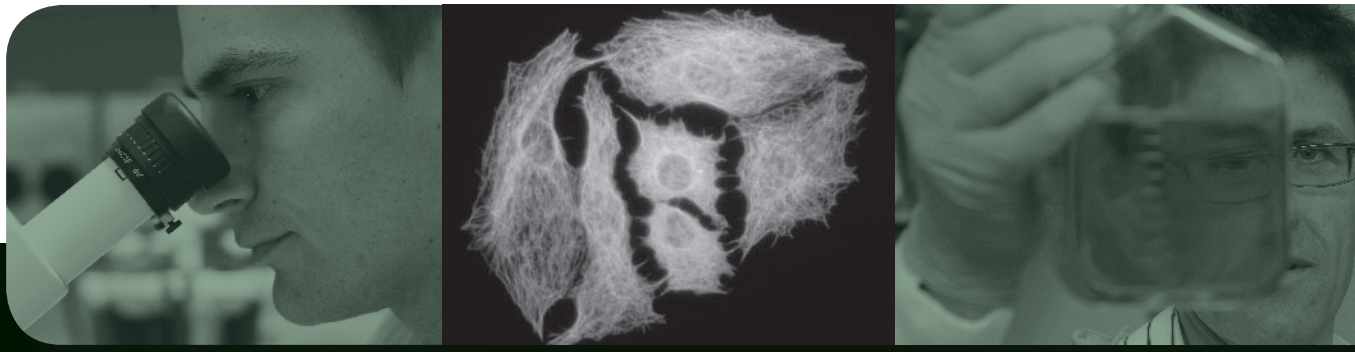
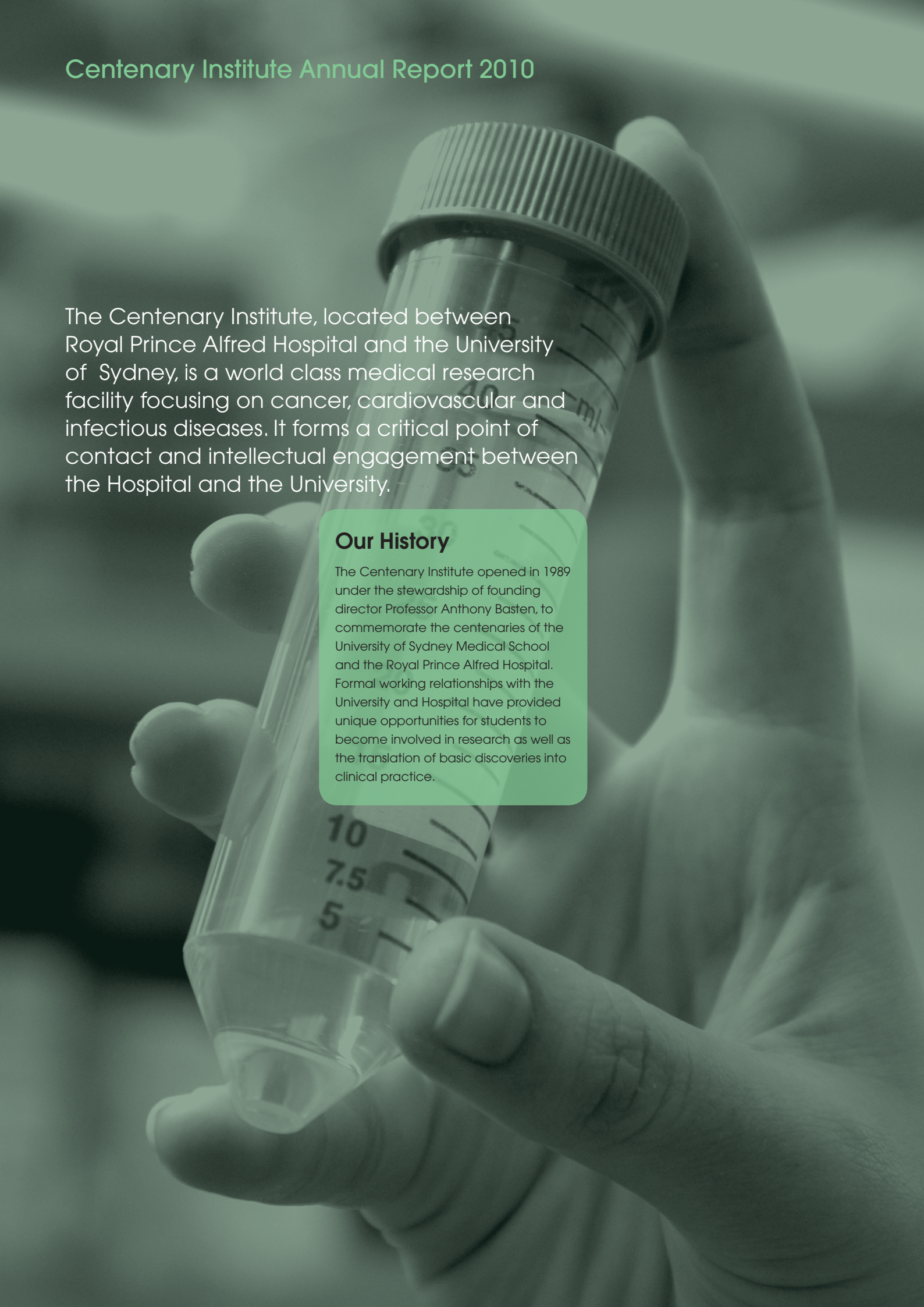
Centenary Institute
research for life



Annual Report **2010**



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.

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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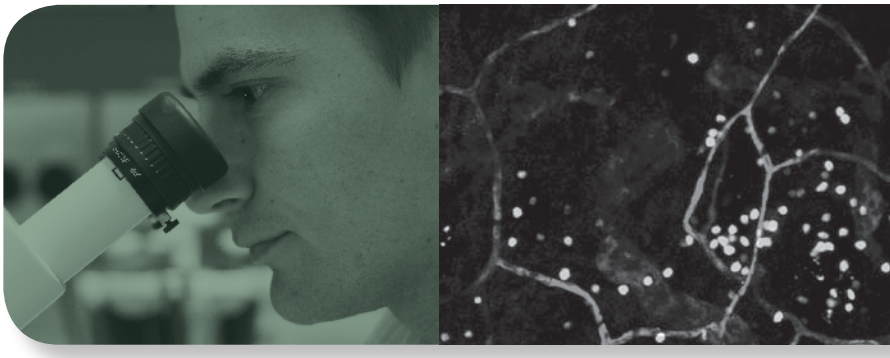


Chairman's Report

The Honourable Michael Egan

First, I would like to thank you.
Yes, you! Because if you are reading this then it is more than likely you are already one of the Centenary Institute's many good friends, and therefore have already played a part in the achievements which this report outlines.

The Centenary has had a very successful year, but only because of help from people like you.

First and foremost among our friends are our medical researchers and administrative staff whose passion for the Institute's work is always an inspiration.

We have great friends too in our next door neighbours, the University of Sydney and its medical faculty and the Royal Prince Alfred Hospital and we collaborate closely with both.

We have always been very grateful for the financial support we receive from the New South Wales and Commonwealth Governments and especially from our many individual friends, good citizens from every walk of life, who have heard about the great work of our medical researchers and want to make their own individual contribution to it.

In many ways the Centenary has always been a "quiet achiever" in the field of medical research, with its excellence and achievements largely unknown to the wider public. We hope to change that and you may have noticed that the Centenary's name has been popping up more and more in the media.

Over the last year our researchers were extremely successful in the very competitive business of winning research grants from the National Health and Medical Research Council, with their applications achieving a success rate of 60% compared to a national average of 23%. We were delighted also when the Centenary's Professor Chris Semsarian's research was declared to be in the "top 10" by the NHMRC.

Importantly, we are also building a strong international presence. No more so than in the area of tuberculosis, a disease that infects a third of the world's population. Professor Warwick Britton's group has established research collaborations in India and Vietnam to work on research into new therapies and also sharing knowledge through student and researcher exchanges.

At the same time, we have increased our staffing to 200. All of the new appointments in the past year are researchers, so we continue to expand our team of leading scientists.

As part of these advances, we have begun to examine ways to expand our research efforts. Those of you who have visited us recently would have noticed the extensive building work being carried out on the neighbouring site. Currently known as the Centre for Obesity, Diabetes and Cardiovascular Disease (CODCD), this will become a landmark research development for the University of Sydney. The Centenary's laboratories will have a link joining them to the new building and we are currently finalising negotiations to allow us to occupy a substantial portion of Level 4 of this Centre. This significant investment will help us capitalise on valuable synergies and collaborations between the two groups. Given that the Centenary and the University will share a considerable amount of infrastructure, as well as students, this will help us with a seamless expansion of our activities.

Similarly, the Centenary-Lifehouse at the RPA Cancer Research Centre will be located in the CODCD until a separate research facility can be built closer to Lifehouse's clinical centre. This is another strategic partnership that will help us increase our research capacity.

Board member Joseph Carrozzi has continued the great work of Neil Lawrence in leading the Centenary Foundation. Joseph has taken on this role with enormous enthusiasm and has achieved some great results in 2010. I would like to thank Neil for his fundamental role in energising this function for the Centenary and his continuing engagement with both the Foundation and the Board.

To celebrate Neil's contribution, the Centenary-Lawrence Creative Award has been established. Neil's long-time friend and colleague Rob Mactier has been instrumental in establishing this national award to recognise creativity in medical research. The inaugural award will be presented in 2011.

After serving on the Centenary Board for almost a decade, the Hon John Brown has stepped down. John has been instrumental in supporting the Centenary through his valuable guidance and contributions, especially in securing financial support to advance the work of our young researchers.

I would also like to thank my fellow board members, for their great support and continuing commitment to the Centenary, and especially our Director, Professor Mathew Vadas for the tremendous leadership he provides to the Institute.

Executive Director's Report

Professor Mathew Vadas

The sight of people with stethoscopes hurrying down the corridors of the Centenary is highly satisfying. Strong clinical links is the main ingredient in translating research discoveries into patient care through a high degree of clinical awareness and understanding what is relevant to patients.

At the Centenary, many of our senior researchers also have clinical responsibilities and our work gets constantly tested for its clinical relevance. This expertise in both clinical and research matters underlie the best of a much quoted concept: 'translation'.

Successful translation saves lives

Successful translation needs incredible focus and foresight; some of the research discoveries made 10 or 15 years ago are only now beginning to save lives. The use of cell and gene therapy has been recognised for a decade, yet the first successful trials are just starting. Centenary's Professor John Rasko has been instrumental in setting up such a unit at RPA Hospital and promises to bring these discoveries to our patient population. Similarly, Professor Chris Semsarian's discoveries about defective genes in the heart are immediately incorporated into diagnostic clinics and preventive strategies that save lives. Professor Geoff McCaughan continues decades of clinical and research work to improve the outcome of liver transplantation. These are all wonderful examples of the translational process working to save and improve lives.

Translation and the ageing process

One area in which translational research has been difficult is ageing. Surprisingly, whilst we happily acknowledge our increasing lifespan, there is little known about the process of ageing. Productive longevity is associated with good nutrition, exercise and mental agility, all in the face of subtly declining physical and mental prowess. Some interesting discoveries at the Centenary are promising to shed new light on the process of ageing.

Ageing is often associated with subtle signs of inflammation. This is a process that Professors Wolfgang Weninger and Barbara Fazekas de St Groth's groups have been investigating and discovering new strategies for its prevention. Another process associated with ageing is the senescence of cells. Professor Jennifer Gamble's group has discovered a new gene that appears to be a central player in the senescence pathway, again opening up a new way of looking for ways to moderate ageing.

Building on our strengths

A major event in 2010 was an independent review from the esteemed researchers on our Scientific Advisory Board (SAB). After three intensive days meeting with our heads and future leaders, the SAB provided a positive report to indicate we are on track to make a significant contribution towards medical advances. The SAB also made some great suggestions for further improvements to our research and outcomes.

Each year, as Centenary's scientific output and grant performance gets stronger, we become more convinced that our distinctive 'formula' – clinicians doing basic medical research, on a campus near RPA and the University of Sydney – needs to be fostered and

Executive Director's Report (continued)

Professor Mathew Vadas

strengthened. We are especially keen on working with Sydney Medical School to foster a new degree in both research and medicine as these students will lay a firm foundation for the best medical care in the long run.

Centenary continues to build a strong team of very talented researchers from our students right through to our inspirational Associate Faculty and Faculty members. It is an honour and privilege to work with our researchers to improve our understanding of disease, to improve prevention, diagnosis and treatment of cancer, cardiovascular disease and infectious diseases.

We were also most fortunate in recruiting Suzie Graham to head up our fundraising and marketing team. Suzie has extensive experience in this area, especially in social media networks, most recently at the Australian Cancer Research Foundation (ACRF). Amongst a number of innovations, we look forward to an increasing digital presence and an interactive website.

Suzie replaced Sally Castle, who has been our energetic and inspirational Fundraising and Marketing Manager for the last three years. Sally decided to gain experience in a different area of pro-bono activity in carbon management. We thank her for her wonderful work and wish her the very best in this new career.

I thank the other key members of our Executive for their dedicated efforts in 2010. This includes our two Assistant Directors, Professors Wolfgang Weninger and Chris Semsarian, our Chief Operating Officer Nick Pearce and Human Resources Manager Nanette Herlihen. Professor Weninger finished his two year term as Assistant Director at the end of 2010 and I thank him for his valuable contribution and commitment to this important role.

Finally, I also wish to extend my heartfelt thanks to all of our supporters. Our life-saving work simply wouldn't be possible without the generous financial support of granting bodies, private trusts, companies and individual donors who invest in our researchers.

Board of Governors

The Honourable Michael Egan (Chairman)

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

Mr Egan is currently the Chancellor of Macquarie University, Chairman of Australian Fisheries Management Authority Commission, Chairman of the Australian Day Council of NSW and is a former Treasurer of NSW. During his 25-year parliamentary career, Mr Egan held a number of ministerial positions and remains the longest serving Treasurer of NSW (1995-2005).

Mr John Samaha (Deputy Chairman)

Appointed Governor in 2003

Mr Samaha is a leading Sydney litigation lawyer. He established his own specialist litigation practice in 2009. Before that, he was a senior litigation partner at first tier law firm, Mallesons Stephen Jaques, where he acted for a wide range of that firm's institutional and corporate clients, predominantly industry sector leaders.

Dr Teresa Anderson

Appointed Governor in 2007

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

Mr Ken Cahill

Appointed Governor in 2009

Mr Cahill is currently the Executive Director of Royal Prince Alfred Hospital and has held a number of senior management positions in New South Wales Health. Prior to his current appointment he was General Manager of the Central Coast Health Service. He was formerly a Radiographer and was Chief Radiographer at Royal Prince Alfred Hospital from 1990 to 1997. Mr Cahill has a Master of Public Health from Western Sydney University.

The Honourable John Brown AO (retired July 2010)

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 Joseph Carrozzi

Appointed Governor in 2008

Mr Carrozzi is a National Managing Partner at accounting firm PricewaterhouseCoopers. He is responsible for managing relationships with some of the largest organisations in Australia, both ASX100 listed companies and also a number of major multi-nationals operating in Australia. Mr Carrozzi has led PwC's client service program in Australia, focusing on the strategy for growth and service quality. He has supported a number of the firm's charity partners such as Juvenile Diabetes Research Foundation. He is admitted as a Barrister at Law in NSW, a member of the Institute of Chartered Accountants in Australia and a Fellow of the Tax Institute of Australia. He is also a member of the Board of Italian Chamber of Commerce in Australia and the Corporate Board of European Australian Chamber of Commerce (EABC).

Mr Alastair Davidson

Appointed Governor in 2004

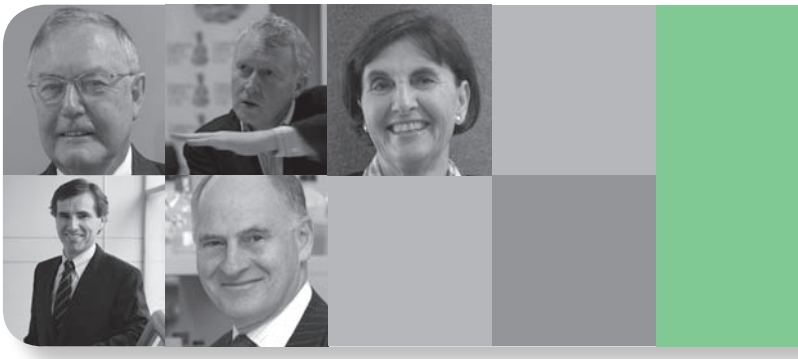
Mr Davidson has held executive positions in the banking and financial services industry for 24 years in the UK, US and Australia. He is currently Managing Director of Aurora Funds Management in Sydney. Prior to this, Mr Davidson was at Citibank, Australia in Sydney, where he spent eight years as co-head of its new product group. He is also a non-executive director of Biotech Capital, an ASX-listed investment company.

Professor John Horvath AO

Appointed Governor in 2007

Professor Horvath was the Australian Government Chief Medical Officer from 2003 - 2009. He is currently continuing to advise the Department of Health & Ageing and the School of Medicine, the University of Sydney and holds the position of Honorary Professor of Medicine. Professor Horvath is currently a member of the Council of the NHMRC and Chairman of the Healthcare Committee. He is a Fellow of the Royal Australasian College of Physicians and is a distinguished practitioner, researcher and teacher. Professor Horvath was previously Clinical Professor of Medicine at the University of Sydney and a specialist renal physician at Royal Prince Alfred Hospital (RPAH), and Area Director of Renal Services for the RPAH and Concord Repatriation General Hospitals. He is also known as a leader in a range of medical training and workforce organisations. He is also a former President of the Australian Medical Council and the NSW Medical Board.

Board of Governors (continued)



Mr Graham Kelly

Appointed Governor in 2006

Mr Kelly is a non-executive Chairman of Tishman Speyer Office Trust, Centrebet International Limited, Infigen Energy Limited and a non-executive director of several companies including FreshFood Australia Holdings Pty Limited and Oasis Fund Management Limited. He is a consultant to Freehills law firm, and was until recently the Inspector of the Independent Commission Against Corruption and a Director of the Medical Research and Compensation Foundation.

Mr Neil Lawrence

Appointed Governor in 2006

Mr Lawrence is the founder of Lawrence Creative Strategy, as well as the Executive Creative Director of STW, Australia's largest communications group. Mr Lawrence was the strategic and creative mind behind the Australian Labor Party's winning 'Kevin 07' advertising campaign, for which he was recognised as 'Australian Marketer of the Year' in 2007. In 2009, Neil was responsible for the marketing campaign behind Anna Bligh's bid to be elected Australia's first female Premier. In 2010, he ran the Minerals Council of Australia's successful campaign opposing the resources super tax to 'Keep Mining Strong.' His work combines creative flair with a deep understanding of highly complex, strategic political and corporate issues. This approach has also been used on corporate positioning and merger and acquisition campaigns for clients such as Wesfarmers, AGL, and BHP Billiton. More recently, Neil's pro bono campaign for indigenous nonprofit GenerationOne was viewed by 6 million Australians in one night, resulting in 2.4 million hits to the movement's website and a 20% boost in national awareness of GenOne. Neil has represented Australia internationally as the Chairman of Judges at the Irish International Advertising awards and on the film jury at Cannes. He writes regular columns analysing campaign strategy for The Australian, and appeared on ABC TV's series Gruen Nation and The Drum focusing on political campaigns.

Dr Susan Pond AM

Appointed Governor in 2009

Dr Pond has a strong scientific and commercial background having held executive positions in the biotechnology and pharmaceutical industry for 12 years, most recently as Chairman and Managing Director of Johnson & Johnson Research Pty Limited (2003-2009). Dr Pond has a Bachelor of Medicine and Surgery (Hons 1) degree from the University of Sydney, a Doctor of Medicine degree from the University of New South Wales and Doctor of Science and Doctor of Medicine *honoris causa* degrees from the University of Queensland. As a specialist physician, Dr Pond was a faculty member of the Department of Medicine at the University of California San Francisco and the University of Queensland thereafter, where she was appointed to a Personal Chair. Dr Pond has a very extensive publication and patent filing record. She has held Board positions including Chairman of the Australian Drug Evaluation Committee (ADEC), Executive Director of Johnson & Johnson Pty Limited and nonexecutive Director & Chairman of AusBiotech Limited. Currently, Dr Pond serves on the Board of Commercialisation Australia and the Board of Trustees for Australia's Virtual Herbarium.

Professor Bruce Robinson

Appointed Governor in 2007

Professor Robinson is Dean of the Faculty of Medicine, the 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 up a significant research enterprise in Adelaide. He was a chief initiator and Inaugural Director of the Hanson Centre for Cancer Research (now Hanson Institute). Professor Vadas has contributed strongly to the Australian biotechnology sector, being involved variously as founder, Chair of the Scientific Advisory Board and acting CEO of two ASX listed biotechnology companies. He serves as chair or member of many pro bono research related enterprises including NHMRC and Australian Cancer Research Foundation. He also currently serves on the Board of Governors of the Arts & Health Foundation.

Research Perspective

PhD Scholar Mei Li Ng, Signal Transduction

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

Cancer

With one in two Australians diagnosed with cancer before the age of 85, cancer remains a major concern for most people.

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 cardiovascular disease each year. Death rates have declined in the past decade but more than 3 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 three 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 almost 1.7 million people are dying each year from the disease.

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 four questions:

- Why do latent TB infection progress to active disease?
- 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

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

The blood vessel is composed of multiple layers of highly specialised cells, with a single layer of endothelial cells acting as a barrier between the blood and the tissue. The endothelial cells maintain the non-inflammatory, selectively permeable, non-adhesive and non-clotting surface of vessels. The endothelial cells also contain all the information necessary to make new blood vessels through a process known as angiogenesis. In adults, blood vessels normally do not proliferate except during the female reproductive cycle. However, in certain medical conditions, such as solid tumour growth and cardiovascular diseases, uncontrolled angiogenesis combined with abnormal and penetrable endothelial cells are hallmarks of these diseases.

The Vascular Biology program is focused on understanding how mature endothelial cells maintain their anti-inflammatory and non-leaky surface plus the signals essential for promoting angiogenesis. Our studies will provide insight into the changes that occur in the vessels upon ageing and in disease.

Highlights of 2010

We have identified a new source of control for angiogenesis and inhibiting vascular leak. This finding will impact on our understanding of diseases such as cancer, cardiovascular disease and rheumatoid arthritis.

MiRNAs are endogenous non-coding RNAs, originally thought to be derived from pieces of "junk" DNA. We now know that they exert major control over differentiation and developmental programs within cells. MiRNAs 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.

We have identified a group of miRNAs which are all decreased in their levels of expression during blood vessel formation. We have demonstrated that one miRNA when overexpressed can inhibit angiogenesis, control vascular permeability and target a specific endothelial cell adhesion molecule. This miRNA acts to inhibit angiogenesis under normal conditions, that is, it is an anti-angiogenic miRNA. Angiogenic stimulation results in a decrease in the levels of the miRNA, thus removing this inhibitory force. We have entered into a collaboration with a biotechnology company to test antagomirs and mimics to this miRNA to determine whether they are effective in regulating angiogenesis and permeability in diseases.

Major Projects

1. Investigating a key gene for heart disease, cancer and ageing

Senescence is a permanent and irreversible ageing of cells that inhibits uncontrolled cell proliferation and activation. Having identified and characterised the gene SENEX as being important in the induction of senescence in endothelial cells, we are now interested in:

- Molecular events that govern its expression.

Left to right: Research Officer – Paul Coleman; Research Officer – Angelina Lay, Senior Research Officer – Mai Tran; Research Officer – Joshua Moses, PhD Scholar – Garry Chang, Faculty – Professor Jennifer Gamble, Research Assistant – Jai Li; PhD Scholar – Garry Chang, Research Assistant – Jia Li and Research Officer – Joshua Moses.

- Structure-function of SENEX (in collaboration with the Structural Biology group at the Centenary Institute).
- Identifying interacting partners of SENEX that may modulate its activity and localisation.
- Determining the up and downstream signalling pathways that impact on SENEX and senescence.
- Determining the expression and involvement of SENEX in diseases such as cardiovascular diseases, tumour development and ageing. The development of mutant mice and the impact of deletion or overexpression of SENEX will aid in these studies.
- Investigating the identity and functional consequences of microparticle release from senescent cells.

2. Identifying the role of senescence in tumour growth

Senescence is a control mechanism to inhibit tumour growth. SENEX is also expressed outside the vascular system particularly in epithelial cells. Furthermore, it is induced by factors that are involved in tumour development. Dr Matthew Grimshaw has initiated work to determine the role of SENEX in cancer development, particularly in breast development and in breast cancer progression.

3. Investigating miRNAs in endothelial cells

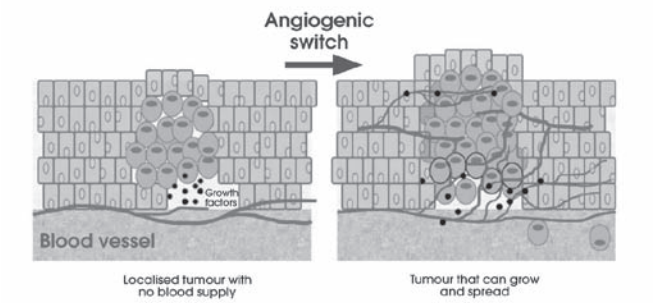
Building on our work that identified a group of miRNAs that are rapidly suppressed when angiogenesis occurs, the major focus of our research now is to:

- Understand the mechanism of their coordinated downregulation.
- Understand how they interact to control angiogenesis.
- Delineate their major targets.
- Determine the impact of using an external agent to regulate these miRNAs in disease.

4. New drugs to halt vascular leak

Vascular leak (permeability) is one of the key functional changes that cause many inflammatory diseases and cancer. For example, leaky blood vessels are responsible for the ability of the cancer cells to enter the blood stream and metastasize at distant sites away from the primary tumour. Therefore, effective methods of decreasing vascular permeability are likely to reduce or prevent metastatic spread.

The opportunity to develop drugs targeting vascular permeability has come from a refinement of our understanding of the factors and intracellular signals that maintain the selectively impermeable nature of blood vessels. In collaboration with Professor Michael Parker at St Vincents' Research Institute in Melbourne, we are developing small molecule inhibitors to target the critical signalling protein PKC, which is known to inhibit vascular leak.



How will this research impact community health?

The goal of the Vascular Biology group is to be able to manipulate the vascular system as an avenue of disease control.

New blood vessel formation and endothelial cell leakiness are essential features of solid tumour growth and are involved in spreading the cancer throughout the body (metastasis). Targeting both the tumour cells and the expanding network of blood vessels is proposed as a two-pronged approach to new anti-cancer therapies. Our goal is to understand the normal process of angiogenesis, identify major control pathways and identify possible targets for drug development.

Our research also has significant implications for cardiovascular disease. With age there is an increase in cardiovascular disease. Understanding what age means to the function of endothelial cells will potentially allow us to identify individuals at greatest risk of disease and develop novel approaches for intervention.

T Cell Biology

Professor Barbara Fazekas de St Groth

The number of people with autoimmune and allergic diseases has more than doubled in the past 20 years. Research by the T Cell Biology group aims to understand how the immune system normally prevents these diseases and which environmental factors are required to maintain immune function.

Such a rapid rise in these immune-mediated diseases must have been caused by changes in environmental factors, as the genes within our population cannot change that quickly. Our long-term goal is to return our immune systems to health by restoring their normal environmental factors.

One of the theories that seeks to explain the epidemic of immune disease is called the hygiene hypothesis. This theory suggests that too much cleanliness in early life causes these diseases by reducing contact between the immune system and environmental micro-organisms. Recent evidence points to the harmless micro-organisms that populate our gut and skin, collectively termed the "human microbiome", as an important regulator of immune function via a small but crucial population of T cells called regulatory T cells (T regs).

We are studying how T regs influence immune function in humans and in animal models. We are particularly interested in how they control the threshold at which the immune system becomes activated. Autoimmune and allergic diseases occur when the threshold is too low, which allows the body to recognise and over-react to harmless substances that should be ignored.

Highlights of 2010

- Discovered that regulatory T cells can prevent the activation of naturally arising self-reactive T cells by fine-tuning the stimulatory capacity of dendritic cells.
- Demonstrated that regulatory T cells act most potently at the sensitisation phase of the asthma response.
- Showed that T regs can prevent islet graft rejection mediated by T cells that are already primed against the graft at the time of transplantation.
- Identified a unique population of dendritic cells that bring tumour antigens to the lymph nodes where they activate tumour-specific T cells and T regs.

Major Projects

1. Immune regulation in mouse models

Fine-tuning dendritic cell stimulatory capacity by T regs: we are reconstituting immune-deficient mice with pure populations of T regs in order to measure their function in vivo. We have shown in immune-deficient mice that lack T regs that dendritic cells over-express many costimulatory molecules from the B7 and tumour necrosis factor families. This abnormality can be seen as early as two weeks of age. Transfer of regulatory T cells

Left to right: Faculty – Professor Barbara Fazekas de St Groth, PhD Scholar – Georgina Kalodimos, PhD Scholar – David Hancock, PhD Scholar – Yik Wen Loh, PhD Scholar – Lauren McKnight, Research Assistant – William Hey-Cunningham, PhD Scholar – Holly Bolton, Research Assistant – Cindy Zhu; Research Assistant William Hey-Cunningham; and PhD Scholar – Holly Bolton.

into these animals not only reduces the expression of costimulatory molecules but prevents the activation of self-reactive T cells. In contrast, transfer of conventional naïve T cells increases the expression of costimulatory molecules and augments the activation of self-reactive T cells, leading to autoimmune disease. In these experiments, we found it is critical to achieve the normal ratio of regulatory T cells to dendritic cells in order to normalise the level of costimulation, suggesting that the number and activation state of regulatory T cells are an important determinant of normal immune function. These studies provide the intellectual basis for our studies of human regulatory T cells.

Thymus gland selection of T regs: using a unique, genetically modified mouse model in which T cell receptor expression is modulated within the thymus, we have shown that T regs are selected at the double positive stage by signals with an avidity between that required for positive and negative selection.

T regs control sensitisation to allergens in asthma: by transferring genetically-marked T regs and allergen-responsive cells into normal mice, we have shown that antigen-specific T regs stop allergen-responsive cells from differentiating into effector cells that can generate an asthmatic lung response. This suppressive effect not only prevents the production of the Th2 cytokines IL-4 and IL-5, but also reduces production of IFN-gamma and IL-17 from higher affinity allergen-reactive T cells.

Organ transplantation: our work in skin and pancreatic islet cell transplantation continues to provide evidence supporting a new paradigm in which organ graft rejection cannot proceed without an initial attack by primed, cross-reactive T cells. We have now shown that effector but not central memory cells are capable of generating such an attack. We have also optimised techniques for visualising graft rejection using microscopy of living tissue. We found T regs can prevent rejection of islet but not skin grafts.

Anti-tumour immune responses: we have established a new mouse model to study interactions between T cells, dendritic cells and T regs during the immune response against tumours. In our model, transfer of regulatory T cells into animals with tumours accelerated tumour growth. This is consistent with the correlation between poor prognosis and an increase in circulating regulatory T cells in cancer patients. We have also identified a unique subset of dendritic cells that traffics through tumours, contains tumour-derived material and can activate tumour-specific T cells. These dendritic cells are not present in healthy animals.

2. Human regulatory T cells

Developing a comprehensive picture of T regs: In a collaborative project with Becton Dickinson, we are adapting our human T reg analysis to take advantage of the range of lasers available on the new custom-built 10-laser LSR analyser. Our aim is to develop ten colour panels to provide a comprehensive picture of the activation and differentiation state of T regs in healthy controls and patients with immune-mediated diseases. We are also developing bioinformatic approaches to optimise the analysis of the complex data acquired from these 10-colour analyses.

Investigating T reg abnormalities

Our current focus is on T reg abnormalities in patients with inflammatory bowel disease, multiple sclerosis, Graves' disease and psoriasis.

We are also analysing immune cells in patients with systemic lupus erythematosis (SLE) to correlate abnormalities in B cells, T cells and T regs. The aim of this research is to determine whether patients generally show abnormalities in all three cell populations or have subset-specific abnormalities that may distinguish between SLE arising from different causes.

How will this research impact community health?

Our research aims to understand how the immune system is regulated and define the abnormalities present in patients with diseases caused by the immune system. We hope this will provide new insights into the specific environmental changes responsible for these problem in our community.

Structural Biology

Dr Mika Jormakka

Membrane proteins account for up to 70% of all drug targets. By understanding membrane protein anatomy, structure and function, the Structural Biology group hopes to develop tailored drugs with better outcomes and less side effects.

Membrane proteins play a critical role in many normal cellular processes. They pump specific molecules across the otherwise impenetrable shield (membrane bilayer) that surrounds all cells and organelles. Alterations in the function of membrane proteins can cause many human diseases and disorders; thus, an intricate understanding of their structures remains a critical objective for biological research.

To recreate the structure of membrane proteins, the Structural Biology group uses a complex technique involving synchrotron radiation sources (particle accelerators) called X-ray crystallography. This allows us to develop a precise and detailed model of the protein to help us understand how a protein functions and provide a route to the discovery of structure-based drugs. This can be likened to mapping out the design of a lock or keyhole to create the matching key rather than conducting a lengthy, imprecise trial-and-error process to find a key that works.

Highlights of 2010

- We have initiated structural studies of membrane transporters involved in prostate cancer development and progression. This included setting up the infrastructure for eukaryotic membrane protein expression, which has been a major hurdle in the field. By using baculovirus infected insect cells for our expression, we have been able to obtain purified protein of the targeted transporters.
- We have continued our work on the prokaryotic iron transporter FeoB – a major virulence factor for many infectious bacteria. Early studies in 2010 indicated a potassium-dependent activation of the transporter. We have now proved this through both functional and structural characterisation. We discovered this potassium activation occurs through a unique structural feature on the protein, which could be targeted for structure-based drug design and provide novel antibiotic treatment for gastric ulcers, cystic fibrosis and severe gum disease (peridontitis).

Major Projects

Membrane proteins constitute roughly a third of the genes in genomes and perform numerous essential cellular functions. Their importance is reflected by the fact they represent 50-70 per cent of the targets of all current therapeutic drugs. Our group is particularly interested in structural studies of membrane proteins involved in the transport of molecules across the membranes of cells.

1. Switching off drug-resistant transporters

Membrane transporters are involved in the input and output of nutrients, ions and drugs across cell membranes. This plays a key role in maintaining normal cell functions but it is also linked to bacterial virulence and drug resistance, which has important implications for cancer and anti-microbial drugs.

Left to right: Associate Faculty – Dr Mika Jormakka;
PhD Scholar – Miriam-Rose Ash, Research Assistant – Samuel Tourle,
PhD Scholar – Amy Guilfoyle and Associate Faculty – Dr Mika Jormakka.

We continue to focus our studies on multi-drug transporters belonging to the novel 'multi-drug and toxin extrusion' (MATE) family. This family of transporters is found in both bacterial and mammalian species, where they are involved in eliminating the cell of toxic compounds, such as norfloxacin, ciprofloxacin and ethidium bromide.

2. Determining the structure of nutrient transporters

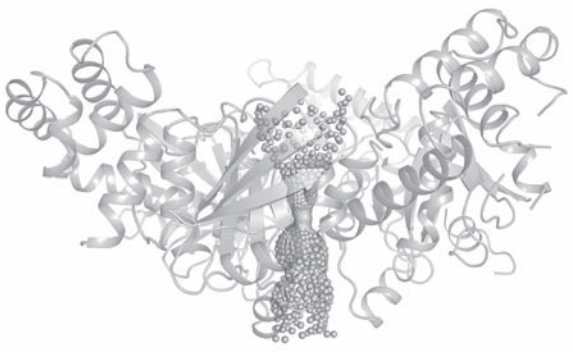
Nutrient intake by our cells is a normal, ongoing process. When the intake is regulated and balanced it helps our cells function properly. In cancer, many balanced processes are thrown into disarray and the specific transport levels are altered to allow cancer cells to develop and progress.

Of particular interest to our group are transporters that are upregulated in prostate cancer. These transporters are specific for amino acids (leucine) that enable the cells to grow rapidly. With Dr Jeff Holst from the Origins of Cancer group, we are conducting structural studies that target two transporters (LAT1 and LAT3) found to be important for the development and progression of prostate cancer. By determining the anatomy of these transporters it will provide a platform for therapeutic design.

How will this research impact community health?

The global effort researching the structural biology of membrane proteins is revealing critical information about the mechanism and architecture of these medically important proteins.

Our long-term aim is to provide high-resolution structures to help structure-based drug discovery. This will allow us to move away from a trial-and-error process of drug discovery to a scenario where we first identify the structure so we can design a 'perfect' drug. This would potentially provide drugs that hit the target with more precision and reduce unwanted side-effects. Structure-based drug design would also lead to far cheaper drugs and shorten the time from discovery to patient use.



Structural representation of metal funneling in a membrane transporter

Signal Transduction

Associate Professor Pu Xia

With a goal of understanding how cells communicate in response to various challenges, our research explores new strategies to alter cellular communication pathways to prevent and treat diseases in a more targeted and potent way.

With up to 75 trillion cells in our body, incorporating hundreds of thousands of specialised functions, good communication between cells is essential for good health. Every cell constantly receives information from the surrounding environment and then transmits signals within the cell or to its neighbours to keep our body functioning. Such communication, also called signal transduction, is processed by cellular languages that consist of numerous molecules and/or biochemical reactions. Our research aims to decode these cellular languages and understand how cells communicate. We also seek to identify faults in the communication process that cause diseases, such as cancer, diabetes and cardiovascular disease.

Our earlier work identified a key signal transduction pathway that is mediated by the enzyme sphingosine kinase (SphK). Activation of this communication pathway is important for cell survival and growth. We found SphK is often overproduced by cells that are inflamed or malignant. Remarkably, blocking this enzyme with chemical or genetic inhibitors, significantly reduces inflammation and slows down or stops cancer cell growth.

On the other hand, cell survival is essential for normal cells to maintain their functions. For instance, pancreatic beta cells produce insulin. When a defect occurs in beta cell survival (leading to insufficient insulin production) it causes diabetes. Interestingly, we found that a single molecule is a key signal for beta cell survival, especially under certain medical conditions such as obesity.

We aim to explore these findings in more clinically relevant settings and to develop new drugs that alter the SphK signalling pathway in a tissue-specific manner for the treatment of cancer, diabetes and inflammation-associated diseases.

Highlights of 2010

- We uncovered FTY720, an analogue of sphingosin, as a promising new drug to kill ovarian cancer cells in a unique way. Current anti-cancer treatments, such as cisplatin, kill ovarian cancer cells by programming cell death (known as apoptosis) but this can be reversed by cancer cells. However, FTY720 kills cells through an irreversible process, known as necrosis, so cancer cells cannot resist, repair and return.
- We identified that autophagy is regulated by sphingolipids, which mediates cancer cells resistant to chemotherapy. Blockage of autophagy is an ideal strategy to help anti-cancer drugs, such as cisplatin, kill cancer cells more effectively.
- We created a novel mechanism through activation of a single molecule to protect pancreatic beta cells against death under certain medical conditions. By altering this pathway we may be able to prevent obesity-associated diabetes.

Left to right: Faculty – Associate Professor Pu Xia; "The Kiss" photo taken by Research Fellow, Eileen McGowan; Faculty – Associate Professor Pu Xia and Research Assistant – Dominik Kaczorowski; and PhD Scholar – Mei Li Ng.

Major Projects

1. SphK in inflammation and cancer development

Many types of cancers are associated with chronic inflammation, particularly liver cancer. Working with the Liver Immunobiology and Vascular Biology groups, we aim to understand how inflammation leads to cancer and explore new strategies to prevent liver cancer. We will use multiple molecular and genetic tools to examine the role of SphK in inflammation and cancer development. This study will allow us to develop new strategies and may lead to the discovery of new cancer treatments.

2. Preventing pancreatic beta-cell death for treatment of diabetes

Cell suicide or apoptosis that destroys pancreatic beta-cells is a common cause for both type 1 and type 2 diabetes. Thus, protecting beta-cells against death and rescuing their insulin function is emerging as a new strategy for managing diabetes.

Our research will examine how pancreatic beta-cells communicate in order to survive, especially under stressful conditions such as high levels of blood sugar or lipids. We will also explore the intersecting pathways that support beta-cell survival and insulin secretion. By using several cell culture models, we have provided strong supporting evidence of a protective role for a single molecule in combating beta-cell death. We are now studying gene-deficient mice to determine whether pancreatic cell death is increased or accelerated in different medical conditions. This research could reveal a new signalling pathway to regulate beta-cell function and survival that could help develop a new therapeutic target for diabetes.

3. Mechanisms of diabetes associated cardiovascular disease

Our early work has demonstrated three novel signalling events that are critically involved in diabetic vascular complications, including (i) diacylglycerol kinase, (ii) SphK and (iii) protein S-nitrosylation. These findings help us to understand why people with diabetes or obesity have a greater risk of developing heart disease when they become insulin resistant. We are now examining if changes in SphK1 can disrupt the normal activity of insulin within blood vessel cells and cause heart disease. This could lead to a potential drug target to halt or slow down the progression of diabetes and obesity associated cardiovascular diseases.

4. Protein S-nitrosylation in health and disease

Building on our previous findings that cells exposed to high-glucose decrease the protein S-nitrosylation, we are investigating the effect of S-nitrosylation on proteins critical to cell movement and survival. Dysregulated S-nitrosylation has been implicated in numerous disease states including cancer and diabetes. This research aims to identify the signalling pathways disrupted by dysregulated S-nitrosylation to help develop novel targeted therapies.

How will this research impact community health?

Many current drugs have issues with drug resistance and unwanted side effects. Our research focuses on understanding cell communication and finding the faults or switches in the signalling networks that can cause or control disease. This will help us to identify molecular targets for the development of more effective therapies that specifically shut down the disease-causing signals so we can treat or prevent the disease at its root.

Molecular Cardiology

Professor Christopher Semsarian

Identifying potentially fatal genetic faults in families with heart disease is the cornerstone of developing new treatment and prevention strategies, with the ultimate aim to save lives both now and in future generations. Cardiovascular disease affects one in five Australians and one out of two families. Yet many genetic causes of heart disease remain unknown.

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

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

Highlights of 2010

2010 was a very exciting and productive year for the Molecular Cardiology team. Our cutting-edge research was published in 10 peer-reviewed, high-quality international journals. Our work was further recognised on the international stage through a series of invited presentations in the field of genetic heart diseases. In addition, Professor Semsarian was awarded a prestigious 2010 NHMRC 10 of the Best Award, which recognises the top 10 researchers in Australia across all medical research fields.

- Professor Semsarian and his team have commenced a world-first, NHMRC-funded national study focused on sudden cardiac death in the young. This prospective study aims to identify the clinical and genetic basis of sudden death, and to initiate treatment and prevention programs to reduce sudden death among young Australians.
- Emily Tu completed her PhD on fascinating and ground-breaking research into the genetic factors which predispose young people with diabetes or epilepsy to sudden death. Ms Tu presented her research at the prestigious Cardiostim Scientific Meeting in France and will continue her research in Professor Semsarian's team in 2011.
- Dr Christine Chiu, also as a PhD student, was awarded the Axel Ullrich Award for the research paper with the highest impact factor at the Centenary Institute. Her research, published in the highly ranked Journal of the American College of Cardiology, identified a muscle protein (Actinin-2) as a new cause of hypertrophic cardiomyopathy using a genome-wide approach.
- Dr Jipin Das received the extremely prestigious Endeavour Prime Minister's Australia Asia Award to commence his PhD studies under the mentorship of Professor Semsarian in 2011.

Major Projects

The Agnes Ginges Centre for Molecular Cardiology is focused on the translation of basic laboratory research to improve 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.

Left to right: Faculty – Professor Christopher Semsarian; Research Officer – Emily Tu and Faculty – Professor Christopher Semsarian; Faculty – Professor Christopher Semsarian, Research Officer – Richard Bagnall, Research Officer – Emily Tu, Genetics Counsellor – Laura Yeates, PhD Scholar – Matthew Kelly; and Genetics Counsellor – Laura Yeates.

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.

Examining three key areas

The aims of the research program are to:

1. **Identify new gene abnormalities in patients with heart disease**
2. **Understand the molecular basis of how these gene mutations lead to disease**
3. **Investigate how these disease-causing 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.

Sudden cardiac death in the young

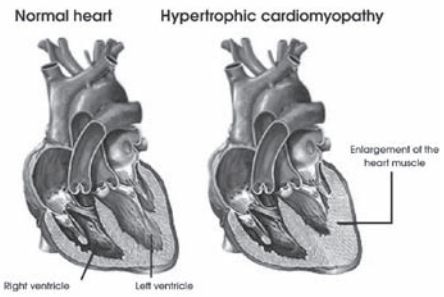
A number of diseases are being studied, ranging from structural heart disorders such as cardiomyopathies to primary arrhythmogenic diseases such as long QT syndrome. A specific area of study is in sudden cardiac death, particularly in the young. These studies include novel gene discovery, genetic diagnosis,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

Investigating hypertrophic cardiomyopathy

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

HCM is characterised by marked thickening of the heart muscle and occurs in approximately one in 500 people, making it the most common genetic heart disorder known. Our research program has seen and collected clinical information and DNA in over 600 HCM 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 HCM, as well as cell culture models to evaluate the cellular effects of specific gene mutations.

These models are likely to provide the keys to unlock the mysteries of genetic heart diseases and their complications, including heart failure and sudden death.

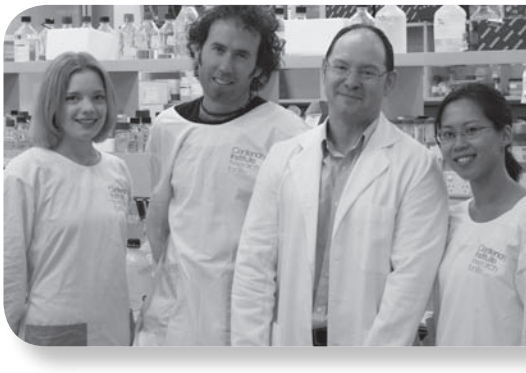


How will this research impact community health?

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 window for initiation of treatments and prevention strategies.

Our work will also be used to identify the people in our community who have a higher risk of developing 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), potentially identifying new targets for pharmacological therapy.

Gene and Stem Cell Therapy



Professor John Rasko

The revolutionary platform technologies involving gene therapy and the use of stem cells could effectively cure many human diseases, including some cancers as well as genetic and infectious diseases, diabetes and heart disease.

The Gene and Stem Cell Therapy group are looking to overcome the barriers to successfully implement innovative technologies, develop models to understand the biology of adult stem cells and discover the causes of diseases such as cancer and genetic disorders. The group undertakes research in five areas: gene therapy; stem cell biology; molecular mechanisms of gene control; genetic disorders; and cancer biology.

Specific staff are allocated to each of these areas but the best outcome is achieved by building project-based organic collaborations to take advantage of the core technologies we have developed at Centenary. For example, understanding the mechanisms of how a normal cell becomes cancerous is a daunting task that needs a multi-faceted approach. By studying proteins and RNA molecules present in different cancers, we reveal the basic biology of cancer that could lead to new therapies. Studying transcription factors and microRNAs help define the biochemical pathways and inter-molecular machinery involved in cancer. Bioinformatics and non-coding RNA molecules (so-called 'junk' DNA) also contribute to our overall understanding of how cancer develops.

Highlights of 2010

We achieved a major breakthrough in 2010 with an internationally-acclaimed discovery on how to maintain and expand the number of blood-forming stem cells grown outside the body. These cells have been used to cure individuals suffering from leukaemia, lymphoma and multiple myeloma for over 50 years. Yet obtaining sufficient numbers of these remarkably rare cells remains a major challenge in stem cell transplantation.

To help overcome this issue, we used the most elastic biological substance available to prove stem cells prefer to be in a stretchy, flexible environment rather than a solid, hard one. We found this substance tripled the number of blood-forming stem cells that we could grow outside of the body. Since these stem cells are the critical component of bone marrow and cord blood transplants, our finding could increase the effectiveness and safety of these transplants to treat diseases such as leukaemia, lymphoma and multiple myeloma.

Published in the highest ranked biotechnology journal Nature Biotechnology, this novel idea also paves the way for technologies designed to expand the use of these cells beyond bone marrow transplantation.

Other highlights include:

- We showed mutations in the solute transporter SLC1A1 cause a rare kidney disorder known as dicarboxylic aminoaciduria. This is a recessive human disorder of urinary glutamate and aspartate transport that can also impair mental capabilities. Published in the prestigious Journal of Clinical Investigation, this discovery was widely covered by media due to the possible link with obsessive compulsive disorder (OCD).
- Completed the first analysis of amino acid transporter distribution during

Left to right: PhD Scholar – Jessamy Tiffen, Senior Research Officer – Chuck Bailey, Faculty – Professor John Rasko, Research Assistant – Cynthia Ng; Faculty – Professor John Rasko; and Senior Research Officer – Chuck Bailey.

embryonic development. In another related study with collaborators in Canada, we showed how these nutrient transporters are involved in kidney damage, which is an important finding for kidney transplantation and organ rejection.

- Conducted a comprehensive analysis of miRNAs in primary chronic myeloid leukaemia samples before and after treatment.
- We demonstrated the in vivo luminescent imaging technology (IVIS) is an effective system for tracking cancer cells. This important and expensive device was purchased from grants coordinated through our program.
- We showed that genetic modification of cells that line blood vessels – endothelial cells – can lead to improved function following heart attacks.

Major Projects

1. Unique way to grow stem cells

We will build upon our collaborative work with groups in Texas, USA and the School of Molecular and Microbial Biosciences at the University of Sydney. This important work delivered a major breakthrough in 2010 with our research proving that blood-forming stem cells prefer to be in a stretchy, flexible environment. This provides a unique tool to study cell biology and offers a valuable dimension to future biomaterial design for culturing cells outside the body.

The quest to expand the number of stem cells outside the body is one of the 'holy grails' of adult stem cell biology. This finding will also contribute to future ex vivo cell manipulation strategies and gene therapies.

2. Essential cell functions in cancer

Our collaboration with the group of Victor Lobanenkov at the National Institutes of Health (NIH) in Washington DC, USA continues to examine the role of the tumour suppressor gene CTCF and its related cancer/testis gene BORIS. BORIS is normally only expressed in the testis, however it is over-expressed in many different types of tumours.

3. Complex analysis of gene expression

An understanding of the way blood cell production is regulated in the body has immediate relevance to understanding and treating diseases like leukaemia. We are studying regulatory molecules, known as microRNAs, to discover their hidden functions in normal blood cells and leukaemia in humans. To understand these better, we will advance our work on building a reliable compilation of miRNA and mRNA expression data to compare multiple tissue types. This research links into the online resource mimiRNA we developed to integrate gene expression data and visualisation. This resource has received an overwhelming response from the international research community. Ultimately, this project may lead to novel treatments involving gene therapy and bone marrow transplantation.

How will this research impact community health?

Our work in the use of blood-forming stem cells could increase the effectiveness and safety of treatments for diseases such as leukaemia, lymphoma and multiple myeloma, since these cells are the critical component of bone marrow and cord blood transplants.

The safe introduction of healthy genes into patients with genetic disorders could effectively cure inherited genetic disorders such as some cancers, haemophilia and degenerative disorders as well as infectious diseases such as HIV. Improving gene delivery to stem cells may assist in both expanding the potential number of diseases amenable to treatment, as well as improving their effectiveness.

With the development of new therapeutics for cancers including antibodies and small molecules, it has become increasingly important to identify novel targets. These technologies, previously thought to be impractical, have now been proven to provide effective new approaches for the treatment of cancers. For example, the small molecule known as imatinib (Glivec) has revolutionised the treatment of chronic myeloid leukaemia.

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, few studies measure the effects of nutrition on disease.

Indeed, there is growing evidence linking obesity with diabetes, cardiovascular disease and cancer. Tumours require a constant supply of nutrients to grow and cancer cells consume more nutrients than normal cells. There are over 350 different nutrient transporters that can transport a variety of substrates, including amino acids. Additionally, the expression of specific amino acid transporters are increased in many primary cancers. Increased understanding of the metabolic requirements of tumours and the role of these transporters may lead to new treatments for cancer.

Highlights of 2010

We have been funded over the past three years by the Prostate Cancer Foundation of Australia (PCFA), which continues in 2011. Dr Kevin Wang, a talented postdoctoral scientist in the group, has generated impressive data showing the role of two separate nutrient transporters in prostate cancer.

Highlights include:

- Showing for the first time a link between testosterone signalling pathways and one of our amino acid transporters. We now know why this transporter is increased in prostate cancer. We aim to publish these findings in 2011.
- Publishing in Nature Biotechnology our work showing how haemopoietic stem cells respond to the physical forces generated by an elastic surface (see page 21 for more details).
- Publishing in Molecular Cancer the first paper from the Centenary Institute using the in vivo imaging system (IVIS-100). Our work definitively showed that use of this tracking technology does not adversely influence the cancer cells, thereby making it an effective method with which to monitor cancer development and treatments.
- Publishing 5 other collaborative papers including EMBO Journal with St Jude Children's Research Hospital (USA), Nature Structural and Molecular Biology with Institute of Molecular Bioscience (QLD), Cellular Signalling with the University of Newcastle (NSW), Haematologica and Biochemical Journal with Gene & Stem Cell Therapy group.
- Dr Holst gave an invited presentation at the PCFA Annual Meeting.
- A PCFA project grant with Dr Mika Jormakka in Structural Biology, which provides $250,000 toward determining the structure of the amino acid transporters as potential therapeutic targets.

Major Projects

1. The role of amino acid transport in melanoma, breast and prostate cancer

Approximately 70% of prostate cancer patients have alterations in a single pathway necessary for cell growth. This is similar for melanoma. Decreased expression of one member of this pathway (PTEN) leads to increases in the activity of another member (mTOR) which drives increased cell growth. Amino acids such as leucine have been shown to activate mTOR, which contribute to uncontrolled growth of cancer cells.

We continue to investigate how these nutrient transporters may promote cancer growth and how they are regulated. This will be studied using various cancer cell lines and a prostate cancer mouse model. Analysis of the genes involved in the onset and progression of cancer will be determined in these models.

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 cancer. Alternatively, these transporters may be targeted for therapeutic intervention, designed to 'starve the cancer'. Our latest work together with Dr Jormakka will help us to develop these drugs in the future.

Bioinformatics

Dr Nicholas Shackel and Dr Mathew Harrison

The Bioinformatics group uses complex computer-based approaches to quickly and effectively analyse the vast amount of data generated by researchers across the Centenary Institute. Bioinformatics interpretation of this wealth of data increases the pace of medical discoveries.

Fundamental highly significant biological questions pivotal to understanding human disease require complex computational bioinformatics analysis. Contrary to traditional research methods, bioinformatic approaches are used to understand the multiple complex interactions that are the basis of most disease. Bioinformatics uses computational analysis of large complex data sets, representing data in new and unique ways to enable researchers to understand the intricate basis of many human diseases including cancer, heart disease, tuberculosis and liver cirrhosis.

Initially founded in 2009 from the Centenary Institute Foundation's fundraising efforts, our group uses bioinformatic approaches to examine complex interactions within the whole human genome to determine how cardiac disease results in sudden cardiac death as well as understanding how liver cancer develops.

The computational requirements of modern Bioinformatic approaches are considerable and our group has established server infrastructure to support the Bioinformatics requirements of all researchers within the Centenary Institute.

Highlights of 2010

- Dr Mathew Harrison was appointed as Foundation Fellow in Bioinformatics
- Delivered the first Centenary Colloquia on Bioinformatics to inform and educate researchers from various institutes about the latest trends in this vital approach to research.
- Aimei Lee was awarded Class Honours and an Australian Postgraduate Award to study the modification of the protein CD147 by the addition of sugars and what role this has in the development of scarring of the liver and liver cancer.
- Bioinformatics was awarded a Roche Pillar Grant in collaboration with Associate Professor Michael Beard from The University of Adelaide to characterise Hepatitis C (HCV) viral diversity and its relationship to interferon gene expression by using ultra deep sequencing. This project aims to determine the mechanisms by which HCV is cleared by the body.

Major Projects

Our studies are currently focused on two main Bioinformatic areas of research:

1. Finding the genetic signature of diseases

We are working on determining the genetic signature of diseases to enable the prediction of outcomes. We have developed a novel computational means of analysis, which will enable us to profile and more importantly, individualise predication of outcomes in disease states.

2. Investigating Glycosylation in disease

Glycosylation is the process of adding sugars to proteins. We are studying the variation of this process and how it may contribute to disease. We believe that this process will vary and contribute to the development of pathogenic processes such as cirrhosis and liver cancer.

How will this research impact community health?

Most common human diseases such as heart disease and cancer are now recognised to have multiple causative factors that cumulatively lead to disease resulting in human suffering. Bioinformatic approaches are essential to understanding how these diseases evolve and specifically answer the question of how these multiple and complex interactions cause disease.

Mycobacterial

Professor Warwick Britton

Tuberculosis (TB) continues to be a major health problem worldwide with 9 million new cases and more than 1.7 million deaths each year. The Mycobacterial research program contributes to tuberculosis control by understanding the immune response to the TB bacteria, developing more effective vaccines and new drugs and identifying new ways to manage tuberculosis in countries with high levels of this devastating disease.

Mycobacterium tuberculosis infection is also an important model of intracellular bacterial infections. Therefore the discoveries we make about TB infection provide new information on how the immune system controls many different types of infections in humans.

Mycobacterium tuberculosis infection is also an important model of intracellular bacterial infections. Therefore the discoveries we make about TB provides new information on how the immune system controls many different types of infections in humans.

The Mycobacterial laboratory consists of three key groups that work on different approaches to stopping tuberculosis:

- Mycobacterial Immunology led by Professor Warwick Britton
- Host Response to Tuberculosis led by Dr Bernadette Saunders
- Vaccine Development and Pathogenesis led by Dr Nick West

Highlights of 2010

As part of our Wellcome Trust-funded Infection and Immunity Genetic Consortium, we have used the new technology of next generation sequencing to identify the causative mutation in a novel line of genetically modified mice, which have increased susceptibility to M. tuberculosis. This work, carried out by Professor Britton's and Dr Saunders' group, has provided exciting new information on how the immune system controls tuberculosis. This technology will increase the rate we can identify mutants that cause increased susceptibility to the disease.

In our vaccine studies we have discovered that modified BCG vaccine expressing the cytokine GM-CSF modulates the immune system in the lung and enhances protective immunity against tuberculosis infection. We have collaborated with the Aeras Foundation in Washington to develop strains of their new BCG vaccine that express mouse and human GM-CSF for further evaluation of this novel vaccine strategy. Building on our work developing a new sub-unit vaccine based on the fusion of cutinase-like proteins, we have discovered it protects mice against pulmonary tuberculosis infection. Sub-unit vaccines reduce the chance of an adverse reaction by using only the antigen components that trigger T cells to respond to the infection.

We have made substantial advances in our studies on drug targets for tuberculosis. Continuing our work on a secreted lipase essential for the growth of both M. tuberculosis and Mycobacterium leprae, studies with collaborators at Monash University have identified the three dimensional structure of the homologue of this lipase in Mycobacterium smegmatis. Inhibition of this lipase kills M. tuberculosis so we are working with Dr Richard Payne in the School of Chemistry at the University

Left to right: Faculty – Professor Warwick Britton; Associate Faculty – Dr Nick West, Associate Faculty – Dr Bernadette Saunders, Faculty – Professor Warwick Britton; Associate Faculty – Dr Nick West, PhD Scholar – Erin Shanahan; and Research Officer – Jennifer Huch.

of Sydney to make new more effective inhibitors of this enzyme. Dr West, Professor Britton and Dr Payne have received new NHMRC funding to make and test new TB drugs targeting this enzyme. We have also been testing inhibitors of two other essential enzymes of M. tuberculosis, which have been synthesised by Dr Payne's group.

We initiated a new project on studying the interactions of mycobacterial infections and influenza in the lung. We have demonstrated for the first time that co-infection with BCG and influenza changed the T cell response to both organisms. These studies resulted in the award of a new NHMRC project to Professor Britton, Dr Jamie Triccas and Dr Manuela Florido with a collaborator, Dr John Stambas at Deakin University.

In 2010 we launched our study on the role of active case finding from proving tuberculosis control in Vietnam. This NHMRC-funded study is a five year, collaborative study between the Centenary and Woolcock Institutes and the National Tuberculosis Program in Vietnam. It will examine the benefits and cost effectiveness of active case finding in the contacts of tuberculosis patients diagnosed across the country. A series of workshops were conducted in centres throughout Vietnam covering the 70 districts, which have been randomised to this intervention.

Major Projects

1. Understanding immunity to improve vaccines

We continue to focus on understanding how the host responds to infection with M. tuberculosis and how to make more effective vaccines against this infection. Further studies are continuing on our sub-unit vaccine and investigating mycobacterial lipoproteins as vaccines against tuberculosis.

2. Developing new drugs

We are also expanding on our efforts to explore how the tuberculosis bacterium responds during infection of the host by changing the genes it expresses and the functions of selected proteins. The genes, which are essential for the survival of M. tuberculosis, are the targets for the development of new drugs.

3. Investigating latent tuberculosis

Latent TB infection is now a major topic of research within the group. It is estimated that a third of the world's population have latent TB infection, which is not infectious and does not cause illness. However, this group is at risk of developing active TB. Understanding latency is vital to the development of drugs, which will work on non-replicating organisms which persist in the lungs of people that have latent tuberculosis infection. More effective, shorter treatment for latent TB would be a major tool for the long term control of tuberculosis.

4. Risky genes and public control studies in Vietnam

We will also build on the great foundations we have developed in Vietnam over the past two years with the National Tuberculosis Program and the National Lung Hospital in Hanoi. We will carry out critical work on searching for genes that make a person more susceptible to tuberculosis. Vietnam-based PhD researcher Dr Greg Fox will help with this project by working with Professor Britton and Professor Guy Marks from the Woolcock Institute to roll out the active screening project.

How will this research impact community health?

Over 2010 there has been further emergence of multiple and extensively drug resistant (XDR) strains of M. tuberculosis in our region. The first cases of XDR-TB were also recently reported in Australia. This worrying trend in drug-resistant TB and the increased spread of HIV means that tuberculosis infection will remain a major problem in our region for decades. New control measures are urgently needed. The development of more effective vaccines and anti-TB drugs will be essential to controlling tuberculosis and improving human health worldwide.

Host Response to Tuberculosis

Dr Bernadette Saunders

TB was once commonly known as 'Consumption' because it seemed to consume people from within.

The current TB vaccine does not provide lifelong immunity and no new antibiotics have been listed for the treatment of TB in over 50 years. The development of new treatments, or a more effective vaccine, requires a greater understanding of the factors that regulate immunity to TB.

Our group is examining the functions of macrophages – a white blood cell that is the major cell type responsible for controlling TB. Our focus is to identify genes within the macrophages that regulate immunity and define how macrophages communicate with one another. We are also working to uncover and examine new genes that modulate resistance or susceptibility to TB infection. The aim of these studies is to increase our understanding of the biology of this disease, which we hope will lead to new biomarkers for identifying TB and new therapy targets to treat this devastating infection.

Highlights of 2010

We identified a gene mutation in mice that makes the animals more susceptible to TB, this mutation also occurs in humans causing a debilitating periodic fever syndrome. This finding was part of an ongoing collaborative project with Professor Goodnow and colleagues at ANU (Canberra) and Oxford (UK).

With two new NHMRC grants starting in 2010 new staff joined our group. Dr Brian Chan began work examining how human macrophages control TB infection and Ms Caitlin Gillis started investigating the role of the molecule SSB2 in control of TB infection.

Our collaboration with the National Lung Hospital in Hanoi, Vietnam, made significant progress. We have now collected blood from more than 800 TB patients and people without TB (controls) in Vietnam to test for mutations in genes that may increase a person's risk of developing TB infection.

Major Projects

The primary focus of our group is to understand the factors that regulate protective immunity to TB infection.

1. Controlling TB with white blood cells

Principally we are examining white blood cells known as macrophages. TB resides in macrophages, the very cells that must be activated to kill the TB bacteria. We are studying the mechanisms used by human macrophages to control TB infection. We will continue to build on a recent exciting discovery that macrophages infected with TB communicate with other surrounding cells through the release of small molecules known as microparticles. This research may lead to the development of alternative therapies to treat TB infection.

2. Identifying high-risk genes

We also have current ongoing projects to identify genes that influence resistance and susceptibility to TB. As part of our collaborative project with colleagues at the National Lung Hospital in Vietnam, we will continue to analyse the DNA of TB patients for gene mutations that may increase a person's risk of developing TB. Further, we will keep screening mutant mice for new genes that affect immunity to TB as part of a Wellcome Trust-funded project with collaborators at ANU, Oxford and Paris.

Vaccine Development and Pathogenesis

Dr Nick West

In order to design more effective vaccines to prevent the spread of TB and develop drugs to improve the outcome for people already infected, we need to know more about how the bacterium causes disease. This is why research within the group is aimed at identifying the bacterial genes which are essential to the survival of M. tuberculosis. Additionally, we are focused on how the bacterium is able to live within the host for the life of the host, usually without causing any symptoms at all.

With this knowledge we can make better decisions regarding drug development to treat both acute and chronic infections, ultimately shortening treatment from months to just weeks.

Highlights of 2010

- Key findings from the group resulted in publication success with peer-reviewed articles on vaccines, drug development, protein biochemistry and cellular microbiology.
- The group has again achieved significant funding through the NHMRC with a new research grant (>$700,000) aimed at drug discovery and development.
- Dr West was one of only 10 researchers in the country to be awarded an NHMRC Career Development Fellowship - Level 2 (biomedical).
- Ms Erin Shanahan, A PhD scholar in the group, was selected as one of 16 students worldwide to attend a training course on Advanced Bacterial Genetics at the world-renown Cold Harbor Laboratories in New York.
- The NSW Minister for Science and Medical Research issued a media release highlighting the drug development work performed by the group. This had considerable international print media coverage and national radio exposure, including the ABC.
- Dr West, Professor Britton and Dr Payne (University of Sydney) filed a provisional patent, protecting our lead anti-TB drug candidates. The compounds target an enzyme of M. tuberculosis, which the bacteria cannot live without, representing a genuine advance for new anti-TB drug therapy.

Major Projects

Our focus is to investigate the processes of disease development (pathogenesis) to improve vaccines and treatments for tuberculosis. We are committed to understanding bacterial contributions to disease.

1. Screening for essential genes

We endeavour to identify the gene set required to colonise the lung and spread to distant organs. Furthermore, we are searching for essential genes required by the bacterium to persist long-term within the host, i.e. during latent TB infection. We have established new mechanisms to examine this latent form of TB and have begun screening our extensive library of mutants for those which are unable to establish chronic infection. This is a very exciting project with great potential to yield vital information about this important aspect of disease.

2. Creating better vaccines

We continue to make progress towards vaccine improvement. An active program exists in the laboratory to deliver vaccines as harmless, protein subunit-vaccines and as non-replicating viruses. These next generation vaccine strategies offer promise for use to boost primary immunisations.

Additionally, we are investigating and trialing other non-living vaccines including those which can directly influence the human immune system, making it stronger and more responsive to infection.

Immune Imaging

Professor Wolfgang Weninger

The Immune Imaging program uses cutting-edge microscopy and innovative models to discover how the immune system fights tumour cells and invading microbes.

The principle approach of the group is the use of multiphoton microscopy – a state-of-the-art imaging technique to track the minute workings of cells and molecules within living tissues. We can now study the dynamics of cell movements and interactions at a level of resolution that has not been previously reached. Using this approach, we investigate fundamental questions related to infections and tumours.

The distinct project groups within the Immune Imaging group include:

- Immune Imaging led by Professor Wolfgang Weninger
- Tumour Microenvironment led by Dr Paulus Mrass
- DNA Repair led by Dr Chris Jolly
- Experimental Melanoma Therapies led by Dr Nikolas Haass

One of the major interests of the Immune Imaging group led by Professor Weninger is studying the role white blood cells (leukocytes) play in the immune system's ability to protect the body against disease. Multiphoton microscopy enables us to conduct real-time studies in living tissue to examine how leukocytes detect and destroy tumour cells and microbes, such as viruses, bacteria and parasites.

Highlights of 2010

We have discovered a novel population of skin-resident lymphocytes, which belong to the subclass of gamma-delta T cells. We have found that these cells are essential in the defence against mycobacterial infections of the skin, in part by their production of the pro-inflammatory cytokine IL-17. These findings have important implications for our understanding of skin immunity and help develop new vaccination approaches and strategies against skin inflammation.

For the first time, we have visualised how Herpes simplex virus enters the skin and how the immune system responds to this infectious agent. Published in The Journal of Immunology, this finding has enabled us to define the sequence of events that occur when immune cells successfully reject the virus.

Major Projects

1. Early immune responses to skin infections

Innate immune cells are the first cells of the immune system to sense and fight infectious agents (pathogens). This group includes dendritic cells and macrophages, gamma-delta T cells and neutrophils. We have very limited understanding as to how these innate cells behave after they encounter an infectious agent. We have recently developed an intravital multiphoton microscopy model that allows us to directly visualise these cells in living skin under normal and disease conditions.

Using a combination of genetically engineered mice and infectious agents, such as Leishmania major parasites, Herpes simplex virus, Staphylococcus aureus and mycobacteria, we continue to investigate how innate immune cells behave during the early phase of immune responses. We will build on our findings into how invading

Left to right: Assistant Director, Faculty – Professor Wolfgang Weninger; and Associate Faculty – Dr Paulus Mrass

infectious microbes are recognised and transported from the skin to draining lymph nodes. These studies have implications for the development of vaccines against infections.

2. Studying the immune response to influenza virus

Influenza is an acute febrile respiratory illness caused by the 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 have a limited understanding of exactly how cells within the immune system interact to launch an anti-influenza response. We are using multiphoton microscopy in living tissue to uncover how innate immune cells activate antigen specific T cells in the lung-draining lymph nodes during infection. In-depth insight into this process not only increases our knowledge of regulatory pathways of anti-viral immunity but may lead to the development of improved vaccines against this disease.

How will this research impact community health?

Cancer and infectious diseases are leading causes of serious illness and death worldwide. We still have a limited understanding of our own body's response to these diseases.

Additionally, there is a great need for developing innovative treatments and vaccinations against these diseases. Our novel imaging approach provides a new angle for studying fundamental questions about how the immune system defends us against microbes and cancer cells. Our studies of targeted treatments will also help us understand their mode of action so we can improve therapeutic strategies for patients.

"Research gives me hope that others won't suffer from **ovarian and prostate cancer** the way my parents did."

– Allan Miller

Experimental Melanoma Therapy

Dr Nikolas Haass

Melanoma is the most aggressive and deadly form of skin cancer. Melanoma has a particularly high incidence in Australia, where it is the most common cancer in young adults.

Patients with advanced melanoma have very low survival rates and until recently, the only standard chemotherapeutic agent had poor response rates.

Over the past few years we have contributed significantly to international efforts to develop new targeted therapies – two of which are currently undergoing clinical trials with very promising results. Our research focuses on understanding melanoma cell subpopulations responsible for drug resistance and the optimisation of targeted therapies.

Highlights of 2010

- Dr Haass and Professor Weninger received an NHMRC project grant to track cell cycle progression of different melanoma cell subpopulations to study drug resistance. Dr Haass and his collaborators at the Brain and Mind Research Institute (BMRI), Associate Professor Ittner and Professor Götz, received an ARC discovery grant for a study to investigate the biological and pathological functions of two possible new drug targets.
- As part of an international collaboration with Professor Meenhard Herlyn from the Wistar Institute, we characterised the pharmacological properties of an inhibitor of the BRAFV600E oncogene (PLX4032/vemurafenib). This and a previous study have set the basis for the current clinical trials of vemurafenib, which have shown unprecedented high response rates but there is also emerging evidence of drug resistance.
- An international collaboration with Dr Johanna Brandner from the University of Hamburg revealed the impact of melanoma on intercellular communication in the tumour microenvironment.
- Dr David Hill found new approaches of targeted therapy by endoplasmic reticulum (ER) stress-induced cell death in melanoma.
- Dr Haass co-convened the very successful 7th International Melanoma Research Congress of the Society for Melanoma Research in Sydney – the first International Melanoma Research Congress in Australia.

Major Projects

Melanoma is the most aggressive skin cancer and highly therapy-resistant, reasons of which are poorly understood. We hypothesise that differences in the growth capacity of melanoma cells in different tumour regions contribute to therapy resistance. We have established a novel microscopic system that allows us to visualise a division of individual melanoma cells in intact tumours in real time. Using this system, we test the effects of targeted therapies on melanoma cell growth and survival.

1. Real-time imaging of melanoma cells

Unrestricted growth is a cancer hallmark, however, the geometry and dynamics of cell cycle progression of individual tumour cells are not known. Using a sophisticated system, Andrea Anfosso, Dr David Hill and Dr Kimberley Beaumont examine melanoma cell cycle behaviour in real-time during proliferation, migration and response to targeted therapy drugs.

2. New therapies for advanced melanoma

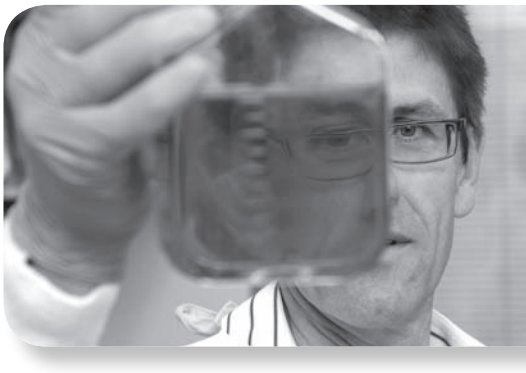
- A collaborative study with Professor Peter Gunning from UNSW investigates a class of novel anti cancer compounds which target the actin cytoskeleton of tumour cells.
- In collaboration with Dr John Allen, PhD student Nethia Mohana-Kumaran investigates the role of the cell death regulators, PUMA, NOXA and McL-1, in melanomagenesis and their modulation as a strategy for sensitising melanoma to the BH3-mimetic drug ABT-737.
- Masters student Paula Nascimento characterises the phototoxic and non-phototoxic anti-melanoma effects of the xanthene dye Rose Bengal.
- In collaboration with Associate Professor Ittner and Professor Götz from BMRI, visiting scientist Ann-Kathrin Reuschl examines the key functions of the proteins TDP-43 and fused in sarcoma (FUS) in melanoma to unveil new drug targets.

3. Cell interactions in the tumour microenvironment

An international collaboration with Dr Johanna Brandner, University of Hamburg, Germany, investigates the role of tight junctions in melanoma and the tumour microenvironment.

DNA Repair

Dr Chris Jolly



Poor repair of DNA damage is a major cause of cancer. Understanding of DNA repair pathways should enable us to prevent early stage cancer from progressing.

Growth and replacement of tissues involves the exact duplication of nuclear DNA and its equal division between daughter cells. This is because nuclear DNA encodes the genes essential for cell function. However, DNA is continuously damaged by irradiation, chemicals and even by inborn replication mistakes.

The DNA Repair Group aims to understand how the many DNA repair pathways interact and how they respond to different types of gene damage.

We focus on "B" lymphocytes (involved in immunity to viruses and bacteria) because these are highly proliferative cells in which inborn replication errors can cause cancer. We have developed a unique and powerful model in which we can manipulate and analyse DNA damage and repair in particular phases of the cell cycle at the single cell level in vivo.

Damage to DNA contributes to most cancers so understanding DNA repair pathways and defects that arise to initiate cancers could stop the progression of early stage cancers.

Highlights of 2010

- In late 2010, the DNA Repair group joined the Immune Imaging Program to take advantage of common interests in the regulation of cell physiology by the cell cycle.
- Our unique single cell in vivo model of DNA damage and repair was published in the prestigious journal Nucleic Acids Research.
- We discovered that restored expression of a single DNA repair gene normally suppressed in proliferating B lymphocytes reduces DNA damage in those cells by a startling 74%. This exciting discovery has not been published as we plan to conduct further studies relating this finding to cancer.
- We showed that a "housekeeping" DNA repair pathway critical for genome stability in all cells, called uracil excision repair, is active in only one phase of the cell cycle. This work has been submitted for publication in 2011.

Major Projects

1. Investigating antibody gene mutations

Examining the mutation of antibody genes in B cells (white blood cells that secrete antibodies) as a physiologically-relevant model of DNA damage is a major area of focus for our group.

Antibody gene mutation is a natural process of extremely accelerated DNA damage and gene mutation called hypermutation that occurs in lymph nodes during immune responses. Antibody hypermutation is essential for effective immune responses but occasionally the antibody mutation machinery targets the wrong genes (referred to as "bystander" genes) and causes cancer. We will continue our research on how mutation of bystander genes by the antibody mutation machinery is implicated in the majority of adult B cell lymphomas and leukaemias.

2. Repairing DNA in cancer patients

Building on our discovery of a very promising effect of a single DNA repair gene, major efforts will now focus on finding a way to induce expression of this gene in cancer cells to slow cancer progression.

Tumour Microenvironment

Dr Paulus Mrass

To improve our understanding of cancer, we need to generate tools that allow us to closely analyse tumour biology by studying the behaviour of cells when they are inside the tumour (tumour microenvironment). Our group has established an innovative tumour imaging model that enables us to observe cellular behaviour within living tumour tissues by capturing snapshots of the tumour in rapid succession. This approach leads to the generation of movie sequences that visualise individual T cells at high subcellular resolution. This model provides a direct view of the dynamic interplay between distinct tumour components within their authentic microenvironment.

Our goal is to use this resource to generate data that provides novel mechanistic insights into tumour development to provides a foundation for novel anti-tumour therapies.

Highlights of 2010

Awarded a highly competitive ARC discovery project grant for the real-time analysis of tumour-infiltrating T cells using novel analytical tools.

NHMRC project grant for a collaboration with Professor Phil Bird from Monash University to investigate the role of granzyme B as lymphocytes migrate through the body.

Major Projects

1. Visualisation of T cell behaviour in live tumours

To study basic tumour biology, we have developed a mouse model that allows targeted tumour destruction by boosting the immune system through intravenously injected killer T cells. By using two-photon microscopy, we can look through the surface of tumours to visualise both targeted tumour cells and the infiltrating T cells. Using this model, our group was the first in the world to succeed in directly visualising killer T cells navigating through and interacting with real tumours. Furthermore, we captured images of the complete disintegration of the tumours.

2. Improving the tumour-scanning ability of T cells

We continue to build on our work to understand tumour growth and rejection. Our laboratory has established tools so we can genetically manipulate killer T cells to use in tumour-bearing mice. We have used these tools to identify a molecular cue (CD44) that is crucial for T cells to migrate towards and infiltrate tumours. We also showed that reduced migration of CD44-deficient T cells is associated with an impaired anti-tumour effect, which has defined a new checkpoint for immune response. Building on this knowledge, we now aim to engineer killer T cells with an improved capacity to scan for tumour cells to create an effective way to reduce tumour growth.

We also continue to use genetic tools to dissect the molecular basis of interactions between tumour-infiltrating T cells and target cells within the tumour-microenvironment. Specifically, we are exploring differences in interactions of killer T cells with tumour cells and tumour-associated-stromal cells.

3. Developing new image-analysis software

The generation of movie sequences with two-photon microscopy leads to vast amounts of visual information. Visual inspection of the image-sequences gives a general impression of the behaviour of the captured cells but it does not allow for an unbiased interpretation or rapid processing of the data (high-throughput screening). Therefore, more systematic and objective analytical tools are required. Our group continues work on developing custom-made software that will enable automatic shape recognition and measurement of cellular and non-cellular (e.g. extracellular matrix) components of these detailed image sequences. This software is helping us to analyse results faster and in a more economical manner. Furthermore, this custom-designed software enables us to address questions where more subjective approaches fail.

Liver Immunology

Dr Patrick Bertolino and Dr David Bowen

Faculty – Dr Patrick Bertolino

The Liver Immunology group aims to understand immune response within the liver and why liver transplants are better tolerated than other organ transplants. Understanding the mechanisms of intrahepatic immunity (immunity within the liver) is critical to two important clinical areas: liver transplants and infection by viruses predominantly affecting the liver, such as hepatitis B and C viruses (HBV and HCV).

Preventing immunity in the liver would improve the outcome of liver and other solid organ transplantation. Unlike other solid organs, liver transplants are spontaneously accepted through unknown mechanisms. Understanding how this tolerance is established would help us develop new strategies to prevent rejection of other solid organs. In contrast, we are also investigating how to enhance immunity to develop improved treatments that would lead to clearance of HBV and HCV infections.

Highlights of 2010

Dr Patrick Bertolino was invited to present the work of his group on liver transplantation at the prestigious Falk Symposium in Germany for 2011.

Several members of the group have presented their results at a range of national meetings (7th Australasian Viral Hepatitis Conference; Australian Gastroenterology Week ; Annual meeting of the Australian and New Zealand Society of Immunology; and Annual meeting of the Australian and New Zealand Society of Immunology NSW).

Dr Patrick Bertolino was awarded a competitive NHMRC project grant of $500,000. Starting in 2011, this project will investigate the mechanisms of liver transplantation in mice.

Dr Patrick Bertolino was invited to be an honorary member of the international advisory board of the 21st Congress of the Asian Pacific association for the study of the liver (APASL 2011) for 2011.

Major Projects

1. Identifying critical factors for liver transplant tolerance

To understand parameters of immunity within the liver, we continue to use mouse models to examine how the liver induces tolerance and we are investigating how to manipulate these mechanisms to induce a persistent immune response.

Our results have demonstrated the liver can retain and activate naive CD8+ T cells, therefore acting as a site of primary activation. This finding contradicts the general accepted view that primary T cell responses can only be initiated in lymph nodes. Our results suggest the site of initial T cell activation is a critical determinant of the outcome of immune responses. Unlike T cells activated in the lymph nodes, most liver-activated T cells become poor effectors and die rapidly, leading to tolerance. A more recent discovery found that most T lymphocytes activated in the liver are destroyed by liver cells before they can divide and be harmful. These findings have important implications for liver transplantation and HCV research.

2. Building carriers to manipulate genes

We have also started a collaboration with Professor Ian Alexander (Children's Medical Research Institute, NSW) to engineer vectors used in gene therapy able to express or silence genes of interest in the liver. These vectors will not only be powerful tools to characterise the molecules critical for intrahepatic tolerance but can also provide some important clues to improve the success of human gene therapy.

3. Hepatitis C and liver transplant outcomes

We are also undertaking human studies in people undergoing liver transplantation for disease related to HCV infection, which is associated with universal re-infection of the transplanted organ with varying outcomes. By studying the immune response to HCV in this group of patients, we aim to gain important insights into factors that could improve treatment outcomes.

Liver Immunobiology

Professor Geoff McCaughan

Chronic liver damage affects up to one in five Australians causing serious illness and death through liver failure and the development of liver cancer. Liver cancer is one of the fastest growing and deadly diseases in Australia.

The research groups within Liver Immunobiology work together for a common purpose: to understand, at the cellular and molecular level, the key issues that cause liver damage and cancer. The groups use a combination of animal models and human tissue samples, which are shared among all groups to maximise understanding of disease pathways.

The distinct research groups are:

- Liver Immunobiology led by Professor Geoff McCaughan
- Molecular Hepatology led by Associate Professor Mark Gorrell
- Liver Cell Biology led by Dr Nicholas Shackel and Dr Fiona Warner

In addition to these project areas, the Liver group has major clinical collaborations nationally and internationally in the fields of antiviral treatment outcomes for hepatitis C and Hepatocellular Carcinoma (primary liver cancer).

Highlights of 2010

Liver transplantation

In liver transplantation, we observed that progressive injury due to the hepatits C virus is associated with intrahepatic (liver) stem cell responses. We also completed studies on the effect of differing immunosuppressive drugs on outcomes with findings to be published next year.

Alcoholic Liver Disease

One of our major collaborations, now in its tenth year, is with Dr Devanshi Seth and Professor Paul Haber at the Drug Health Services RPAH, Sydney South West Area Health Service and the University of Sydney. This has been a highly successful venture in terms of findings, publications, collaborations, grants and students. The main projects involve identifying novel diagnostic and therapeutic targets by investigating the development of alcohol-induced liver injury and the genetic predisposition of alcoholics to alcoholic cirrhosis.

Alcoholic Liver Disease (ALD) remains one of the leading causes of diseases and injury associated with alcohol. ALD is a multi-stage, multi-factorial disease established on long-term alcohol misuse. In Australia, ALD is responsible for 50% of the total liver disease burden, 15% of liver transplants and significant co-morbidities.

Identifying new markers for ALD

There are no specific diagnostic markers or effective treatments for ALD so it is necessary to investigate for new biomarkers and genetic markers in order to understand how ALD develops.

We first identified elevated Secreted Phosphoprotein 1 (SPP1, aka osteopontin) pathway (including SPP1 receptors CD44 and integrin v, in patients with ALD). We have also shown SPP1 isoforms and receptors are increased in liver cell culture models of alcohol. Subsequently, we found alcohol-induced Erk and Akt phosphorylation and cell migration in hepatic stellate cells (HSCs) is mediated via SPP1. Blocking SPP1 pathway by neutralising antibodies (SPP1 aptamer and silencing SPP1 mRNA) inhibited Erk and Akt phosphorylation and migration in hepatic stellate LX2 cells. In addition, alcohol-induced plasmin activation is also inhibited by blocking SPP1 pathway, which suggests SPP1 plays an important role in HSC-mediated ALD pathogenesis. Furthermore, expression of several fibrogenesis (TGFß, collagen-1), extracellular matrix (ECM) (MMP2, MMP3, MMP9) and fibrinolytic molecules (urokinase plasminogen activator (uPA), tPA) induced by alcohol in LX2 were inhibited by silencing SPP1 RNA. SPP1 is a cytokine involved in ECM remodelling and metastasis in cancer, including hepatocellular carcinoma, and thought to be involved in plasmin activation via increased uPA in breast cancer. We believe specific SPP1 isoforms are involved in Akt and Erk signalling, which contributes to the progression of alcoholic liver injury by activating HSCs, TGFß and collagen, and resolve injury by inducing plasmin and pro-fibrinolytic profile. We are now confirming our in vitro findings by investigating the role of SPP1 in vivo in models of acute alcohol using wild type and SPP1 gene deficient mice.

Driving a world-first international study

We are also working on identifying genetic risk factors in a genome wide association study (GWAS) for ALD. Led by Dr Seth, this project has grown from a pilot study in Sydney, funded by the Alcohol Health and Grants Research Scheme, to a major international project with five years funding from a highly competitive National Institutes of Health (NIH)/National Institute on Alcohol Abuse and Alcoholism (NIAAA) project grant. This is the first project in the world to be conducted across multi-centres in a large cohort of

Left to right: Assistant Director, Faculty – Professor Geoff McCaughan; Associate Faculty – Associate Professor Mark Gorrell, Senior Research Officer – Dr Fiona Warner, Associate Faculty – Dr Nicholas Shackel; and PhD Scholar – Michelle Vo.

thousands of alcoholic patients using the GWAS to identify single nucleotide polymorphisms that may predispose some moderate to heavy drinkers to liver cirrhosis. Dr Seth has established the GenomALC consortium consisting of eminent alcohol researchers from the USA, UK, Germany, France and Switzerland to conduct this study. We have made significant progress to establish protocols, develop questionnaires, acquire ethics approvals and finalise the framework. We also recruited a total of 80 participants in the pilot study that will become part of the NIH-funded cohort from Australia. This Australian-led study aims to build a significant resource of clinically well characterised cohorts, blood and DNA biobank and generate important information for the first genetic architecture for alcoholic liver cirrhosis.

Major Projects

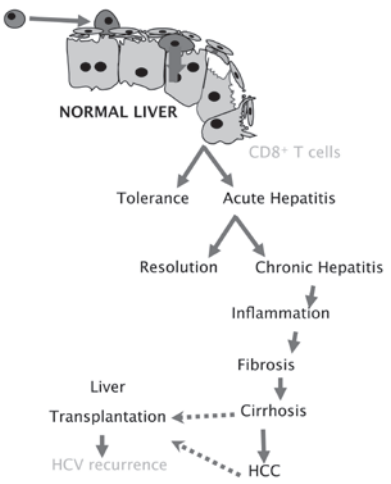
In addition to the projects already mentioned, we also have two other major areas of research:

1. Examining the Hedgehog (Hh) family in progressive liver injury

The Hh pathway has been identified as an important molecular mediator during foetal development and cancer. We have seen increased levels of the Hh pathway in experimental cirrhosis and identified the pathway is activated by hepatic growth factors and inflammatory cytokines. The pathway is activated within a niche in the liver at the edge of the portal tract which is the key site of injury induction. We have shown that injured hepatocytes interact with hepatic stem cells .We are now examining whether this drives further injury, predisposes someone to liver cancer or acts as a repair mechanism.

2. Identifying key miRNAs in liver injury and cancer

EMT (Epithelial Mesenchymal Transition) is a process that occurs in cancer development. Cancer (and non-cancer) cells expressing an EMT phenotype are more likely to migrate and in the case of cancer, invade and spread to other organs. We have identified a single miRNA that can reproduce TGFb-induced EMT in liver cells. This miRNA shows increased expression in experimental and human cirrhosis. Currently we are looking at what genes are targeted by this miRNA and whether inhibition of such pathways can alter progression of progressive liver injury and potentially liver cancer.



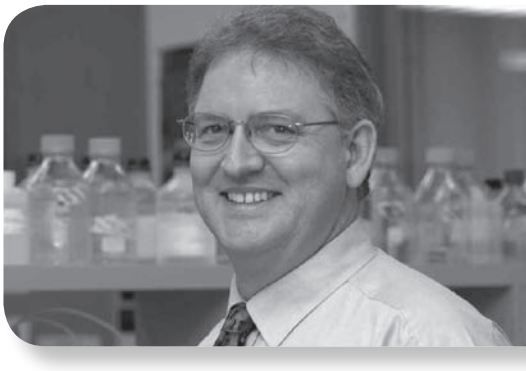
How will this research impact community health?

Liver disease remains a major cause of illness and death in Australia and worldwide. Our research provides valuable insight into the causes of liver damage and cancer along with new ways to improve diagnosis and treatment options for people with liver disease.

Our focus on understanding how liver injury occurs will help us develop new therapeutic strategies to stop the progression of liver injury and the development of liver cancer.

Our studies to understand why liver transplants are not rejected like other solid organ transplants will help us design new strategies to prevent rejection of liver transplants and improve patient outcomes. Our findings may also shed light on ways to improve transplant acceptance rates of other solid organs.

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 find ways to arrest and reverse these processes of chronic liver injury. Such new therapies would prevent cirrhosis and liver cancer. Hepatitis C virus infection and severe fatty liver, which is associated with obesity and the metabolic syndrome, 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 (DPP) IV, DPP8 and DPP9 exhibit heightened expression by liver cells in disease and are involved in cell movement, growth and death. FAP is under investigation as a therapeutic target for liver and lung diseases, arthritis and some cancers. DPP-IV is especially interesting because it is the target of a new diabetes therapy called incretin therapy. Discoveries on DPP-IV and related genes that we published a decade ago significantly assisted the development of this new type 2 diabetes therapy. We believe that diabetes-therapeutic DPP-IV inhibitors will also prove to be useful in combating liver disease.

Highlights of 2010

- Dr Fiona Keane identified four bioactive peptides as major targets of FAP. These peptides are molecules important in neurons, heart and immune cells.
- Publication of our patent application on targeting FAP as a therapy for type 2 diabetes and the metabolic syndrome.
- We showed that the huge influence of DPP-IV on specific immune responses does not depend upon DPP-IV enzyme activity. This means that DPP-IV inhibitors used to treat diabetes are not likely to impair a person's immunity to infections.
- Publication of four reviews on the DPP-IV gene family in diabetes, fatty liver disease, cancer and normal cell functioning. All lab members were authors; special thanks to Dr Denise Yu.
- Finding by Ms Sumaiya Chowdhury that DPP9 and DPP-IV are upregulated together in mouse models of chronic liver injury.
- The discovery by Ms Tsun-Wen SheenaYao that DPP9 is a regulator of cell death in certain conditions.
- Discovered that mice lacking FAP exhibit improved regulation of blood glucose when they eat a high-fat-high-calorie diet (Ms Chowdhury and Mrs Margaret Gall).

Major Projects

The DPP-IV family of enzymes consists of DPP-IV, DPP8, DPP9 and FAP. We continue to build upon our understanding of these enzymes, the role they play in liver scarring and discovery of molecules to reduce their damaging effects.

We are doing this by:

1. Studying mouse strains that lack individual genes of the DPP-IV gene family.
2. Upregulating DPP-IV family genes in cell cultures.
3. Making isolated enzymes to discover bioactive molecules that they inactivate.

1. Controlling a liver/brain enzyme in Alzheimer's

Collaborative work with Dr W. B. Church of the Pharmacy Faculty at the University of Sydney on the liver/brain enzyme Kynurenine Aminotransferase 1 (KAT-1) has leapt forward. PhD student N.A. Nadvi has made crystals of KAT-1 that gave him data on the protein structure and how it interacts with an inhibitor. This research is developing compounds that will control KAT-I in the brain of Alzheimer's sufferers and thereby alleviate their illness.

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 cell types have distinct roles in normal liver functioning and liver disease states. We aim to understand the development of liver disease, particularly the development of inflammation and the formation of scar tissue within the liver. These injury insults lead to liver cancer and we have elected to focus on the main cell type and functional unit of the liver – the hepatocyte.

We believe our research will help in understanding how liver injury occurs. This 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 whom it is most likely to benefit. Our research aims to help develop novel diagnostic and prognostic tests to enable personalised and tailored therapy in liver disease.

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

Highlights of 2010

- Honours Student Alison Potter was awarded first class honours and the University Medal for her research on the role of the cyclophilins in inflammatory liver disease.
- Ms Carleen Fernandez was awarded an Australian Postgraduate Award to study the role of bone marrow stem cells in liver disease and cancer.
- The addition of two talented research officers to our group, Dr Victoria Wen and Dr Alison Morgan, that have contributed significantly to our research of EMMPRIN in liver disease

Major Projects

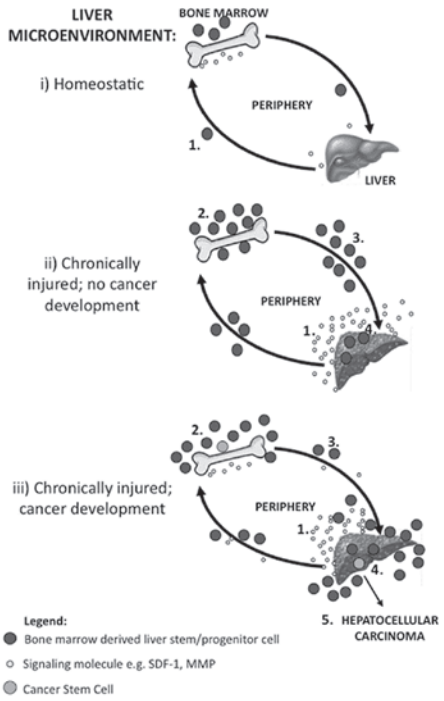
Our studies are currently focused on two main aspects of progressive liver disease.

1. Investigating the role of EMMPRIN in liver scarring

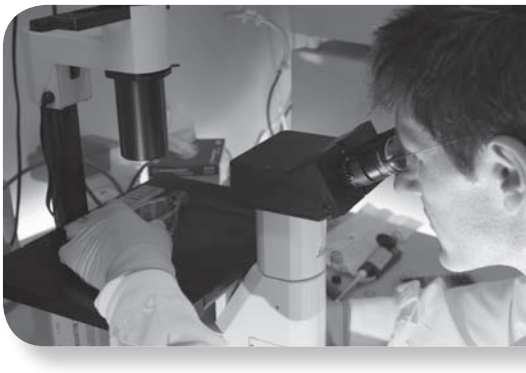
The role of molecule EMMPRIN and the hepatocyte and inflammatory cells in liver fibrogenesis. This project is helping understand how this molecule on hepatocytes seems to regulate the inflammatory process and the remodeling of the scar matrix that is the hallmark of cirrhosis.

2. Stem cells in liver injury and cancer

We are looking at how stem cells contribute to liver injury and cancer. This project will answer the question: *Do liver stem cells mobilised with injury contribute not only to regeneration but also the development of liver cancer?*



Core Facilities



Cytometry and Imaging

Flow Cytometry

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

Flow cytometry allows researchers to rapidly analyse large populations of cells. Individual cells are examined and a wide variety of properties of each cell can be recorded. Researchers tag the cell populations with fluorescent dyes and then use the flow cytometer to pass the cells through a beam of laser light one at a time. This laser light is scattered by the cells and provides a way to measure physical properties of the cell such as size. The laser also excites the different fluorescent dyes attached to cells. These dyes produce light of different colours and allow the researchers to count and analyse the cell types that are present. By examining the cells one by one, researchers can find minute characteristics of the cells to get an accurate profile of rare disease-causing cells. Some flow cytometers extend this analysis by sorting the cells into different fractions at high speeds to enable purification of rare cell populations for further study.

Highlights of 2010

We continued close collaboration with the flow cytometry resources on the University of Sydney campus, which resulted in Centenary hosting a number of workshops and user group meetings for researchers from across Sydney. In 2010, this collaboration (with researchers from UNSW) resulted in the purchase of two new high-end cytometry instruments for the University/Centenary campus.

One of these instruments was the world-first BD LSRII equipped with 9 lasers. The extra lasers on this instrument gives researchers the ability to measure more characteristics of each cell as it passes through the laser. This allows all the relevant information to be gleaned from one sample rather than several, which leads to considerable savings both in time and the amount of sample required. We already have plans to add another laser in 2011.

The second instrument is a BD Pathway High Content Bioimager. This extends the cell analysis capabilities of the facility in imaging by providing the ability to automatically acquire images of thousands of cells and then extract meaningful biological information from those pictures.

Funding in excess of $1.1 million was provided for these two systems by the Australian Research Council (ARC), National Health and Medical Research Council (NHMRC), the University of Sydney, University of New South Wales and the Centenary Institute.

The Centenary Institute also received close to $1 million from the Cancer Institute NSW and the NHMRC, to help purchase a next-generation high speed cell sorter. This investment demonstrates the importance of flow cytometry to cancer researchers and highlights the pre-eminence of Centenary as the key reference facility for cytometry and cell sorting in NSW. In 2010 we conducted an extensive selection process to determine the best possible instrument. The new cell sorter is expected in mid-2011 and it will be another world-first instrument offering increased speed and power to detect more features of different cell types. It will also include the biosafety features required for the isolation of cells from human samples.

The major Australasian cytometry conference was held in Sydney in 2010. Centenary staff presented at this conference and played a significant role organising and hosting this major event. Dr Adrian Smith (Facility Manager) was elected as the 2010-2011 President of the Australasian Flow Cytometry Group at this conference. Dr Smith also attended and presented at the International Society for the Advancement of Cytometry's international congress in the United States. Mr Robert Salomon (Cytometry Support Coordinator) attended the 33rd Annual Advanced Cytometry Course at Boudoin College in the US. This engagement in the Australian and international flow cytometry community represents Centenary's continued commitment to best practice research techniques.

Imaging

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

LaVision Biotec TriMscope

This cutting-edge multiphoton microscope enables researchers unprecedented access to the secret workings of living tissues at the cellular and molecular level. Our multiphoton

microscope has two unique features – its imaging mode and laser. The unique imaging mode uses multiple laser beams and means fast moving objects and dynamic processes in living tissue can be viewed. The laser has been enhanced with a unit called an OPO that produces longer wavelengths of light than those used in other microscopes. This enables researchers to look deeper into living tissue than ever before.

In 2010, we upgraded the multiphoton facility with an additional laser and a second microscope with advanced detection technologies. These additions have added considerable capabilities and flexibility to our imaging of living tissues and keep us at the cutting-edge of multiphoton imaging.

Confocal microscope

We are equipped with 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.

Live cell microscopy

To supplement the multiphoton and confocal microscope systems, we received funding in 2010 from the Cancer Institute NSW, Perpetual Trustees and the Ramaciotti Foundation to purchase an additional microscope system dedicated to the imaging of living cells. This exciting new system is expected in mid-2011.

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' remains a high priority for the Centenary Institute. Our facility is the longest established in the state and one of the most productive in Australia in terms of the number 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 multiphoton microscopy, small animal imaging and flow cytometry.

Genomics Facility

Genomics represents the new age in how we diagnose, assess risk and treat patients with a range of diseases. Genomics approaches promise to lead to more optimal and cost-effective treatment in patients with cancer, cardiovascular and infectious diseases and more effective preventative strategies for those at risk. The promise of personalised medicine will be realised using Genomics approaches.

The Centenary Institute houses the latest Affymetrix Gene Array platform (supported by funding from the Cancer Institute NSW) and NimbleGen Array platform. These platforms will create a better understanding of the molecular basis of cancer, cardiovascular and infectious diseases and will help develop new therapies. We have also embraced and used even newer technologies profiling microRNA expression as well as "deep sequencing".

These technologies promise to be highly significant in realising personalised, pre-emptive, predictive and participatory healthcare. The wealth of data we are generating can now be analysed within our own Bioinformatics Group.
The Genomics Facility and Bioinformatics Group are integrated to provide a core facility of data acquisition and in-depth data analysis within the Centenary Institute.

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

In addition, there is a mouse exercise facility (running and swimming) that 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 that 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 2010, we made significant progress expanding the PC3 facility. This development is critical to supporting our increasing level of research.

Animal Facility

Genetically modified mouse lines are bred under Level 2 Specific Pathogen Free conditions in the Animal Facility. Individually ventilated cages, 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.

Foundation Report

2010 marked an exciting year of growth and change for the Centenary Institute Medical Research Foundation's fundraising and marketing.

The Foundation is honoured by the growing number of people and companies who generously support our research projects. We are touched by their kindness and belief in our researchers and the amazing work they do to help Australians and people worldwide live better, longer lives.

On behalf of the Foundation and our researchers, we thank everyone who has supported us in 2010 for their incredible generosity and commitment to Centenary.

Ms Sally Castle managed the Foundation until late 2010. She has left a legacy of committed, loyal supporters - including a large contingent of new supporters – together with a strongly-enhanced reputation of excellence. We commend her stellar performance.

We are especially grateful to Inghams Enterprises, PriceWaterhouse Coopers, Mrs Jessica Hore, the Andrew Cameron Family Foundation, Dr Max & Mrs Tess Hooper, Lifestyle Financial Services, Ms Beverly Sarvay, Dr Mary- Anne Sutherland, Lady AJ Loewenthal, Mr John & Mrs Felicity Atanaskovic and Mrs Patricia Lee.

Our appreciation also goes to our community fundraisers for their exceptional fundraising efforts, participating in events like the City2Surf, the Great Ocean Road Bike Ride or the Surf Swim from Perth Shores to Rottnest Island. Others coordinated golf days, dinners, trivia nights and other special events. We extend our sincere thanks to Jenny and Rick Bamford, Leeann Richards, Kimberly Curtis, Louise Stevenson, Stephanie Arnold, Martin Whitham, CWA Wyalong, the Rotary Club of Roseville East and the Rotary Club of Cronulla.

Throughout the year Centenary welcomed over 230 new Research Partners to our regular giving program. This valuable program enables a select group of supporters to donate automatically on a monthly basis and it's cost efficiency ensures we are able to plan more effectively.

The generosity of our dedicated supporters was matched by the people who so kindly shared their personal experience dealing with the diseases which are the focus of Centenary's work. Those stories put a human face to the work of our 200 dedicated scientists who are seeking new cures and treatments for cancer, cardiovascular and infectious diseases. A special thank you goes to Zoe van Middeldyk, Leesa Adams, Norma Jackson-Snow, Dylan Fox, Ron Smith and Beverly Mylcreest who shared their personal experiences to help raise vital funds and awareness about how Centenary's research makes a critical contribution to people living with life-threatening diseases.

The second Annual Foundation Dinner, held in June and convened by the Foundation and their colleagues was a major success. Thank you to our sponsors PriceWaterhouse Coopers, Torbreck Vintners, Mount Mary Vineyards, Hardy's and Yarra Yering for helping make this such a memorable evening. The dinner raised over $130,000 to fund the second

Left to right: Associate Faculty – Dr Nicholas Shackel, Associate Faculty – Dr Mika Jormakka, Associate Faculty – Dr Paulus Mrass, Foundation Fellow – Dr Mathew Harrison; Carl Riseley, Kirsten Ford; Associate Faculty – Dr Nikolas Haass, Associate Faculty – Dr Jeff Holst, Her Excellency Professor Marie Bashir Governor of NSW, Associate Faculty – Dr Nick West; and Chaiman – Joseph Carrozzi.

year of our Bioinformatics Fellowship. This invaluable position, held by Dr Mathew Harrison, has accelerated the pace of our work in the past year by helping our researchers find new, faster ways to analyse the huge amount of data generated from their projects.

Guests enjoyed fine food and wine with entertainment provided by Australian Idol artist Carl Riseley. We thank our guests for their fantastic support as well as all those individuals and businesses that donated art and an array of fantastic items for our live and silent auctions. Green & Black's Organic Chocolate, Rockford Wines, Small Luxury Hotels of the World, Australian Aerospace, Nick Mount Glass & Sabbia Gallery, EcoTraining Australia, Annette Larkin Fine Art, Jonty Rumbold from Urban Monk and Albert Jangtong from Lawrence Creative Strategy.

Centenary opened its doors for our first Science Week Open Lab Tour Evening. Over 80 people attended, including Her Excellency Professor Marie Bashir AC CVO, Governor of NSW. Guests listened to three researchers talk about their work before experiencing an exciting behind-the-scenes tour of our research labs.

The third Annual Foundation Cocktail Reception was held at the home of Justice Margaret Beazley AO. Guests had the chance to meet members from our Scientific Advisory Board, who are world-renowned scientists and leaders in their field of research.

The Foundation relied on a small and wonderful team of fundraisers who worked hard throughout the year to raise money and awareness for Centenary's work. Congratulations and thank you to LauraBeth Albanese, Leisl Holterman, Barbara Smith, Jeff Wai-Yee, and Tanya Sarina. Thanks also to all our wonderful volunteers. Particular thanks go to Sudipta Dev and Wei-wei Tan who volunteered regularly.

Finally, we thank our Foundation for the big personal commitment which makes so many of our achievements in 2010 possible. The vision, passion and talent of the individuals who lead our Foundation are making so many of our achievements possible.

We feel honoured by the generosity of all our supporters and thank them most sincerely.

Joseph Carrozzi
Chairman

Suzie Graham
Head of Fundraising,
Marketing and Communications

On behalf of the Centenary Institute Medical Research Foundation

Justice Margaret Beazley AO
Joseph Carrozzi (Chair since June 2010)
Julie Ford
Graham Kelly
Caroline Lawrence
Neil Lawrence (Chair until June 2010)
The Late Lady (Sonia) McMahon
John Samaha
Andrew White
Julia Wokes

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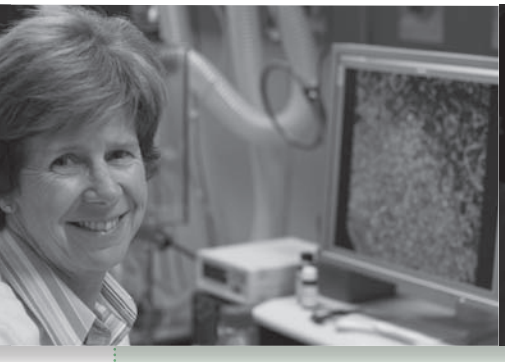
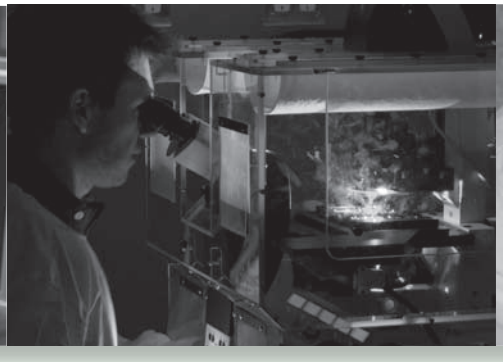


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Xia P, Wadham C. *Sphingosine 1-phosphate, a key mediator of the cytokine network: juxtracrine signaling.* **Cytokine Growth Factor Rev**. 2011 Feb; 22(1):45-53. Epub 2010 Nov 3.

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2010 Invited Presentations

International

Britton W, Workshop Chair, Immunomodulation of Tuberculosis, Mycobacterial Granulomas: Where Microbiology meets Pathology, Borstel Research Institute, June 2010, Hamburg, Germany

Fazekas de St Groth B, DC2010: Forum on Vaccine Science, 11th International Symposium on Dendritic Cells in Fundamental and Clinical Immunology, September 2010, Lugarno, Switzerland

Gamble J, 2nd affiliated Hospital of Anhui Medical University, October 2010, Anhui, China

Gamble J, International Vascular Biology Conference, June 2010, Los Angeles, USA

Gamble J, Biology of Aging, Gordon Research Conference, August 2010, Les Diablerets, Switzerland

Grimshaw M, Oncogene-induced Senescence in Breast Cancer Suppression and Progression, 3rd Annual World Cancer Congress, April 2010, Shaghai, China

Haass N, Modification of the sphingosine kinase pathway as a novel therapeutic approach for melanoma, Workshop Experimental Dermatological Oncology, 37th Annual Meeting of the Arbeitsgemeinschaft Dermatologische Forschung, March 2010, Lübeck, Germany

Haass N, Inhibition of MCL1 dramatically sensitises melanoma cells to the small molecule BH3-mimetic ABT-737, Workshop Experimental Dermatological Oncology, 37th Annual Meeting of the Arbeitsgemeinschaft Dermatologische Forschung, March 2010, Lübeck, Germany

Haass N, Xanthoma Disseminatum with extensive bone involvement, Joint Meeting between the Australasian College of Dermatologists and the Österreichische Gesellschaft für Dermatologie und Venerologie, November 2010, Vienna, Austria

Haass N, Real-time imaging of cell cycle progression in melanoma, Department of Dermatology at the University Hospital Erlangen, November 2010, Erlangen, Germany

McCaughan G, Liver Transplantation in Australia, APASL Annual Meeting, March 2010, Beijing, China

McCaughan G, Liver Transplantation for HBV: HBIG or not? APASL Annual Meeting, March 2010, Beijing, China

McCaughan G, The liver allograft tolerance effect, ILTS Annual Meeting, June 2010, Hong Kong

McCaughan G, Hepatocellular Cancer: The role for new immunosuppressive strategies, ILTS, June 2010, Hong Kong

McCaughan G, HCV in the setting of liver transplantation: insight and challenges, APASL single topic conference on Hepatitis C, December 2010, Tokyo, Japan

McCaughan G, What will the Direct antiviral drugs the IL28 polymorphisms mean for APASL HCV treatment guidelines, APASL single topic conference on Hepatitis C, December 2010, Tokyo, Japan

Rasko J, K Pratap Memorial Speaker, A coming of age for gene and cell therapies, 9th Annual General & Scientific Meeting, College of Pathologists Academy of Medicine, June 2010, Malaysia

Rasko J, RNA in neoplasia - beginning to make sense ... and antisense?, 17th Hong Kong International Cancer Congress, November 2010, Hong Kong

Semsarian C, Risk factors for sudden cardiac death in HCM: Does genotyping help? 17th World Congress, Cardiostim 2010, June 2010, Nice, France

Semsarian C, Insights on establishing a national collaboration in HCM, Genetics, CMRI and Cardiomyopathies, 2010, Genoa, Italy

Semsarian C, Hypertrophic and dilated cardiomyopathies, World Congress of ISHR, May 2010, Kyoto, Japan

Semsarian C, Genetic testing and counselling in HCM families, American Heart Association Meeting, November 2010, Chicago, USA

Semsarian C, Getting to the heart of sudden death, Heart and Mind Meeting, September 2010, Prato, Italy

Vadas M, International Vascular Biology Meeting, June 2010, Los Angeles, USA

Vadas M, Ageing in Endothelium, University of Illinois, July 2010, Chicago, USA

Vadas M, Anahui Medical University Symposium, October 2010, Anahui, China

Weninger W, Austrian Society for Dermatology Annual Scientific Meeting, Vienna, Austria

Xia P, ER stress response and lipotoxiocity in pancreatic cells: Role in type 2 diabetes. ISSFAL 2010: Lipids in Metabolic Health and Disease Conference, May 2010, Maastricht, Netherlands

Xia P, Role of sphingosine kinase 1 in cancer: Non-oncogene addiction. Institute of Pharmacology and Structural Biology, June 2010, Toulouse, France

National

Bowen D, Immunological determinants of HCV control and clearance, 7th Australasian Viral Hepatitis Conference, September 2010, Melbourne, VIC

Britton W, Wunderley Oration, Taming the Tubercle: Translating Tuberculosis research into improved control of Tuberculosis, Thoracic Society of Australia & New Zealand, March 2010, Brisbane, QLD

Britton W, Functional genomics of mycobacteria to identify drug and vaccine targets, 7th Indo-Australian Conference on Biotechnology, October 2010, Brisbane, QLD

Britton W, Current approaches to improving vaccination against Tuberculosis, Australasian Society of Immunology Annual Scientific Meeting, December 2010, Perth, WA

Fazekas de St Groth B, 33rd Annual Meeting of the Australasian Flow Cytometry Group, November 2010, Sydney, NSW

Fazekas de St Groth B, Australasian Society for Immunology Conference, December 2010, Perth, WA

Gamble J, Australian Vascular Biology Meeting, September 2010, Lorne, VIC

Gamble J, Cell Signalling Conference, Garvan Research Institute, October 2010, Sydney, NSW

Haass N, The role of melanoma stem cells in melanomagenesis, Cure Cancer Australia Foundation, January 2010, Sydney, NSW

Haass N, Experimental melanoma therapy, Rotary International, Inner West, January 2010, Sydney, NSW; Rotary International, Marrickville, April 2010, Sydney, NSW

Haass N, Melanoma Models from Centenary to Millennium, Westmead Institute for Cancer Research, Westmead Millennium Institute, April 2010, Westmead, NSW

Haass N, Modification of the sphingosine kinase pathway using dimethyl-sphingosine or sphingosine kinase inhibitor 2, has differential effects on the cell cycle behaviour of melanoma cells, 7th Annual Scientific Meeting of the Australasian Society for Dermatology Research, June 2010, Cairns, QLD

Haass N, In vitro 3D tumour microenvironment models for anti-melanoma drug discovery, Diamantina Institute for Cancer, Immunology and Metabolic Medicine, June 2010, The University of Queensland, Brisbane, QLD

Haass N, In vitro 3D tumour microenvironment models for anti-melanoma drug discovery, School of Medical Science, Griffith University, August 2010, Gold Coast, QLD

Haass N, Real-time imaging of cell cycle progression in melanoma, 7th International Melanoma Research Congress of the Society for Melanoma Research, November 2010, Sydney, NSW

Haass N, Real-time imaging of cell cycle progression in melanoma, Centenary Colloquium VII - In Search of Melanoma's Achilles' Heel – Signalling, Death Mechanisms and Tumour Immunology, November 2010, Sydney, NSW

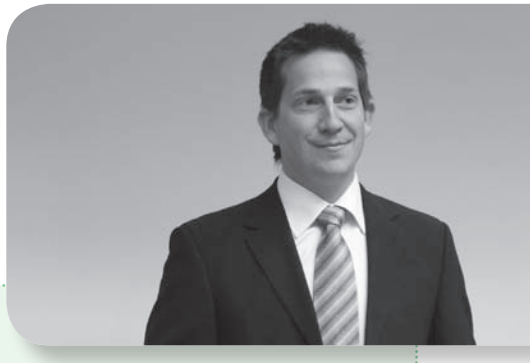
Holst J, Prostate Cancer Foundation of Australia Annual Meeting, 2010, Gold Coast, QLD

Ingles J, Hypertrophic cardiomyopathy and genetics, Cardiomyopathy Association of Australia Annual General Meeting, August 2010, Sydney, NSW

Ingles J, Genetic counselling and inherited cardiomyopathies, Heart Failure and Cardiac Genetics Satellite Meeting, 58th CSANZ Annual Scientific Meeting, August 2010, Adelaide, SA

McCaughan G, Emerging role of novel laboratory methods for HCV assessment: IL28 polymorphisms, National Hepatitis C Meeting, May 2010, Melbourne, VIC

2010 Invited Presentations



McCaughan G, Advanced liver disease: Pathogenesis and clinical features. National Adv Trainees Meeting, July 2010, Melbourne, VIC

McCaughan G, Molecular signatures in HCC, ALA Master Class, August 2010, Sydney, NSW

McCaughan G, Interaction between HCV recurrence and allograft rejection in liver transplantation. South Australian Annual Transplant Meeting, November 2010, Adelaide, SA

Rasko J, Towards cellular therapy with a spring in your step!, Pathology Update 2010, Melbourne, VIC

Rasko J, Cell-substrate interactions at the molecular level, University of Western Australia, 4th Margaret River Region Forum and ISCT-Australia, Pathways Towards Molecular and Cellular Therapy, April 2010, Bunker Bay, WA

Rasko J, The Future of Living Longer – The new age of medicine and what it means for you, Garvan Institute of Medical Research, 11 November 2010, Sydney, NSW

Rasko J, Enter the matrix-cell therapy towards the clinic, Australian Institute of Medical Scientists, 6 December 2010, Brisbane, QLD

Semsarian C, Genetics of cardiovascular disease, FRACP RPA Training Course, 2010, Sydney, NSW

Semsarian C, Genetics of sudden cardiac death, Cardiac Arrhythmia Educational Weekend, 2010, Sydney, NSW

Semsarian C, Genetic testing in adult cardiomyopathies and sudden death, 58th CSANZ Annual Scientific Meeting, August 2010, Adelaide, SA

Semsarian C, Multiple mutations in mice and humans with familial HCM, 58th CSANZ Annual Scientific Meeting, August 2010, Adelaide, SA

Semsarian C, Risk stratification in hypertrophic cardiomyopathy, 58th CSANZ Annual Scientific Meeting, August 2010, Adelaide, SA

Semsarian C, Getting to the heart of sudden death. State-of-the-art Symposium: SCD – New Insights, August 2010, Adelaide, SA

Semsarian C, Genetic testing and sudden death, RNSH Cardiology Grand Rounds, 2010, Sydney, NSW

Semsarian C, Workshop: Unusual cardiomyopathies, Specialist CV Symposium, 2010, Sydney, NSW

Tsoutsman T, Key role of connective tissue growth factor (CTGF) in familial cardiomyopathy and heart failure, Australian Heath and Medical Research Congress, November 2010, Melbourne, VIC

Vadas M, Cronulla Rotary, April 2010; Chatswood Sunrise Rotary, June 2010; North Sydney Sunrise Rotary, September 2010; Pearls, October 2010; Sydney, NSW

Vadas M, Lowy Symposium – Discovering Cancer Therapeutics, May 2010, Sydney, NSW

Vadas M, Chair, Australian Vascular Biology Conference, September 2010, Lorne, VIC

Weninger W, 2010 Australasian Dermatopathology Society, Annual Scientific Meeting, Sydney, NSW

Weninger W, OzBio 2010 Conference, Melbourne, VIC

Weninger W, Seminar Series, University of Canberra, Canberra, ACT

Weninger W, Seminar Series, Peter MacCallum Cancer Centre, Melbourne, VIC

West N, Vaccine and Novel Chemotherapy Development for Tuberculosis, Australian Society for Microbiology, July 2010, Sydney, NSW

West N, Development of vaccines and treatments for the causative agent of Tuberculosis, Mycobacterium tuberculosis, March 2010, University of Queensland, Brisbane, QLD

Yeates L, The challenges of growing up with a genetic heart disease. NSW Genetic Counsellors Meeting, March 2010, Sydney, NSW

Yeates L, Hypertrophic cardiomyopathy and genetics, Cardiomyopathy Association of Australia Annual General Meeting, August 2010, Sydney, NSW

Postgraduate Training Program

The Centenary Institute maintains its commitment to the development of Australia's next generation of brilliant scientists. 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 2010.

Doctor of Philosophy (Medicine) (PhDs) Awarded 2010

Student	Supervisor	Thesis Title
Frances Chow	Professor Warwick Britton	Molecular approaches to the control of leprosy
Jessica Vanslambrouck	Professor John Rasko	The expression of renal and intestinal amino acid transporters during development and disease

Masters Awarded 2010

Student	Supervisor	Thesis Title
Sumaiya Chowdhury	Associate Professor Mark Gorrell	Dipeptidyl Peptidase IV (DPIV) Gene Family and the Metabolic Load

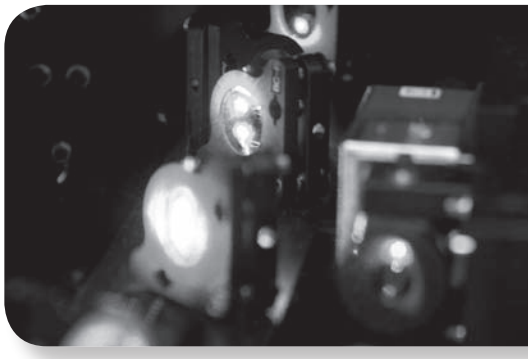
2010 Grants Awarded

Investigators	Project title	Granting body
W Weninger, M Vadas, P Gunning, D Richardson, B Fazekas, J Gamble, G McCaughan, J Rasko, N Shackel, N Haass	High speed 3D live cell imaging of cancer genesis, growth, metastasis and death.	Cancer Institute NSW
W Weninger	Live Cell Imaging System	Perpetual Trustees
T Guy	Strategies to enhance CD4 T cell-mediated anti-tumour immunity	Cancer Institute NSW
D Hancock	Targeting dendritic cells for cancer immunotherapy	Cancer Institute NSW
P Mrass, W Weninger	Real-time Analysis of Tumour-Infiltrating T Cells Using Novel Analytical Tools	ARC
P Bertolino	Mechanisms of liver allograft tolerance	NHMRC
C Jolly	When and how do cells repair damaged genes?	NHMRC
B Fazekas	How Treg cells stop islet graft rejection	NHMRC
B Fazekas	T cell-mediated control of allergic lung inflammation	NHMRC
B Fazekas, E Shklovskaya	Tregs in cancer	NHMRC
N Haass	Real-time Imaging of cell cycle progression in melanoma	NHMRC
W Weninger	Neutrophil migration	NHMRC
W Britton, J Triccas, Florido, Stambas	Impact of Influenza A on immunity to tuberculosis	NHMRC
N West, W Britton, R Payne	Genes to drugs for TB	NHMRC
N West	Determining the bacterial contributions to tuberculosis and identification of drug targets	NHMRC
J Holst, M Jormakka	Structural analysis of amino acid transporters that regulate the mTOR pathway	Prostate Cancer Foundation
D Sieveking (J Rasko)	NCE based Strategy for Nuclear Reprogramming and Regenerative Medicine	NHMRC
R Padang (C Semsarian)	Clinical, Pathological and Genetic Basis of Familial Valvular Heart Disease	Heart Foundation



Investigators	Project title	Granting body
J Holst	Nutrition and prostate cancer	Rebecca L Cooper Foundation
C Semsarian	Genetic causes of heart failure	Rebecca L Cooper Foundation
W Britton	Genetic modulation of Mycobacterium tuberculosis and macrophages to enhance TB killing	Rebecca L Cooper Foundation
J Gamble, M Vadas	Ageing and the Vascular System	Heart Foundation
Padang (C Semsarian)	Clinical, Pathological and Genetic Basis of Familial Valvular Heart Disease	NHMRC
W Weninger, B Fazekas (through WISTAR Institute)	Protective Immunity In Special Populations	National Institute of Health (US)
J Rasko, W Ritchie, J Holst	Small non coding RNAs in alternative splicing	Cancer Council (NHMRC)
J Rasko, C Bailey	Dissecting the multi-component machine that controls chromatin architecture	Cancer Council (NHMRC)
N West, J Triccas	Genetic Basis of Ethionamide Resistance in Mycobacterium tuberculosis	International Program Development Fund - University of Sydney Office of the Deputy Vice-Chancellor (International) and Sydney Medical School
L Shewan, C Semsarian	Prevalence of rheumatic hear disease in rural Cambodia. An echocardiography-based pilot study.	International Program Development Fund - University of Sydney Office of the Deputy Vice-Chancellor (International) and Sydney Medical School

Financial Highlights



In 2010 both total and research income was similar to that received in 2009. NHMRC and ARC funding continued to grow (up 22%) while non-government peer reviewed income decreased by 27%. Foundation income grew by 65% - a very pleasing result.

Income	2010 in '000	2009 in '000
Research Income		
Federal - NHMRC + ARC	5,989	4,928
NSW Government	1,331	1,202
Other Research Grants	3,999	5,475
Total research income	11,319	11,605
Fundraising		
Donations, events + other	1,198	888
Bequests	1,346	657
Total fundraising	2,544	1,545
Commercial	32	86
Other	3,456	3,742
Total Income	**17,351**	**16,978**
Expenditure		
Research Activities	12,625	11,370
Fundraising	870	580
Administration	1,606	1,602
Building operations	1,684	1,649
Total Expenditure	**16,785**	**15,201**

** The complete annual accounts are available on request*

Overall income grew by 2% whilst expenditure grew by 10%. The growth in expenditure was predominantly on research with a small increase in Foundation expenses. Administration and the building operations costs were similar to 2009.

An exciting development in 2010 was the arrival of a world-first research system called the BD LSR-9 Flow Cytometer. This system with its nine lasers gives medical researchers in Australia a new weapon in the fight against cancer, cardiovascular and infectious diseases. This installment continues Centenary's strategy to invest heavily in its core facilities of cytometry, imaging, animal and PC3.

My thanks to the Federal Government (Department of Health and Aging and ARC), State Government (OSMR, Cancer Institute NSW), non government granting bodies and the general community for their ongoing financial support of Centenary's research.

Finally my thanks to all the science support staff for their continued hard work in 2010.

Nick Pearce
Chief Operating Officer

Organisational Chart 2010

Board of Governors — **Foundation**

Executive Director

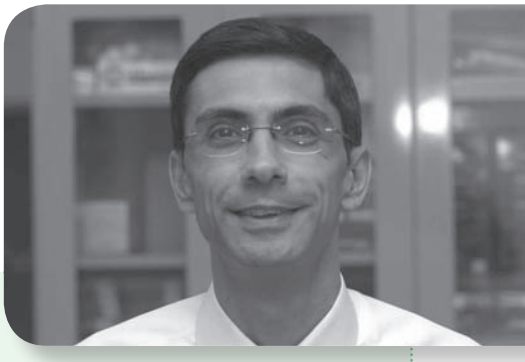
Research Groups

- Bioinformatics
- Gene and Stem Cell Therapy
- Immune Imaging
- Liver Immunobiology
- Molecular Cardiology
- Mycobacterial
- Signal Transduction
- Structural Biology
- T Cell Biology
- Vascular Biology

Scientific Support

- Chief Operating Officer
- Animal Facility
- Building and OHS
- Cytometry and Imaging
- Finance
- Fundraising and Marketing
- Human Resources
- Information Technology
- Administration

Scientific Support Staff



Executive Director & Faculty
Mathew Vadas

Administration Assistant/Reception
Michael Greensmith

Administration Assistant/Reception
Rachel Wolfenden

Animal Attendant
Danielle Moyes

Animal Attendant
David Herne (From Oct)

Animal Attendant
Hannah Walters

Animal Attendant
Leah Miller

Animal Attendant
Megan Kavazos (From Jul)

Animal Attendant
Matthew Blissett (Jul - Oct)

Animal Attendant
Michael Damjancuk

Animal Attendant
Sandra Martin (Until Aug)

Animal Attendant
Victor Truong

Animal Technician
Carol Juaton

Assistant Accountant
Chelsea Wang

Assistant Accountant
David Chow (From Jul)

Building Services Assistant
Bob Thorburn

Chief Operating Officer
Nick Pearce

Communications Manager
Tanya Sarina (From Jul)

Cytometry Support Coordinator
Robert Salomon

Director's PA / Office Support Mgr
Helen Warwick

Donor Services Assistant
Jeff Wai-Yee (From May)

Donor Services Coordinator
Barbara Smith

OHS & Operations Manager
Jeff Crosbie

Facility Assistant
Gary Black

Facility Assistant
Rebekah Hutchinson

Finance Manager
Viraf Variava

Finance Officer
Willie Entona

Fundraising & Marketing Manager
Sally Castle (Until Sep)

Fundraising Coordinator
Leisl Holterman

Head of Fundraising, Marketing and Communications
Suzie Graham (From Nov)

HR Assistant
Eric Suchy

HR Manager
Judith Barry (Until Feb)

HR Manager
Nanette Herlihen

IT Support
Owen Hoogvliet

IT Support
Sam Tardif (Until Mar)

IT Systems Administrator
Robert Middleton

Microinjectionist
Michelle Brownlee

Microinjectionist
Rain Kwan (From Jul)

Philanthropy Coordinator
LauraBeth Albanese

Receptionist
Katie Doyle

Manager – Cytometry, Imaging & IT
Adrian Smith

Grants Manager
Nick Keilar (From Nov)

Research Support Officer
Sonja Bates (Until Sep)

Senior Technical Officer
Marisa Mourelle

Technical Support Officer
Steven Allen

Veterinary Manager
Maria Wynne

Research Staff

Bioinformatics

Associate Faculty
Nicholas Shackel

Foundation Fellow in Bioinformatics
Mathew Harrison (From Jun)

Cancer Drug Resistance

Associate Faculty
John Allen

Gene and Stem Cell Therapy

Faculty
John Rasko

Associate Faculty
Jeff Holst

Editorial Research Officer
Carl Power

GMP Honours Student
Margaret Shaw

GMP Honours Student
Phoebe Matthews

GMP Honours Student
Renuka Balasubramaniam

Masters Student
Dadi Gao (From Sep)

PhD Scholar
Fiona Guan

PhD Scholar
Jessamy Tiffen

PhD Scholar
Liane Khoo

PhD Scholar
Megha Rajeskhar (Until May)

Research Assistant
Annora Thoeng

Research Assistant
Cynthia Ng

Research Assistant
Jessica Vanslambrouck

Research Assistant
Kinsha Baidya (From Mar)

Research Assistant
Maria Gonzalez (From Oct)

Research Assistant
Sarah Watson (Until Mar)

Research Assistant
Vineet Minhas (Until Dec)

Research Assistant
Xuebin Dong

Research Officer
Justin Wong

Research Officer
Kevin Wang

Research Officer
Michelle O'Han (Until Nov)

Research Officer
William Ritchie

Senior Research Officer
Chuck Bailey

Visiting Scientist
Ryuichi Aikawa (Until Mar)

Visiting Scientist
Stephen Larsen

Visiting Scientist
Tang Yi (Until Apr)

Immune Imaging

Assistant Director, Faculty
Wolfgang Weninger

Associate Faculty
Chris Jolly

Associate Faculty
Paulus Mrass

Associate Faculty
Nikolas Haass

GMP Honours Student
Kate Johnson

GMP Honours Student
Mark Taylor

Masters Student
Paula Nascimento

PhD Scholar
Edwin Lau

PhD Scholar
George Sharbeen

PhD Scholar
Nethia Kumaran

Research Assistant
Christine Yee

Research Assistant
Andrea Anfosso

Research Assistant
Ben Roediger

Research Assistant
Eunice Tan (Until Oct)

Research Assistant
Jenna Langfield (From Aug)

Research Assistant
Jim Qin

Research Assistant
Mary Mouawad

Research Assistant
Sumedha Gattani (Until May)

Research Officer
Arby Abtin

Research Officer
David Hill (From Aug)

Research Officer
Ichiko Kinjo

Research Officer
Nital Sumaria

Research Officer
Rohit Kumar Jain (From Mar)

Research Officer
Saparna Pai

Research Officer
Sioh Yang Tan

Research Officer
Stephanie Arnold (Apr - Jul)

Senior Research Officer
Lois Cavanagh

Visiting Scientist
Ann-Kathrin Reuschl (Aug - Nov)

Visiting Scientist
Celine Loh (Jan - Jun)

Liver Immunobiology

Assistant Director, Faculty
Geoff McCaughan

Associate Faculty
David Bowen

Associate Faculty
Mark Gorrell

Associate Faculty
Nicholas Shackel

Associate Faculty
Patrick Bertolino

Honours Student
Aimei Lee

Research Staff

Honours Student
Alastair Duly

Honours Student
Alison Potter

Honours Student
Elizabeth Hamson

Masters Student
Fady Akladios

Masters Student
Sumaiya Chowdhury (Until Apr)

Occupational Trainee
Louise Barbier (Until Oct)

PhD Scholar
Auvro Mridha

PhD Scholar
Candice Grzelak

PhD Scholar
Carleen Fernandez

PhD Scholar
Emilia Prakoso

PhD Scholar
Michelle Vo

PhD Scholar
Naveed Nadvi

PhD Scholar
Sarah Calabro

PhD Scholar
Sheena Yao (Until Sep)

PhD Scholar
William D'Avigdor

PhD Scholar
Yiqian Chen

Research Assistant
Ana Julia Viera de Ribeiro

Research Assistant
Bharvi Maneck (From Oct)

Research Assistant
Bramilla Patkunanathan

Research Assistant
Brenna Osborne (Until Aug)

Research Assistant
Claire McGuffog

Research Assistant
Geetha Rao (Aug - Sep)

Research Assistant
Maggie Lee (Until Sep)

Research Assistant
Margaret Gall

Research Assistant
Nicole Wood

Research Assistant
Sheena Yao (Sept - Oct)

Research Assistant
Sumaiya Chowdhury (From Apr)

Research Officer
Alison Morgan

Research Officer
Denise Yu (Until Jul)

Research Officer
Eamon Breen (From Mar)

Research Officer
Fiona Keane

Research Officer
Jennifer Brockhausen

Research Officer
May La Linn

Research Officer
Munif Allanson (Until Jan)

Research Officer
Nicholas Sigglekow (From Aug)

Research Officer
Szun Tay

Research Officer
Victoria Wen

Senior Research Officer
Fiona Warner

Snr Scientist / Clinical Snr Lecturer
Devanshi Seth

Work Experience
Zane Wang

Molecular Cardiology

Faculty
Christopher Semsarian

Genetics Counsellor
Laura Yeates

Genetics Research Coordinator
Diana Khodr (From Feb)

GMP Honours Student
Natalie Tan

Honours Student
Louise Waterhouse

PhD Scholar
Emily Tu (Until Oct)

PhD Scholar
Jodie Ingles

PhD Scholar
Matthew Kelly

PhD Scholar
Rhian Shephard

Research Assistant
Emily Tu (From Nov)

Research Assistant
Natalie Wong (Until Dec)

Research Officer
Richard Bagnall

Research Officer
Tatiana Tsoutsman

Mycobacterial

Faculty
Warwick Britton

Associate Faculty
Bernadette Saunders

Associate Faculty
Nick West

Admin Officer
Lalita Narayan

Affiliate Faculty
Jamie Triccas

Honours Student
Michael Grima

Occupational Trainee
Jens Kieckbusch (Until Mar)

PhD Scholar
Carlyn Kong

PhD Scholar
Erin Shanahan

Phd Scholar
Francis Chow (Until Mar)

PhD Scholar
Frank Kao

PhD Scholar
Gayathri Nagalingam

PhD Scholar
Greg Fox

PhD Scholar
Jonathan Nambair (Until Sep)

Research Staff

PhD Scholar
Mercedes Monteleone

Research Assistant
Germaine Chua (Until Mar)

Research Assistant
Lisa Leotta

Research Assistant
Liz Randall (Until Dec)

Research Assistant
Tuyet Tran (From Apr)

Research Officer
Heidi Schilter (Apr - Oct)

Research Officer
Jennifer Huch (From Apr)

Research Officer
Manuela Florido

Research Officer
Rachel Pinto

Research Officer
Shaun Walters

Research Officer
Wendy Lin (From Nov)

Senior Technical Officer
Paul Reynolds

Signal Transduction

Faculty
Pu Xia

Masters Student
Dona Wethsinghe

PhD Scholar
Elise Jackson

PhD Scholar
Jacob Qi

PhD Scholar
Mei Li Ng

Research Assistant
Daniel Yagoub (Until Dec)

Research Assistant
Dominik Kaczorowski

Research Fellow
Eileen McGowan (Until Dec)

Research Officer
Jinbiao Chen (From Sep)

Senior Research Officer
Carol Wadham (From Feb)

Technical Officer
Lijun Wang

Structural Biology

Associate Faculty
Mika Jormakka

PhD Scholar
Amy Guilfoyle

PhD Scholar
Kimberley Vincent

PhD Scholar
Miriam-Rose Ash

Research Assistant
Samuel Tourle

Research Fellow
Megan Maher

Research Officer
Aaron McGrath (From Nov)

Research Officer
Chandrika Deshpande (From Nov)

Research Officer
Josep Font (From Sep)

T Cell Biology

Faculty
Barbara Fazekas de St. Groth

Occupational Trainee
Kathrin Buffin (From Oct)

PhD Scholar
David Hancock

PhD Scholar
Georgina Kalodimos

PhD Scholar
Holly Bolton

PhD Scholar
Lauren McKnight

PhD Scholar
Loretta Lee

PhD Scholar
Thomas Guy

PhD Scholar
Yik Wen Loh

Research Assistant
Cindy Zhu

Research Assistant
Suzanne Asad

Research Assistant
William Hey-Cunningham

Research Officer
Michael Kuligowski (From Jul)

Senior Research Officer
Elena Shklovskaya

Vascular Biology

Faculty
Jennifer Gamble

Honours Student
Amanda Khoury

Honours Student
Anna O'Halloran

PhD Scholar
Garry Chang

PhD Scholar
Ilana Lichtenstein

PhD Scholar
Jennifer Young (Until Dec)

Research Assistant
Andrej Brummer (Until May)

Research Assistant
Danesh Kumar (Until Jan)

Research Assistant
Emie Roy (From Mar)

Research Assistant
Jia Li (From Jul)

Research Assistant
Paul Coleman

Research Assistant
Ying Lu

Research Officer
Angelina Lay

Research Officer
Joshua Moses (From Feb)

Senior Research Officer
Mai Tran (From Feb)

Senior Research Officer
Matthew Grimshaw

Technical Officer
Elena Zaporoshenko (From Feb)

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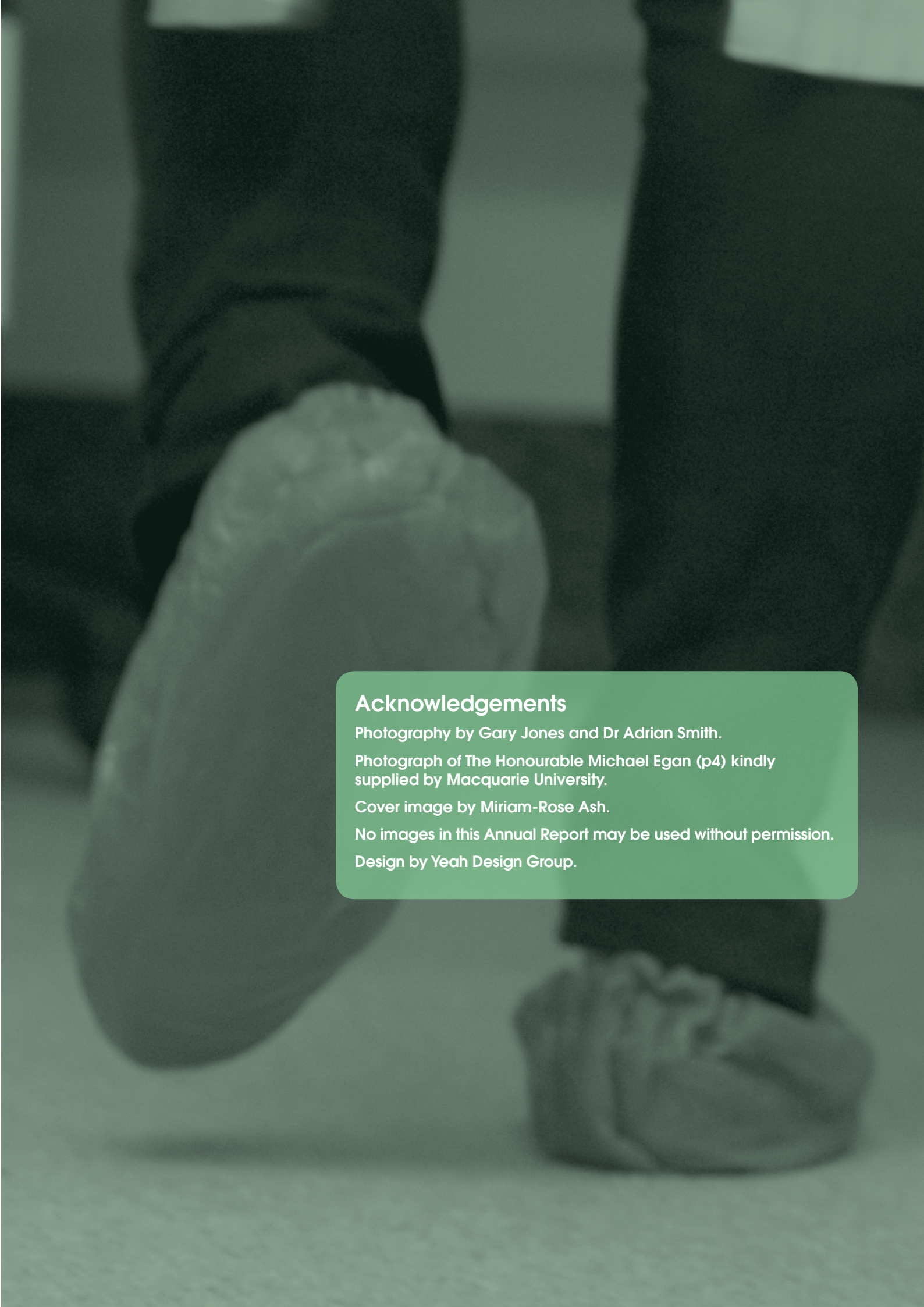

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