. Medizinische Universitätsklinik Freiburg; 2008 Dec; Freiburg, Germany.

Bertolino P. T cell tolerance in the liver: new insight into an old question. Centre d'Immunologie et Biologie Parasitaire, Inserm U547 - Université Lille 2 "Schistosomiase, Paludisme et Inflammation", Institut Pasteur de Lille; 2008 De; Lille, France.

Britton W. Immune Mechanisms in Leprosy Reactions. International Leprosy Congress; 2008 Jan; Hyderabad, India.

Britton W. HIV and Leprosy Interaction: Future Challenges. International Leprosy Congress; 2008 Jan; Hyderabad, India.

Britton W. Tuberculosis. Immuno-compromised Host Society Scientific Congress; 2008 Jun 22-26; Thessaloniki, Greece.

Britton W. Intranasal delivery of BCG secreting GM-CSF increases the number of dendritic cells, anti-mycobacterial T cell responses and protection against Mycobacterium tuberculosis. 43rd US-Japan Tuberculosis/ Leprosy Conference; 2008 Jul; Baltimore, USA.

Britton W. Improving BCG the APC way. Immunobiology Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health; 2008 Jul; Bethesda, USA.

Britton W. Taming the tubercle: Manipulating host responses to Mycobacterium tuberculosis through the IL-12/23 axis and the purinergic receptor P2X7. National Hansen's Disease Research program, Dept of Microbiology, Louisiana State University; 2008 Jul; Baton Rouge, USA.

Britton W. Tuberculosis and Transplantation. XXII International Congress of The Transplantation Society; 2008 Aug; Sydney Australia.

Britton W. Risks for developing tuberculosis: Influence of environmental and genetic factors. National Hospital for Tuberculosis and Lung Diseases; 2008 Oct; Hanoi, Vietnam.

Devanshi S. Alcohol, Signaling and ECM turnover. International Society for Biomedical Research on Alcohol (ISBRA) & Research Society on Alcoholism (RSA) Joint Scientific Meeting; 2008 Jun 28-Jul 2; Washington DC, USA.

Devanshi S. 3rd International symposium on Alcoholic Liver and Pancreatic Diseases and Cirrhosis; 2008 Jul 17-18; Bilbao, Spain.

Fazekas de St Groth B. Regulatory T cells in human health and disease. International Society for Laboratory Haematology, XXIst International Symposium on Technological Innovations in Laboratory Hematology; 2008 Apr 28 - May 1; Sydney, Australia.

Fazekas de St Groth B. Identifying human regulatory T cells in health and disease. XXII International Congress of the Transplantation Society; 2008 Aug 10-14; Sydney, Australia.

Gamble J. Sphingosine Kinase-1 regulates basal and angiopoietin-1 mediated endothelial cell permeability. 15th International Vascular Biology Meeting; 2008 Jun 1-5; Sydney, Australia.

Gorrell M. The biology of dipeptidyl peptidases explored in gene knockout mouse models. 3rd International Symposium on Dipeptidyl Peptidases and Related Proteins; 2008 Apr 22-25; Antwerp, Belgium.

Gorrell M. Dipeptidyl peptidase IV inhibitor selectivity. Symposium on Incretin Therapies. 44th Annual Meeting of the European Association for the Study of Diabetes; 2008 Sep 7; Rome, Italy.

Gorrell M. Dipeptidyl peptidase IV inhibitor selectivity. Symposium: Clinical Crossroads in Type 2 Diabetes Management: Optimizing Treatment Success. International Congress of Endocrinology; 2008 Nov 7; Rio de Janiero, Brazil.

Holst J. Discussion Panel Presentations. 4th PacRim Breast and Prostate Cancer Conference; 2008 Aug; Whistler, Canada.

McCaughan G. Ethical issues in medical research involving humans. Asia Pacific Association for the Study of Liver; 2008 Mar 23-26; Seoul, Korea.

McCaughan G. Importance of HBV DNA levels in the management of chronic HBV infection. Vietnamese Society for Liver and Gall; 2008 Mar; Ho Chi Min, Vietnam.

McCaughan G. Liver transplantation for HBV: Where are we up to? International Liver Transplant Society (ILTS) Special Conference: Advances in Liver Transplantation "A Western and Eastern Perspective"; 2008 Apr 5-6; Hong Kong, China.

McCaughan G. The role of the ILTS in global liver transplantation. ITLS Special Conference: Advances in Liver Transplantation "A Western and Eastern Perspective"; 2008 Apr 5-6; Hong Kong, China.

McCaughan G. Immunovirology of HCV recurrent post liver transplant. Edmonton Transplantation Service Meeting; 2008 May; Edmonton, Canada.

McCaughan G. Treatment for HCV post liver transplant – the no case. ILTS Annual Meeting; 2008 Jul 9-12; Paris, France.

McCaughan G. Liver transplantation: Improving long-term outcomes. International TTS Meeting; 2008 Aug, Sydney, Australia.

McCaughan G. The interaction between HCV recurrence and allograft rejection post liver transplantation. International TTS Meeting; 2008 Aug, Sydney, Australia.

McCaughan G. Workup of the liver transplant recipient. International TTS Meeting; 2008 Aug, Sydney, Australia.

McCaughan G. Omics in the 21st century – applications in liver disease. American Association for the Study of the Liver Annual Meeting; 2008 Nov; San Francisco, USA.

Rasko J. Introduction to microRNAs in Haemopoiesis. NZ Branch of the Haematology Society of Australia and New Zealand Update Meeting; 2008 Aug; Queenstown, New Zealand.

Saunders B. Granuloma development and the TNF superfamily in tuberculosis. New Zealand Society for Immunology Annual Meeting. 2008; Jun 4-6; Wellington, New Zealand.

Semsarian C. Inherited heart disease – from molecule to mouse to man. 60th Annual Scientific Meeting of the Paediatric Society of New Zealand; 2008 Nov 26-28; Waitangi, New Zealand.

Semsarian C. The emerging role of genetic testing in heart disease. Starship Children's Hospital; 2008; Auckland, New Zealand.

Vadas M. Keystone Symposium. Eicosanoids and other mediators of chronic inflammation; 2008 Jan 8; Montana, USA.

Weninger W. Patterns and mechanisms of intratumoral T cell migration. 50th Symposium of the Society of Histochemistry, 2008 Oct 1-4; Interlaken, Switzerland.

Xia P. Sphingosine kinase, a potential anti-cancer target. 1st World Cancer Congress in China; 2008 Jun 12-16; Shanghai, China.

Xia P. The role of sphingosine kinase-1 in cancer: oncogene or non-oncogene addiction? Sino-Australian Symposium: Cancer Research in the 21st Century; 2008 Jun 24-25; Shanghai, China.

National

Allen J. Understanding and predicting response to proteasome inhibitors in multiple myeloma. Sydney Cancer Conference, University of Sydney, 2008 Jul 24-26; Sydney, NSW.

Britton W. New solutions to the challenges of vaccines for tuberculosis. Sir Mark Oliphant Conference on Vaccines and Immuno-therapy Technologies, Australian Academy of Sciences; 2008 Apr; Canberra, Australia.

Britton W. The immunological challenges presented by tuberculosis in the 21st century. Annual Scientific Meeting of the Australasian Society of Immunology; 2008 Dec; Canberra, ACT.

Chiu C. Genome-wide linkage in a family with HCM. HGSA National Meeting; 2008 Aug 2-6; Adelaide, SA.

Devanshi S. Models of alcohol induced liver disease. Using Animal Models to Study Human Diseases, Royal Prince Alfred Hospital; 2008 Aug; Sydney, NSW.

Fazekas de St Groth B. How do dendritic cells program T cells for both tolerance and immunity? 12th Australasian Autoimmunity Workshop; 2008 Aug 15-16; Sydney, NSW.

Fazekas de St Groth B. Regulatory T cells and inflammatory bowel disease. Mater Medical Research Institute Mucosal Diseases Program Symposium; 2008 Oct 20-21; Brisbane, Queensland.

Fazekas de St Groth B. Obligatory tolerance induction by epidermal Langerhans cells. Australian Health & Medical Research Congress, 2008 Nov 16-21; Brisbane, Queensland.

Fazekas de St Groth B. Effect of cancer chemotherapy on human regulatory T cells. Tumour Immunology Workshop, Australasian Society for Immunology Annual Meeting; 2008 Dec 7-11; Canberra, ACT.

Gamble J. Sphingosine kinase regulates the rate of differentiation of endothelial progenitor cells. ComBIO; 2008 Sep 21-25 September; Canberra, ACT.

Haass NK. In vitro 3D tumour microenvironment models for anti-cancer drug discovery. Matrix Biology Society of Australia and New Zealand (MBSANZ) Annual Scientific Meeting; 2008 Oct; Ettalong, NSW.

Haass NK. Novel kinase inhibitors to target the melanoma's Achilles' heel, Sydney Melanoma Unit; 2008 Aug; Sydney, NSW.

Haass NK. 3D models for the identification of novel candidates for targeted therapy of melanoma. University of Queensland; 2008 Aug; Brisbane, Queensland.

Haass NK. Targeted therapy of melanoma: Novel kinase inhibitors with potent and specific anti-melanoma activity. Queensland Institute of Medical Research; 2008 Jul; Brisbane, Queensland.

Haass NK. Novel kinase inhibitors to target the melanoma's Achilles' heel. Grand Rounds, University of Sydney; 2008 Jun; Sydney, NSW.

Haass NK. Inhibition of MEK with AZD6244 is cytostatic as a monotherapy in melanoma, but cytotoxic when combined with docetaxel leading to tumour regression in vitro and in vivo. 5th ASDR Annual Scientific Meeting; 2008 May; Sydney, NSW.

Haass NK. Novel kinase inhibitors to target the melanoma's Achilles' heel. 41st ACD Annual Scientific Meeting; 2008 May; Sydney, NSW.

Jolly C. Antibody hypermutation: AID can fool all DNA repair pathways some of the time. Children's Medical Research Institute; 2008 Jun 30; Westmead, NSW.

Jolly C. Antibody hypermutation: AID can fool all DNA repair pathways some of the time. St Vincent's Medical Research Institute; 2008 Aug 11; Melbourne, Victoria.

Lam L. Proteomic studies in normal and cardiomyopathic mice. ISHR/CSANZ Meeting Young Investigator Prize; 2008 Aug 7-10; Adelaide, SA.

Ling S. Understanding and Predicting Sensitivity of Myelomas to Proteasome Inhibitor bortezomib. HSANZ: Haematology Society of Australia and New Zealand; 2008 May 14; Sydney NSW.

McCaughan G. Are there standard listing criteria for liver transplantation in Australia? ALF Annual Scientific Meeting; 2008 Aug; Sydney, NSW.

McCaughan G. The national transplant reform agenda – why did the government change its mind? St George Hospital Annual Medical Conference; 2008 Nov; Sydney, NSW.

Ng LG. Visualisation of dendritic cell responses in the skin. Australia Society of Immunology, NSW branch meeting; 2008 Oct 16; Sydney, NSW.

Ng LG. Visualisation of dendritic cell responses in the skin. Young Investigators Seminars, Central Clinical School, University of Sydney; 2008 May 30; Sydney, NSW.

Ng LG. Migratory dermal dendritic cells act as rapid sensors of protozoan parasites. 5th ASDR Annual Scientific Meeting; 2008 May; Sydney, NSW.

Rasko J. Gene therapy in haematology. Pathology Update; 2008 Mar; Sydney, NSW.

Rasko J. Gene therapy coming to a pharmacy near you? Society of Hospital Pharmacists; 2008 Apr; Sydney, NSW.

Rasko J. CTCF and BORIS: paralogous zinc-finger proteins competing in cancer? New Directions in Leukaemia Research; 2008 Mar; Sunshine Coast, Queensland.

Rasko J. Gene transfer and gene medicine? Australian Society of Medical Research XVII NSW Scientific Meeting; 2008 Jun; Sydney, NSW.

Rasko J. Gene and cell therapies - are we there yet? University of Queensland Centre for Clinical Research, University of Queensland; 2008 Jul; Queensland.

Rasko J. MicroRNAs. Royal Perth Hospital Haematology Department; 2008 Aug; Perth, Western Australia.

Rasko J. Stem cells. Diseases of the Third Age Meeting; 2008 Aug; Hobart, Tasmania.

Rasko J. Baboons and blood: is it worth the trouble? Celebrating 25 Years of Primate Research, National Baboon Colony; 2008 Aug; Wallacia, NSW.

Rasko J. Gene and cell therapies - are we there yet? Ludwig Institute for Cancer Research Melbourne Centre for Clinical Sciences, 2008 Sep; Melbourne, Victoria.

Rasko J. Gene and cell therapies - are we there yet? Johnson and Johnson Research, 2008 Nov; Sydney, NSW.

Roediger B. Identification and Characterisation of Dermal Dendritic Cell (DDCs) Precursors In Vivo. NSW Flow Cytometry Prize; 2008 Nov 28; Sydney, NSW.

Semsarian C. Causes of sudden cardiac death in the young. Cardiomyopathy Association of Australia Meeting, Royal North Shore Hospital; 2008; Sydney, NSW.

Semsarian C. Double mutations in the cardiac sarcomere: a link between hypertrophic and dilated cardiomyopathies. Australian Health and Medical Research Congress; 2008 Nov 16-21; Brisbane, Queensland.

Semsarian C. Overview of cardiology research at the University of Sydney. Peking University Health Science Centre visit; 2008; Sydney, NSW.

Semsarian C. Genetic testing in CV disease. Workshop, CV Forum; 2008; Gold Coast, Queensland.

Semsarian C. Genetic testing in structural heart disease. 56th CSANZ Scientific Meeting; 2008 Aug 7-10; Adelaide, South Australia.

Semsarian C. Hypertrophic cardiomyopathy in 2008. 56th CSANZ Scientific Meeting; 2008 Aug 7-10; Adelaide. South Australia.

Semsarian C. Early diagnosis and management of the myopathic heart. ASEANZ; 2008; Melbourne, Victoria.

Semsarian C. Sudden death in the teen years – what is the cause? Advances in Device Therapy Symposium; 2008; Byron Bay, NSW.

Semsarian C. Genetic basis of hypertrophic cardiomypathy: an update. Asia-Pacific Heart Failure Congress; 2008; Melbourne, Victoria.

Vadas M. Tumour angiogenesis: protagonists and antagonists. Solid tumours are characterised by a chaotic, hypoxic and leaky blood vessels. Pfizer Oncology Forum; 2008 Apr 5; Melbourne, Victoria.

Vadas M. Sydney Cancer Centre Conference; 2008 Jul 25; Sydney, NSW.

Vadas M. AusBiotech Luncheon, 2008 Sep 26.

Vadas M. The role of sphingosine kinase in cancer and inflammation. Westmead Millennium Institute; 2008 Oct 31; Westmead, NSW.

Weninger W. Visualising immune responses in tumours and infections using two-photon microscopy. Diamantina Institute, University of Queensland; 2008 Mar 4; Brisbane, Queensland.

Weninger W. Visualising immune responses in tumours and infections using two-photon microscopy. Garvan Institute; 2008 Mar 18; Sydney, NSW.

Weninger W. Visualising immune responses in tumours and infections using two-photon microscopy. Centre for Vascular Research, UNSW; 2008 May 14; Sydney, NSW.

Weninger W. Role of CD44 in intratumoral T cell migration. 41st Australasian College of Dermatologists Annual Scientific Meeting; 2008 May 21; Sydney, NSW.

Weninger W. Real-time imaging of immune responses to tumours and during infections. John Curtin School of Medical Research, ANU; 2008 Aug 29; Canberra, ACT.

Weninger W. Visualising immune responses with 2-photon microscopy. Westmead Millennium Institute; 2008 Sep 12; Sydney, NSW.

Weninger W. Imaging the immune system in real time using 2-photon microscopy. 22nd Annual International Congress of the Transplantation Society; 2008 Aug 9; Sydney, NSW.

Weninger W. Visualising immune responses in infections and tumours. University of Canberra; 2008 Nov 5; Canberra, ACT.

Weninger W. Visualising immune responses in infections and tumours. Hansen Institute; 2008 Nov 27; Adelaide, South Australia.

Weninger W. Visualising dendritic cell responses in the skin. 4th ANHMRC Conference; 2008 Nov 17; Brisbane, Queensland.

Xia P. The sphingosine kinase signaling pathway: potential anti-cancer targets. Kolling Institute, University of NSW; 2008 Aug 22; Sydney, NSW.

Yeates L. Case presentation. Australian Society Genetic Counsellors, Human Genetics Society of Australia Meeting; 2008 Aug 2-6; Adelaide, South Australia.

POSTGRADUATE TRAINING PROGRAM

The Centenary Institute maintains its commitment to the development of Australia's next generation of brilliant scientists. In 2008, university students accounted for 28 per cent of Centenary staff. Students in the Postgraduate Training Program come from a wide range of ethnic and academic backgrounds to work with Australia's leading medical researchers at the Institute.

The Centenary Institute congratulates the following students for their achievements in 2008.

Doctor of Philosophy (Medicine) (PhDs) Awarded 2008

Student	Supervisor	Thesis title
Katerina Ajami	Associate Professor Mark Gorrell	Functional characteristics of DP8 and DP9
Keefe Chng Teck Leong	Professor John Rasko	A non-human primate model of mesenchymal stromal cell gene transfer and cell therapy
Sandhya Limaye	Professor Antony Basten AO	The role of the TRAF2 in lymphocyte responses

Master of Science in Medicine awarded 2008

Student	Supervisor	Thesis title
Sultana Mahmuda	Professor Warwick Britton	Interaction of mycobacterial Mpt83 and the host immune response

GRANTS AWARDED 2008

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

Investigators	Title	Granting Body
S Broer, J Rasko	Amino acids as nutrients - the molecular basis of amino acid absorption in kidney and intestine	Australian Research Council (ARC)
BD Hambly, S Bao, GA Bishop, J Black, IL Campbell, Q Dong, MD Gorrell, GE Grau, NH Hunt, NJ King, DJ March, KL McDonald, SV McLennan, KJ Rodgers, D Seth	Dako ACIS III Cellular Image Acquisition and Analysis System	ARC
M Jormakka, M Rapp	A rational approach to a high-resolution structure of the multidrug transporter EmrE	ARC
J Rasko, J Holst	Dissecting BORIS Function In Neoplasia	Cancer Council NSW
M Maher	Platinum drug resistance: structural and functional studies of the Ctr proteins	Cancer Institute NSW
E McGowan	Identification of new molecular targets for the treatment of breast cancer	Cancer Institute NSW
J Selwyn (J Rasko)	The role of the tumour suppressor CTCF and its paralogue BORIS in carcinogenesis	Cancer Institute NSW
M Gorrell	Gene expression	Ceramisphere Ltd
J Allen, S Ling	Predicting response to proteasome inhibitors	Cure Cancer Australia
S Ling, J Allen	Renewal: Role of XBP-1 in the drug resistance of multiple myeloma	International Myeloma Foundation
S Ling (J Allen)	Predicting and understanding the response of myeloma to proteasome inhibitors	Leukaemia Foundation
P Bertolino	Research Fellowship	National Health and Medical Research Council (NHMRC)
D Bowen	Hepatitis C virus-specific cellular immune responses post-liver transplantation	NHMRC
W Britton, J Triccas, N West	Regulation of pulmonary immune responses to subunit vaccines against tuberculosis	NHMRC
J Gamble, M Vadas	Development of inhibitors pf PKCzeta for targeting vascular leak	NHMRC
M Gorrell, C Semsarian, P Xia, J Allen, M Jormakka, G McCaughan, J Rasko, M Vadas, F Warner, D Seth, T Tsoutsman, J Holst, S Ling	Advanced multiparameter quantitation stations	NHMRC
M Gorrell	Therapeutic potential of the dipeptidyl peptidase IV gene family	NHMRC
M Grimshaw	Defining the role of senescence in tumour associated endothelial cells	NHMRC
C Jolly, J Manis, F Alt	Antibody mutation promotes translocation: a natural cause of cancer	NHMRC
M Kelly (C Semsarian)	Clinical and molecular consequences of multiple gene mutations in familial hypertrophic cardiomyopathy	NHMRC

Investigators	Title	Granting Body
NJ King, BD Hamley, S Bao, GA Bishop, J Black, IL Campbell, Q Dong, MD Gorrell, GE Grau, NH Hunt, R Markham, DJ Marsh, KL McDonald, SV McLennan, KJ Rogers, D Seth	Dako ACIS III Cellular Image Acquisition and Analysis System	NHMRC
E Lau (C Jolly)	Mechanisms for the development of leukaemia via antibody hypermutation	NHMRC
J Rasko, J Holst	Dissecting BORIS Function In Neoplasia	NHMRC
N Shackel, S McLennan, F Warner	Role of the hepatocyte in extracellular matrix interactions in liver fibrogenesis	NHMRC
W Weninger, L Cavanagh	Interplay of innate and adaptive immunity to influenza A virus	NHMRC
W Weninger, P Mrass	Mechanisms of T cell migration and interactions in tumours	NHMRC
T Tsoutsman	Multiple mutations in familial cardiomyopathy: haracterization and treatment studies	National Heart Foundation
J Holst	Role of nutrient amino acids in prostate cancer	Prostate Cancer Foundation of Australia
R Martiniello-Wilks	Tri-modal targeted stem cell gene therapy for prostate cancer metastases	Prostate Cancer Foundation of Australia
J Holst	Gene regulation by nutrient amino acids in prostate cancer	Ramaciotti Foundation
N Shackel	Illumina	Ramaciotti Foundation
M Vadas, M Gorrell, C Semsarian, P Xia, J Allen, M Jormakka, G McCaughan, J Rasko, W Britton, B Fazekas de St Groth, W Weninger, J Gamble, N West, F Warner, C Jolly, D Seth, C Bailey, J Holst	Fluorescence polorisation reader with high performance luminescence	Ramaciotti Foundation
W Britton, B Saunders	Genetic control of tuberculosis (plate reader)	Rebecca L Cooper Foundation
W d'Avigdor (N Shackel)	Understanding the pathobiology and interferon treatment responses in chronic hepatitis C using an analysis of gene expression in peripheral blood mononuclear cells	Rebecca L Cooper Foundation
C Jolly	Development of novel human antibodies for use as therapeutics in arthritis and other autoimmune disorders (Nucleofector)	Rebecca L Cooper Foundation
J Rasko	Generation of viral vectors for gene transfer (QIAcube)	Rebecca L Cooper Foundation
P Bertolino	Understanding the role of resident and donor leucocytes in liver and solid organ transplantation	Roche Organ Transplant Research Fund
C Semsarian	Prevention of sudden death in the young	RT Hall Trust
S Ling (J Allen)	Predicting response to a new drug for multiple myeloma	Royal College of Pathologists of Australasia
B Fazekas de St Groth	Effects of cancer chemotherapy on regulatory T cells	Sydney Cancer Centre
R Martiniello-Wilks	Improving cell-based gene delivery to organ-confined and prostate cancer metastases	Sydney Cancer Centre

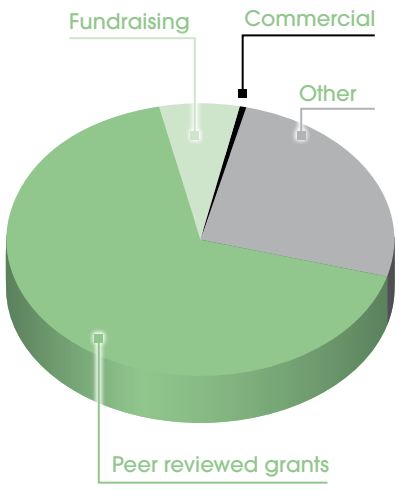
Investigators	Title	Granting Body
E McGowan, P Xia	The role of progesterone and shpingosine kinase 1 in the regulation of endocrine responsiveness in breast cancer cells	Sydney Cancer Centre
N Shackel, F Warner	Novel gene discovery in progressive liver injury and hepatocellular carcinoma development	Sydney Cancer Centre
N Tran, J Gamble	The expression and function of micro-RNA (miRNA) genes in tumour angiogenesis	Sydney Cancer Centre
D Bowen	Dendritic cell phenotype and function in chronic hepatitis C infection	Sylvia & Charles Viertel Charitable Foundation
N Shackel	Analysis of gene expression in peripheral blood mononuclear cells in chronic hepatitis C infection	Sylvia & Charles Viertel Charitable Foundation
C Jolly	AID-induced DNA damage, DNA repair and the cell cycle	University of Sydney
M Jormakka	Equipment: Liquid handling robot	University of Sydney
A Lay	Role of sphingosine kinase-1 in the dysfunction of endothelial progenitor cells in diabetes	University of Sydney
W Weninger, L Ng	Real-time visualisation of innate immune responses during cutaneous Leishmania infection	University of Sydney
J Young (J Gamble)	Role of miRNAs in the control of angiogenesis	Wenkart Foundation

FINANCIAL HIGHLIGHTS

	2008 in '000	2007 in '000
INCOME		
Peer reviewed grants		
Federal - NHMRC + ARC	4,222	3,159
NSW Government	1,559	1,193
Other Research Grants	3,739	2,496
Total grants	9,520	6,848
Fundraising		
Donations, events + other	708	558
Bequests	239	24
Total fundraising	947	582
Commercial	65	148
Other	3,582	3,042
Total Income	14,114	10,620
EXPENDITURE		
Research activities	9,080	5,807
Foundation	320	223
Infrastructure	1,738	1,196
Building operations	1,677	1,594
Other	427	55
	13,242	8,875

** The complete annual accounts are available on request.*

INCOME 2008



Peer reviewed income grew strongly in 2008 (up 39%). This partially reflects the expansion strategy put in place in 2007. NHMRC funding increased by 29%. Non government peer reviewed income grew by 50%. Grant income from International grants (National Institutes of Health, USA and Wellcome Trust UK) and the Cancer Institute NSW were the main contributors to this growth. Overall both income and expenditure grew by more than 30% reflecting the strong organisational growth mentioned in the Chairman's Report.

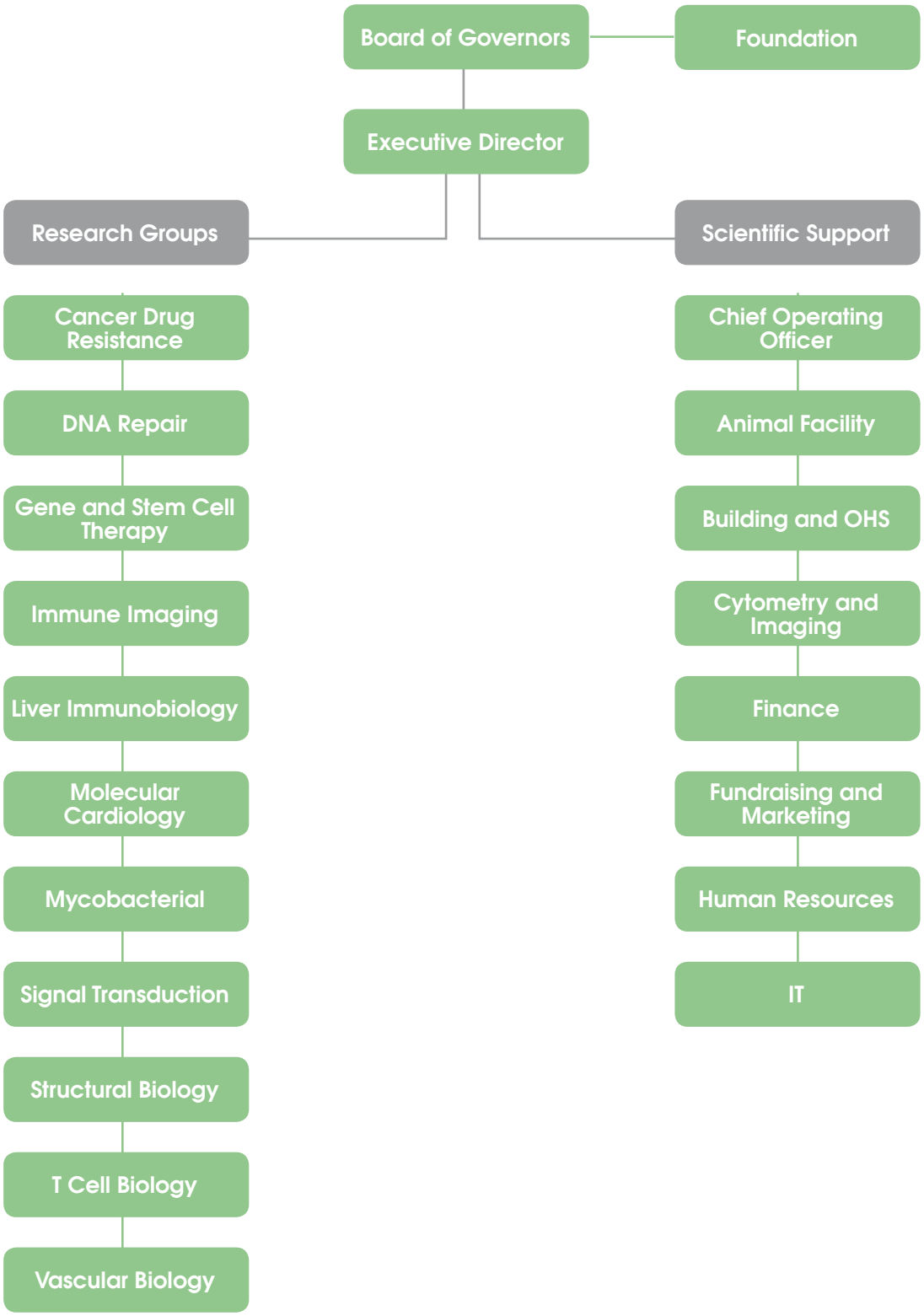
The rapid growth of the Centenary Institute since 2007 will see us top 200 people in 2009. Whilst this is an exciting milestone it brings new challenges given our building was designed for approximately 150 people. The coming years will see the Centenary Institute develop new research facilities in collaboration with key stakeholders.

The expansion of our animal, flow and imaging facilities as discussed in the Director's Report, was particularly pleasing. My thanks to the Federal Government (Department of Health and Ageing), State Government (Cancer Institute NSW), and non-government granting bodies for their financial support in this area. These core facilities underpin the cutting-edge research performed by the Centenary Institute researchers.

Finally my thanks to all the science support staff for the hard work in 2008.

Nick Pearce
Chief Operating Officer

ORGANISATIONAL CHART



SCIENTIFIC SUPPORT STAFF

Executive Director
Mathew Vadas

Accounts Officer
Wilfredo Entona

Administration Assistant
Eric Suchy (from Mar)

Animal Attendant
Robert Agostino
Mladen Damjancuk
Dale Farrell (Mar-Jul)
Jenna Glasgow (from Sep)
Sandra Martin
Jason Martin-Powell (until Aug)
Claire McGoffog
Danielle Moyes (from Jul)
Sarah Murray (from Sep)
Belinda Porchera (Jul-Oct)
Karen Ridgeway
Tan Truong

Animal Technician
Brad Harper (until July)
Carol Juaton (from Sep)

Assistant Accountant
Chelsea Wang

Building Services Assistant
Bob Thorburn

Chief Operating Officer
Nick Pearce

Communications Coordinator
Jane O'Dwyer (until Feb)
Erin Sharp (from Mar)

Director's PA/Office Support Manager
Helen Warwick

Donor Services Coordinator
Sonny Liang (from Oct)
Dianne Missiris (until May)

Facilities and Resources Manager
Jeffrey Crosbie

Finance Manager
Viraf Variava

Fundraising and Marketing Manager
Sally Castle

Fundraising Coordinator
Suzanne Dyson (Oct-Dec)
Rebecca Monk (May-Aug)

Human Resources Manager
Nanette Herlihen

IT Support
Owen Hoogvliet (from Dec)
Sam Tardiff

IT Systems Administrator
Robert Middleton

Librarian/Administrative Support
Mary Linnane (until July)

Microinjectionist
Michelle Brownlee

Receptionist
Catherine Axford

Research Facilities and IT Manager
Adrian Smith

Research Support Officer
Sonja Bates

Senior Technical Support Officer
Christopher Brownlee (until May)

Technical Officer
Marisa Mourelle

Technical Support Officer
Steven Allen (from July)
Robert Salomon

Veterinary Manager
Maria Wynne

RESEARCH STAFF

Cancer Drug Resistance

Associate Faculty
John Allen

Research Officer
Ammira Al-Shabeeb (from May)

Research Assistant
Kun Kan (Edwin) Lau (until Feb)
Angela Nikolic (May-Dec)

PhD Scholar
Lye Lin Ho
Nethia Kumaran
Keryn Lucas
Silvia Ling

Technical Officer
Tom Davis (Until Feb)

DNA Repair

Associate Faculty
Chris Jolly

PhD Scholar
Kun Kan (Edwin) Lau
George Sharbeen

Gene and Stem Cell Therapy

Faculty
John Rasko

Associate Faculty
Jeffrey Holst

Research Scientist
Ryuichi Aikawa

Senior Research Officer
Charles Bailey

Research Officer
Stephane Flamant (until Dec)
Michelle O'Han (from Jun)
William Ritchie
Qian (Kevin) Wang (from Feb)
Ayako Yamaura (from Nov)

Editorial Research Officer
Carl Power

Research Assistant
Cynthia Ng
Fiona Guan
Gemma Meyers
Sarah Watson
Wilfred Leung (until Dec)

Visiting Scientist
Stephen Larsen

Rosetta Martiniello-Wilks
Nick Viiala
Amittha Wickrema (Nov-Dec)

PhD Scholars
Megha Rajasekhar
Jennifer Randall
Jessica Selwyn (until November)
Shawna Tan
Jessamy Tiffen
Jessica Vanslambrouck

Honours Student
Renuka Balasubramaniam
(Graduate Medical Program)
Phoebe Matthews
(Graduate Medical Program)
Margaret Shaw
(Graduate Medical Program)

Immune Imaging

Faculty
Wolfgang Weninger

Senior Research Officer
Lois Cavanagh
Nikolas Haass

Research Officer
Lai Guan Ng
Nital Sumaria (from Feb)
Sioh Yang Tan (from May)

Research Assistant
Garth Douglas (from Feb)
Mary Mouawad
Jim Qin (from Feb)

PhD Scholar
Ben Roediger

Masters Scholar
Keiko Matsuzaki

Honours Student
Mark Taylor
(Graduate Medical Program)

Liver Immunobiology

Faculty
Geoffrey McCaughan

Associate Faculty
Patrick Bertolino
David Bowen
Mark Gorrell
Nicholas Shackel
Fiona Warner

Research Scientist
Devanshi Seth

Research Officer
Katerina Ajami (Feb-Julyl)
Volker Benseler
Fiona Keane (from Dec)
Sunmi Song (from July)
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