Centenary Institute research for life

Annual Report 2009

The Centenary Institute, located between Royal Prince Alfred Hospital and Sydney University, 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

In this past year, it has been a pleasure to see how the Centenary's staff and scientists have faced the financial turmoil with equanimity, optimism and energy. Given the long lead time for scientific discoveries to reach clinical utility, researchers are selected for their tenacity and capacity to work through difficult times

Indeed our performance has if anything strengthened, with our total grant income climbing from $13 Million to $15 Million and an undiminished impact of our publications. At the same time, the Centenary grew in numbers with our staff reaching 200, a remarkable increase of 100% in 3 years.

The Board of the Centenary welcomed Professor Sue Pond AM and Mr Ken Cahill to the Board of Governors. Professor Pond brings to the Board superb commercial and scientific experience, while Mr Cahill brings a wealth of experience in management of major health facilities.

One of the many things we pride ourselves on at the Centenary is our capacity to synergise with our neighbours. A lot of effort in this regard has come to fruition with the planning of a new building for the Centre for Obesity, Diabetes and Cardiovascular Diseases. The Centenary will have a significant role in this research centre, which will be staffed by 1,000 scientists. In addition, the Boards of the Centenary and LifeHouse have agreed to progress their joint support of cancer research with the formation of the Centenary-Lifehouse Cancer Research Centre. This will initially be housed over two sites, with wet research supported by the infrastructure provided by the Centenary and dry research being nearer the patients in the new LifeHouse building. Eventually, these will be united when Stage B of the LifeHouse is erected adjacent to their clinical suites.

The Board is very pleased with progress in our fundraising efforts and with the Foundation. With the leadership of our Board Member Mr Joseph Carrozzi, we look forward to a wonderful year. We have also been very fortunate that Ms Jill Weekes, the former CEO of the Starlight Children's Foundation, has agreed to assist the Foundation in their activities.

The issue of adequately funding infrastructure is central to the successful operations of the Centenary, and indeed all medical research institutes. For this reason we are very grateful for the MRSP scheme of the NSW Government, which provides a vital component of our infrastructure funding. Ultimately, we strive for a system that ensures $0.60c infrastructure in each $1 of research income.

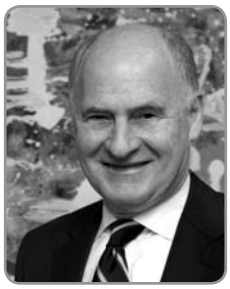
Assistant Directors have become a vital part of the management of the Institute. The Board thanked Professor Geoff McCaughan for his services as Assistant Director, a position that rotates after two years, and welcomed Professor Chris Semsarian to this post.

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

The Honourable Michael Egan

EXECUTIVE DIRECTOR'S REPORT

What is the most satisfying outcome of a visit to the doctor? It is definitely not hearing: 'I am not sure what is wrong,' or 'I'm sorry, there is nothing I can do for you'. It is the definition of the illness and hearing 'I have just the treatment for you'. This is what medical research, and the Centenary is about- finding effective diagnostics and therapies for diseases.



Researchers across the world have made remarkable progress in 2009. Diseases like melanoma, often resistant to drugs, now have an effective therapy. New drugs are being approved for rheumatoid arthritis and cancer. These advances have each taken 10-15 years of work and hundreds of millions of dollars to deliver, but their success is a testament to the persistence and vision of researchers and drug developers.

Our work at the Centenary is motivated by finding treatments for cancer, cardiovascular and infectious diseases and the progress has been, as highlighted in this Annual Report, highly gratifying. I would specifically draw your attention to the work of Professor Chris Semsarian which has had a significant impact on community health. Professor John Rasko has also done remarkable work in understanding the role of small RNA molecules in cancer.

What is particularly satisfying about being the Director of an independent medical research institute (MRI) is that whilst we compete with other entities, we also collaborate for the greater good. A good example this year of collaboration was the purchase of a microscope for our multi-photon facility. This microscope allows an unprecedented detail of analysis of cells and tissues. The microscope was funded by grants totalling $600k in which were joined by the University of Sydney, University of NSW, Children's Cancer Institute Australia and Royal Prince Alfred Hospital.

Of course the Centenary is most fortunate, by virtue of its location, to be at the epicentre of medical research in Sydney. This allows us to interact with our neighbours and generate synergistic outcomes. We are involved in two key developments on either side of our building - on the west, the Centre for Obesity, Diabetes and Cardiovascular Diseases, and on the south, LifeHouse. As is detailed in the Chairman's Report, our association with these developments will provide the much needed space and infrastructure capacity to propel the Centenary into its next phase of growth and activities. The performance at the Centenary already comfortably puts us amongst the top 5 MRI in Australia. With the addition of 150 staff we are also on the verge of joining in size the major research Institutes.

Another advantage of MRIs is a single mindedness, and speed in bringing the latest technologies to bear on problems. A clear skill set that has been holding us back has been the lack of a coordinated and in-depth analysis of the data that is arising from genomics. In the past, experience and intuition were the only tools we had to decipher patterns and trends in biology. This is no longer the case, as the new art or science of 'computational biology' or 'bioinformatics' serves to organize and disseminate scientific knowledge, thus accelerating the pace of medical research. The Centenary has grasped this field in an exemplary fashion.

EXECUTIVE DIRECTORS REPORT CONT.

In June, Centenary's Foundation mounted a magnificent effort to raise funds to support a Bioinformatics Fellowship. In addition, our Faculty has agreed to contribute time and effort in order to start a new Laboratory of Bioinformatics. I congratulate Dr Nick Shackel in becoming the inaugural leader of this laboratory and see it as not only providing Centenary the necessary skills to succeed, but also becoming an invaluable campus-wide resource.

There have been significant developments in our international interactions as well. We have signed agreements with Vietnam to progress our research on tuberculosis, and with Nara Institute in Japan to collaborate in the longer term. In addition, we have also set up a study in Vietnam addressing sudden death in that community.

Satisfyingly, our discoveries are having an effect in our indigenous communities as well. Prof Chris Semsarian has set up an Indigenous Heart Disease Clinic, addressing the problem of sudden cardiac death in peripheral centres.

We have also had a strong year in funding, with 32 new grants and 3 Fellowships awarded to our researchers. Our publications continue to be cited at a level amongst the highest in Australia (a mean of approximately 10 citations per paper per year).

Managing our growth over the next three years represents a challenge we are ready to meet head on. The Centenary will use this opportunity to promote the very talented Associate Faculty, to recruit skills that add to and complement our existing strengths, and to ensure the changes result in a steady strengthening of our financial position. In 2010, our Scientific Advisory Board will spend three very intensive days reviewing our vision and performance, our plans and aspirations and advise on our future leaders in the Centenary.

I wish to acknowledge the superb help provided by the Executive of the Centenary: the two Assistant Directors, Professors Geoff McCaughan and Wolfgang Weninger, the Chief Operating Officer Nick Pearce, the Fundraising and Marketing Manager, Sally Castle and the Human Resources Manager Nanette Herlihen. Professor McCaughan finished his rotation as Assistant Director, a position that holds a two year term, at the end of 2009. He will join the Executive as a member of the Centenary-LifeHouse Cancer Research Centre management team.

I want to congratulate Professor Semsarian for receiving the Royal Prince Alfred Hospital Foundation Medal. This prestigious medal is awarded yearly and it is the 4th time that workers at the Centenary have been successful.

Professor Mathew Vadas

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.

The Honourable John Brown AO

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 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.

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 John 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, 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 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.

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. He was the strategic and creative mind behind the successful 'Kevin 07' advertising campaign. His work for Kevin Rudd and the Australian Labor Party was recognised by The Australian newspaper, which awarded him the 'Australian Marketer of the Year' in 2007. In 2009, he was responsible for the marketing campaigning behind Anna Bligh's successful bid to be elected Australia's first female Premier. More recently, he worked with the Football Federation of Australia's bid strategy for the nation's bid to win hosting rights for the 2018-2022 FIFA World Cup, and was the Creative Director of the launch film. Mr Lawrence has represented Australia internationally as the Chairman of Judges at the Irish International Advertising awards and on the film jury at Cannes.

Dr Susan Pond AM MBBS MD DSc, FTSE

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 non-executive 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, 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 served as chair of the Medical Research Advisory Committee of the Australian Cancer Research Foundation for five years before stepping down in 2007. He currently serves on the Board of Governors of the Arts & Health Foundation and the Sydney Institute of Health and Medical Research.

RESEARCH PERSPECTIVE

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

Cancer

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

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

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

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

Cardiovascular disease

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

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

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

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

Infectious diseases

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

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

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

- Why do latent TB infection progresses 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 selective barrier between the blood and the tissues. Furthermore, endothelial cells are the key to maintaining the non inflammatory, non adhesive and non clotting surface of vessels.

In adults, blood vessels normally do not proliferate except during the female reproductive cycle. However, in pathologies such as solid tumour growth and cardiovascular diseases, uncontrolled blood vessel growth and dysfunctional endothelial cells are hallmarks of these diseases.

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

Highlights of 2009

- Age is the greatest risk factor for the development of cardiovascular disease. We have discovered a gene, which we have called, SENEX (from the Latin meaning old age or old man), that causes endothelial cells to age prematurely through a process known as senescence. Senescent endothelial cells do not replicate but remain alive for months, outside the control of their normal survival mechanisms. The exciting finding is that the senescent endothelial cells display an altered phenotype, being anti-inflammatory in response to the normal inflammatory stimuli such as cytokines.

  We have shown that SENEX expression and senescence can be induced by oxidative stress, which has also been linked to atherosclerosis development. We propose that the induction of senescence in the vasculature may be a defense mechanism, designed to limit or control chronic inflammatory conditions (of which atherosclerosis is one). Indeed SENEX levels are increased in areas of atherosclerotic plaques taken from a model of disease development.

Major Projects

Senescence in the vasculature

Having identified and characterised the gene SENEX, we are now interested in the molecular events that govern its expression, its structure-function (in collaboration with the Structural Biology group at the Centenary Institute) and its expression and involvement in diseases such as cardiovascular diseases, including atherosclerosis and diabetes. The development of mutant mice and the impact of deletion or overexpression of SENEX will aid in these studies.

The Role of senescence in tumour growth

Senescence is a control mechanism to inhibit tumour growth. SENEX is also expressed in epithelial cells and, when over-expressed, induces senescence. Furthermore, it is induced by factors, which are involved in tumour development. Dr Matthew Grimshaw has initiated work to delineate the role

Professors Mathew Vadas and Jennifer Gamble, the Vascular Biology group, PhD Scholar Jennifer Young

of SENEX in breast development and in breast cancer progression.

Blood vessel formation

Angiogenesis is a process of new blood vessel growth from preexisting vessels. Endothelial cells, during angiogenesis must undergo events such as proliferation, migration re-organisation and differentiation.

miRNAs

miRNAs are endogenous non-coding RNAs which are expressed as long hairpin-forming precursor RNAs that are further processed to 21-23 nucleotide RNA molecules.

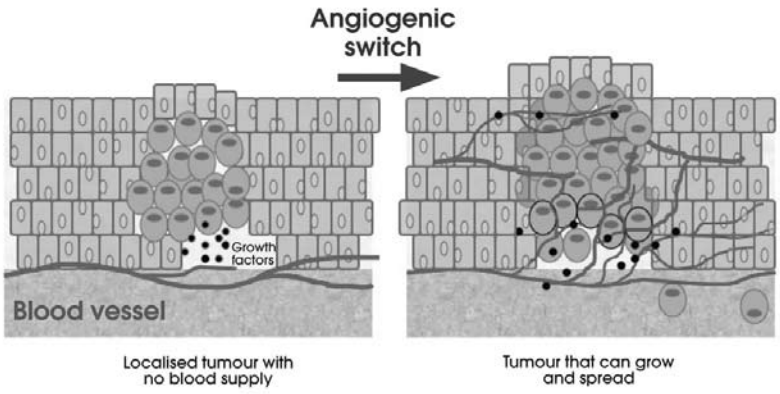
miRNAs regulate gene silencing generally by post-transcriptional mechanisms and are regulators of key differentiation and developmental processes. We are investigating the control of angiogenesis by miRNAs and have identified a group of miRNAs which are regulated during blood vessel formation and which control two major signalling pathways essential for angiogenesis.

Further work is directed to understanding the regulation of these specific miRNAs, the expression of these in normal vessels and diseases where angiogenesis is a key feature.

Differentiation of Endothelial Progenitor Cells (EPC)

Endothelial cells are derived from progenitor cells (EPC) that are present in the bone marrow, vessel wall and circulation. EPCs are increased in number upon vascular stress or damage and are thought to contribute to vascular repair.

An understanding of what drives and controls EPC maturation may aid in the development of novel strategies in diseases, such as diabetes where there is a deficit of EPC. We have identified a set of miRNAs, which are regulated in their expression during EPC to endothelial maturation. Further characterisation of these miRNAs has demonstrated that some act as a block to the differentiation process and maintain the progenitor state. Their targets and mechanism of action is now under investigation.



How will this research impact community health?

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

New blood vessel formation is an essential feature of solid tumour growth and is involved in metastatic spread. Targeting both the tumour cells and the expanding vasculature in combination, is proposed as a two- pronged approach to new anti-cancer therapies. Understanding the normal process of angiogenesis should expose what goes wrong in disease and identify possible targets for drug development.

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 to intervention.

T CELL BIOLOGY

Professor Barbara Fazekas de St Groth

Diseases caused by immune imbalances such as allergies and autoimmune diseases are on the rise. Immune imbalance may also be involved in many chronic health problems such as heart disease, obesity and diabetes. The T Cell Biology Research program seeks to find the underlying causes of these immune imbalances and to work towards new treatments and preventive strategies.

The increase in inflammatory diseases is believed to be due to lifestyle changes that have made the environment too 'hygienic' to allow the immune system to function normally. We are studying how the immune system interacts with the environment so that we can pinpoint the factors that are adversely impacted by 'hygiene'.

At the heart of the immune response is a network of cells that perform 3 distinct functions: sampling and 'presentation' of molecules from microorganisms and the body itself (performed by dendritic cells), activation of the immune effector cell arm (performed by effector and memory T cells), and regulation of responses to minimise their negative effects on health (performed by regulatory T cells).

Our group is working to understand how cells with these 3 different functions interact during normal and abnormal immune responses. To do this we use animal models to identify and manipulate each cell type and environmental factors. We also study the immune abnormalities present in human immune-mediated diseases, including inflammatory bowel disease, asthma, type 1 diabetes, rheumatoid arthritis, multiple sclerosis, Graves' disease and psoriasis.

Highlights of 2009

- Demonstrating for the first time that the most superficial dendritic cells in the skin, known as Langerhans cells, are pre-committed to inducing immune tolerance, even when exposed to highly inflammatory stimuli.
- Showing that regulatory T cells function in an antigen-specific manner to prevent asthma in a mouse model.
- Showing that subsets of human regulatory T cells, identified by expression of chemokine and adhesion receptors, are abnormal in patients with multiple sclerosis, psoriasis, Graves' disease and inflammatory bowel disease.
- Publishing the findings from a collaboration with the University of Sydney Department of Paediatrics, showing that the ratio between regulatory T cells and pro-inflammatory interleukin-17-producing T cells is increased in normal pregnancy but not in preeclampsia.

Major Projects

Immune regulation in mouse models

We are using genetically modified mouse models to track the interactions between dendritic cells, T cells and regulatory T cells. A major focus is how the behaviour of different subsets of dendritic cells affects the T cell response. Led by Dr Elena Shklovskaya, we have shown that Langerhans cells, the dendritic cell subset within the epidermis

Professor Barbara Fazekas de St Groth, the T Cell Biology group, PhD Scholar Lauren McKnight

the most superficial layer of the skin are pre-committed to induction of immune tolerance. This is the first direct in vivo evidence of such pre-commitment of a dendritic cell subset and defines a new means of regulating the immune response.

These novel findings shed light on how the immune system distinguishes between commensal organisms, which do not disturb the structural integrity of the epidermal/dermal barrier and pathogens which breach the barrier and thereby interact with immunogenic dermal dendritic cells in the deeper skin layers. The work supports a new paradigm in which tolerogenic and immunogenic responses are driven not by changes in the function of individual dendritic cells but by different combinations of dendritic cells pre-committed to either tolerance or immunity.

A second parameter that controls the ability of dendritic cells to stimulate T cells is the expression of costimulatory molecules. These molecules appear to enhance the stimulatory capacity of dendritic cells without changing their fundamental ability to program T cells for tolerance versus immunity.

We have shown that a reduction in the number of regulatory T cells causes dendritic cells to over-express many costimulatory molecules from the B7 and tumour necrosis factor families. This in turn allows relatively low affinity self-reactive T cells to become activated, leading to autoimmune disease.

We have now shown that transfer of regulatory T cells into these animals can reduce the expression of costimulatory molecules. In these experiments, 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 of regulatory T cells is an important determinant of normal immune function. These studies provide the intellectual basis for our studies of human regulatory T cells (below).

We have also shown that antigen-specific regulatory T cells can prevent the development of asthma in a murine model. So far this effect has been limited to the priming phase of the response but we are now testing whether regulatory T cells will work at later stages of the response after appropriate pre-activation.

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.

Human regulatory T cells

This year we have developed new antibody cocktails to distinguish subsets of circulating and tissue-derived regulatory T cells. Based on the hypothesis that the number of regulatory T cells in any particular tissue is the crucial determinant of immune control at that site, we have counted the number of regulatory T cells expressing the homing molecules required for entry into particular tissues.

Comparison of healthy controls with patients suffering from inflammatory bowel disease, multiple sclerosis, Graves' disease and psoriasis has indicated significant differences in circulating subsets of regulatory T cells within patients. Importantly, these changes were not seen within non-regulatory T cells. These results suggest that we may be able to design new tests for autoimmune disease, based on counting regulatory T cell subsets within blood samples.

How will this research impact community health?

Our ultimate goal is to arrest or reverse the increase in immune-mediated diseases by identifying and changing the environmental factors responsible for the problem. While we work towards this objective, our research will generate potential benefits for community health.

Our studies of how regulatory T cell and dendritic cells control the immune response will provide the basis for the development of new vaccination therapies for cancer, allergy and autoimmune disease. Our transplantation studies will define new mechanisms that can be targeted to stop the rejection of organ grafts.

Our studies of human regulatory T cells should lead to new tests for diagnosis and monitoring of human immune-mediated disease.

STRUCTURAL BIOLOGY

DR MIKA JORMAKKA

By understanding the anatomy of membrane proteins and their structure function relationship, we hope to be able to tailor drugs to increase their efficiency and to reduce side effects. We are focused on structural studies of membrane proteins involved in signal transduction and transport. Of particular interest is transporters involved in cellular drug extrusion, the proteins that 'pump' drugs out from the cell and therefore reduce the efficiency of, for example, cancer chemotherapy and antibiotics.

The structural biology group is using synchrotron sources (particle accelerators) to determine structures by X-ray crystallography. This technique has been used for many decades for structural determination of soluble proteins, proteins that are found in the cytoplasm of the cells. In recent years, technical development and increased funding has paved the way for structural determination of membrane proteins.

Highlights of 2009

- We determined the structure of the G protein domain (GTPase) of a bacterial metal transporter critical for virulence in many pathogenic organisms. This provided information of G protein coupled membrane processes in general, and the transport mechanism of this protein in particular (Guilfoyle et al., EMBO Journal, 2009).
- Functional studies of the metal transporter show a potassium dependent activation, leading to a unique structural feature on the surface of the protein. This structural feature could provide a novel therapeutic target for gastric ulcers, which is currently being investigated.

Major Projects

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

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

Transporter derived drug resistance

Membrane transporters are involved in cellular influx and efflux of nutrients, ions and drugs. They fill an essential niche in cellular homeostasis and are, in many cases, implicated in bacterial virulence, as well as drug

Dr Mika Jormakka, the Structural Biology group, PhD Scholar Amy Guilfoyle

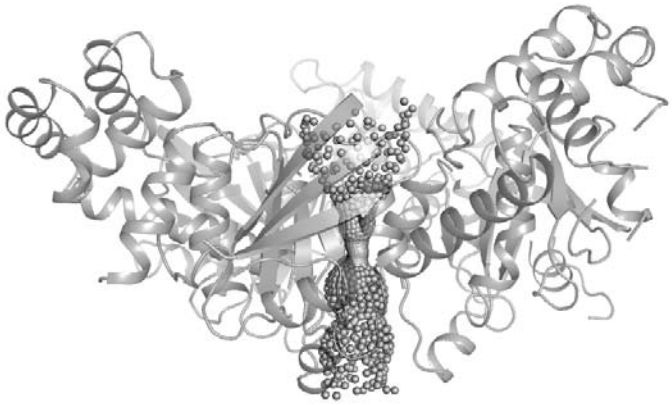
extrusion, with important implications for cancer and anti-microbial drug resistance.

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

G-protein coupled membrane processes

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

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



Structural representation of metal funneling in a membrane transporter

How will this research impact community health?

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

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

SIGNAL TRANSDUCTION

ASSOCIATE PROFESSOR PU XIA

Research in the Signal Transduction program aims to understand how cells communicate in our body to maintaining normal functions, and how such communication goes wrong leading to the development of human diseases, such as cancer, diabetes and cardiovascular disease.

To keep our body functioning normally, cells in our body are capable of consistently sensing and responding to any stimuli or environmental changes through a proper communication process called signal transduction.

A new enzyme named sphingosine kinase is often overproduced by cancer cells. We found that numerous cancer cells are able to utilise this enzyme to generate potent growth signals, leading to accelerated and uncontrolled cancer cell growth. Remarkably, we have found that blocking this enzyme and thus abolishing the growth signals by using either chemical or genetic inhibitors, significantly slows down or stops the uncontrolled cancer cell growth. This finding will help to develop various types of therapeutic agent for the treatment of human cancers, such as breast cancer.

Highlights of 2009

- Following our previous finding that sphingosine kinase 1 (SphK1) is a key mediator of estrogen and growth factor signalling, we have found that SphK1 is an important contributor to endocrine resistance in breast cancer cells. Inhibition of this enzyme not only profoundly sensitised cancer cells responding to tamoxifen, but also restored the sensitivity to the drug in the resistant cells, leading to the cancer cell death. This work provides a new strategy that will be more effective and safer for the treatment of breast cancer.
- Collaboration with the University of Turin has been initiated, with an aim to investigate whether SphK1expression can be used as a predictor or diagnostic marker for patients who will respond properly or become resistant to endocrine therapy.
- In collaboration with clinicians in China, we have reported a novel therapeutic potential for ovarian cancer by using a synergist of cisplatin with a traditional Chinese medicine compound, arsenic trioxide.
- Collaborations with the Liver Research and Vascular Biology groups have been established in the Centenary Institute, conducting a new NHMRC program to investigate inflammation, angiogenesis and cancer in the next 5 years.

Major Projects

Identification of a new anticancer target

Since we, for the first time, reported a potential oncogenic role for SphK1, a growing body of evidence has now suggested that SphK1 plays a critical role in the development of various human cancers, such as that of breast, lung, liver, prostate and others.

We have recently found that SphK is able to promote cell growth in breast cancer and help the cells escaping

Associate Professor Pu Xia, Research Assistant Dominik Kaczorowski

from death after treatment with anti-cancer drugs. We now seek to further understand how cancer cells use SphK for their communications to survival, and whether blockade of this signalling pathway could provide an effective way to specifically kill cancer cells without damaging normal cells.

Endocrine resistance in breast cancer

We have demonstrated a key role of SphK1 in tamoxifen resistance of breast cancer. Our challenge is to translate this knowledge into the clinic to improve diagnosis and treatment for breast cancer patients with endocrine resistance. Ongoing work in the laboratory is to determine if SphK inhibitors can be used in combinational therapy to kill resistant breast cancer cells and not normal cells. Additionally, in collaboration with the University of Turin, we are determining whether SphK1 can be used as a predictor or diagnostic marker for patients who will respond properly or become resistant to endocrine therapy.

Preventing pancreatic beta-cell death for treatment of diabetes

Diabetes is now a serious global health problem. Currently, more than one million Australians suffer from diabetes and this number will be doubled by 2015. Dysfunction or destruction of pancreatic beta-cells caused by cell suicide, namely apoptosis, is a common pathogenic factor for both type 1 and type 2 diabetes. Thus, attempting to protect beta-cells against death and rescue their insulin secretory function is emerging as a strategy for the management of diabetes.

We aim to examine how pancreatic beta-cells communicate for their survival especially under cellular stress, such as high levels of blood sugar or lipids. We also seek to understand the interrelationship between molecular mechanisms underlying defects in beta-cell survival and insulin secretion. This study will not only reveal a novel signalling pathway in the regulation of beta-cell function and survival, but may also provide a potential target to create new therapeutic strategy for diabetes.

Insulin resistance and cardiovascular disease

Due to the current and growing trends of obesity and type 2 diabetes throughout the wider community, insulin resistance represents a key metabolic determinant underlying the development of cardiovascular diseases, such as heart attack and stroke. We are attempting to understand why people with diabetes or obesity have a greater risk of developing heart disease when they become insulin resistant.

The main cause of diabetes is a defect in the actions of insulin, the hormone that promotes sugar metabolism. Insulin also has a number of beneficial effects associated with maintaining a healthy heart. However, the heart-protective effects of insulin are often devastated in diabetes or obese people, leading to the development of heart disease. Currently, researchers believe that this is caused by disruptions in the communication between and within cells.

Our recent work has uncovered that the enzyme SphK1 can be used by cells for their communications in response to insulin. The current study is designed to examine if changes in this enzyme can disrupt the normal activity of insulin within the cells that make up the blood vessels and how this could contribute to the development of heart disease. By working on this project, we hope we can provide a potential drug target for intervention to halt or slow down the progression of diabetes and/or obese-associated cardiovascular diseases.

How will this research impact community health?

Today, most therapeutic agents are still problematic and often have side effects. For example, the drugs currently used for chemotherapy that kill cancer cells also often kill or damage normal cells, leading to a poor outcomes for patients. Therefore, the development of innovative chemotherapeutic agents is urgently needed for increasing patient survival rates.

Our research has focused on understanding how the communication networks in cancer cells differ from that in normal cells, and finding key nodes of the signalling networks that control cancer cell growth. This will allow us to identify molecular targets for the development of new therapeutics that specifically and effectively kill cancer cells without harming normal cells, and ultimately improve the patient's outcomes.

MOLECULAR CARDIOLOGY

PROFESSOR CHRISTOPHER SEMSARIAN

One of the great benefits of identifying potentially fatal genetic diseases in families is the opportunity it provides to help save lives for future generations. Cardiovascular disease affects one in five Australians and one out of two families. However, many of the 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, genetic technologies and clinical medicine will ultimately reduce human heart diseases and prolong life. We hope through our research to realise these goals in the coming years.

Highlights of 2009

- 2009 was an extremely productive year for the Molecular Cardiology team, with their cutting edge research resulting in 12 peer-reviewed publications in high-quality international journals. In addition, Professor Semsarian was awarded 3 prestigious NHMRC project grants for research commencing in 2010, as well as receiving the 2009 RPA Foundation Medal, for excellence in medical research.
- Professor Semsarian and his team have commenced a national study focused on sudden cardiac death in the young. This prospective study is not only aimed to identify the clinical and genetic basis of sudden death, but to initiate treatment and prevention programmes to reduce sudden death among young Australians.
- Dr Lien Lam was awarded her PhD in 2009 and was accepted to undertake her postdoctoral fellowship at the Department of Genetics at Harvard Medical School in Boston, USA. Her outstanding research during her PhD studies involved understanding the key protein changes in the development of cardiomyopathies.

Major Projects

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

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

Furthermore, studies have shown marked variability in the degree of clinical expression of the abnormal gene. There are many examples of affected individuals within the one family who are carrying

Professor Christopher Semsarian, the Molecular Cardiology group

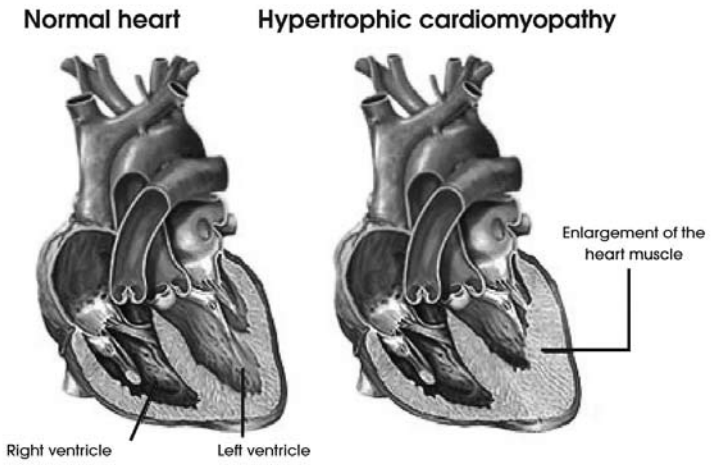
the same gene (DNA) defect, having vastly different clinical features and outcomes. This suggests modifying factors, both environmental (e.g. exercise, diet) and secondary genetic influences, play an important role in modifying the clinical phenotype in genetic cardiac disorders.

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

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

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

HCM is characterised by marked thickening of the heart muscle and occurs in approximately one in 500 people, making it the most common genetic heart disorder known. Our research program has seen and collected clinical information and DNA in over 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, including diabetes, HIV and heart disease. We are looking to overcome the barriers to successfully implement these technologies, develop models to understand the biology of adult stem cells and discover the causes of diseases such as cancer and genetic disorders.

The Gene and Stem Cell Therapy Program undertakes research in five areas: gene therapy; stem cell biology; molecular mechanisms of gene control; genetic disorders; and cancer biology. Each of these areas have specific staff allocated to projects, but a true synthesis is achieved by building project-based organic collaborations that take advantage of the core technologies we have introduced to the Centenary Institute.

For example, understanding the mechanisms by which a normal cell becomes cancerous is a daunting task that demands a multi-faceted approach. By studying proteins and RNA molecules that increase or decrease in different cancers, we have pursued the basic biology of cancer and possible future therapeutic opportunities that will arise.

Studying both the transcription factors and microRNAs will help to define the biochemical pathways and complex inter-molecular machinery involved in cancer.

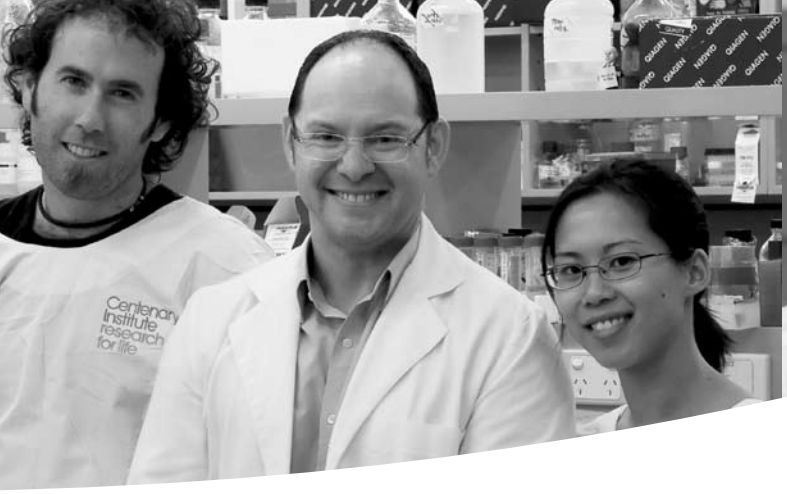
A major initiative within the Program established several years ago is now producing internationally-acclaimed discoveries in the area of bioinformatics.

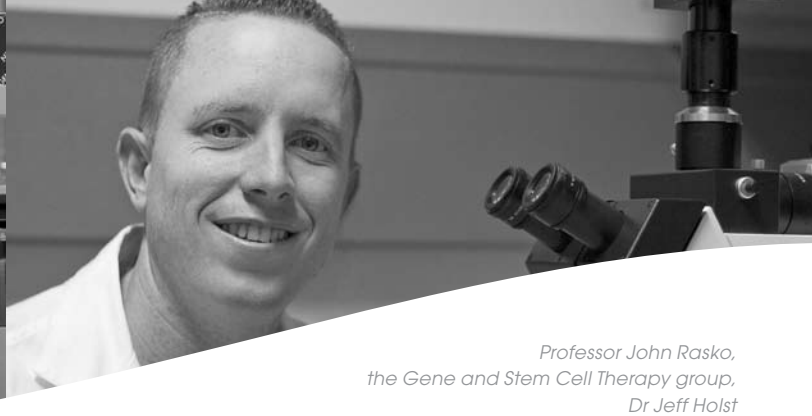
Highlights of 2009

The major highlight of 2009 was a series of internationally-acclaimed discoveries in the field of bioinformatics. This relatively new area arises from the ability to generate vast amounts of biological data from new DNA sequencing technologies and its availability online. Our research has led to the creation of a website, which we called mimiRNA. It serves the international research community by providing a novel tool to analyse small RNA molecules that were the subject of the 2006 Nobel Prize in Physiology or Medicine.

Other highlights include:

- Graduation of several doctoral students, all of whom have been appointed to tertiary Institutions of learning and medicine.
- Visits extending 2-12 months by sabbatical scientists from the USA and China.
- Chairing the inaugural meeting and establishing the International Society for Cellular Therapy – Australia to be the peak industry voice in developing stem cell and other cell-based treatments
- Appointment as Chair of the American Society of Cellular and Gene Therapy International Committee
- Award of 2nd place in the inaugural Centenary Image Prize to graduate





Professor John Rasko, the Gene and Stem Cell Therapy group, Dr Jeff Holst

student Jessica Vanslambrouck for her microscopic analysis of kidney amino acid pumps

Major projects

Stem cells and their environment

In order to provide advances in stem-cell based therapies we need to understand the essential components of their environment. A major limitation in stem cell therapy is our inability to expand them outside of the body. While there have been major advances by Australian research in understanding growth factors required to maintain cells, we sought to explore an entirely new dimension in collaboration with groups in Texas, USA and the School of Molecular and Microbial Biosciences at the University of Sydney.

We have demonstrated for the first time that blood stem cells are capable of responding to their physical surroundings. We have made use of the most elastic biological substance available to prove that stem cells prefer to be in a stretchy and flexible environment, rather than a solid and hard one. Our work not only provides a unique tool to study cell biology, but it also offers an additional dimension to biomaterial design for the culture of cells outside the body.

Essential cellular functions and cancer

For the last decade, we have collaborated with the group of Victor Lobanenkov at the National Institutes of Health (Washington DC, USA), examining the role of the tumour suppressor gene CTCF and its related cancer/testis gene BORIS. BORIS is normally only expressed in the testis, however it is over-expressed in many different types of tumours. We have shown that CTCF and BORIS share a number of protein interactors, whilst also maintaining unique binding proteins. This analysis has led to the development of novel tools to study normal and cancerous cell growth. We have also shown for the first time the function of BORIS when it is expressed in cells.

Computer analysis of gene expression (Bioinformatics)

An understanding of the way blood cell production is regulated in the body has immediate relevance to diseases like leukaemia and the way they are treated. MicroRNAs were recently identified to be of profound importance in controlling patterns of gene expression and have been shown to be intricately involved in cell development and differentiation. To understand these patterns, a reliable compilation of miRNA and mRNA expression data is required to compare multiple tissue types.

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

We have developed mimiRNA, an on-line resource that integrates gene expression data and permits its visualisation <mimirna.centenary.org.au/>. The research community response to this website has been overwhelming. Its importance has been recognised as a 'research highlight' by the journal Nature Methods and, within the first month, we processed over one thousand jobs requested from ten different countries.

How will this research impact community health?

The safe introduction of healthy genes into patients with genetic disorders could effectively cure inherited genetic disorders such as some cancers, haemophilia and immunodeficiency disorders as well as infectious diseases such as HIV. 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 there are not many studies measuring the effects of nutrition on disease.

It is known that the expression of specific amino acid transporters are increased in many primary cancers, and indeed there is growing literature that obesity can be linked with diabetes, cardiovascular disease and cancer. Tumours require a constant supply of nutrients to maintain their growth advantage and it has been shown that cancer cells consume more nutrients than normal cells. Increased understanding of the metabolic requirements of tumours may lead to new treatments for cancer.

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

Highlights of 2009

The Prostate Cancer Foundation of Australia awarded a four-year $475,000 grant to this project, which started in 2008. 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 the link between a common gene mutation/deletion and two different amino acid transporters in prostate cancer cell lines.
- An invitation for Dr Holst to speak at the 10th National Prostate Cancer Symposium in Melbourne, August 2009 and at the Prostate Centre, Vancouver General Hospital, Canada.
- A Prostate Cancer Foundation of Australia equipment grant together with Prof. John Rasko, Dr Rosetta Martiniello-Wilks and Dr Qihan Dong providing $40,000 toward the purchase of a new in vivo imaging system.
- Hiring a new research assistant, Vineet Minhas, to work with Dr Wang on the project.

Major Projects

The role of amino acid transport in prostate cancer

Approximately 70% of prostate cancer patients have alterations in a single pathway necessary for cell growth. Decreased expression of one member of this pathway, PTEN, leads to increases in 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 prostate cancer cells.

We are investigating how transporters may promote prostate cancer. This will be studied using prostate cancer cell lines and a prostate cancer mouse model crossed with a new knockout mouse model. Analysis of the genes involved in the onset and progression of prostate cancer will be determined in these models.

Understanding this complex network may provide new insights into the effect of diet (particularly red meats and dairy which are high in leucine) on the development and progression of prostate cancer. Alternatively, these transporters may be targeted for therapeutic intervention, designed to 'starve the cancer'.

Dr Nicholas Shackel

BIOINFORMATICS

DR NICHOLAS SHACKEL

The Bioinformatics group will collect and make sense of the data generated by Centenary Institute's labs – quickening the pace of medical research.

The formation of the Bioinformatics Department was made possible by the Centenary Institute Foundation's fundraising efforts. The group will address questions raised by a broad range of medical and biological research projects.

Fundamental, highly significant biological questions, pivotal to understanding human disease require complex computational Bioinformatics analysis. The group will provide specialist bioinformatics services to researchers within the Institute and external collaborators, including the University of Sydney.

Bioinformatics approaches utilise computational analysis of large complex data sets, representing data in new and unique ways. This enables researchers to understand the complex basis of many human diseases including cancer, heart disease, tuberculosis and liver cirrhosis.

Recent Highlights

- Appointment of the Head of Bioinformatics: Dr Nicholas Shackel
- Appointment of the Foundation Fellow in Bioinformatics
- Appointment of Bioinformatics Steering Committee
- Appointment of a Bioinformatics Interest Group

Major Projects

- To provide core essential Bioinformatics services to Centenary Institute research groups
- To establish collaborations within the research precinct
- To undertake novel research, including understanding the pathogenesis of human viral hepatitis liver injury (in collaboration with the Liver Biology group) and understanding gene differences between immune cells (in collaboration with the Immune Imaging group).

Centenary Staff for 2010

Dr Nicholas Shackel
– Head and Associate Faculty

Foundation Fellow in Bioinformatics
– Dr Mathew Harrison

Dr Victoria Wen
– Post-doctoral Researcher

Ms Maggie Lee
– Research Assistant

How will this research impact community health?

We believe bioinformatics is essential to the development of personalised approaches in medicine. Bioinformatics analysis will enable researchers to understand the complex and multifaceted nature of human disease. This will quicken the pace of medical research, bringing new therapies and treatments to light faster.

MYCOBACTERIAL

PROFESSOR WARWICK BRITTON

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

Mycobacterium tuberculosis infection is an important model of intracellular bacterial infection. Studying TB infection provides new information about how the immune system controls many different types of infections in humans.

Highlights of 2009

- We established collaborative research projects with a National Tuberculosis Program in Vietnam to study how to improve the control of TB in the community and the genetic regulation of TB infection. With Professor Marks at the Woolcock Institute and Vietnamese colleagues we obtained NHMRC funding for a five year randomised trial on the benefits of active case-finding for TB control in Vietnam.
- As part of the Wellcome Trust-funded Infection and Immunity Genetic Consortium we have identified new lines of genetically modified mice with increased susceptibility to *M. tuberculosis*. These will help identify genes essential for controlling tuberculosis infection.
- We started new collaborations to develop novel drugs to control TB infection. We identified a secreted lipase shared by *M. tuberculosis* and *Mycobacterium leprae,* which is essential for mycobacterial growth.

  We are working with Dr Richard Payne in the School of Chemistry, University of Sydney, to make new inhibitors of this enzyme. Professor Britton and Dr Payne received new NHMRC funding to make and test new TB drugs targeting other essential enzyme pathways in *M. tuberculosis.*
- The development of new subunit vaccines against TB based on fusion constructs of the cutinase-like proteins of *M. tuberculosis,* which we have recently identified.
- The discovery that the number of bacteria following infection with *M. tuberculosis* or the BCG vaccine controls the priming of CD8 T cells, a type of lymphocyte essential for protective immunity against TB.
- The discovery that rBCG expressing the cytokine GM-CSF when given intra-nasally influences the function of immune cells in the lung and is more protective against pulmonary TB than when given subcutaneously.
- We reported that *M. tuberculosis* has the dominant effect in controlling gene expression in human macrophages co-infected with *M. tuberculosis* and HIV.
- Nerve damage in leprosy is caused by infection of Schwann cells by *M. leprae* and we have identified the host genes that are switched on during this infection.

Professor Warwick Britton,
Dr Nick West,
Dr Bernadette Saunders,
PhD Scholar Erin Shanahan

Major Projects

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

We are also exploring how the bacterium responds during infection of the host by changing the genes it expresses and the function of selected proteins from *M. tuberculosis* and *M. leprae*.

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

Estimated new TB cases (all forms) per 100 000 population

How will this research impact community health?

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

HOST RESPONSE TO TUBERCULOSIS

DR BERNADETTE SAUNDERS

Tuberculosis is primarily a disease of the respiratory system. Our own immune response to TB often leads to the development of damaging inflammation in the lungs. For centuries the disease was known as 'Consumption' as people's lungs were literally 'consumed' by the damaging effects of their own immune response to TB.

Understanding how the immune response to TB develops and is regulated is essential for the development of new therapies to treat the infection and moderate the damaging inflammation. Our group is examining the factors that control protective immunity to TB, focusing on the development of the inflammatory response. Furthermore, we are identifying genes that influence this response, and mutations in these genes that may increase a person's risk of developing TB.

We are working to uncover new genes that influence resistance or susceptibility to MTB infection and determining how these genes regulate these processes. We are also working to understand the chemical messengers, called cytokines that are important in controlling inflammation. We are determining the pattern of cytokine expression in the lungs during infection and how this controls subsequent inflammation.

Our major focus is on the cytokines that are produced by, or modulate, macrophage function. Macrophages are the immune cells in which the MTB bacteria reside within the host, they are also the cell responsible for killing the invading MTB. Increasing the capacity of macrophages to kill MTB is our major long term goal.

Highlights of 2009

- Dr Saunders received 2 new NHMRC grants with collaborators at the University of Queensland and WEHI to fund new projects examining; 1, how human macrophages control TB infection and 2, the role of the molecule SSB2 in control of TB infection.
- We have established a productive collaboration with the National TB hospital in Hanoi, Vietnam. Professor Britton and Dr Saunders have both visited Vietnam this year and we have collected blood from our first TB patients and controls in Vietnam for analysis of mutations in genes that may influence susceptibility to MTB infection.

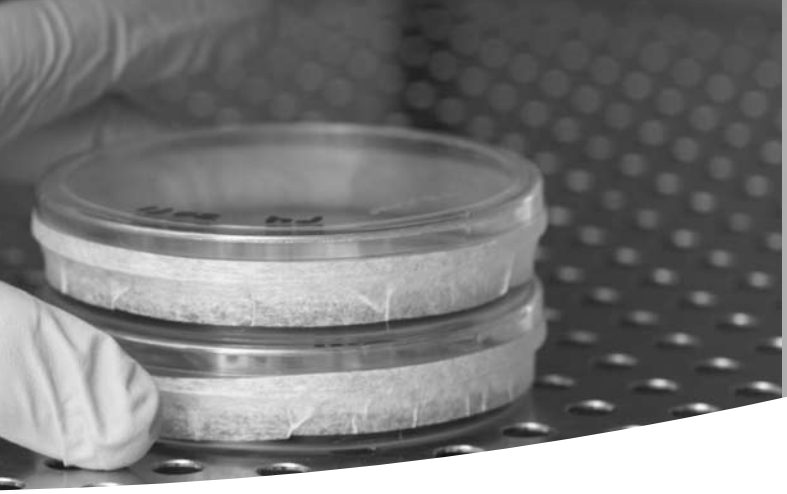
Major Projects

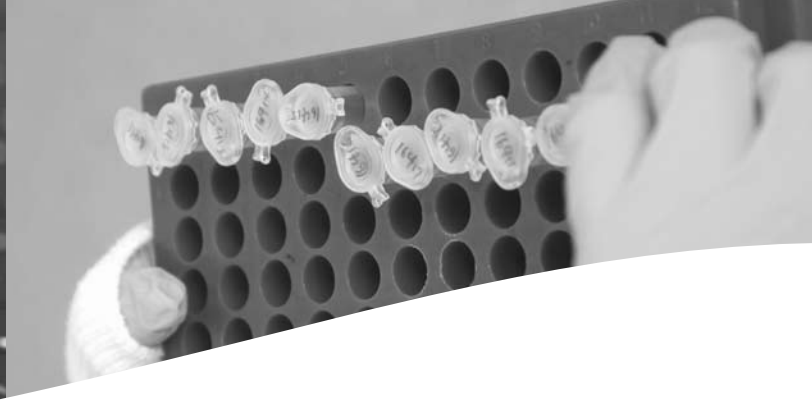
Our group is investigating the cellular and genetic factors that regulate protective immunity to MTB infection.

We are dissecting the mechanisms used by macrophages to control MTB infection. Further, we are using macrophages with specific genes deleted to determine the function of these genes in resistance to MTB infection. We hope this research may lead to the discovery of alternative therapies to treat MTB infection.

We are identifying host genes that influence resistance and susceptibility to TB. This involves both a program to screen mutant mice for novel genes that control immunity to TB with collaborators at ANU in Canberra, Oxford and Paris.

In addition, we have established an exciting project with collaborators in Vietnam to analyse the DNA of TB patients for mutations in genes that may influence susceptibility to TB. These exciting projects should uncover new factors that regulate resistance and susceptibility to TB.





VACCINE DEVELOPMENT AND PATHOGENESIS

DR NICK WEST

A better understanding of *M. tuberculosis* and how it causes disease will allow us to design more effective vaccines to prevent the spread of TB and to develop drugs that will improve the outcome for those already infected. This is why research within the group is aimed at identifying the genetic repertoire possessed by the bacterium, which is essential to its survival. Additionally, we are concerned with 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 will be better placed to make informed decisions regarding drug development to treat both acute and chronic infections, ultimately shortening the duration of treatment to just weeks instead of months. Furthermore, knowing what pathways are essential to the bacterium may also provide new vaccine candidates.

Highlights of 2009

- Importantly, an *M. tuberculosis* mutant library has been completed, comprising 12,000 individual, single gene mutants. This library is a valuable resource and a prerequisite for projects of genetic discovery.
- The group has again achieved significant funding to equip the lab with specialist equipment required to realise these important project goals.

Major Projects

Our focus is to investigate the processes of pathogenesis to improve vaccines and treatments for tuberculosis. We are committed to understanding the disease, from a bacterial perspective. We endeavor 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. 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.

Another active research project includes screening of drug candidate molecules against an essential enzyme of *M. tuberculosis*, which we have recently characterised. We believe this enzyme, which the bacteria cannot live without, represents a genuine target for new anti-TB drug therapy. We continue to make progress towards vaccine improvement.

An active program exists in the laboratory to deliver vaccines as harmless, non-replicating viruses. This next generation vaccine strategy offers promise in delivery of long lasting vaccines, which could also be used 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 group studies basic questions related to cancer and infectious diseases. We are using cutting-edge microscopy techniques to determine how the immune system fights tumour cells and intruding microbes. We are further interested in developing targeted therapies against melanoma by visualising cell cycle dynamics in real time.

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

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

A second interest of the group relates to the pathogenesis of melanoma, the most aggressive and often therapy-resistant form of skin cancer with a particularly high incidence in Australia. We are using a new approach to visualise the dynamics of cell cycle progression in melanoma models in vitro and in vivo. Our aim is to use multi-photon microscopy to characterise the effects of targeted therapies on the cell cycle in this tumour.

Highlights of 2009

- For the first time, we have visualised how malignant T cells from a lymphoma enter the skin (Hoeller et al, Cancer Res, 2009). This has enabled us to define the molecular requirements of these cells to interact with the blood vessel wall in the skin. This information may be used for novel therapeutic strategies against this disease.
- In collaboration with colleagues in the United States, we have found that the aggressiveness of tumours, defined as its metastatic potential, is determined by the interaction of tumour cells with the surrounding extracellular matrix (Levental et al, Cell, 2009). This provides completely new insight into the metastatic process of cancer and a potential new angle for therapies.

Major Projects

Orchestration of innate immune responses following skin infections

Innate immune cells, including dendritic cells and macrophages, gamma-delta T cells, and neutrophils, are the first cells of the immune system to sense and fight intruding pathogens. We currently have very limited understanding as to how these innate cells behave in space and time after pathogen encounter. We have recently

Professor Wolfgang Weninger, Dr Paulus Mrass, Dr Nikolas Haass

developed an intravital multi-photon microscopy model that allows us to directly visualise these cells in intact skin under normal and pathologic conditions.

Using a combination of genetically engineered mice and infectious agents, such as Leishmania major parasites, Herpes simplex virus and mycobacteria, we are investigating how innate immune cells behave during the early phase of immune responses. We are further studying how pathogens are recognised and transported from the skin to draining lymph nodes. These studies have implications for the development of vaccines against infections.

Interplay of innate and adaptive immune cells during influenza virus infection

Influenza is an acute febrile respiratory illness caused by influenza virus infection and may trigger potentially life-threatening complications especially in the young and elderly. Immunity against influenza virus involves integration of the innate and adaptive immune system. However, we currently have a poor understanding as to how the interactions between the cellular components of the anti-influenza immune response are orchestrated in space and time. We are making use of intravital multi-photon microscopy to study how innate immune cell subsets induce the activation of antigen specific T cells in the lung draining lymph nodes during infection. In-depth insight into this process is not only important for increasing our knowledge of regulatory pathways of anti-viral immunity but may, in the long-term, lead to the development of improved vaccine strategies against this disease.

Role of melanoma cell subpopulations in melanomagenesis (Group leader "Experimental Melanoma Therapy": Nikolas Haass)

We are testing the hypothesis that melanomas recur after chemotherapy because certain melanoma cell subpopulations are chemoresistent and can reinitiate tumour growth.

The central idea of our current work is that all distinct melanoma cell subpopulations need to be targeted simultaneously to cure melanoma. We have developed three-dimensional melanoma culture models, which recreate the correct interactions of the melanoma with its tumour microenvironment. This predicts the effects of drugs on the tumour in a much better way than conventional two-dimensional cell culture. These models are used in combination with in vivo mouse models and multi-photon microscopy to study the interactions of melanoma cell subpopulations with their microenvironment.

We are further investigating cell cycle dynamics in melanoma and are assessing the effects of chemotherapeutic drugs on these processes. From these experiments, we hope to develop novel therapeutic concepts for this devastating disease.

The principle approach of the Immune Imaging group is the use of a state-of-the-art imaging technique called multi-photon microscopy. This cutting-edge technology allows for visualisation of fluorescently-tagged cells and molecules within the context of living tissues.

How will this research impact community health?

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

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

TUMOUR MICROENVIROMENT

DR PAULUS MRASS

Cancer remains a major cause of mortality. To improve our understanding of this disease, we need to generate tools that facilitate the analysis of tumour biology in the context of an intact tumour-microenvironment. Our group has established an innovative tumour-imaging model, enabling us to observe cellular behaviour within intact tumour-tissues at high temporal and spatial resolution. This model provides a direct view of the dynamic interplay between distinct tumour components within their authentic microenvironment.

Our goal is to utilize this resource to generate data that provide novel mechanistic insights into tumour development as well as to provide a foundation for novel anti-tumour strategies.

Highlights of 2009

- Dr Mrass joined the Immune Imaging group at the Centenary in January and was promoted to Associate Faculty.
- Dr Mrass received the Cancer Institute NSW Career Development and Support Fellowship – Future Research Leader (AUD$1,167,710 over 5 years).
- The imaging experience of our group has led to collaborations with various labs, leading to publications in top journals.

Major Projects

Imaging model of intact tumours

To study the basics of tumour biology, we have developed a mouse model, enabling targeted tumour destruction by intravenously injected killer T cells. By using two-photon microscopy, it is possible to look through the surface of those tumours, and visualize both targeted tumour cells and the infiltrating T cells. Using this model, our group was the first in the world to succeed in directly visualizing killer T cells navigating through real tumours, preceding interactions with tumour cells. Furthermore, we captured interactions between killer T cells and tumour cells, followed by complete disintegration of the target.

Molecular characterization of killer T cell behaviour in intact tumours

To obtain a mechanistic understanding of tumour growth and rejection, our laboratory has established tools that enable genetic manipulation of killer T cells before injection into tumour-bearing mice. With those tools, we succeeded in defining a molecular cue, CD44, which is crucial for optimal migration of tumour-infiltrating killer T cells. We further demonstrated that reduced migration of CD44-deficient T Cells is associated with an impaired anti-tumour effect, and thus define a novel checkpoint of an immune response.

Currently, we utilize such 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, respectively.

Image analysis and mathematical modelling

The generation of movie sequences with two-photon microscopy leads to an extensive accumulation of visual information. While visual inspection of the image-sequences allows a general appreciation of the behaviour of the captured cells, this approach precludes rapid processing of the data (high-throughput screening) and is subject to biased interpretation. Therefore, more systematic and objective analytical tools are required. To this end, our group is developing custom-made software, enabling automatic shape recognition and measurement of cellular and non-cellular (e.g. extracellular matrix) components of the image-sequences.

Dr Chris Jolly,
The DNA Repair group

DNA REPAIR

DR CHRIS JOLLY

Poor repair of DNA damage is a major cause of cancer. Understanding 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 replication mistakes.

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

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

Highlights of 2009

In 2009, the DNA Repair laboratory achieved two major outcomes:

- We used our unique in vivo experimental system to test a compelling model for the mechanism of gene mutation in B cells first proposed by UK researchers in 2005. Our data has eliminated this model from further consideration and provided insights allowing us to devise a new model submitted for publication in December to the prestigious journal PLoS Biology.
- We have identified a new mitotic DNA repair gene, showing that mice carrying defective copies of this gene are unable to repair some forms of DNA damage correctly. Mice carrying two defective copies of this gene rarely survive to birth. Mice carrying only one defective copy superficially appear to be healthy but nonetheless have subtle DNA repair defects which may predispose them to cancer.

Major Projects

The DNA Repair group uses the mutation of antibody genes in B cells (white blood cells that secrete antibodies) as a physiologically-relevant model of DNA damage. We also treat mouse embryonic fibroblasts (MEFs) with DNA-damaging chemicals to investigate DNA repair pathways not used by B cells.

Antibody gene mutation is a natural process of extremely accelerated gene mutation (i.e. hypermutation) that occurs in lymph nodes during immune responses in order to increase the diversity of antibodies, which neutralise infectious organisms. Antibody hypermutation is essential for effective immune responses, but occasionally, the antibody hypermutation machinery targets the wrong genes (referred to as "bystander" genes) and causes cancer. In fact, mutation of bystander genes by the antibody hypermutation machinery is implicated in the majority of adult B cell lymphomas and leukaemias.

How will this research impact community health?

Comprehension of DNA repair pathways underlies a full understanding of the causes of cancer, because damage to DNA contributes to most, if not all cancers. In the future it may be possible to prevent early stage cancers from progressing by identifying DNA repair defects that initiate cancers in the first place.

LIVER IMMUNOBIOLOGY

PROFESSOR GEOFF MCCAUGHAN

Chronic liver damage affects up to 20 percent of Australians and results in significant ill health and fatality through liver failure and the development of liver cancer. In addition, liver cancer is one of the fastest growing and deadly diseases in Australia.

The distinct research groups within the Liver Immunobiology program come together through 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 to achieve these aims. Such models and tissues are shared among all groups to maximise understanding of disease pathways.

The distinct research groups are:

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

In addition, to these project areas, the Liver group at the Centenary has major clinical collaborations with nation-wide hepatitis C clinical studies in the fields of antiviral treatment outcomes. We have been partners in 3 major studies reporting improved treatment outcomes for mild chronic hepatitis C, acute hepatitis C and hepatitis C post liver transplantation. A virological cure has been obtained in 60% of some groups.

In liver transplantation, we have observed that high-peak virological responses are associated with poor outcomes. This leads to protocols that attempt to limit such surges either via manipulation of immunosuppression or antiviral treatments.

We also have a major collaboration 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, in identifying molecular pathogenesis of alcohol induced liver injury.

Of more than 60 types of diseases and injury associated with alcohol, Alcoholic Liver Disease (ALD) remains the most prominent, second only to alcohol dependence. ALD is a multi-stage and multi-factorial disease that is established on long-term alcohol misuse. In Australia, ALD is responsible for 50% of the liver factors for ALD and treatment options for alcohol induced injury.

Molecular targets in ALD include Osteopontin (Opn). We have shown Opn isoforms and cell surface receptors (CD44, integrin $\alpha 5\beta$) are induced in human ALD as well as in liver cell culture models of alcohol.

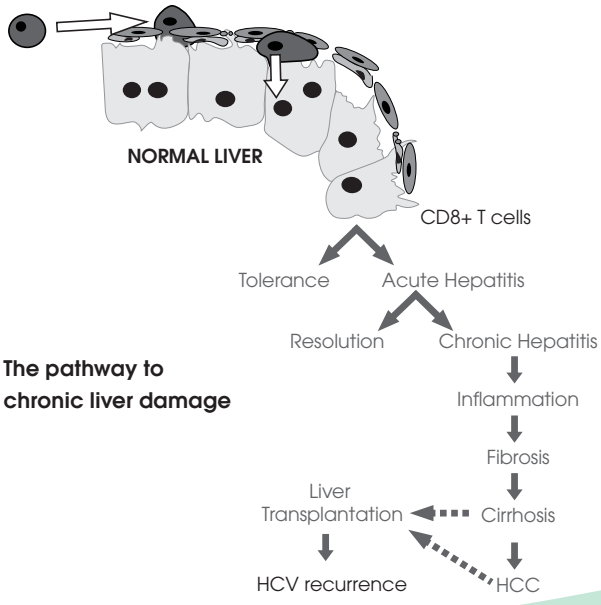
We also found that alcohol increased cell signalling pathways such as a Erk and Akt phosphorylation, uPA expression and plasmin activity, which was abrogated by alcohol dehydrogenase inhibitor, 4-methylpyrazole (4MP). In LX2 stellate cells, prominent players in liver fibrogenesis blocking antibodies to Opn inhibited this activation. Conversely, Opn overexpressing hepatocytes inhibited the effect of alcohol and decreased Erk and Akt phosphorylation and plasmin activity. This suggests a complex

Professor Geoff McCaughan, Dr Mark Gorrell, Dr Fiona Warner, Dr Nick Shackel and Dr Patrick Bertolino, PhD Scholar Michelle Vo

interaction between alcohol and Opn and a "negative feedback loop" mechanism for this pathway.

We discovered that in vitro inhibition of Opn (Opni) increased uPA expression in both stellate and hepatocyte cells, underscoring the negative feedback mechanism. We are breeding Opn knockout mice to investigate the role of Opn in vivo as well as actively studying the functional roles/mechanisms of Opn isoforms in liver cell signalling, migration, plasmin and fibrogenesis.

The second main area, driven by Dr Seth, is to identify genetic risk factors in a genome wide association study (GWAS) for ALD, as part of the multi-centre international GenomALC Consortium for which NIH funding is currently being sought. In addition, the Alcohol and Health Research Grants Scheme pilot study in Australian cohort commenced in September 2009 and is progressing well. We have appointed Sarah Johnson, Registered Nurse as part-time Research Assistant on this project and we have conducted interviews, collected data and blood samples from subjects from Liver Clinics and Drug Health Services at RPAH and Liverpool Hospital.



The pathway to chronic liver damage

The distinct research groups within the Liver Immunobiology program come together through a common purpose: to understand at the cellular and molecular level the key issues that cause liver damage and cancer.

How will this research impact community health?

In animal models, liver transplants are spontaneously accepted. Understanding why liver transplants are not rejected like other solid organ transplants would help us to design new strategies to prevent rejection of liver transplants in the clinic and significantly improve the outcome of liver transplantation. Additionally, this may shed light on possible ways to use this property of the liver to induce acceptance of other solid organs that are normally rejected.

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

LIVER IMMUNOLOGY

DR PATRICK BERTOLINO AND DR DAVID BOWEN

The Liver Immunology group aims to understand immune response within the liver and why these are biased towards the induction of tolerance. Understanding the mechanisms of intrahepatic immunity is critical to two important clinical areas: transplantation and infection by viruses that predominantly infect the liver, such as the Hepatitis B and C viruses (HBV and HCV).

Preventing immunity in the liver would improve the outcome of liver and other solid organ transplantation. In contrast to other solid organs, liver transplants are spontaneously accepted through unknown mechanisms. Understanding how this tolerance is established would help us to develop new strategies to prevent rejection of other solid organs. In contrast, chronic infection with HBV and HCV are associated with complications that are extremely costly to the community. Enhancing immunity to these viruses would allow clearance of these infections.

Highlights of 2009

- Dr Patrick Bertolino was invited to present the work of his group at the prestigious Falk Symposium in Hannover, Germany.
- Our group presented at the Australian Gastroenterology Week in Sydney and at the Annual meeting of the Australian and New Zealand Society of Immunology in the Gold Coast.
- Dr David Bowen delivered an invited address on "Pathogenesis of Autoimmune Hepatitis" at the 2009 Australian Hepatology Masterclass.
- Dr Patrick Bertolino was one of the 5 Centenary Institute investigators who were awarded a very competitive program grant of $8.2 Million by the NHMRC, starting in 2010, to investigate the mechanisms leading to inflammation and cancer in the liver.

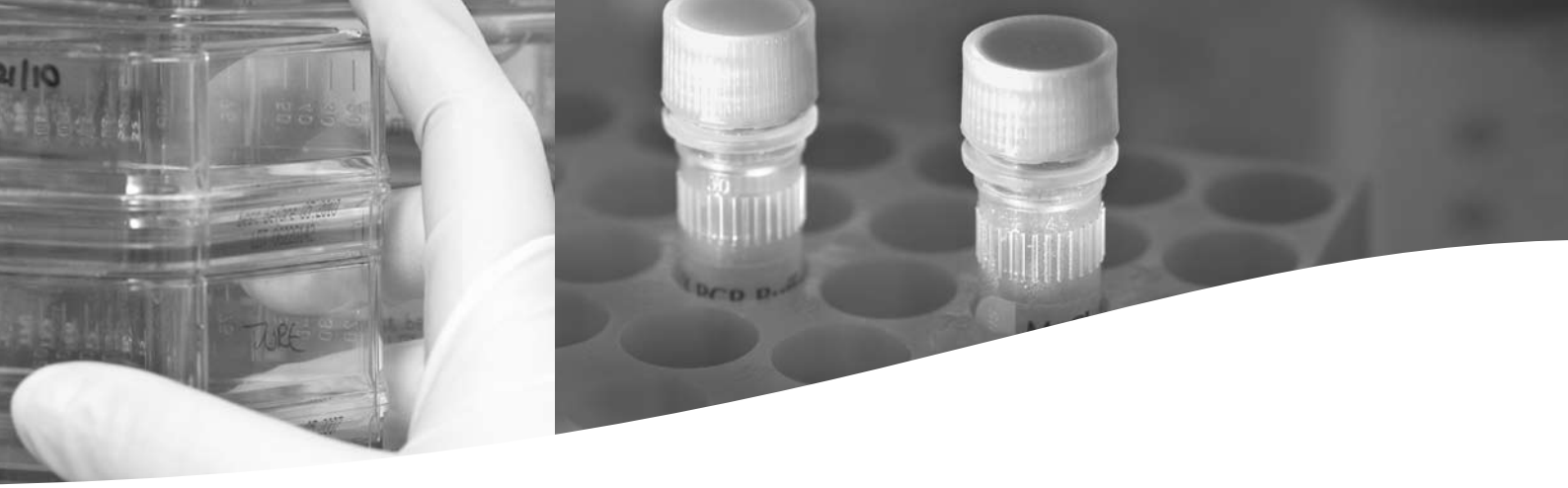
Major Projects

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

Our results have demonstrated that due to its unique structure, the liver can retain and activate naïve CD8+ T cells, therefore acting as a site of primary activation. This finding contradicts the general accepted view that primary T cell responses can only be initiated in lymph nodes (LN). Our results suggest that the site of initial activation of T cells is a critical determinant of the outcome of immune responses, with activation within the liver and LN programming T cells towards different fates. Unlike T cells activated in LN, which become effective cytotoxic T lymphocytes, most liver-activated T cells become poor effectors and die rapidly, leading to tolerance.

This is the first demonstration that a non-lymphoid organ can be the site of primary activation, a seminal finding with important implications for liver transplantation and HCV research.

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



MOLECULAR HEPATOLOGY

ASSOCIATE PROFESSOR MARK GORRELL

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

We have discovered that in the injured liver the genes fibroblast activation protein (FAP), dipeptidyl peptidase (DP) IV, DP8 and DP9 exhibit heightened expression by liver cells and are involved in cell movement and proliferation. FAP is under investigation as a therapeutic target for liver and lung diseases and some cancers. DPIV is especially interesting because it is the target of a new diabetes therapy. Our published discoveries on DPIV and related genes significantly assisted the development of this new type 2 diabetes therapy.

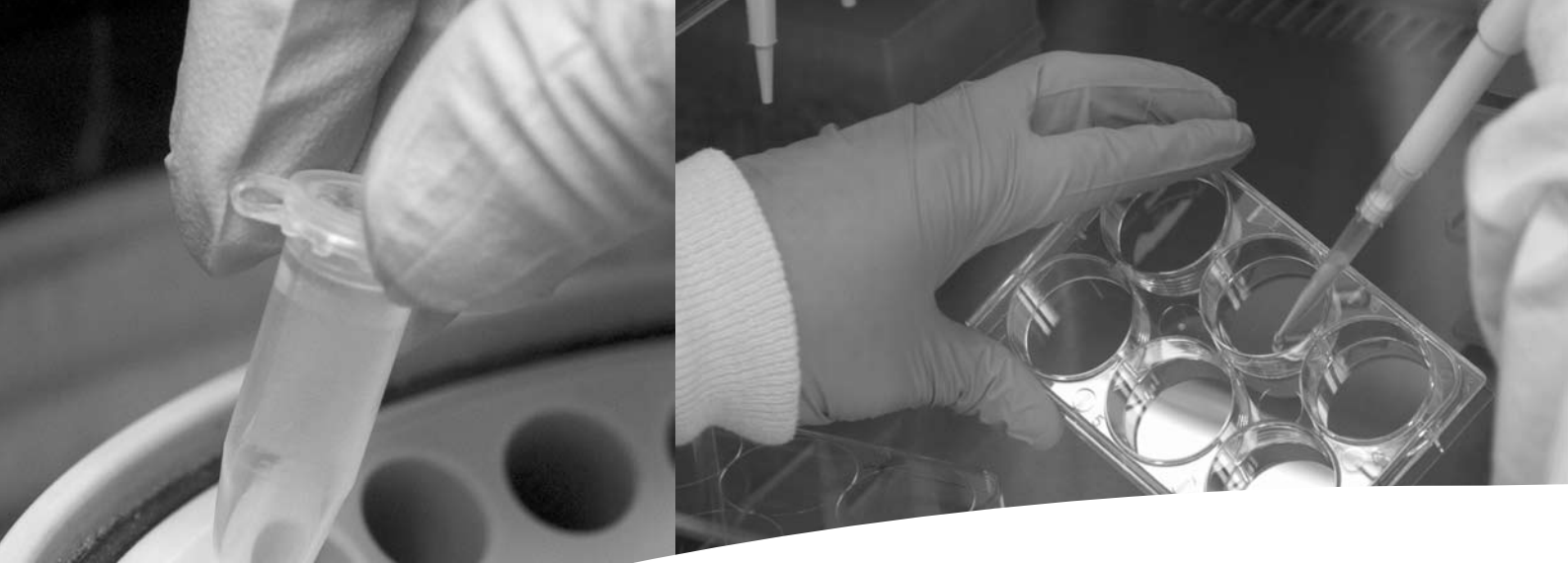
Highlights of 2009

- Completion and publication of our discoveries on where DP8 and DP9 are made in the body, which includes liver, gut and immune organs.
- In conjunction with other experts in Australia, USA, Germany and Denmark, we wrote four reviews and commentaries that will be published in 2009 and 2010 on the topics of the DPIV gene family in diabetes, fatty liver disease, cancer and normal cell functioning.
- A/Prof Gorrell appeared as an expert on DPIV at a US Food and Drug Administration Advisory Committee hearing in Washington DC on the safety and efficacy of a new DPIV inhibitor as a type 2 diabetes therapeutic.
- Our group, primarily Dr Denise Yu, ran a successful DPIV workshop in the International Proteolysis Society conference.
- We discovered that:
  - DP9 is upregulated in mouse models of chronic liver injury.
  - DP9 downregulates a specific growth factor pathway within cells.
  - Energy metabolism is disregulated in mouse models of chronic liver injury, but alleviated by the absence of DPIV.
  - Established a new mouse model of diabetes - related non-alcoholic fatty liver disease (with A/Prof S. Twigg and A/Prof S. McLennan of the Bosch Institute).

Major Projects

The DPIV family of enzymes consists of DPIV, DP8, DP9 and FAP. We have obtained evidence that these enzymes have roles in liver scarring and are discovering key molecules that mediate the DPIV family roles. We continue to increase this mechanistic understanding. We are doing this by studying mouse strains that lack individual genes of the DPIV gene family, by upregulating DPIV family genes in cell cultures and by examining isolated enzymes.

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) continues to develop more effective methods of making and purifying this protein. The research is directed towards discovering compounds that will control KAT-I in the brain of Alzheimer's sufferers and thereby alleviate their illness.



LIVER CELL BIOLOGY

DR NICK SHACKEL AND DR FIONA WARNER

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

Highlights of 2009

- Dr Shackel was awarded the CARG research award from Roche for research into predicting HCV treatment responses to interferon treatment.
- Honours Student Candice Grzelak was awarded an Australian Postgraduate Award and Cancer Institute NSW Scholar award to study a PhD in the role of the Hedgehog Pathway in Progressive Liver injury and hepatocellular carcinoma development.
- William d'Avidgor was awarded a scholarship from the Rebecca L. Cooper Foundation to study novel gene expression in progressive liver injury and hepatocellular carcinoma.
- 1st year PhD student, Candice Grzelak was runner up for the June Halliday Young Investigator Award for Basic Research by the Gastroenterology Society of Australia for her presentation entitled, `Hedgehog pathway activity within hepatocytes following progressive liver injury'.
- In 2009 our work was accepted and presented at the Asia Pacific Association for the Study of Liver Disease in Hong Kong, the American Society for the Study of Liver Disease Annual Meeting in Boston, USA, and Australian Gastroenterology Week in Sydney.

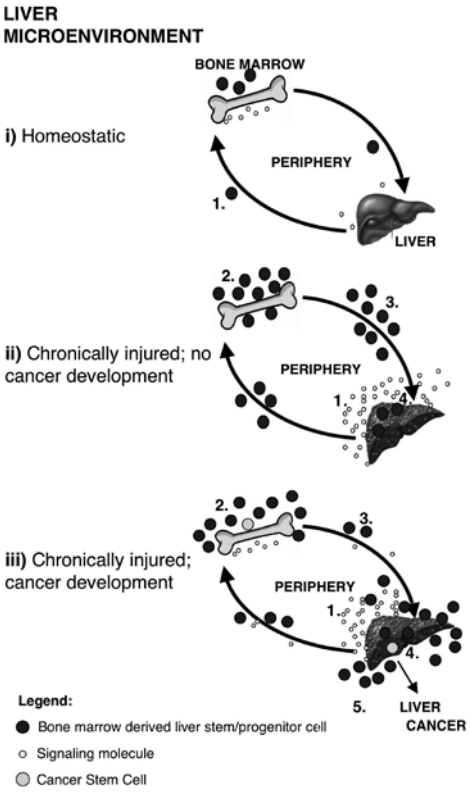
Major Projects

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

Analysis of liver disease using a functional genomics approach.

The role of molecule EMMPRIN and the hepatocyte and imflammatory cells in liver fibrogenesis.

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



Dr John Allen,
PhD Scholar Nethia Kumaran

CANCER DRUG RESISTANCE

DR JOHN ALLEN

Chemotherapy is a grueling form of treatment that fails all too frequently but we take inspiration from the fact that it sometimes works very well. We can make this the rule if we understand why some cancer cells are resistant to treatment with chemotherapy drugs.

The Cancer Drug Resistance group works to improve chemotherapy. We take particular interest in understanding resistance to new anticancer drugs employed against common, recalcitrant cancers, such as melanoma (a scourge in Australia), and multiple myeloma.

If we can get the treatment right the first time, it gives the patient the best chance of survival. For example, identification of molecular markers that predict whether an individual cancer will respond to a drug, or exhibit resistance, would allow the best treatment to be chosen from the options available.

Highlights of 2009

- Drs Silvia Ling and Keryn Lucas were awarded their PhDs.
- Dr Ling identified a molecular marker, which predicts response of multiple myeloma patients to a new drug, the proteasome inhibitor Velcade, which is revolutionising treatment of this intractable disease

Major Projects

Drug resistance in melanoma

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

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

Drug resistance in multiple myeloma

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

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

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

How will this research impact community health?

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

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

CORE FACILITIES

CYTOMETRY AND IMAGING

Flow Cytometry

Flow cytometry and cell sorting are key technologies that are used extensively by most of the research groups at the Centenary Institute. The cytometry facility at Centenary is well-equipped with 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 make optimal use of this significant infrastructure investment.

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

Highlights of 2009

- The attendance of facility staff members at the major Australasian cytometry conference, representing a continued commitment to best practice research techniques at the Centenary Institute. At this conference, Sydney was selected to host the 2010 conference, and Centenary staff will play a significant role in organising and hosting this important event.
- Continuing close collaboration with the flow cytometry resources on the University of Sydney campus, resulting in Centenary hosting a number of workshops for researchers from across Sydney. In 2008, this collaboration (with researchers from UNSW) resulted in a successful Australian Research Council LIEF grant application for the acquisition of two new high-end cytometry instruments for the University/ Centenary campus.

Work on selecting the best possible instruments continued through 2009 and the new instruments are expected in early 2010.The Centenary Institute was also successful in obtaining grant funding n excess of $1M from the Cancer Institute NSW to support the acquisition of a next generation high speed cell sorter and continuing employment of the Facility Manager, Dr Adrian Smith.

This major ongoing investment by the Cancer Institute demonstrates the importance of flow cytometry to cancer researchers and highlights the pre-eminence of the Centenary Institute as the key reference facility for cytometry and cell sorting in NSW. The new cell sorter will be the first of its kind in Australia and will offer increased speed and add power to detect more features of different cell types. It will include the biosafety features required for the isolation of cells from human samples.

Imaging

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

LaVision Biotec TriMscope

This cutting edge multi¬-photon microscope enables researchers unprecedented access to the secret workings of living tissues at the cellular and molecular level. The multi-photon microscope at the Centenary Institute has two unique features, its imaging mode and laser. The unique imaging mode uses multiple laser beams 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, which enabls researchers to look deeper into living tissue than ever before.

A highlight in 2009 was the attendance of the facility manager (Dr Adrian Smith) and a key post-doctoral researcher (Dr Lai Guan Ng) at the LaVision BioTec User Meeting held in Berlin, Germany. This meeting, along with associated visits to labs in Berlin and Hannover (Germany) and Nijmegen (Netherlands), facilitated the exchange of technical and scientific ideas and techniques and will help to ensure that the Centenary multi-photon imaging facility remains at the forefront of this exciting field. Dr Smith's trip was funded by a grant from the ARC/NHMRC Fluorescence Applications in Biotechnology and Life Sciences (FABLS) Network.

Late in 2009 work commenced on a major upgrade of the multiphoton facility with an additional laser and a second microscope with further advanced detection technologies. Now in early 2010 these additions add flexibility to our imaging of living tissues and keep the facility on the cutting-edge of multi-photon imaging.

Confocal microscope

The Centenary Institute is 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.

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

MICROINJECTION FACILITY

The use and development of the latest transgenic (over expression of a single gene) and knockout (deletion of a single gene) technology, collectively called genetically modified, has for many years been a high priority for the Centenary Institute. Centenary's facility is the longest established in the state and one of the most productive in Australia in terms of 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, control and assess risk, and treat patients with a range of diseases. Genomics promises to lead to more optimal and cost-effective treatment in patients with cancer, cardiovascular and infectious disease and more effective preventative strategies for those at risk.

The Centenary Institute houses the latest Affymetrix Gene Array platform (supported by funding from the Cancer Institute NSW). This platform will create a better understanding of the molecular basis of cancer, cardiovascular and infectious development and will aid in the development of new therapies. In addition, we have embraced and utilized 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 Unit. The Genomics Facility and Bioinformatics Unit 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 including:

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

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

PC3 LABORATORY

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

The facility contains equipment permitting cell culture, genetic manipulation of bacteria and aerosol exposure system for animal infection models. In 2010, a larger PC3 facility will be commissioned to accommodate increased levels of research.

ANIMAL FACILITY

Genetically modified mouse lines are bred under Level 2 Specific Pathogen Free conditions in the Centenary Institute 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.

CENTENARY INSTITUTE FOUNDATION REPORT

2009 was a year of tremendous growth for the Centenary Institute Medical Research Foundation's fundraising efforts.

Guests at the Centenary Institute Foundation Dinner enjoying the evening's events

The Foundation has a growing number of people and companies that support our research projects with substantial contributions. Their generosity and belief in our vision will serve to enhance the health of our global community. Thank you to Inghams Enterprises, Mr & Mrs Cameron, PriceWaterhouse Coopers, Mrs Hore, Mr Cheung, the Cheung Foundation, Dr Hooper, Mrs Michaelis, Mrs Bamford, The Wine Society, Mr & Mrs Cawsey, Ms Englman, Lifestyle Financial Services, Mrs Brown, Mr & Mrs Atanaskovic, Dr Juratowitch, Swiss Re and the Levy Foundation.

Due to a successful donor acquisition program we welcomed 5,000 new donors in 2009, doubling the size of Centenary's donor community.

The generosity of our donors was matched by that of the people who so kindly shared their experience of the diseases that Centenary's scientists work on as part of our appeals program.

Every day the 200 scientists at Centenary come to work seeking new cures and treatments for cancer, cardiovascular and infectious diseases. People like Nicole, Jillian, Julie, Olivia, Sumith, Ron and Leesa who bravely shared their experiences to raise vital funds for medical research continue to inspire us.

Our fundraising team also launched a bequest program in September, which has helped to discover 11 exceptional people who have left the Centenary Institute a gift in their Will.

The Foundation Trustees held their first Annual Foundation Dinner, sponsored by Pricewaterhouse Coopers and Yarra Yering Vineyard. The evening featured a three-course menu built around some of Australia's finest wines and a special performance by Christine Anu. In addition to the art auction, generous donations to the live auction from Song Zu, Qantas and Small Luxury Hotels of the World helped raise $130,000.

Professor Jennifer Gamble presents her work to guests at the Centenary Institute Foundation Cocktail Reception

Chairman of the Foundation Neil Lawrence with Justice Margaret Beazley

All proceeds from the night were used to fund the first year of a new Bioinformatics Fellowship at the Institute. This is a position that our scientists unanimously agreed is the Institute's highest need. The Fellowship will provide Centenary with a dedicated specialist who will find new ways to interpret the vast amounts of data generated by modern medical research, accelerating the pace of our work.

The second Annual Foundation Cocktail Reception at Government House was held in October. The event was a perfect start to spring. Throughout the night, attendees had the opportunity to meet some of the Institute's talented young scientists who are making exciting discoveries in their fields.

Our Guest of Honour Professor Jim Bishop AO, Australia's Chief Medical Officer, spoke about the importance of medical research to global community health. His speech was followed by a presentation from Head of the Vascular Biology group at Centenary, Professor Jenny Gamble, who discussed her lab's investigation into the process of blood vessel formation and survival and its role in cancer and cardiovascular disease.

The Foundation relies on a small but dedicated staff who worked tirelessly throughout the year. Congratulations and thank you to Sonny Lang, Leisl Holterman, LauraBeth Albanese and Barbara Smith. Thanks also to the wonderful volunteers who helped out in the office to keep our costs down. Particular thanks go to Jeff Wai Yee and Duncan Smith who have each contributed hundreds of hours and many good times to the team.

Finally, I want to thank the efforts of the Foundation Trustees whose dedication have made the achievements of this year possible. It is their vision, talent, and sense of fun that have made 2009 one of exceptional growth.

The simple truth is that we could not conduct the quality of research that we do here at the Centenary Institute without the support of our community. On behalf of all of us and the people whose lives our work will benefit in the future, I would like to offer our deepest thanks for your ongoing support.

Sally Castle
Fundraising and Marketing Manager

2009 PUBLICATIONS

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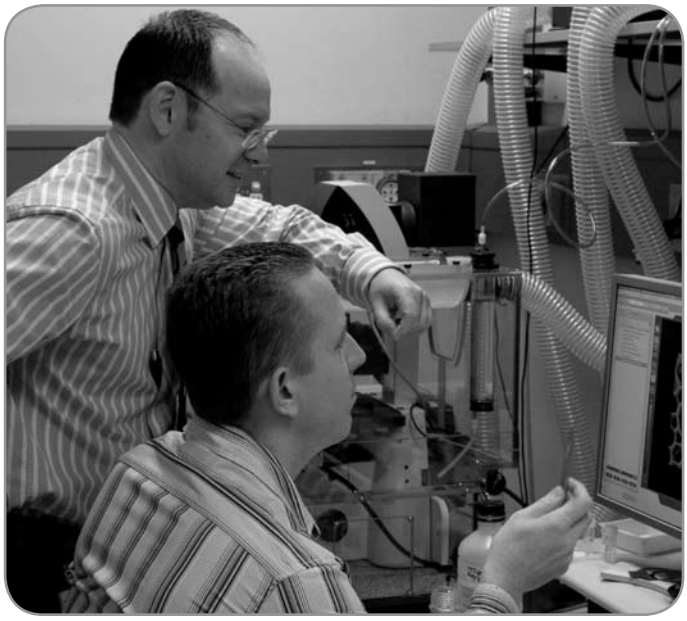

Professor John Rasko and Dr Jeff Holst, Gene and Stem Cell Therapy group

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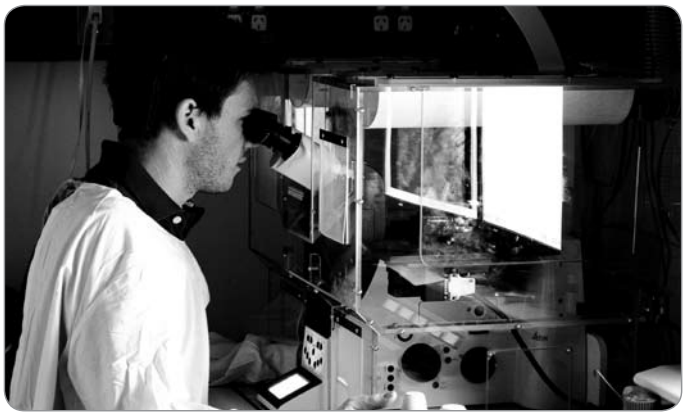

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2009 INVITED PRESENTATIONS

International

Benseler V, Suicidal emperipolesis mediates deletion of T cells undergoing primary activation in the liver, 2009 International Congress of the International Liver Transplantation Society, July 2009, New York, USA

Bertolino P, Suicidal emperipolesis mediates deletion of autoreactive T cells in the liver, Falk Symposium: Immunology of the liver, October 2009, Hanover, Germany

Fazekas de St Groth B, Dendritic cell initiation and regulation of the CD4 T cell response, Singapore Immunology Network, 2009, Immunopolis, Singapore

Fazekas de St Groth B, Regulation of the CD4 T cell response in vivo, Institutes of Biomedical Sciences, Fudan University and State Key laboratory on Infectious Disease Prevention and Control, China CDC, Jin Shan, 2009, Shanghai, P.R. China

Gamble J, Senescence and the Vascular System, European Vascular Biology Conference, September 2009, Marseille, France

Gorrell M, 2009. Role of DPP-4 and FAP in liver disease. Symposium: NAFLD, NASH and liver fibrosis. Marbach, Höri, Germany.

Haass NK. Melanoma Down-under: NOXA inhibits melanoma growth and invasion in 3D models. Colloquium (host: Ashani Weeraratna), National Institutes of Health, National Institute on Aging, Biomedical Research Center; November 2009, Baltimore, MD, USA

Haass NK. Melanoma Research Down-under. Seminar host: Meenhard Herlyn, The Wistar Institute, May 2009, Philadelphia, PA, USA

Haass NK., Novel small molecule kinase inhibitors with potent and specific anti-melanoma activity, Experimental Dermatological Oncology Workshop XXXVI ADF Annual Meeting, March 2009, Heidelberg, Germany

Haass NK. The induction of connexins 26 or 30 in the epidermis adjacent to melanoma is a valuable biomarker for diagnosis and prognosis. Experimental Dermatological Oncology Workshop XXXVI, ADF Annual Meeting, March 2009, Heidelberg, Germany

Jormakka M, Structure and function of Polysulfide reductase, Molybdenum & Tungsten enzymes, Gordon Research

Conference, July 2009, Lucca, Italy

McCaughan G, Retreatment for chronic HCV: What are the options?, APASL, February 2009, Hong Kong, China

McCaughan G, Liver transplantation for HBV infection, APASL. February 2009, Hong Kong, China

McCaughan G, Advancing Treatment for HCV: What are the challenges in current standard therapy? Asian Pacific R-C3 meeting, May 2009 Shanghai, China

McCaughan G, Outcome from the ANZ Liver Transplant Data, ILTS, July 2009, New York, USA

McCaughan G, Immunological aspects of HCV, autoimmunity and liver allograft acceptance: Insights from a transgenic model. Banff Pathology Conference, August 2009, Banff, Canada

McCaughan G, Liver Allograft Tolerance, British Association for the Study of the Liver, September 2009, London, UK

McCaughan G, Genomics and Liver Disease, New Zealand Gastroenterological Society meeting, November 2009, Wellington, New Zealand

McCaughan G, The Liver Tolerance Effect: Where are we up to in humans?, New Zealand Gastroenterological Society meeting, November 2009, Wellington, New Zealand

McCaughan G, Current HCC Management: Liver

transplantation versus other options, New Zealand Gastroenterological Society meeting, November 2009, Wellington, New Zealand

McCaughan G, Managing the complications of cirrhosis, New Zealand Gastroenterological Society meeting, November 2009, Wellington, New Zealand

Rasko J, Auckland Blood Club, April 2009, Auckland, New Zealand

Rasko J, 2009 Invited Speaker and session chair, Biomedical Transporter Conference, August 2009,Thun, Switzerland

Rasko J, A physical dimension to ex vivo expansion, Tutorial ISCT Somatic Meeting, Innovations in Cord Blood and MSC Therapies, September 2009, Bethesda, Maryland, USA

Saunders B, Protective role of Th17 cells during Mycobacterium tuberculosis infection, Singapore Immunology Network, February 2009, Singapore

Semsarian C, From Down Under: Insights on establishing a national HCM center in a "small" country. International HCM Summit IV, 2009, Minneapolis, USA.

Shklovskaya E, Epidermal Langerhans cells inhibit the immune response and induce obligatory CD4 T cell tolerance, 11th International Workshop on Langerhans cells, September 2009, Funchal (Madeira), Portugal

Vadas M, Novel concepts in angiogenesis, Australia China Biomedical Research Conference, April 2009, Tiangin, China.

Vadas M, The Young and Old of Endothelium, Cleveland Clinic, Molecular Cardiology, Lerner Research Institute, May 2009, Cleveland, OH, USA

Vadas M, Drivers of Angiogenesis and of senescence in endothelial cells, CNIO Spanish National Cancer Research Institute, June 2009, Madrid, Spain

Weninger W, Seminar Series, Singapore Immunology Network, 2009, Singapore

Weninger W, ASI New Zealand Branch Meeting, 2009 Wellington, New Zealand

Weninger W, Seminar Series, Institute of Molecular Biotechnology, 2009, Vienna, Austria

Weninger W, Seminar Series, University of Salzburg, 2009, Salzburg, Austria

Weninger W, 7th World Congress of Melanoma, 2009, Vienna, Austria

Weninger W, ComBio 2009 Conference, 2009, Christchurch, New Zealand

Xia P, Targeting the sphingosine kinase signalling pathway for cancer therapy, 2nd Australia-China Biomedical Research Conference, April 2009,Tianjin, China

Young J, The Regulation of Angiogenesis by miRNAs, Invited talk selected from abstracts, Keystone Symposium, June 2009, Keystone, CO, USA

National

Bertolino P, Suicidal emperipolesis mediates deletion of autoreactive T cells in the liver, ASI NSW retreat, September 2009, Bowral, NSW

Bertolino P, Suicidal emperipolesis mediates deletion of autoreactive T cells in the liver Australasian Liver Association meeting, May 2009, Yarrah Valley, VIC

Bertolino P, Suicidal emperipolesis mediates deletion of autoreactive T cells in the liver, ACH2 annual meeting, June 2009, Terrigal, NSW

Bertolino P, Suicidal emperipolesis mediates deletion of T cells undergoing primary activation in the liver, AGW 2009, October 2009, Sydney, NSW

Bowen D, Control of hepatitis C virus replication by CD8+ T cells during prolonged low level viraemia. Australasian Liver Association meeting, May 2009, Yarrah Valley, VIC

Bowen D, Control of hepatitis C virus replication by CD8+ T cells during prolonged low level viraemia , ACH2 annual meeting, June 2009, Terrigal, NSW

Bowen D, Pathogenesis of autoimmune hepatitis. Australian Hepatology Masterclass, July 2009, Sydney, NSW

Fazekas de St Groth B, Identification and characterisation of human regulatory T cells, BD Symposium: Celebrating 30 years of Flow Cytometry in China, 2009

Fazekas de St Groth B, Dendritic cell initiation and regulation of the CD4 T cell response, Mater Medical Research Institute Dendritic Cell meeting, 2009 Brisbane, QLD

Fazekas de St Groth B, Effect of cancer chemotherapy on human regulatory T cells, Tumour Immunology Group Annual Scientific Meeting, 2009, Perth, WA

Fazekas de St Groth B, A Brief History of Tolerance: From Theory to Therapy, Ian Mackay Lecturer, 13th Australasian Autoimmunity Workshop, 2009, Adelaide, SA

2009 INVITED PRESENTATIONS CONT.

Fazekas de St Groth B, Defining regulatory T cell subsets for studies in cancer immunotherapy, National Centre for Asbestos-Related Diseases Annual Scientific meeting, 2009 Sydney, NSW

Fazekas de St Groth B, Regulatory T cells, Federation of Immunological Societies of Asia Advanced Immunology Training Course, 2009, Tangalooma Island Resort, QLD

Fazekas de St Groth B, Dendritic cell initiation and regulation of the CD4 T cell response, Garvan Institute of Medical Research, 2009, Sydney, NSW

Gamble J, The Differentiation and Aging of the Vascular System, Hunter Cell Biology Meeting, March 2009, Hunter Valley, NSW

Haass NK. In vitro 3D tumour microenvironment models for anti-cancer drug discovery. Seminar (host: Peter Gunning), University of New South Wales, November 2009, Sydney, NSW

Haass NK. Experimental melanoma therapy, Rotary International, October 2009, Sydney, NSW

Haass NK. The role of melanoma stem cells in melanomagenesis, Cure Cancer Australia Foundation, August 2009, Sydney, NSW

Haass NK. The induction of connexins 26 or 30 in the epidermis adjacent to melanoma is a valuable biomarker for diagnosis and prognosis, 6th ASDR Annual Scientific Meeting, May 2009, Surfers Paradise, QLD

Holst J, Amino acid transport in the regulation of prostate cancer, 10th National Prostate Cancer Symposium, August 2009, Melbourne, VIC

Jormakka M, G protein coupled Fe2+ transport, SCANZ (Society of Crystallographers in Australia and New Zeeland), 2009 conference, April 2009, Barossa, SA

McCaughan G, The "ins and outs" of T cells and the Liver, Melbourne Liver Group, February 2009, Melbourne, VIC

McCaughan G, Management of HCC, Melbourne Liver Group, February 2009, Melbourne, VIC

McCaughan G, IL-6 and the Liver, Roche Dinner Meeting on Anti-IL-6 and Rheumatoid Arthritis, March 2009, Brisbane, QLD, Melbourne, VIC and Sydney, NSW

McCaughan G, Bring back the liver biopsy: a debate, Australian Roche Viral Hepatitis meeting, June 2009, Sydney, NSW

McCaughan G, Management of HCC-where are we at?, Australian Roche Viral Hepatitis meeting, June 2009, Sydney, NSW

McCaughan G, IgG4 Disease, Roche Masterclass, July 2009, Sydney, NSW

McCaughan G, Advances in Viral Hepatitis: 50 years of Australian Gastroenterology, AGW, September 2009, Sydney, NSW

McCaughan G, "Omics": Applications in Liver Disease, AGW, September 2009, Sydney, NSW

McCaughan G, Liver Transplantation: Current Challenges, Feschrift for Dr Katrina Watson, St Vincent's Hospital, November 2009, Melbourne, VIC

Rasko J, Did the Ancient Greeks foreshadow regenerative medicine?, Royal Australasian College of Physicians, Physicians Week 2009 Congress, May 2009, Sydney, NSW

Rasko J, Cell and Gene Therapy: a marriage made ...?, Regenerative Medicine: Opportunities and challenges Conference, Kolling Institute, Royal North Shore Hospital, July 2009 Sydney, NSW

Rasko J, Practical Pharmacogenomics - Ethical & Scientific Issues, Australian Pharmacogenomics Summit, July 2009, Sydney, NSW

Rasko J, Gene Therapy for Haemophilia: What's the holdup?, 15th Australian and New Zealand Haemophilia Conference, October 2009, Brisbane, QLD

Rasko J, Report from Australian Regional ISCT Meeting, Bone Marrow Transplant Scientists Association of Australia Meeting, October 2009, Adelaide, SA

Rasko J, Bouncing stem cells into the clinic, 1st Annual Regenerative Medicine Symposium at Sydney University, October 2009, Sydney, NSW

Rasko J, Heart Cell Therapy: Lost in Translation?, Victor Chang Cardiac Research Institute, 11th International Symposium in conjunction with St Vincent's Hospital "Cardiology at the Frontier: Development, Stem Cells and Heart Failure", October 2009, Sydney, NSW

Saunders B, Pattern Recognition Receptors in Health and Disease: Extracellular ATP modulates P2X7 receptor phagocytic activity and mycobacterial killing, TLROZ 2009, October 2009, Gold Coast, QLD

Saunders B, The effect of defective Roquin on immunity to Mycobacterium Tuberculosis, Gayathri Nagalingam: Workshop

Oral Presentation, ASI Annual Conference December 2009, Gold Coast, QLD

Semsarian C, Do HCM and DCM have a mechanistic link? CSANZ 2009, 2009, Darling Harbour, Sydney, NSW

Semsarian C, SCD Clinics: expanding role in Australia. CSANZ 2009, 2009, Darling Harbour, Sydney.

Semsarian C, The molecular postmortem: investigating sudden death in the young, Sydney Fornesic Medicine & Science Network, University of Sydney, 2009, Sydney, NSW

Semsarian C, Sudden cardiac death in the young, Flinders University Medical Grand Rounds, 2009 Adelaide, SA

Semsarian C, Emerging role of genetics in cardiovascular disease, Flinders Medical Centre Cardiology Grand Rounds, 2009 Adelaide, SA

Executive Director Professor Mathew Vadas

Semsarian C, Medical disorders in pregnancy: heart disease, RACP Physicians Week 2009, 2009, Darling Harbour, Sydney. NSW

Semsarian C, Emerging role of genomics in cardiovascular disease, Cardiac Club Meeting, 2009. Sydney, NSW

Semsarian C, Genomics and beyond, Cardiology 2009, 2009, Sydney, NSW

Semsarian C, Genetics and TRAGADY, XXV World Congress of Pathology and Laboratory Medicine, 2009, Sydney, 2009

Semsarian C, Genetics and heart disease, Australasian Cardiovascular Nursing College, 2009, Coogee, Sydney, NSW

Shklovskaya E, Epidermal Langerhans cells inhibit the immune response and induce obligatory CD4 T cell tolerance, ASI 2009, Dec 2009, Gold Coast, QLD

Vadas M, Invited to give Occasional Address, Science Graduation Ceremony, University of Sydney, June 2009, Sydney, NSW

Vadas M, The molecular basis of inflammation, AVBS Conference as an Award Lecturer, September 2009, Canberra, ACT

Vo M, Role of suppressor of cytokine signaling-1 (socs-1) in intrahepatic immune responses, Australasian Liver Association meeting, May 2009; Yarrah Valley, VIC.

Vo M, Role of suppressor of cytokine signaling-1 (socs-1) in intrahepatic immune responses, AGW 2009, October 2009, Sydney, NSW

Weninger W, Sydney Advanced Light and Optical Microscopy Meeting, 2009 Sydney, NSW

Weninger W, Seminar Series, Institute for Molecular Bioscience, University of Queensland, 2009, Brisbane, QLD

Weninger W, Seminar Series, University of New South Wales School of Medical Sciences, 2009, Sydney, NSW

Weninger W, Brisbane Immunology Group Annual Retreat, 2009, Gold Coast, QLD

Weninger W, TLROZ 2009 Conference, 2009, Gold Coast, QLD

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 2009.

Doctor of Philosophy (Medicine) (PhDs) Awarded 2009

Student	Supervisor	Thesis title
Christine Chiu	Professor Chris Semsarian	Novel gene discovery in hypertrophic cardiomyopathy
Jennifer Margo Randall	Professor John Rasko	The Utilisation of KoRV and RD114 Envelopes for Retroviral Vector Pseudotyping
Keryn Maree Lucas	Professor John Allen	The contribution of defective apoptosis to drug resistance of melanoma
Lauren Elise Holz	Dr Patrick Bertolino	Characterising the phenotype and fate of liver-activated CD8+ T cells

GRANTS AWARDED 2009

Investigator	Title	Granting Body
R Aikawa, J Rasko, DAllen, C Semsarian, E Kizana, T Tsoutsman	Gene therapy for cardiac diseases	University of Sydney Medical Foundation
M Vadas	Polarstar omega fluorescence polarisation reader with high performance luminescence	Clive & Vera Ramaciotti Foundation
L Ng	Visualising the structural changes in the lung during inflammatory responses by multiphoton microscopy	Clive & Vera Ramaciotti Foundation
B Fazekas, W Weninger	Real-time imaging of the initiation of adaptive immunity in vivo	ARC
M Grimshaw	Definition of the role of senescence in tumour-associated endothelial cells.	NHMRC
J Triccas, W Britton	Chronic bacterial infection and the generation of T cell memory: implication for vaccination against tuberculosis	NHMRC
W Weninger, L Ng	Real-time visualisation of dendritic cell responses during cutaneous Leishmania infection	NHMRC
B Saunders, W Britton, G Grau	Cytokine and macrophage determinants of pulmonary inflammation during tuberculosis	NHMRC
E Shklovskaya	Role of dendritic cell subsets in the generation of CD4 T cell memory	NHMRC
B Fazekas	The role of primed T cells in graft rejection	NHMRC
M Jormakka	Molecular basis of Fluoroquinolone resistance	NHMRC
C Jones, W Weninger	Defining the dynamics and function of dendritic cells after cutaneous HSV infection in vivo	NHMRC
C Semsarian	Practitioner Fellowship	NHMRC
D Bowen	Dendritic cell phenotype and function in chronic	
hepatic C virus infection	Sylvia & Charles Viertel Charitable Fdn	
P Xia	Identification of a new mechanism for insulin resistance in the vasculature	Heart Foundation
J Gamble, M Vadas	Endothelial Aging and Vascular Disease	Heart Foundation
N Haass	Role of Melanoma stem cells in melanomagenesis	Cure Cancer / Cancer Council
C Jolly, M McKay, J Manis, H Xu	Understanding AID-induced cancer: Unraveling complex mutation and repair pathways	Cancer Council
F Kao (W Britton)	Viral based prophylactic vaccine against M. tuberculosis	GlaxoSmithKline Australia
G Sharbeen (C Jolly)	Selective killing of mismatch repair deficient cancer cells	Cancer Institute NSW
M Gorrell	Fluorescence polarization reader with high performance luminescence.	Rebecca L Cooper Foundation
W Britton	Identification of genetic components essential for Mycobacterium tuberculosis to cause pulmonary disease	Rebecca L Cooper Foundation

GRANTS AWARDED 2009 CONT.

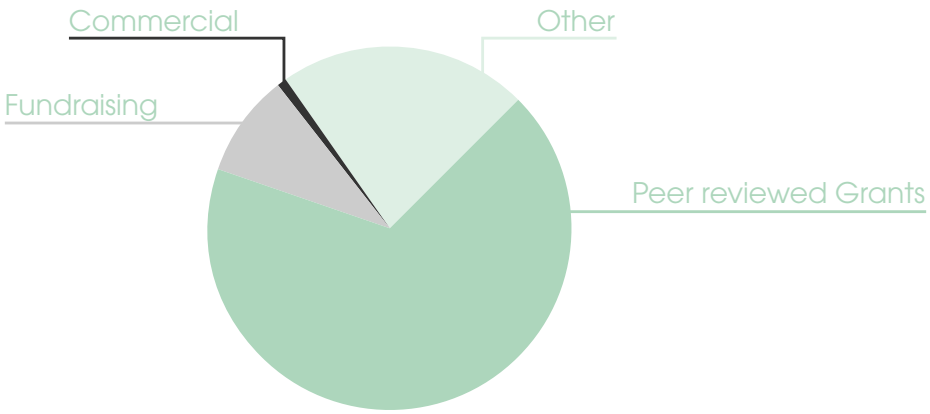
Investigator	Title	Granting Body
W Weninger	Multi-photon microscope for intravital imaging	Cancer Institute NSW
P Mrass	Direct visualization of T cell-tumour stroma cell interactions to dissect the molecular mechanisms of immune system-mediated tumour destruction	Cancer Institute NSW
N Haass	Intravital cell-cycle imaging as a novel approach to design combined targeting strategies of independent signalling pathways in melanoma	Cancer Institute NSW
W Weninger	Ultrafast tunable laser for multi-line, multi-photon intravital imaging	University of Sydney
Y Qi (P Xia)	Role of sphingosine kinase-1 in beta cell survival and function.	NHMRC
D Seth, P Haber,	Genetic factors that predict liver disease amongst excessive alcohol drinkers: a pilot genome-wide analysis	Alcohol & Health Research grants Scheme
W Ritchie	Exploring roles for microRNAs in cancer using bioinformatics and gene expression tools.	NHMRC
M Vadas, G McCaughan, J Gamble, P Xia, P Bertolino	Inflammation, Angiogenesis and Cancer	NHMRC
R Shephard (C Semsarian)	Familial cardiomyopathy and severe heart failure caused by multiple gene mutations: from molecular pathogenesis to disease prevention	Australian Rotary health
B Fazekas, M Vadas, J Gamble, J Rasko, W Weninger, G McCaughan, G Halliday, L Khachigian, S Clarke, M Norris, P Xia, N Shackel, J Holst, N Haass, S Byrne, R Martiniello-Wilks, P Mrass, P Beale, C Jones	Next generation high speed cell sorter for cytometry and imaging facility	Cancer Institute NSW
M Vadas, B Fazekas, J Allen, S Byrne, S Clarke, R Christopherson, Q Dong, J Gamble, N Haass, G Halliday, J Holst, P Hogg, C Jolly, L Khachigian, R Mason, R Martiniello-Wilks, G McCaughan, M Norris, J Rasko, Richardson, N Shackel, F Warner, W Weninger, P Xia, P Beale, C Jones, P Mrass	Manager Imaging and Cytometry and Imaging Specialist for expanded Centenary Institute flow and imaging facility	Cancer Institute NSW
N Mohana-Kumaran (J Allen)	Apoptosis pathways in the drug resistance and pathogenesis of melanoma	Cancer Institute NSW
C Grzelak (F Warner)	Role of the hepatic hedgehog pathway in injury and hepatocellular carcinoma	Cancer Institute NSW
C Semsarian	Prevention of sudden unexplained death in children in Australia	Thrasher Research Fund (USA)
M Vadas	Inverted microscope and laser for MP facility	Perpetual Trustees

FINANCIAL HIGHLIGHTS

	2009 in '000	2008 in '000
INCOME		
Research Income		
Federal - NHMRC + ARC	4,928	4,222
NSW Government	1,202	1,559
Other Research Grants	5,475	3,739
Total research income	11,605	9,520
Fundraising		
Donations, events + other	888	610
Bequests	657	239
Total fundraising	1,545	849
Commercial	86	65
Other	3,742	3,582
Total Income	16,978	14,016
EXPENDITURE		
Research Activities	11,370	9,080
Foundation	580	320
Infrastructure	1,602	1,738
Building operations	1,649	1,677
Other		329
Total Expenditure	15,201	13,142

** The complete annual accounts are available on request*

INCOME 2009



Research income grew strongly in 2009 (up 22%). NHMRC and ARC funding continued to growth (up 17%). Non government peer reviewed income grew by 46%. International grants (National Institutes of Health, USA and Wellcome Trust UK), Cancer Council, the Cancer Institute NSW in particular $760,000 for a new cell sorter), the National Heart Foundation and the Charles and Silvia Viertel Foundation were the main contributors to non NHMRC/ ARC growth.

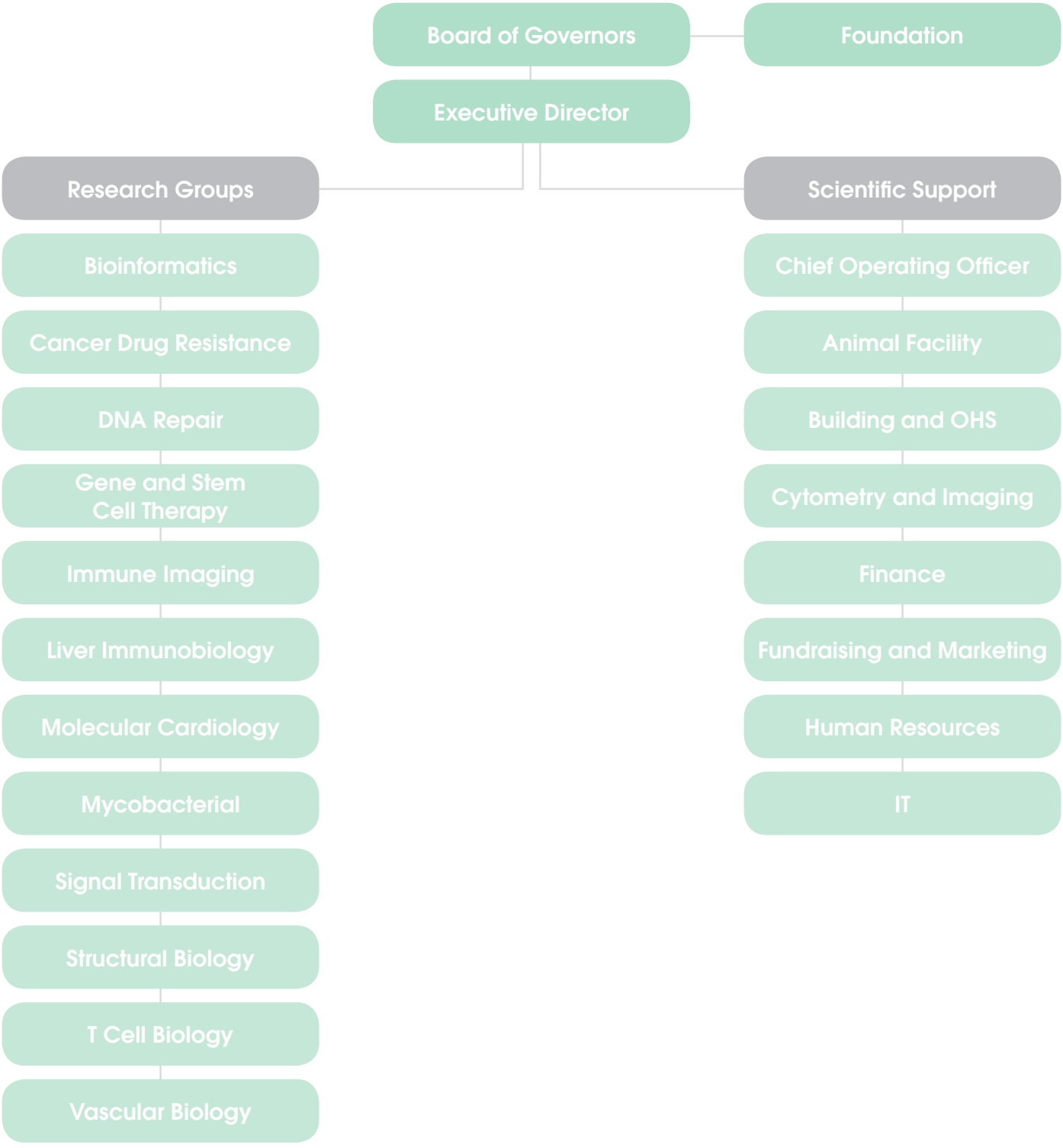
Overall income grew by 18% whilst expenditure grew by 12%. It is pleasing to report that whilst expenditure on research activities grew in line with increase in income expenditure on infrastructure and the building operations were slightly less than 2008, a reflection of improved efficiencies in the scientific support area.

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

Finally my thanks to all the science support staff for their continued hard work in 2009.

Nick Pearce
Chief Operating Officer

ORGANISATIONAL CHART



SCIENTIFIC SUPPORT STAFF

PhD Scholar Jonathan Nambiar, Mycobacterial group

Executive Director
Mathew Vadas

Administration Assistant
Catherine Axford (Until March)
Michael Greensmith (From March)
Rachel Wolfenden (From May)

Animal Attendant
Danielle Moyes
Hannah Walters (From November)
Jenna Glasgow (Until October)
Leah Miller (From April)
Robert Agostino (Until May)
Sandra Martin
Victor Truong

Animal Facility Assistant
Gary Black (From May)
Cassandra Cox (March-April)
Rebekah Hutchinson (From Dec)
Sarah Murray (Until September)
Selina Colosi (March-April)

Animal Technician
Michael Damjancuk
Carol Juaton

Assistant Accountant
Chelsea Wang

Building Services Assistant
Bob Thorburn

Chief Operating Officer
Nick Pearce

Communications Coordinator
Erin Sharp (Until April)

Cytometry Support Coordinator
Robert Salomon

Director's PA / Office Support Manager
Helen Warwick

Donor Services Coordinator
Barbara Smith (From October)
Sonny Liang (Until August)

Facilities & Resources Manager
Jeff Crosbie

Finance Manager
Viraf Variava

Finance Officer
Elvin Certeza (June-Oct)
Willie Entona

Fundraising & Marketing Manager
Sally Castle

Fundraising Coordinator
Leisl Holterman (From April)

HR Assistant
Eric Suchy

HR Manager
Judith Barry (From June)
Nanette Herlihen

IT Support
Owen Hoogvliet
Sam Tardif

IT Systems Administrator
Robert Middleton

Manager - Cytometry, Imaging & IT
Adrian Smith

Marketing Coordinator
LauraBeth Albanese (From April)

Microinjectionist
Michelle Brownlee

OHS and Operations Manager
Jeff Crosbie

Receptionist
Katie Doyle (From January)

Research Support Officer
Sonja Bates

Senior Technical Officer
Marisa Mourelle

Technical Support Officer
Steven Allen

Veterinary Manager
Maria Wynne

RESEARCH STAFF

Cancer Drug Resistance

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PhD Scholar
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Chris Jolly

PhD Scholar
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George Sharbeen

Gene and Stem Cell Therapy

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Jeff Holst

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Phoebe Matthews
Margaret Shaw

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Jessamy Tiffen
Jessica Vanslambrouck
Megha Rajasekhar
Shawna Tan

Research Assistant
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Fiona Guan (Until March)
Gemma Meyers (Until January)
Vineet Minhas (From July)
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Mark Tan (Aug-Dec)
Annora Thoeng
Sarah Watson

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Michelle O'Han
Qin (Kevin) Wang
Justin Wong (From March)
Ayako Yamaura (Until November)

Research Scientist
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Visiting Scientist
Rosetta Martiniello-Wilks (Until December)
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Tang Yi (From April)

Immune Imaging

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Paula Nascimento (From August)

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Garth Douglas (Until February)
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Mary Mouawad
Ben Roediger (From July)
Eunice Tan (From September)

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Arby Abtin (From October)
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Saparna Pai (From September)
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Lauren Holz (Until April)
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Auvro Mridha (From February)
Naveed Nadvi

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Yanfei Qi

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Lijun Wang

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Structural Biology

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Amy Guilfoyle (Until July)

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Natalie Wong

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David Hancock

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Jennifer Young
Ivy Zhang

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Garry Chang (Jan-July)
Danesh Kumar (From July)
Ying Lu

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Carlos Cassano (Until November)
Nham Tran (Until December)

Senior Research Officer
Matthew Grimshaw

Visiting Scientist
Zhou Zhaoxiang (Feb-May)

Dr Chris Jolly, Research Assistant Christine Yee and PhD Scholar George Sharbeen, DNA Repair group

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