C-type lectin-mediated antigen loading to dendritic cells using immunoliposomes

We aim to develop a strategy for delivering antigens to DC by targeting DEC-205 and DCL-1 expressed on DC surfaces using immunoliposomes, membranous microparticles coated with anti-C-type lectin monoclonal antibodies. This DC targeting method is likely to increase the efficiency of antigen uptake by DC, therefore inducing strong antigen-specific immune responses. Our monoclonal antibodies against DEC-205 and DCL-1 are now being tested for their ability to do this.

Biology of a novel intracellular protein AHCYL1

We discovered AHCYL1 during the search for proteins expressed specifically in DC but not other white blood cells. AHCYL1 is present not only in humans but also other species, including rodents, fish and insects, and is likely to be an important protein to mediate intracellular signalling that controls cell function and differentiation. Using a molecular genetics approach, we have shown that AHCYL1 modulates intracellular calcium release, suggesting that AHCYL1 is important for calcium-based intracellular signalling. AHCYL1-deficient mice are being produced to explore its function in a mammalian system. Because of the extensive knowledge of mouse genetics and immunology, the AHCYL1-deficient mice will contribute to understanding AHCYL1 function in both development and also DC biology and the immune response.

Team Members

Dr Masato Kato PhD – Team Leader
Ms Kylie MacDonald BBiomedSc(Hons) – Research Assistant
Mr Hiroaki Michiue – Honours student

External Collaborators

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Dr Ian Ross, Institute for Molecular Bioscience, UQ
Dr Nigel Davis, Pharmacy, UQ
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Research Highlights

- The launch of our Phase I clinical trial for a prostate cancer vaccine.
- World-first finding that the number of activated dendritic cells (DC) in the blood is a predictive factor for graft versus host disease (GVHD). This finding has enabled us to develop a predictive blood test for this major complication of bone marrow transplantation and has opened the door to developing new strategies to prevent it.
- Pioneering finding that low DC counts in blood are associated with diabetes. This has stimulated a major Brisbane collaborative research effort in this disease.
- Showed for the first time that there is a link between inappropriate synthesis of the Muc2 protein (misfolding / ER stress) and intestinal inflammation in mouse models and human inflammatory bowel disease.
- Developed a novel technique for screening breast cancer genes, enabling up to 2000 genes to be tested at once.

Operational Highlights

- 23 new scientific publications (5 in press) and 3 book chapters authored by MMRI scientists.
- A total of almost $600,000 in philanthropic support was raised to support research at the MMRI.

Corporate Highlights

- Record success with funding from the National Health and Medical Research Council, being allocated almost $2 million.
- $1 million funding from the US Army to fund a second Phase I clinical trial for a prostate cancer vaccine, using a novel antibody.

Highlights of 2006
About us

The Mater Medical Research Institute (MMRI) is a world-class facility conducting research aimed at improving health care.

Established by the Sisters of Mercy in 1998, the MMRI attracts scientists and collaborators from all around the world to work on its leading research projects, which have already led to many novel discoveries and world-first innovations in health care.

Co-located on the Mater Hospital campus in Brisbane, the Institute focuses on translational research, boasting a close working relationship with clinicians from the Mater and employing double-trained clinician scientists to ensure this goal is met.

Researchers at the MMRI specialise in cancer biology, immunotherapy and dendritic cells, mucosal diseases, and biotherapies including adult stem cells.

Their research is making a difference to health care and the treatment of illnesses and diseases including:

- Cancers including breast, prostate, ovarian, lung, bowel, leukaemia, lymphoma, and multiple myeloma
- Inflammatory bowel diseases such as Crohn’s disease and ulcerative colitis
- Diabetes
- Heart disease
- Stroke
- Acute renal failure and other diseases requiring organ transplant
- Infectious diseases including Hepatitis C and HIV
- Bone marrow transplantation complications
- Psoriasis

Mission
Based on a commitment to academic medicine, we are building a world-class medical research institute to discover, develop, translate, and commercialise medical research that integrates with relevant areas of excellence within Mater Health Services.

Vision
Exceptional medical research to innovate and enhance health care for the benefit of the community
Chairman’s report
Professor Ian Zimmer

2006 has been a year of exceptional achievement for the Mater Medical Research Institute, marking a turning point for the Institute.

A major project for 2006 was the successful incorporation of the MMRI as an independent medical research facility. Supported by its founders, the Sisters of Mercy and Mater Health Services, incorporation allows the Institute to access the federal and state government infrastructure funding that is vital to the Institute’s future development.

As part of incorporation, the Institute has appointed a Board of Directors to oversee its corporate governance and strategic direction. The board replaces the previous MMRI Council. On behalf of the Institute, I would like to thank the members of the Council for their service to the MMRI. I would like to particularly acknowledge the commitment of the previous Chair, Professor Geoffrey Kiel, in guiding the growth of the Institute and congratulate him on his success in providing a strong platform from which to launch the next phase for the Institute. Professor Kiel remains a member of the Institute’s Board.

A major initiative set to play a pivotal role in the future of the MMRI is the creation of a new research facility in Brisbane. The MMRI and in particular its Director Professor Derek Hart have been instrumental in driving the vision for the centre. The MMRI will expand its research activities to join other world-class Queensland research institutes in this new facility when it is completed in 2009. A founding pledge of $100 million from the Queensland Government has ensured the vision will become a reality and I would like to thank the Government for their support.

In the coming year, the MMRI aims to further develop its business, commercial, and philanthropic activities to cement its financial security and provide a solid foundation for the expansion of its facilities and research activities.

I would like to acknowledge the Director of the MMRI, Professor Derek Hart, for his commitment to research and academic medicine, which have driven the activities of the Institute since its inception. Again in 2006, his leadership has helped ensure the Institute’s success.

Throughout the year, we have strengthened our collaborations with clinicians at the Mater hospitals. The relationship between the Mater and the MMRI became even closer in 2006, with CEO of MHS, Dr John O’Donnell, being appointed to the MMRI Board. This will enable greater synergies between the research and health care being carried out at the Mater in the best interest of patients.

Finally, I would like to thank all the Institute’s supporters. Looking ahead, I see a very exciting future for the Institute which I look forward to sharing with you all.

Professor Ian Zimmer
Chairman of the MMRI Board
A message from...

In 2006, the Mater Medical Research Institute has continued to play an important role in the Sisters of Mercy’s commitment to serve the community by providing quality health care.

The Sisters of Mercy’s objective in establishing the Mater Medical Research Institute was to foster an environment of academic medicine, whereby scientists work alongside clinicians to ensure discoveries are translated into clinical practice.

The Mater Medical Research Institute has made great progress over the past 12 months in achieving this goal as well as achieving scientific discoveries which hold great hope for improving health care and quality of life of patients everywhere.

Research has always been regarded as a vital component of compassionate and high quality patient care, and continues to play an important role in the development of medicine practised and taught at each of the hospitals within the Mater complex.

A strong working relationship between the MMRI and Mater Health Services through the contribution of MMRI scientists and Mater clinicians to scientific inquiry is providing a vital link between medical research and clinical application.

It is in this tradition of caring for the sick and needy and a strong connection with the history, mission and values of the Sisters of Mercy and Mater Health Services that the MMRI stands out from other research facilities.

A great spirit of social and scientific innovation is embodied in the Institute’s vision of exceptional medical research to innovate and enhance health care for the benefit of the community.

On behalf of the Sisters of Mercy, I would like to congratulate Professor Hart and his team of scientists, clinicians, research students and support staff for their exemplary work and their continued commitment to our mission.

An important element of Mater Health Services’ approach to providing exceptional clinical care is to ensure close collaboration between clinicians and researchers.

This unique Mater partnership brings the laboratory research directly to the bedside, by ensuring researchers and clinicians work together to deliver the best possible outcomes to the patients. This synergy between researchers and clinicians creates the ideal environment for scientific discoveries.

The partnership with the Mater Medical Research Institute (MMRI) strengthened during the year, with Mater Health Services becoming a co-owner of the newly incorporated MMRI Ltd, in conjunction with the MMRI founders, the Sisters of Mercy.

Mater has committed to $2 million per year infrastructure support for the MMRI to ensure the Institute can fulfill its role in supporting research on the Mater campus.

Throughout the year, Mater has been truly excited by the significant breakthroughs that the MMRI has delivered through their world-first prostate cancer vaccine trials and breast cancer research.

This medical research has the potential to revolutionise health care around the globe and Mater is committed to supporting the MMRI as it continues to break new ground which will ultimately benefit the community.

Sister Sandra Lupi
RSM
Congregational Leader,
Sisters of Mercy

Professor John McAuliffe AM
Chair,
Mater Health Services Board
Patron’s report

Professor Peter Doherty

Scientific Patron for the MMRI
1996 Nobel Prize winner in Physiology and Medicine
1997 Australian of the Year

The Mater Medical Research Institute is internationally recognised for its research and its commitment to pushing the boundaries of medical science and stimulating interaction between research, teaching, and health care practice to bring new biological therapies into clinical practice.

As Scientific Patron of the MMRI since its inception in 1998, I am proud to have watched the Institute grow to become a world-class facility.

Led by Professor Derek Hart and a remarkable team of scientists and clinicians, the Institute has established an internationally-renowned research program in the areas of dendritic cell research, mucosal diseases, biotherapy and adult stem cells, cancer biology, and most recently, clinical trials.

As any researcher will attest, scientific discovery is never an overnight phenomenon and requires hard work, dedication, persistence, and patience. It is very much a team effort and I congratulate each and every member of the MMRI team who have all excelled in their research over the past year.

By being co-located on a major hospital campus, the Institute successfully unites science and medicine in a model of academic medicine and translational research. This ensures scientific discovery is taken out of the laboratory and into the clinic and community as quickly as possible for the benefit of patients.

I believe 2006 has been a particularly significant year for the MMRI, with the Institute gaining momentum that will see it emerge as a driving force in medical research in Australia in the coming years.

The research being carried out at the Mater Medical Research Institute is vital and deserves strong support. The Institute is making a difference to health care practices through continuous discovery, innovation, and translation and I look forward being a part of the MMRI’s future.
The research activities of the Mater Medical Research Institute have flourished in 2006, with outstanding scientific results and new national and international collaborations.

Our vision is for exceptional medical research to innovate and enhance health care for the benefit of the community. We set out to achieve this through a commitment to academic medicine; discovering, developing, translating and commercialising new biological solutions to disease to benefit patients everywhere.

While the progress of our Phase I clinical trial for a new prostate cancer vaccine is a measure of our success in achieving this vision, it really is just the tip of the iceberg. The science underpinning our trial is unique and very exciting. Once proven, it will have far-reaching implications world-wide for exploiting the immune system to treat not only cancer but other diseases such as diabetes, inflammatory diseases and the complications of transplantations.

Throughout 2006, we have continued to make great strides in all our basic research programs. These programs have been given a major boost thanks to the MMRI’s success with two major initiatives in 2006.

The first was the success of our joint application for $30 million federal funding to establish the Cooperative Research Centre for Biomarker Translation (CRC-BT). The MMRI is one of seven leading national and international research, health and pharmaceutical bodies that have come together to form the CRC–BT. Its vision is to develop new antibodies that will transform the diagnosis and treatment of cancer and autoimmune disease. MMRI will play a role in all areas of research activity from molecule discovery through to clinical trials and commercialisation. The partnerships we have formed with other Australian research institutes, and commercial partners Becton Dickinson Biosciences and Amgen Inc, will have significant benefits for all our research projects.

The second major initiative is the development of the Translational Research Institute (TRI) in Brisbane, which is a one in a hundred year opportunity for research in Queensland. A $100 million commitment from the Queensland Government, the result of a great deal of groundwork from the MMRI and other stakeholders, provided the final impetus to get this project off the ground.

It brings together a proposed expansion of the MMRI with other stakeholders and will address a vacuum in Australia for the infrastructure critical to effectively translating scientific research into clinical practice. The TRI will feature a fully functioning scale-up manufacturing facility for biopharmaceutical and cell therapeutics, which will be the only facility of its kind in the southern hemisphere and one of only a handful in the world with this capacity not dedicated to a single commercial entity’s needs. This a milestone not only for the MMRI but for all Australian researchers who will be able to carry their projects through all stages of clinical trial in Australia, as opposed to shipping the intellectual property overseas for production.

These two initiatives firmly establish the MMRI on the world research stage. I would like to acknowledge the state and federal governments for their support in establishing these initiatives.

2007 is shaping up to be a very exciting year. We will start the practical planning of the Translational Research Institute and commence our research activities as part of the CRC-BT. In 2007 we hope to establish a funding base from which to launch a clinical trial for a therapeutic vaccine for multiple myeloma as well as advancing other research projects to the clinical stage. In particular, we aim to commence a Phase I clinical trial using adult (mesenchymal) stem cells with unrelated cord blood to accelerate the rate of engraftment of cord blood transplant and commence a second Phase I trial of our prostate cancer vaccine using an MMRI-developed antibody. An international study involving the Fred Hutchinson Cancer Centre (Seattle) and European Bone Marrow Transplant colleagues will extend our studies on DC in bone marrow transplantation into an international study.

We acknowledge and give heartfelt thanks to all our partners, collaborators and the funding bodies, who have supported our research for 2006. In particular, I would like to thank the Mater Foundation for their dedication in raising the essential additional philanthropic support for the MMRI’s research.

Finally – and by no means least - I would like to thank the magnificent team at the Institute. Research is a team effort and the achievements of the past year would not have been possible without the hard work, dedication and passion of everyone at the MMRI.

I am looking forward to the next phase of the Institute’s development and we look forward to sharing our achievements with you.
MMRI Board and Council 2006

**Professor Ian Zimmer**
MMRI Council until September 2006  
Chairman since October 2006

**Professor Geoff Kiel**
Chair of MMRI Council until September 2006  
Director since October 2006

**Dr John O’Donnell**
Director since October 2006

**Professor Peter Brooks**
MMRI Council until September 2006  
Director since October 2006

**Sister Deirdre Gardner RSM**
Director since October 2006

**Mr John McAuliffe**
MMRI Council until September 2006

**Sister Anne Hetherington RSM**
MMRI Council until September 2006
Dendritic Cell (DC) Program

How does the immune system respond and can we exploit DC, the cells that initiate the immune response, to develop vaccines against cancers and problem infections? Can we also control DC activity to facilitate transplantation and modify inflammatory/autoimmune disease?

These are the questions which drive the researchers in the DC program.

DC are specialised white blood cells that play important roles in initiating immune responses against foreign and infectious agents. DC are involved in virtually every organ in the body and therefore their role in health and disease is potentially relevant to every medical specialty.

The goal of the DC teams is to develop new preventative vaccines against major infections and therapeutic vaccines against cancers; improve the results of organ and bone marrow transplantation; and switch off destructive autoimmune responses associated with diseases such as psoriasis, arthritis, SLE and diabetes.
The goal of the DC Antigens Team is to discover, characterise, and develop applications for new molecules associated with DC to help in the immunotherapy treatment for cancer and transplantation.

Specifically, the DC Antigens Team aims to:

- Discover novel molecules expressed by DC and to determine the role they play in DC immunobiology
- Develop a therapeutic antibody that targets DC for the control or prevention of graft versus host disease (GVHD)
- Identify the antigens recognised by the DC activation marker antibodies CMRF-44 and CMRF-56
- Determine the functional role of the DC activation antigen CD83 and to develop potential applications

**Monitoring of activated DC for prediction of GVHD**

GVHD is a very common and often serious complication of bone marrow transplants (BMT) for leukaemia and other haematological disorders.

We have recently found that we can predict which BMT patients will develop GVHD by monitoring activated DC in blood. This is an important advance because it will enable patients who are going to develop GVHD to be given pre-emptive immunosuppressive treatment and allow clinicians to delay or minimise prophylactic immunosuppression for those who are not going to develop GVHD.

**Human-SCID mouse model of GVHD**

The DC Antigens Team has recently shown that targeting activated DC with antibody prevents GVHD in a chimeric human-SCID mouse model of the disease. In the same study we showed that protective T cell memory is not impaired by activated DC antibody treatment, in contrast to conventional immunosuppression which impairs both immunity to infection and the graft versus leukaemia effect which is the main purpose of BMT.

**Identification/characterisation of DC molecules – PEDF, CD83**

The role of CD83 (expressed on the surface of activated DC) in immunity is only now becoming clear. It seems to be important for efficient generation of antigen specific antibody and T cell responses, via interaction with an as yet unidentified ligand.

The DC Antigens Team is generating a panel of antibodies that recognise different parts of the CD83 molecules, which will contribute to our understanding of their role in DC function.

**Therapeutic anti-DC antibody development – CMRF-44, CD83**

The team is developing therapeutic antibodies for the control of GVHD. The CMRF-44 monoclonal antibody has been humanised and is currently undergoing affinity maturation to obtain efficacy. New high affinity monoclonal antibodies to CD83 are being generated, and the best of these will also be humanised and compared with the humanised and affinity matured CMRF-44 antibody. One of these will be tested on BMT patients in a Phase I clinical trial.

**Collaborators**

Professor Anne Dickenson, University of Newcastle-Upon-Tyne
Dr Katleen Braet, University of Queensland
A/Professor Ken Bradstock, Westmead Millennium Institute
A/Professor Ross Barnard, University of Queensland
“Understanding the molecular mechanisms of DC function is the key to developing strategies for manipulating and optimising immune responses for vaccination and immunotherapy.” - Dr Masato Kato

**Team leader**
Dr Masato Kato

**Team members**
Ms Kylie MacDonald, Research Assistant
Ms Elisabetta D’Aniello, Research Assistant
Ms Hiroaki Michiue, Honours student

**Funded by**
National Health and Medical Research Council

DC reside in peripheral tissues, take up pathogens as antigens, process them, and migrate to lymph nodes for presenting the processed antigens to other immune cells such as T cells and B cells for the antigen-specific immune responses.

The Gene Discovery Team is investigating molecular mechanisms of DC function, particularly the functions of novel C-type lectin molecules (DEC-205 and DCL-1) discovered by the MMRI. These molecules appear to function in antigen uptake and processing, pivotal steps for efficiently eliciting immune responses.

**Biology of a novel C-type lectin receptor**
This project aims to understand the function of DCL-1 at molecular levels. Using genetically modified cultured cells expressing DCL-1 (called transfectants), we have shown that DCL-1 associate with cytoskeletons and mediate particle uptake (called phagocytosis). Furthermore, we have shown that DCL-1 is likely to be involved in cell adhesion and migration. These functions are relevant to DC function. We are currently investigating DCL-1 function using genetically modified mice lacking DCL-1.

The understanding of DCL-1 at molecular levels is important to develop an effective strategy for vaccination and immunotherapy.

**DEC-205-mediated antigen loading to DC using immunoliposomes**
This project aims to develop a strategy to deliver antigens of interest to DC by targeting DEC-205 expressed on DC surfaces using immunoliposomes, membranous microparticles coated with anti-DEC-205 antibody. As immunoliposomes can capsule a wide range of reagents within their membrane structure, they are ideal to deliver the reagents to DC for modulating DC function.

In collaboration with Dr Nigel Davis, we have shown that anti DEC-205-coated immunoliposomes can be effectively taken up by DC. We are conducting preclinical studies using a new formulation of anti DEC-205 immunoliposomes using DEC-205 monoclonal antibodies (MMRI-7) we have developed.

**Biology of a novel intracellular protein AHCYL1**
We discovered AHCYL1 during the search for proteins expressed specifically in DC but not other white blood cells. AHCYL1 is present not only in human but also other species, including rodents, fish and insects, and is likely to be an important protein to mediate intracellular signalling that controls cell function and differentiation.

Using a molecular genetics approach we have shown that AHCYL1 modulates intracellular calcium release, suggesting that AHCYL1 is important for calcium-based intracellular signalling. Currently we are characterising AHCYL1-deficient mice to explore AHCYL1 function in a mammalian system.

**Collaborators**
Professor Brian Key, University of Queensland
Dr Ian Ross, Institute for Molecular Bioscience
Dr Matthew Sweet, Institute for Molecular Bioscience
Dr Nigel Davis, University of Queensland
“Better understanding the role of CD300 molecules will lead to more effective treatments and improve the quality of life of psoriasis sufferers and hopefully improve the survival rates of patients with acute myeloid leukemia.”
Dr Georgina Clark

Team leader
Dr Georgina Clark

Team members
Dr Ju Xinsheng, Senior Research Officer
Ms Min Rao, Research Assistant
Ms Courtney Modra, PhD Student

Funded by
Leukaemia Foundation of Australia
National Psoriasis Foundation

The Immunoregulation team studies the human CD300 molecules which are a family of six closely related proteins (CD300a, CD300b, CD300c, CD300d, CD300e, CD300f) found on the surface of white blood cells. These proteins have the ability to regulate the extent to which white blood cells respond during an immune response, by amplifying or diminishing an immune response.

By studying the biology of the CD300 molecules, the team plans to determine what role CD300 molecules play in the common chronic inflammatory skin disease, psoriasis, and how they may be used for targeted treatment of acute myeloid leukaemia (AML).

CD300f as a target for antibody mediated therapy of AML
Some CD300 molecules are expressed by the cells altered in AML. We hypothesise that these molecules may act as targets for drug delivery to AML cells in a manner similar to current therapies such as Mylotarg. In particular, CD300f is expressed on myeloid cells and contains the structural motifs to induce negative signalling. We have generated a monoclonal antibody to this molecule and are evaluating CD300f as a target molecule in AML.

Technologies to study human CD300 molecules
We are developing technology to monitor and manipulate the amount of each CD300 molecule expressed by human cells. We aim to identify the ligands for these molecules in order to determine how the cells send signals through the CD300 molecules.

CD300a and CD300c identify a novel CD4+ T cell population
CD300a and CD300c are expressed on a subpopulation of CD4+ T lymphocytes. We are studying CD4+ T cells to understand their role in developing CD4 mediated effector functions in autoimmune diseases, graft versus host disease and other inflammatory scenarios to determine if CD300 molecules are biomarkers for particular immune responses.

CD300 molecules as regulators of DC function
CD300 molecules are expressed by at least one subpopulation of DC. The differentiation and activation of DCs results in changes to CD300 molecule expression simultaneously with CD300 mediated signals effecting DC function. This research is studying how the expression of CD300 molecules by DC populations varies during differentiation and activation, and the feedback mechanisms by which CD300 molecules then control this process.

CD300 molecules in psoriasis
Psoriasis is a chronic inflammatory disorder that affects 2-3% of the population. We have found that the expression of CD300a and CD300c by peripheral blood mononuclear cells is altered in a subgroup of psoriasis patients. We aim to determine the underlying genetic explanations for these observations and how they contribute to the disease. Our research suggests these molecules may be targets for new therapeutics.

CD300e as a monocyte selection marker
CD300e is expressed predominantly on the CD14+ monocytes within the peripheral blood. We have made a monoclonal antibody to CD300e which is able to be used to immunoselect monocytes and to study the function of CD300e on monocytes.

Collaborators
Professor Heddy Zola, Child Health Research Institute
The Growth and Differentiation team is focused on investigating the human DC system in healthy conditions and applying this knowledge to cancer and type 1 diabetes mellitus (T1DM).

Our recent research shows that blood myeloid DC-like cells can be generated from cord blood CD34+ cells in the presence of FLT3-ligand, stem cell factor, interleukin (IL)-3 and IL-6. We have demonstrated that blood myeloid DC and the homeostatic cytokines IL-7 and IL-15 are critical for the maintenance of memory CD4+ T cells with mixed helper and regulatory functions. We suggest that immune insufficiency involving reduced blood DC numbers contributes to autoimmunity in children with T1DM.

Modulation of human DC system in vivo including its development, activation and migration is likely to be an important future therapeutic approach to induce an appropriate immune response in cancer and autoimmune disease. However, modulation of human DC in vivo is severely limited by ethical and technical constraints. Our approach to overcome these limitations involves developing a functional human DC system in humanised (hu)NOD/SCID mice engrafted with haematopoietic stem cells.

Targeting human DC in a multiple myeloma huNOD/SCID model

Effectively targeting DC directly in vivo in cancer patients requires an understanding of how the conditions in the tumour-bearing host influence DC development and function.

We have developed huNOD/SCID mice engrafted with haematopoietic stem cells which support the development and survival of human DC to better understand the development and activation of human DC. We propose to introduce human multiple myeloma (MM) cells into huNOD/SCID mice to generate a MM-huNOD/SCID model, and then to use this MM-huNOD/SCID model to address DC biology in the tumour environment. Once we understand DC biology in the MM host, we will try to reverse any detrimental tumour effects upon DC biology by targeting DC directly in vivo.

**DC biology in Type 1 Diabetes Mellitus (T1DM)**

We suggest that restoration of aberrant DC numbers and survival will be essential for balancing DC-mediated autoimmune and tolerogenic T cell responses and suppression of β-cell autoimmunity in T1DM patients. This project uses a cross-sectional and prospective clinical cohort study design in T1DM patients, close family members (including subjects at risk of T1DM) and healthy controls to analyse the number and composition of blood DC subsets, blood DC survival and underlying survival signalling pathways.

**Human DC-targeted liposome formulations designed to maximise antigen cross-presentation**

This project focuses on manufacturing new DC-targeted liposome formulations capable of co-delivering multiple compounds to DC to facilitate antigen “cross-presentation” by the MHC class I restricted pathway and maximum generation of cytotoxic T lymphocyte responses.

**Mannose binding lectin (MBL)**

MBL is a soluble pattern recognition protein that binds to a number of pathogens in the blood acting as an initial barrier to infection. Low MBL levels due to genetic variation are associated with increased frequency and severity of infection. We are testing how the addition of exogenous MBL regulates innate and adaptive immune responses in MBL sufficient compared to MBL deficient individuals.

**Collaborators**

Dr Laurence Catley, Mater Adult Hospital
Dr Andrew Cotterill, Mater Children’s Hospital
Dr Alfred Lam, Griffith University
Professor Ranjeny Thomas, Diamantina Institute
Dr Nigel Davies, University of Queensland
Dr Robyn Rodwell, Queensland Cord Blood Bank
Australian Red Cross Blood Service
“We aim to develop more potent, less toxic cancer treatments that will be applicable to a broad range of cancer patients by exploiting DC and the ability of the immune system to fight cancer.” Dr Kristen Radford

Team leader
Dr Kristen Radford

Team members
Dr Ray Wilkinson, Senior Research Officer
Dr Roger Lord, Senior Research Officer
Dr Hans Goossen, Masters Student
Mr Andrew Kassianos, PhD Student
Dr Annelie Vulink, PhD Student
Ms Melinda Hardy, PhD Student

Funded by
National Health and Medical Research Council
Queensland Cancer Fund
Susan G. Komen Breast Cancer Foundation (USA)

Immunotherapy using the patient’s own DC instructed ex vivo to initiate and direct anti-cancer immune responses is a new non-toxic strategy with potential to treat a variety of malignancies.

Understanding DC biology will allow us to realise the full potential of these remarkable cells and will lead to continued improvements of this therapy. Our findings will be directly incorporated into future clinical trials and will provide new treatment options for cancer patients.

The role of DC produced cytokines in the induction of T lymphocyte responses

We are investigating cytokine secretion by different human DC subsets in response to a range of stimulatory conditions, and how these can modulate tumour-specific cytotoxic T lymphocyte and naïve CD4+ T helper cell responses. These findings will assist in determining the best stimulatory conditions and type of DC to use to induce tumour specific immune responses for immunotherapy.

We have shown that MoDC derived in IL-15 produce high levels of IFN-γ, whilst MoDC derived in IL-4 produce high IL-12, and the naturally circulating BDC produce high IL-10. These findings are likely to influence the type of DC and activator used for clinical therapy.

Discovery of new tumour associated antigens (TAA) using a novel E.coli-based screening strategy

We have developed a screening method that can rapidly identify new immunogenic cancer proteins from thousands of tumour-specific genes. We are using this strategy to identify new breast cancer TAA and are planning to apply the technology to search for new leukaemia TAA in the near future.

Selection of prostate-antigens for DC immunotherapy

In this project, undertaken in conjunction with Prof Judith Clements (QUT), we have identified immunogenic epitopes from a novel member of the prostate specific antigen (PSA)-related Kallikrein family. This molecule is more specific for prostate cancer than other commonly used targets (PSA, PSMA and PAP) and our data suggest it to be a promising new target for use in immunotherapy of prostate cancer.

Collaborators
Professor Ross Pinkerton, Mater Health Services
Professor Deon Venter, Mater Health Services
Dr Jane Armes, Mater Health Services
Dr Peter Swindle, Mater Health Services
A/Professor Paul Mainwaring, Mater Health Services
Dr Chris Pyke, Mater Health Services
Professor Judith Clements, Queensland University of Technology
Professor Derek Kennedy, Griffith University
Assistant Professor Darren Higgins, Harvard Medical School, USA
Professor Cornelis Melief, Leiden University, Netherlands
Biotherapy Program

The Biotherapy Program consists of four teams: The Adult Stem Cell (ASC), The Haematopoietic Stem Cell (HSC), the Bone Marrow Transplant (BMT) and the Solid Organ Transplant. This program combines a range of biological interventions to address specific issues associated with the delivery of cell therapy to treat a wide range of diseases.

The ASC team focuses on the biology and pre-clinical and clinical application of mesenchymal stem cells (MSC) and other cell populations for the repair of tissues and organs. The HSC team is focused on the biology of stem cell mobilisation and the role of bone in haematopoietic stem cell biology. The BMT team is focused on modulation of graft versus host disease by exploiting immunosuppressive features of MSC and DC populations, as well as active cellular immunotherapy of malignant disease. The Solid Organ Transplant team is focused on the biology and prolongation of kidney transplant survival.
“Our research promises to improve treatment and long-term survival of leukemia patients receiving stem cell transplantation by preventing a potentially fatal complication and relapse.”

Dr Alison Rice

Team leader
Dr Alison Rice

Team members
Dr Janusz Lange, Research Fellow
Mr Andy Hsu, PhD Student
Ms Brie Turner, PhD Student
Ms Melinda Kambouris, PhD Student

Funded by
Leukaemia Foundation of Australia
Perpetual Charitable Planning Services
Queensland Cancer Fund

Not all patients with leukemia will be cured by chemotherapy. Stem cell transplantation improves their chances of survival but requires intensive chemotherapy and radiotherapy to eradicate the underlying disease followed by infusion of healthy stem cells to provide an anti-leukaemic effect (Graft versus Leukaemia [GVL]) and normal blood cells.

We are investigating therapeutic cell based strategies designed to prevent graft versus host disease (GVHD) and leukaemic relapse to allow engraftment of a healthy donor blood system.

Minimising GVHD

Effects of pretransplant conditioning on GVHD onset

Reduced intensity conditioning (RIC) reduces treatment related mortality but the overall incidence of GVHD is unchanged. Understanding and predicting RIC-associated GVHD will provide a window in which to treat and prevent serious GVHD with current and novel therapeutics.

We have established the stem cell transplantation models and for the first time defined a murine model of RIC that mimics the clinical course of transplant recipients. This has enabled us to identify the effects of RIC on DC and gain insight into the reasons for the delayed onset of GVHD seen in transplant recipients.

DC depletion to control GVHD

Current treatment options for GVHD focus mainly on the effector T-cells and cause systemic immunosuppression. Our intention is to shift the focus from elimination of activated T-cells to manipulation of the DC that activate T-cells. Having shown the effects of conditioning on DC has also enabled us to pursue antibody-mediated depletion of DC as a means to attenuate GVHD. While some of our work suggests that survival can be prolonged in transplanted mice when the DC depleting antibody treatment is administered in the peri-transplant period, more detailed studies show that targeting all DC as therapy for GVHD is detrimental. Collaborative work with the MMRI’s DC Antigens team has shown that elimination of activated DC prevents GVHD onset and retains anti-viral immunity in a xenogeneic GVHD model. We aim to eliminate activated DC that interact with donor T-cells to control GVHD but preserve the GVL effect.

MSC-mediated immunosuppression of GVHD

In collaboration with the MMRI Adult Stem Cell team we are investigating the potential of immunosuppressive mesenchymal stem cells (MSC) to attenuate GVHD. Preliminary work suggests that administration of MSC on day +1, but not on the day of transplant (day 0) to mice transplanted with MHC mismatched stem cells alters the kinetics of GVHD onset. We now aim to determine the mechanism of MSC-mediated immunosuppression.

Optimising GVL

Relapse remains the most common cause of death after transplantation. We have developed systems to generate mature DC from CD34+ cord blood (CB) cells. These CD34+DC express costimulatory and activation markers and are able to take up and present antigen. CD34+DC can be effectively electroporated with in vitro transcribed-RNA or total leukemia RNA and these RNA-loaded CD34+DC can generate a strong anti-leukaemic response for both Nalm-6 (ALL cell line) and human ALL xenograft. Anti-surviving CTL responses have also been detected. Using the NOD-SCID mouse model to grow primary ALL in vivo we now show that anti-leukaemic CTL can control ALL growth in vivo. We are now testing to see if the anti-leukaemic response seen in vivo can be enhanced by administration of antigen-loaded DC.

Collaborators
Professor Ross Pinkerton, Mater Health Services
Dr Richard Lock, Children’s Cancer Institute Australia for Medical Research
Adult Stem Cell Team

“Adult stem cells are the body’s repair kit. We believe adult stem cell research holds the key to repairing tissue following illness and injury and has potential for treating heart attacks, strokes, leukaemia and spinal and soft tissue injuries.”

Prof Kerry Atkinson

Team leader
Professor Kerry Atkinson

Team members
Dr Gary Brooke, Senior Research Officer
Ms Konika Chatterjee, Research Assistant
Ms Sarah Barlow, Research Assistant

Funded by
Australian Stem Cell Centre
Inner Wheel Australia

The Adult Stem Cell team is focused on the cell biology and the clinical application of mesenchymal stem cells (MSC) and how they compare to haematopoietic stem cells (HSC), endothelial progenitor cells, and other cell types in the repair and regeneration of new tissues.

We employ animal models of acute myocardial infarction and stroke injury and have approval to start manufacturing human MSC for our first clinical trial.

Research aims
- To determine the molecular mechanisms by which MSCs preferentially migrate to sites of acute inflammation.
- To determine the ability of MSCs and other cell types to improve cardiac function after acute myocardial infarction.
- To explore the capability of MSCs to improve the injury caused by stroke.
- To explore the potential of MSCs to accelerate haematopoietic engraftment after allogeneic HSC transplantation.
- To explore the immunosuppressive potential of MSCs in treating human graft versus host disease following allogeneic HSC transplantation.

Throughout 2006, we have continued our primary project (in collaboration with the Victor Chang Cardiac Research Institute) exploring the molecular homing mechanisms of MSCs to sites of acute inflammation such as an acute myocardial infarction. We have also continued our project exploring the potential role of MSCs in repairing cerebral tissue injured by stroke, a collaboration with the Queensland Brain Institute (University of Queensland).

We have expanded the range of cellular candidates for therapy to repair or regenerate organs and tissues with a comparative study of MCSs, HSCs, endothelial progenitor cells, and pro-angiogenic macrophages in our acute myocardial infarction murine model.

We have received approval from Mater Health Services and Westmead Hospital Human Research Ethics Committee for our first Phase I clinical trial utilising MSCs. These will be co-transplanted with umbilical cord blood in patients with life-threatening diseases such as leukaemia, for which no other treatment is available.

MMRI has obtained full stakeholder status with the Australian Stem Cell Centre (ASCC), receiving initial funding from the ASCC for its cardiac therapeutic focus program. We have also received for a second consecutive year funding from Inner Wheel Australia for our manufacturing of human MSC for clinical trial.

We have determined chemokine receptor display on human bone marrow and human MSC.

Over the next 12 months, we plan to initiate our first Phase I and second Phase I clinical trial, together with obtaining preliminary efficacy data in a murine model of myocardial infarction and murine model of stroke injury on which to base further Phase I clinical studies.

Collaborators
Professor Michael Feneley, Victor Chang Cardiac Research Institute, Sydney
Professor Perry Bartlett, Queensland Brain Institute
Dr Rod Rietze, Queensland Brain Institute
Professor Robert Williamson, University of Melbourne
A/Professor Jean-Pierre Levesque, MMRI
Dr Ingrid Winkler, MMRI
Dr Alison Rice, MMRI
A/Professor Michael McGuckin, MMRI
Solid Organ Transplant Team

“Our research is paving the way for clinical trials using adult stem cells to improve outcomes in organ transplantation.”
Dr Steven McTaggart

Team leader
Dr Steven McTaggart

Team members
Dr Christopher Tracey, Urology Research Fellow
Mr Ben Jones, PhD Student

Funded by
Golden Casket Foundation
Kidney Health Australia
National Health and Medical Research Council
Queensland State Government

The Solid Organ Transplant Team is investigating important pathways involved in the immune response following transplantation. We aim to discover ways to manipulate the immune system during the early stages of a transplant so that an individual becomes ‘tolerant’ to the transplant organ, without the need for ongoing drug therapy.

Mesenchymal stem cells (MSC) in the prevention of solid organ transplant rejection

Organ transplantation is the treatment of choice for severe kidney, liver, heart and lung failure and not only restores the quality of life in seriously ill patients, but also has a significant impact on future health and longevity. However, lifelong treatment with powerful immunosuppressive medications is needed to prevent rejection by the recipient’s immune system.

We are currently exploring the potential of MSC to prevent rejection of solid organ transplants. In contrast to most current pharmacological agents that target only the immunological basis of rejection, cell-based therapies such as MSCs have the potential to target several pathways of rejection. Cell culture studies by us and other groups have shown that MSCs are both non-immunogenic and immunosuppressive. In addition, in a rodent renal transplant model we have been able to show that MSCs track to transplanted kidneys. Further experiments to determine their effectiveness in preventing rejection are currently in progress.

Dendritic cells (DC) and immunological tolerance – the paradox of pregnancy

Tolerance - the ability to accept a transplant from another individual without the need for any ongoing immune suppressant medications – is the ‘Holy Grail’ of transplantation immunology. An example of tolerance that occurs regularly in nature is pregnancy; the foetus that expresses ‘foreign’ antigens from the father is able to develop and is protected from maternal immune attack. One of the mechanisms that promotes tolerance during pregnancy is the expression of indoleamine 2,3-dioxygenase (IDO), an enzyme that modulates the immune system, skewing it towards a more tolerant phenotype. IDO also affects T-cells, the key mediators of transplant rejection, making IDO a strong immunosuppressant.

IDO has also been shown to have an effect on the immune response to malignancy, chronic infections and autoimmune diseases. We propose that IDO may therefore also be able to protect a kidney allograft and are currently studying the role of DC in the production of IDO, and its effects on immune reactions following solid organ transplantation.

Collaborators
Professor Francesco Dazzi, Imperial College, London
A/Professor Yin Xiao, Queensland University of Technology
Professor David Johnson, Princess Alexandra Hospital
A/Professor Glenda Gobe, University of Queensland
Dr Ross Norris, Mater Health Services
Dr David Roberts, Centre for Cancer Research, Bethesda, Maryland, USA
We are studying the cells which are responsible for making our red blood cells and immune cells to find out more about their role in the development of diseases such as leukaemia, anaemia and other immune and bone disorders.

A/Prof Jean-Pierre Levesque
Team leader

A/Professor Jean-Pierre Levesque
Team members
Dr Ingrid Winkler, Senior Research Officer
Ms Bianca Nowlan, Research Assistant
Ms Valerie Barbier, Research Assistant
Mr Florent Peglian, PhD Student
Ms Yi Shen, PhD Student

Funded by
National Health and Medical Research Council
Queensland Cancer Fund

Haematopoietic stem cells (HSC) reside in bone marrow where they make all blood and immune cells. HSC growth, development and migration are tightly regulated to prevent leukaemia, anaemia, and other immune and bone disorders. We are studying these regulations at the molecular level in order to identify new therapeutic targets to treat blood, bone and immune diseases.

Mobilisation of HSC

HSC mobilisation is now commonly carried out to collect large numbers of HSC for transplant into cancer patients after intensive chemotherapy. Transplanted HSC can restore the blood and immune systems destroyed by chemotherapy. However not all patients’ cells mobilise well, thus limiting the number of HSC that can be collected for transplantation. We aim to understand the mechanisms behind HSC mobilisation, so we can improve mobilisation and harvest more HSC for transplantation to improve the survival and recovery of cancer patients.

We have made two significant discoveries: 1) osteoblasts, the cells that form bone, disappear during HSC mobilisation and 2) oxygen is depleted from the bone marrow during HSC mobilisation due to the rapid proliferation of myeloid progenitors that consume a lot of oxygen when they multiply. In response to this oxygen depletion, bone marrow cells make vascular endothelial growth factor (VEGF). This may increase the permeability of blood vessels in the bone marrow thus facilitating the movement of HSC into the blood.

Regulation of HSC

Previously we identified that the cells that form blood and bone regulate one another. This cross-regulation may have major implications for HSC fate (whether HSC decide to survive, grow, migrate or turn into blood cells) as well as on bone turnover which if perturbed leads to bone loss and osteoporosis.

Adhesion molecules that regulate haematopoiesis

Selectins are adhesion molecules essential for the migration of immune cells to organs and into inflamed tissues. We have found that selectins in the bone marrow can dramatically alter HSC turnover and differentiation. Leukaemic cells however do not respond to selectin signalling. These studies will give us a better understanding of how blood formation is regulated and what changes to trigger leukaemia.

Mesenchymal stem cells (MSC)

In collaboration with the MMRI Adult Stem Cell team, we are using our discoveries to better understand how MSCs can be used to repair solid tissues such as bone, cartilage and heart.

Collaborators
A/Professor Ivan Bertoncello, Australian Stem Cell Centre
A/Professor David Haylock, Australian Stem Cell Centre
A/Professor Susan Nilsson, Australian Stem Cell Centre
Professor Christopher Parish, Australian National University
Dr Ljubov Simson, Australian National University
Dr Allison Pettit, Institute for Molecular Biosciences
Dr Liza Raggatt, Institute for Molecular Biosciences
Dr Natalie Sims, St Vincent’s Institute
Dr Louise Purton, Massachusetts General Hospital, Boston, USA
Mucosal Diseases Program

Like common respiratory infections, asthma, inflammatory bowel diseases and common cancers (such as colon and breast cancer), mucosal diseases are major contributors to the burden of disease facing our society.

Mucosal diseases arise in the epithelial tissues that separate our bodies from the often hostile external environment. These tissues are common sites of infection (influenza, the common cold), often develop debilitating inflammation (inflammatory bowel diseases, bronchitis), and after a long period of these insults, cancers may develop in these tissues.

The aim of the Mucosal Diseases Program is to study these diseases with a view to preventing them and improving current treatments. The Mucin and Inflammatory Bowel Disease teams work closely together on basic science and translational research projects with a particular emphasis on gastrointestinal infection, inflammation and cancer.
“By better understanding the mucosal barrier that separates the body from the outside world, we hope to improve treatment or prevent infectious and inflammatory diseases and cancers from developing.”

A/Prof Michael McGuckin

Team leader
A/Professor Michael McGuckin

Team members
Dr Sara Linden, Research Fellow
Dr Penny Jeffery, Research Officer
Ms Debbie Roche, Research Assistant
Ms Kim Driessen, Research Assistant
Ms Thu Tran, Research Assistant
Mr Chad Heazlewood, PhD Student
Mr Ryan Parlett, PhD Student
Ms Samia Taufiq, Honours Student

Funded by
ANZ Trustees
National Health and Medical Research Council
Queensland Cancer Fund

The Mucin Research Team is investigating the biology and clinical applications of a family of genes/proteins known as mucins. We have shown that mucins are a critical component of the barrier to bacterial and viral infection and that mutations in mucin genes can lead to inflammatory disease. We predict that altered function of these mucins will therefore be important determinants of susceptibility to infection and a range of inflammatory mucosal diseases. Mucins also impact on the behaviour of epithelial cancers such as colon, breast and ovarian cancers and therefore our research has important ramifications for cancer treatment.

Our major current goal is to increase our understanding of the mucosal barrier that separates the body from the outside world. Specifically: how it keeps bacteria from infecting the body, how inappropriate inflammation is initiated causing chronic disease, and how this chronic inflammation leads to cancer. Our main focus is on how the mucin genes and proteins are involved in these processes. In the longer term a better understanding of these disease processes is likely to lead to new methods of preventing infectious and inflammatory diseases and preventing cancers developing.

Characterisation of the role of cell surface and secreted mucins as a fundamental component of the mucosal barrier to infection

We now have four distinct murine mucin deficiency models which place us in a unique international position in this field. Dr Sara Linden is leading our in vitro studies to examine interactions between pathogens and cell surface mucins. We have demonstrated that MUC1 limits damage to cells caused by bacterial toxins, that MUC1 interacts with Helicobacter pylori, and that MUC1 limits H. pylori infection.

MUC2 misfolding, endoplasmic reticulum stress in goblet cells and inflammatory bowel disease

We have made an important link between inappropriate synthesis of the Muc2 protein (misfolding/ER stress) and intestinal inflammation in mouse models and human IBD.

Examination of the role of cell surface mucins in regulating growth and metastasis in adenocarcinomas

We have shown that the MUC13 (which we discovered) is present on all colorectal cancers making it a potential target for therapy and that MUC16 mucin is involved in the process of cell division in ovarian cancer. We are also examining whether another mucin, MUC12, which is lost in cancers, is a growth inhibitor and therefore a potential therapeutic agent in cancer.

New therapeutics for Inflammatory Bowel Disease (IBD)

Together with the IBD team we are examining the efficacy of several new drugs with the potential to treat IBD.

Collaborators
Dr Phil Sutton, University of Melbourne
Dr Victoria Korolik, Griffith University
A/Professor J Alejandro Lopez, Queensland Institute of Medical Research
A/Professor Geoff Hill, Queensland Institute of Medical Research
Professor Christopher Goodnow, Australian National University/ Australian Phenomics
Dr Matt Cook, Australian National University
Dr Andreas Obermair, Queensland Centre for Gynaecological Cancer
Dr David Thornton, Wellcome Trust Centre for Cell Matrix Research, Manchester (UK)
Dr Graham Radford-Smith, Queensland Institute for Medical Research
A/Professor George Mendz, University of NSW
Professor Thomas Boren, Umea University, Sweden
Dr Andre Dubois, Uniformed Services University of the Health Sciences, Bethesda (USA)
Inflammatory Bowel Diseases Team

“Our work is focused on understanding why IBD occur, developing better ways to treat them, and helping to make the lives of IBD patients better.”
A/Prof Timothy Florin

Team leader
A/Professor Timothy Florin

Team members
Dr Rajaraman Eri, Research Fellow
Ms Rachel Adams, Research Assistant
Mr Chin Wen Png, PhD Student
Ms Sharise Heazlewood, PhD Student

Colleagues in the Mucin Team

Inflammatory bowel diseases (IBD) – specifically ulcerative colitis (UC) and Crohn’s disease (CD) – affect 50,000 Australians, both adults and children. IBDs are a major cause of chronic disease in the gut causing considerable distress, and are associated with an increased risk of bowel and bile duct cancers and some types of arthritis. The diseases entail inflammation in the intestine that is amplified by recruitment of the immune system. The cause of the inflammation is not known and there is currently no cure.

Mucolytic Bacteria and IBD
The mucus barrier is the primary defence of the intestine against infection from bacteria and viruses. We have novel data that indicates that mucolytic bacteria are increased in IBD. We are studying the relevance of their mucolytic activity in IBD.

Endoplasmic reticulum (ER) stress and inflammation
We have novel evidence that UC is caused by a defect in quality control of the manufacture of mucin, the dominant protein forming the intestinal mucus barrier. The mucin protein is manufactured by the endoplasmic reticulum (ER)-organelles in the cells that line the intestine. We are researching:

- The relationship between ER stress and chronic inflammation
- The relationship between intestinal bacteria, ER stress and mucus
- The spectrum of ER stress in UC and CD
- Genetic predispositions to ER stress in the intestine

Better use of thiopurine therapies to prevent amplification of inflammation by the immune system
Thiopurines discovered by 1989 Nobel Prize winning chemists, Elion and Hitchings, are excellent therapies despite known side effects (that can be avoided with proper use). They are not only useful for IBD, but also autoimmune diseases, rheumatoid arthritis, to aid organ transplantation, and to treat leukaemias.
Unfortunately, approximately 30% of patients cannot use them because of side effects or insufficient response. We are discovering ways to prevent the accumulation of toxic metabolites and aim to identify why there is a much higher risk of life-threatening liver disease with one of the thiopurines, 6-thioguanine, which is otherwise superior to the more commonly used azathioprine or 6-mercaptopurine.

Collaborators
Dr John Duley, Mater Health Services
Mr Kristen Gilshenan, Mater Health Services
Dr Frank Crimmins, Mater Health Services
Dr Mazhar Haque, Mater Health Services
Ms Di Templeton, Brisbane IBD
Professor Linda Blackall, University of Queensland
Dr Sandra Hall, University of Queensland
Dr Bob Simpson, University of Queensland
Dr Beth Fowler, Queensland Institute Medical Research
Dr Graham Radford-Smith, Queensland Institute Medical Research
Ms Lisa Sims, Queensland Institute Medical Research
Ms Nirmala Pandeya, Queensland Institute Medical Research
Professor Dr Wolfgang Petritsch, Prof Dr Walter Reinisch, Austria
Cancer Biology Program

This program is aimed at studying the biology of cancers and the mechanisms that allow their uncontrolled growth and permit them to evade the immune system. Practically, understanding this mechanism is allowing researchers to develop drugs which are becoming increasingly more targeted to individuals.

At present the program has teams investigating the genetic basis of cancers and cancer drug pharmacokinetics. Another project focusing on acute lymphoblastic leukaemia targets for therapeutic antibody productions is being planned with collaborators in Adelaide.
Molecular Genetics Team

“Our research will provide a better understanding of the role of genetics in disease and will hopefully lead to tailored management of diseases.”
Prof Deon Venter

Team Leader
Professor Deon Venter

Team members
A/Professor Jane Armes, Senior Research Officer
Mr Gareth Price, Senior Research Officer
Ms Thu Nguyen, Research Assistant
Mr Christopher Futter, Honours Student

The Molecular Genetics team uses the latest in GeneChip technology to investigate complex diseases and inherited disorders, with a focus on breast cancer, a diverse disease where women present with a range of cancer subtypes. An understanding of the differences in subtypes will lead to more tailored management of each individual patient.

Inherited disorders cannot always be determined by conventional means and the latest generation of GeneChips offers the potential to assess a person’s genetic makeup at unprecedented levels. We have begun testing the use of high-density GeneChip analysis for rare patient samples that are not easily diagnosed by conventional methods.

Breast cancer and novel combinational use of chemotherapy agents
Chemotherapy agents can be used singularly or in combination, the use of which is dictated by their effectiveness in combating a particular cancer type. If two agents are only partially effective used singularly, they may have synergistic effects when combined. Two novel agents have become available at the MMRI and we intend to first demonstrate their effectiveness individually on laboratory models of breast cancer. Once established we will test the agents in combination to explore their combined mode of action and to return to the clinic the best combination of agent doses and treatment periods for maximal tumour destruction.

We have begun this project by acquiring and testing the characteristics of a number of model breast cancer cell lines. Each cell line was assessed for its baseline rate of growth and cell turnover. This preliminary data will give us the basis for all measurements concerning the use of new chemotherapy agents.

Cytogenetics
Conventional diagnostics in determining inherited disease or other suspected genetic change is sufficient for the majority of routine hospital cases. We are working to increase that majority by reducing the minority of cases where a result cannot be determined by current technologies. This research has two major benefits: firstly it will lead to a better understanding of complex inherited diseases/syndromes and secondly, the incorporation of this technology within the Mater complex will make this one of few sites in Australia, if not the world, that has bridged the gap through research into Pathology via the use of GeneChip Cytogenetics.

We have assessed a number of patients with known, unknown or ambiguous results by currently employed technologies. All known results were replicated fully. Unknown or ambiguous results highlighted the usefulness of GeneChips to explore inherited disorders and to define complex genetic changes such as those observed in high-grade cancers.

Collaborators
A/Professor Paul Mainwaring, Mater Adults Hospital
Professor Rob Richards, University of Adelaide
Professor Rob Saint, Australian National University
Pharmacogenetics of vincristine

Vincristine (VCR) is one of the anticancer drugs used most commonly in children with leukaemia and tumours of solid organs. The dose that can be given is limited by its toxicity to nerve cells which can produce serious neurological side effects. There is great variability between patients in the frequency of side effects and it is possible that in some patients higher doses could be given safely, with a greater anticancer effect.

We are proposing that the way the liver breaks down VCR contributes to the level of drug in the blood stream. If the drug is broken down very rapidly then blood levels will be low and side effects will be rare but in this situation there is also the possibility that the levels may be too low to have the maximum anticancer effect. Children who break down VCR rapidly in their bodies may thus benefit from a higher dose than normal. Conversely, if the drug is broken down very slowly by the liver, then blood levels will be high and there may be greater risk of side effects. These patients may benefit from a lower dose.

In two parallel studies we are measuring the blood levels of VCR and its breakdown products.

- The first is to determine if there are links between these levels and the incidence of side effects.
- The second looks in more detail at the reason why there is such variability between children.

Of relevance to VCR response is the cytochrome P450 (CYP) system that is responsible for the breakdown of many drugs in the liver. A specific form of cytochrome P450, CYP3A5, has been identified as being central to VCR toxicity. Our study will attempt to correlate drug levels in the blood with common CYP3A5 mutations.

The hypothesis is that the 10-20% of patients with a particular profile will have lower blood levels of VCR and for these children there may be the potential to escalate drug doses to achieve maximum benefit.

Pharmacogenetics of thiopurines and antimetabolites

‘Thiopurine’ drugs (Azathioprine and Mercaptopurine) are widely used to treat serious diseases such as childhood leukaemia and auto-immune diseases (eczema, arthritis, inflammatory bowel disease), and for kidney transplants.

Due to genetic variation in the way thiopurines are handled by the body, one in 300 patients given these useful drugs will suffer life-threatening suppression of their immune system. A further 10% of the population are susceptible to unpleasant side-effects if exposed to thiopurines. This study is designed to understand in more detail the reasons for variability in thiopurine tolerance and effectiveness.

In addition we have extended our pharmacogenetic research to cover antiviral drugs that are used in the treatment of the HIV (AIDS) virus. Pharmacogenetic research will thus be important to both adults and young children.

Pharmacogenomics Team

Team Leaders
Professor Ross Pinkerton
Dr John Duley

The basis of pharmacogenetics is the variation between individuals in how they respond to drugs. The genetic variation can be caused by rare mutations, but there are also a large number of very common mutations (polymorphisms) that affect drug response.
Clinical Trials

The MMRI’s Clinical Trials Centre is focused on developing and testing immunotherapy, biological and other cell-based therapies which use the body’s immune system and natural biology to fight diseases including cancer.

Medical practitioners have long suspected the immune system and human biology could be used to manage cancers and other diseases, but it is only within the last few decades that real advances have been made towards new treatments.

Compared to other forms of cancer treatment, such as surgery, radiation therapy, or chemotherapy, immunotherapy and biotherapy are still relatively new forms of treatment.

**Biotherapies** at the MMRI involve stem cell transplantation alone, or in conjunction with dendritic cell (DC) treatment, to improve the repair and recovery and reduce the complications of stem cell or solid organ transplantations.

**Immunotherapy** is the treatment of disease by stimulating the body to correct problems within a patient’s immune system. Immunotherapy can be a stand-alone treatment or used as an adjuvant to the effects of the main therapy.

The keys to our research at the MMRI are dendritic cells (DC), specialist white blood cells responsible for initiating the immune response, and adult stem cells, cells which are capable of regenerating human cells to repair damage to tissue or organs.

We aim to use DC vaccination to either develop new, or boost ineffective, immune responses to fight cancer. As these forms of therapy have not been used before, they must first be tested thoroughly to be sure they are both safe and effective.
Prostate cancer is now the most commonly diagnosed cancer in Australia. Our prostate cancer vaccine offers hope to the 11,000 men diagnosed with the disease in Australia each year.

Dr Rebecca Prue
Project Management Team
Professor Derek Hart – Principal Investigator
Dr Rebecca Prue – Project Team Leader
Dr Peter Swindle – Medical Monitor
Dr Robert Coleman – Clinical Urology Fellow
A/Professor Paul Mainwaring – Advisor
A/Professor Mark Bowles – Deputy Director Operations
Ms Georgina Crosbie – Clinical Trials Nurse

Funded by
United States Army (USA)

Just like breast cancer, men are beginning to develop prostate cancer at a younger age. While prostate cancer is usually one of the slower growing cancers, earlier onset means the disease has an extended period of time to progress and become life-threatening unless diagnosed and treated.

One of the most promising new approaches for effective treatments for late stage prostate cancer (PC) is the use of dendritic cell (DC) vaccines. By modulating the patient’s own immune system using our novel DC based therapies, there is real potential to overcome the patient’s failed immune surveillance and allow the patient’s immune system to attack PC cells.

Prostate carcinoma BDCA-1+ blood dendritic cell (BDC) clinical trial
In 2005 we commenced the first MMRI-led investigator-sponsored trial of DC immunotherapy in PC. This initial Phase I clinical trial uses a BDCA-1 selected BDC preparation to stimulate the patient’s immune system. To date, the vaccine has been well tolerated and we expect to complete the trial in 2008.

Monitoring of immune response following BDC vaccination
As part of the DC vaccine trial program we are developing immunological assays to monitor the generation of immune response in patients following vaccination. These tests will help to determine if the immunotherapy has stimulated the body’s immune system and instructed it to fight the cancer.

Prostate carcinoma CMRF-56+ BDC clinical trial
We will commence a second clinical trial of immunoselected BDC for the treatment of PC in late 2007. This trial utilises the MMRI’s own CMRF-56 antibody, which the DC Antigen Team have engineered into a ‘human’ form to enable more repetitive use in patients.

In partnership with QGEN Pty Ltd we have developed a bioprocess for the production of the cGMP grade antibody for clinical use. This cGMP antibody has been produced and we are currently developing a process for isolating BDC from patients.

Optimisation of the migratory function of immunoselected BDC preparations
A critical requirement for successful DC based immunotherapy is the migration of the DC from the injection site to the sites in the body at which anti-tumour responses are generated. We are currently investigating the migratory potential of CMRF-56+ BDC compared to other DC preparations, the relationship between migration and generation of anti-tumour responses, and are also developing ways to enhance the migratory capacity of the BDC. We aim to confirm the migratory behaviour of BDC isolated from prostate patients as this may be abnormal and require correction.

Collaborators
QGEN Pty Ltd
Miltenyi Biotec
**Multiple Myeloma**

“Multiple Myeloma is a debilitating disease affecting more than 800 people in Australia each year. While the treatment options are currently limited, we hope our proposed dendritic cell vaccine will improve the treatment of this painful and deadly disease.”  
**Dr Frank Vari**

**Team leader**
Dr Frank Vari

**Team members**
Ms Jennifer Freeman

**Funded by**
Leukaemia Foundation of Australia
Perpetual Charitable Planning Services
Golden Casket Foundation

Multiple myeloma (MM) is a rare progressive blood cancer which is almost invariably fatal. It is a malignancy of plasma cells which are normally an important part of the immune system to produce antibodies to help fight infection and disease.

In MM, the plasma cells accumulate in the bone marrow and their abnormal proliferation causes significant bone loss, particularly in the vertebrae, leaving the patient severely handicapped and, if left untreated, in considerable pain. While MM generally affects males and females in their middle age (with the greatest incidence in the 60 to 70 age range), there has recently been incidence of MM increasing in younger people aged 35-45 years.

**Immunoselected CMRF-56+ blood dendritic cell (BDC) clinical trial for MM immunotherapy**

We are currently seeking funding to advance this project to trial. Progress in our laboratory studies has allowed us to optimise CMRF-56 preparation for a Phase I MM immunotherapy trial which will include a number of significant advances, new tumour associated antigen targets, activated DC and possibly tracking of the migration of the DC in patients after treatment.

**Selection of new targets for MM immunotherapy**

With our optimised method for preparing and loading BDC, we have established a number of optimised protocols for generation of both anti-tumour associated antigens and anti-myeloma responses. We are currently validating and selecting a number of approaches for generating anti-myeloma responses, including several candidate MM tumour associated antigens (TAA) based on their ability to generate cytotoxic T cell responses. The study proposed can address different TAA candidates’ flexibility and allows for significant collaborator input. The anticipated outcome will be the optimisation of a portfolio of MM TAA for application in subsequent clinical trials.

In a further study we will establish a number of clinically applicable protocols to reliably generate anti-myeloma responses from patient peripheral blood and bone marrow lymphocytes. These studies will focus on generating and expanding cytolytic T cells (CTL) which can kill myeloma cells using optimal concentrations of cytokines or T cell expander beads (Invitrogen). The outcome from this study will be a method for generating anti-myeloma cytotoxic T cells for use in immunotherapy. We would plan to test whether combining these CTL with DC pulsed with appropriate TAA will improve the ability to delay or eliminate the progression of MM in a murine model. This model is currently being developed by MMRI’s DC Growth and Differentiation team. Future clinical trial protocols for MM immunotherapy will be developed as a result of these studies.
“For bone marrow transplantation patients, every day is critical. Our studies suggest our new method could offer a faster recovery and a better chance of survival.”

A/Prof Kerry Atkinson

Project Management Team
Professor Kerry Atkinson, Principle Investigator
Dr Gary Brooke, Production Manager
Mr Tony Rossetti, Project Management Team Leader
Ms Sonia Hancock, Clinical Research Nurse
Ms Nina Ilic, Quality Manager
Ms Patricia Murray, Quality Officer

Funded by
Inner Wheel Australia
Australian Stem Cell Centre

Phase I multicentre, open label, dose-escalation study of unrelated, MHC-unmatched MSC for the treatment of steroid-refractory acute graft versus host disease (GVHD) in recipients of allogeneic haematopoietic stem cell (HSC) transplants

This study has been submitted to MHS HREC and is a similar design to the trial above. Again in collaboration with the Bone Marrow Transplantation program at the Westmead Hospital, the objective is to determine the safety of MSC in this situation with a view to determining their efficacy in treating or preventing GVHD, currently the most serious transplant-related cause of morbidity and mortality after cord blood and living donor bone marrow transplantation.

Collaborators
Bone Marrow Transplant Unit, Westmead Hospital
**Hepatitis C**

“We are participating in trial testing the ability of dendritic cells to induce immune responses in patients with Hepatitis C.”

**Professor Derek Hart**

**Team leader**
Professor Derek Hart

**Funded by**
National Institutes of Health (USA)

**Hepatitis C Project**

The study is approved as a Clinical Trial Exemption (CTX) by the Therapeutic Goods Administration (TGA). HLA A2-positive patients who are persistently infected with HCV and who have not responded to conventional interferon-based therapy form the cohort. Six patients will be enrolled in this dose escalation trial in which the autologous Mo-DC will be pulsed with lapidated peptides which represent HLA A2-restricted cytotoxic T cell epitopes that have been associated with clearance in some HCV-positive individuals. At present, two patients have been treated; neither suffered any adverse events and both developed HCV-specific T cell responses that appeared to be temporally associated with the injection of the peptide-loaded Mo-DC.

The study, headed by Professor Eric Gowans, is a Phase I safety study and will take place in Melbourne with the major input from the Burnett Institute and the Peter MacCallum Cancer Centre.

---

**Palliative Care**

“Our aim is to improve quality of life for patients with advanced disease, for whom there are limited treatment options.”

**Prof Janet Jardy**

**Team leader**
Professor Janet Hardy

Palliative care is defined as the care of patients with active, progressive, far advanced disease, for whom the prognosis is limited and the focus of care is the quality of life. This includes studies of supportive care and the control of pain and other symptoms commonly experienced by patients with far advanced cancer, along with research aimed at improving the care of patients in the terminal phase of disease.

**The efficacy of Haloperidol in the management of nausea and vomiting in patients with advanced cancer**

Haloperidol is the antiemetic used most commonly in palliative care. A recent systematic review has highlighted the complete lack of evidence to support this practice. This is an open Phase 2 trial designed to assess the efficacy of the drug.

**Funded by**
JP Kelly Research Grant

**A double-blind, dose-ranging study to determine the optimal dose of oral morphine needed to treat breakthrough pain for patients on regular opioids**

This trial running in collaboration with the palliative care team based at Flinders University in Melbourne is designed to identify the most efficacious and best tolerated dose when delivering breakthrough medication to patients requiring extra pain relief.

**Funded by**
JP Kelly Research Grant

**Evaluating novel methods for delivering non-pharmacological interventions for dyspnoea in patients with lung cancer**

There is evidence of benefit of patient education programs including breathing exercises and psychological support for helping lung cancer patients to control their dyspnoea. This study will test the effectiveness of a patient education program.

**Funded by**
National Health and Medical Research Council
2006 has been a year of exceptional achievement for the MMRI that would not have been possible without the support of a dedicated and highly-skilled support team.

**Deputy Director, Operations**

A/Professor Mark Bowles

Behind the scenes at the MMRI, our scientific and executive support, information technology, finance and human resources, research administration, fundraising, and marketing and communications staff keep the wheels of research turning.

Thank you to all the research support and administration staff for their hard work and positive attitude during an exceptionally busy year.

**Executive**

A/Professor Mark Bowles, Deputy Director – Operations

**Administration**

Ms Janine Richards, Research Administration Manager
Ms Marnie Nichols, Marketing and Communications Officer
Mr Justin Sharp, Company Secretary

**Executive Support**

Ms Cara Boehm, Executive Assistant
Ms Jenny Lucas, PA to the Director
Ms Megan Winter, Receptionist / Administrative Assistant

**Finance and Human Resources**

Ms Hong-Yi Ong, Executive Officer – Finance and Human Resources
Mrs Cathryn Murray, Finance Officer
Ms Kathryn Peel, Finance Officer

**Scientific Support**

Mr Paul Turley, Laboratory Manager
Ms Ann Burns, Annex Manager
Mr Robert Wadley, Flow Cytometry Technician
Ms Phillip Matthews, Laboratory Operator
Ms Nicola Greer, Tissue Culture Technician
Ms Diane Lee, Laboratory Assistant
Ms Elaine Rattray, Annex Assistant
Ms Emma Rattray, Assistant Laboratory Technician

**Information Technology**

Mr Norbert Konecki, Senior IT Officer
Mr Quentin Morley, IT Officer
Symposia + Seminars

The MMRI believes the continued development of researchers will aid scientific discovery. Each year the Institute hosts two scientific symposia and weekly seminars for leading scientists from Australia and around the world to present their findings. Invitations to these events are open to any interested scientists or clinicians.

8th Annual DC Symposium
“Antigen Processing”
13-14 July 2006
Keynote Speaker: Professor Ken Shortman, Walter and Eliza Hall Institute of Medical Research

3rd Annual Stem Cell Symposium
“Basic Science and Clinical Application of Mesenchymal and Haematopoietic Stem Cells”
9-10 March 2006
Keynote Speaker: Professor Robert Negrin, Stanford University, USA

MMRI Seminar Series 2006

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<thead>
<tr>
<th>Date</th>
<th>Speaker</th>
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<tr>
<td>2/3/06</td>
<td>Ellen Kreijveld</td>
<td>The new immunosuppressive drug FK778 induces regulatory activity in CD4+CD25- T-cells</td>
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<td>31/3/06</td>
<td>Dr Penny Jeffery</td>
<td>The autocrine/paracrine roles of the growth hormone-releasing peptide ghrelin and its cognate receptor in hormone-dependent cancer</td>
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<td>Professor Alfred Lam, Griffith University</td>
<td>Molecular pathology of thyroid cancer</td>
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<td>Professor Hans Ringherz, Nobel Prize Committee Radiology</td>
<td>Characterisation of a novel selective PPARgamma modulator with insulin sensitizing and glucose lowering properties</td>
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<td>21/4/06</td>
<td>Professor George Muscat, IMB</td>
<td>The biology of CA125, a cell-surface mucin, in ovarian cancer immune evasion and progression</td>
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<tr>
<td>28/4/06</td>
<td>Ryan Parlett, MMRI</td>
<td>The biology of CA125, a cell-surface mucin, in ovarian cancer immune evasion and progression</td>
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<td>12/5/06</td>
<td>Dr Scott Burrows, IMB</td>
<td>Epitope selection in the cytotoxic T cell response to viral infection</td>
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<td>26/5/06</td>
<td>Dr Josephine Bowles, IMB</td>
<td>Retinoid signalling determines germ cell fate in mice</td>
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<td>2/6/06</td>
<td>Dr Arne Mould, QIMR</td>
<td>Analysing the function of VEGF-B using transgenic and knockout mouse models.</td>
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<td>9/6/06</td>
<td>A/Professor Alpha Yap, IMB</td>
<td>A cadherin users’ manual: cadherin signalling and the actin cytoskeleton</td>
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<td>16/6/06</td>
<td>Dr Stephen Wood, Child Health Research Institute</td>
<td>The cell biology of USP9X - a “stemness” gene</td>
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<td>23/6/06</td>
<td>Dr Alex Loukas, QIMR</td>
<td>Vaccines against blood-feeding worms</td>
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<td>30/6/06</td>
<td>Dr David Pennisi, IMB</td>
<td>Patterning events in the developing heart</td>
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<td>7/7/06</td>
<td>Lisa Freeman, MMRI</td>
<td>The regulation of immunosuppressive steroids by human monocyte-derived dendritic cells</td>
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<tr>
<td>21/7/06</td>
<td>Dr Jos Malda, QUT</td>
<td>Hypoxia in Tissue Engineering: Friend or Foe?</td>
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<td>4/8/06</td>
<td>Professor Tim Hirst, University of Bristol, UK</td>
<td>Harnessing the properties of cholera-like enterotoxins to create new medicine</td>
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<td>11/8/06</td>
<td>Professor Andreas Suhrbier</td>
<td>The accelerated degradation of retinoblastoma protein mediated by HPV-E7 requires the cystein protease Calpain</td>
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<td>1/9/06</td>
<td>Dr Rajaraman Eri, MMRI</td>
<td>T cell inhibitory small molecule in the treatment of autoimmune diseases.</td>
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<td>8/9/06</td>
<td>Professor Kerry Atkinson, MMRI</td>
<td>Preclinical and clinical studies with mesenchymal stem cells</td>
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<td>15/9/06</td>
<td>Dr Michael Kershaw, Peter MacCallum Cancer Centre</td>
<td>Supernatural T cells in immunotherapy</td>
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<td>29/9/06</td>
<td>Dr Alison Pettit, IMB</td>
<td>Osteoimmunologic mechanisms in bone physiology and disease</td>
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<td>3/11/06</td>
<td>Dr Graham Leggatt, CICR</td>
<td>CD8 T cell tolerance to HPV16E7 protein expressed in epithelial cells</td>
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<td>10/11/06</td>
<td>Dr Zia Mollah, CICR</td>
<td>Abnormal regulation of SHP-1 and NF-kB characterises antigen presenting cells in type 1 diabetes</td>
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<td>24/11/06</td>
<td>Dr Helen Blanchard, Griffith University</td>
<td>Structural investigation of the Rotavirus spike protein carbohydrate-recognising domain VP8* from Sialidase-sensitive and insensitive strains</td>
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<tr>
<td>01/12/06</td>
<td>Dr Tara Roberts, IMB</td>
<td>Cellular activation by cytoplasmic dsDNA - identification of a novel viral detection system</td>
</tr>
<tr>
<td>08/12/06</td>
<td>Dr Wendy Blanshard, Seaworld</td>
<td>Applied Immunology: Respiratory disease in captive koalas</td>
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</table>
Students are our future. Therefore it is essential they are adequately trained, mentored and nurtured to ensure the continued success and progress in unearthing the secrets that science holds.

Since the MMRI was founded in 1998, it has established a vibrant student population.

Throughout 2006 the Institute has hosted 25 PhD, Honours and Masters students and our numbers are frequently boosted by student visitors from interstate and overseas.

**Studying at MMRI is a solid grounding in research...**

MMRI PhD student Brie Turner is in the final stages of writing up her thesis on graft versus host disease (GVHD), finding that the successful application of DC depletion to control GVHD would improve the safety of stem cell transplantation for patients with leukaemia and extend the immune benefits of this curative therapy to the wider patient population.

According to Brie, the most valuable lesson she has learnt while working at the Institute is to trust her instincts.

“I have gained an enormous amount of confidence since starting here a little over four years ago,” Brie says.

“What I like most about the MMRI is that it is small, almost like a family, you can ask anyone questions and there is a lot of time with supervisors and other senior scientists.”

“The friendships I have formed here will last a lifetime; the people that I work with here at the MMRI are what make the place so special.”

While Brie describes the end of her PhD as a ‘whirlwind’ and is still considering her future, she knows she would like work overseas.

**Former MMRI PhD student, Julie McAuley, has done exactly that, and is now working at the internationally-renowned St Jude Children’s Research Hospital, in Memphis, Tennessee.**

Julie credits her experience as a student at the MMRI as being a major factor in securing such a sought-after position overseas. She says the way research is conducted at the MMRI helped her build her research skills and, consequently, her career.

“At the MMRI, people are willing to collaborate, share knowledge and assist in anyway possible. The resources available to me at the MMRI I realise now really were world class and I still use many of the techniques that were taught to me at the MMRI.

“Without the guidance of my supervisor, Mike McGuckin, to give me the confidence to get out there and network, or the ample opportunities that I was given to talk about my work, I would have never wound up at St Jude.”

Julie completed her PhD in the mucin research team at the MMRI in 2005. Julie discovered that the cell surface mucin (MUC1) is involved in protecting the epithelial cell barrier from infection and invading pathogens. Her finding has been important in the ongoing work of the mucin team at the MMRI and has been published in the Journal of Clinical Investigation.

Focused on understanding the relationship of influenza-bacterial synergism in the context of infection of the host, Julie now works with world-renowned scientists such as John McCullers, Richard Webster, Erich Hoffman and Richard Webby who have developed many of the techniques that are used to study influenza around the world.

Julie is still planning her next career move, but hopes to carve out a research niche to focus on… preferably in an exotic location! But wherever her career takes her, Julie admits she will always fondly recall her days at the MMRI, particularly relaxing on the balcony on a Friday afternoon, chatting with friends and enjoying the start to the weekend.

“For an institute that is relatively young and still growing, the MMRI produces great work. It is filled with people that create a great work environment and it was a pleasure to have been a student at the MMRI.”

**2006 Education Committee:**

Dr Georgina Clark (Chair January – October 2006)
Dr Steven McTaggart (Chair November 2006 onwards)
A/Professor Jean-Pierre Levesque (joined November 2006)  
Dr Gary Brooke
Ms Janine Richards (Research Administration Manager)  
Mr John Wilson (Student Representative)
Dr Sara Linden
A Message from Nigel Harris
Executive Chairman, Mater Foundation

The Mater Foundation is committed to investing in a future of exceptional health care and medical research by raising funds and harnessing community support for Mater Health Services and the Mater Medical Research Institute.

Since the Mater was established by the Sisters of Mercy medical research has been regarded as an integral component of high quality patient care.

Today, as scientific discovery paves the way for better treatment, faster diagnosis and cures for life-threatening and debilitating diseases, the Mater’s commitment to research remains as strong as ever.

So does the Mater Foundation’s commitment to funding research programs and I am proud to say that in 2006 the Foundation raised more than $512,000 for the MMRI.

The Mater Foundation’s support for the MMRI comes from individual, corporate and community donors. Some of the highlights of 2006 included:

- Ongoing support of prostate cancer research by Lions Clubs of Australia;
- More than $60,000 received from individuals who chose to support a future of exceptional health care by leaving a bequest in their will;
- Significant donations made by the Pradella family, Mr Leo White, Hutchinson Builders and Mary Ryan’s;
- And a large contribution made through trusts and foundations including a $95,000 commitment from Perpetual Trustees.

Over several years one area which has attracted much support from the community has been MMRI’s world-leading research into prostate cancer. In 2006, MMRI took the next step in developing this exciting research with the commencement of a Phase I clinical trial. This trial represents years of dedication by MMRI scientists and is just one example of how community support plays a vital role in medical research.

There is a growing trend in philanthropic support for the MMRI as many of our donors recognise that one of the most significant ways they can invest in a future of exceptional medical care is to support research. The support from philanthropic donors often provides the seed funding to start new research projects and provides people like Sarah Bowe, Michael Nichols and the Skinner family, whose stories feature in this annual report, hope for a brighter future.

I’d like to take this opportunity to thank all of our donors and supporters who gave so generously to the MMRI in 2006. I’d also like to take this opportunity to thank Professor Derek Hart and the MMRI for their commitment to world-leading research which we at the Mater Foundation are so proud to support.

We look forward to continuing to work with the MMRI in the coming years.

Nigel Harris
Executive Chairman
Mater Foundation
Prostate Cancer Vaccine

Michael Nichols’ personal experience with prostate cancer has made him realise the importance of the research conducted at the Mater Medical Research Institute (MMRI).

“My father passed away from metastatic prostate cancer in November 1994 at the age of 78,” says Michael.

“Then I was diagnosed with prostate cancer in 2003 and had a prostatectomy at the Mater in February 2004.”

While Michael is now doing extremely well and his follow-up tests have given him the all clear, the family history of prostate cancer makes him think about his sons and grandson.

“Medical research is imperative for improving treatment options for prostate cancer, as well as many other diseases. The work being done at the MMRI may just save the life of one of my boys down the track, not to mention thousands of other men around the world.”

The MMRI took a critical step in its world-leading research into developing a prostate cancer vaccine in 2006 with the commencement of a Phase I clinical trial.

Lead researcher Dr Rebecca Prue says the trial, which combines the scientific and medical expertise of the MMRI and the Mater hospitals, should give hope to the one in 10 men who develop prostate cancer each year.

“The research is based on the concept that a man’s own immune system could be the key to a cure for prostate cancer,” says Dr Prue.

The body contains specialised white blood cells, called dendritic cells (DC), which initiate the immune response. These cells direct the body’s fight against invaders like bacteria or foreign bodies, but they don’t always work effectively against cancer.

In MMRI’s vaccine trial, researchers extract DCs from the patient and ‘train’ them to instruct the body to destroy prostate cancer cells.
12 patients will be involved in the Phase I clinical trial, which is designed to test the safety of the vaccine.

“This trial is so exciting because the research has great potential,” says Dr Prue.

“I believe there is no better way to treat people than by using their own immune system. It’s like teaching the body to heal itself.”

While the research is still in the early stages, Dr Prue says to date the results have been very encouraging and the MMRI is eagerly awaiting the outcome of the trial.

“Construction Income Protection Queensland (CIPQ) has supported the MMRI, raising more than $100,000 for prostate cancer research over the last two years at their annual lunch.

Established in 2001, CIPQ provides income protection and portability of sick leave benefits for workers in the building and construction industry.

CIPQ General Manager Bill Wallace says they couldn’t think of a better organisation to support than the MMRI.

“We wanted the lunch to bring members of the building and construction industry together to build awareness and support for medical research into prostate cancer at the Mater,” says Mr Wallace.

“Plans are already underway for next year’s lunch where we hope to attract 500 people,” says Mr Wallace.

“The work being done at the MMRI may just save the life of one of my boys down the track, not to mention thousands of other men around the world.”
Kellie and Michael Skinner describe the weeks after discovering their unborn child had severe kidney damage as a ‘rollercoaster of emotion’. 

Kellie says a routine ultrasound at 18 weeks gestation revealed their baby Frank had swollen kidneys due to an excess build-up of urine.

“Over the next 14 weeks the prognosis ranged from positive to dire and eventually settled somewhere in the middle,” says Kellie.

“Doctors were proactive in trying to salvage Frank’s kidney function, performing numerous procedures in-utero to drain the excess urine before he was delivered at 32 weeks gestation.”

“It was expected Frank would require dialysis before his first birthday, but he managed with 20 percent kidney function until three years of age.”

In 2006, Frank’s kidney function was dropping and Frank’s dad Michael decided to donate one of his own kidneys to his son.

“Although the operation initially went well, we spent several months in the Mater with complications relating to the transplant, as well as battling a few viruses,” says Kellie.

The good news is Frank is doing extremely well and Michael’s precious gift means he now has a bright future ahead of him.

According to Frank’s specialist and MMRI researcher Dr Steve McTaggart, complications following organ transplantation are common.

“For many kidney transplant recipients the remaining hurdle following their operation is a dependence on immunosuppressive medications to prevent rejection of the kidney,” says Dr McTaggart.

The MMRI is working to develop promising new treatments to overcome this final hurdle by investigating how adult stem cells can be used to repair and protect transplanted organs and prevent rejection.

“Research has shown that when mesenchymal stem cells (MSCs), a particular type of adult stem cell known to repair tissue damage, are injected into the blood stream they preferentially travel to transplanted kidneys,” says Dr McTaggart.

“Our findings indicate that MSCs may improve the long-term success rate of kidney transplants by helping to prevent rejection, reducing the demand for donor kidneys and leading to a shorter wait time for those in need of a transplant.”

Kellie and Michael Skinner say they will be forever grateful to the Mater for the care provided to Frank. They hope that breakthroughs made possible by the MMRI will help the 1,500 Australians currently awaiting kidney transplantation to also receive this life-saving gift.

Real estate entrepreneur Patrick Dixon’s love for the Brisbane River and appreciation for medical research led him to create a book, 150 years of Brisbane River Housing, with a goal to raise $225,000 for the MMRI.

Launched in 2004, the river book tells the story of Brisbane’s unique residential riverscape.

“The MMRI’s work is imperative for everyone and we couldn’t think of a better recipient to benefit from a book about our river, the lifeblood of our city,” says Mr Dixon.

The river book has been fully funded by Dixon Partners Quality Property enabling the entire sale price of the book, which retails for $50, to be donated to the MMRI.

“The creation of the river book would not have been possible without the support of photographer David Millar, artist Glenda Holyoake and the property owners whose homes are featured in the book,” says Mr Dixon.

To date more than $108,000 has been raised for the MMRI through the sale of the book.
Kellie and Michael Skinner hope that breakthroughs made possible by the MMRI will help the 1,500 Australians currently awaiting kidney transplantation to also receive this life-saving gift.
Breast Cancer Hope

Dr Kristen Radford and her team at the MMRI are bringing hope to the thousands of women who are diagnosed with breast cancer each year.

Women like Sarah Bowe who was diagnosed with breast cancer in 2005, at the age of 36.

“It was such a shock,” says Sarah. “You hear of young women having breast cancer, but you never think you will be one of them.”

It is now almost a year since Sarah completed her treatment and everything is going well.

When Sarah found out she had breast cancer she was not alone. In Australia each year more than 11,000 women are diagnosed with the disease.

The MMRI researchers are in the pre-clinical stages of developing a new dendritic cell or immunotherapy treatment that they hope could one day stop breast cancer in its tracks.

“Dendritic cell vaccines work by effectively re-training the immune system to seek out and attack the cancer in the same way it would attack a cold or flu,” says Dr Radford.

“Cancer cells are good at hiding from the immune system. Our strategy is to introduce the dendritic cells to cancer proteins in the lab and inject them back into the patient so the body will recognise them in the future and know how to attack them.”

The development of the immunotherapy treatment hinges on the number of cancer-specific proteins scientists are able to identify. A novel technique being developed by the MMRI will enable researchers to find proteins critical to breast cancer immunotherapy more quickly, testing up to 2,000 genes in a matter of weeks.

“The new technique for finding these proteins is dramatically faster, which means we could potentially have a treatment available for patients sooner than we thought,” says Dr Radford.

“While our research is in its early stages, we hope that the treatment could eventually be given to patients following surgery to prevent the cancer recurring.”

Sarah Bowe says having breast cancer and being the mother of a three-year-old daughter have made her realise the importance of medical research.

“Until you or someone close to you has a serious illness I don’t think you appreciate how important the search for a cure is,” says Sarah. “MMRI researchers are at the forefront of the battle against these terrible diseases.”

Former breast cancer and melanoma patient Maureen McGrath has also been touched by her personal experience with cancer and is investing in the health of future generations by leaving a bequest in her will to the MMRI.

“The Mater has always been our ‘family’ hospital and I always planned to remember the Mater in my will,” says Maureen.

“Since having cancer, and benefiting from the care of the Mater Hospitals, I know how important it is to increase knowledge about these diseases.”

According to Mater Foundation’s Executive Director Nigel Harris, Maureen is part of a special group of people who have chosen to support the Mater by leaving a bequest in their will.

“Support like Maureen’s can make all the difference in bringing about new treatments for cancer and other diseases. Giving a gift in your will is an amazingly generous act – and one we are enormously grateful for.”
“Until you or someone close to you has a serious illness I don’t think you appreciate how important the search for a cure is. MMRI researchers are at the forefront of the battle against these terrible diseases.”
## Donor List

### $50000 +

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<td>The Lions Club of Brisbane Hellenic $5,000.00 Mary Ryan's</td>
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<td>A &amp; P Irvine $5,000.00 Lewis Media</td>
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<td>Miriam Devine $2,000.00 Clive Hildebrand</td>
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<td>Brookwater Golf Club $1,100.00 The Waller Unit Trust</td>
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<td>Campbell Brothers Limited $1,100.00 Lionel Morris</td>
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<td>Ladies of Rugby $500.00 Lions Club of Mitcham</td>
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<td>Opus Capital Limited $500.00 Lions Club of Inverell MacIntyre</td>
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<td>McDonald Balanda &amp; Assoc $500.00 Lions Club of Healsville</td>
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<td>Lions Club of Ulverstone $500.00 Lions Club of Glenside</td>
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## Patents

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<th>Countries</th>
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<tr>
<td>PCT/AU03/01038</td>
<td>A method of immunomodulation</td>
<td>15/08/2003</td>
<td>Australia, Canada, Europe, New Zealand, United States</td>
<td>Under Examination, Pending, Under Examination, Pending</td>
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<td>PCT/AU03/01011</td>
<td>A method of immunomodulation</td>
<td>8/08/2003</td>
<td>Australia, Canada, Europe, New Zealand, United States</td>
<td>Under Examination, Pending, Under Examination, Under Examination, Pending</td>
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<td>PCT/AU03/01040</td>
<td>A method of characterising dendritic cells</td>
<td>15/08/2003</td>
<td>Australia, Canada, Europe, New Zealand, United States</td>
<td>Under Examination, Pending, Under Examination, Pending</td>
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<td>PCT/AU03/01113</td>
<td>Generation of dendritic cells from cD34+ precursors</td>
<td>29/08/2003</td>
<td>Australia, Canada, Europe, New Zealand, United States</td>
<td>Under Examination, Pending, Under Examination, Pending</td>
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<td>PCT/AU03/01586</td>
<td>Therapeutic and diagnostic agents</td>
<td>28/11/2003</td>
<td>Australia, Canada, Europe, New Zealand, United States</td>
<td>Under Examination, Pending, Under Examination, Pending</td>
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<td>PCT/AU03/01634</td>
<td>DEC-205 (ly 75)/DCL-1 intergenic splice variants associated with Hodgkin's disease, and uses thereof</td>
<td>5/12/2003</td>
<td>Australia, Canada, Europe, New Zealand, United States</td>
<td>Under Examination, Under Examination, Pending, Under Examination, Pending</td>
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<td>PCT/AU03/01647</td>
<td>In vitro immunisation</td>
<td>9/12/2003</td>
<td>Australia, United States</td>
<td>Under Examination, Pending</td>
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<td>PCT/AU04/001493</td>
<td>Isolated CD4+ T-cell defined by CMRF-35 and CD45RO</td>
<td>28/10/2004</td>
<td>Australia, Europe, United States</td>
<td>Pending, Pending, Pending</td>
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<td>PCT/NZ97/00068</td>
<td>Dendritic cell receptor</td>
<td>29/05/1997</td>
<td>Australia, Europe, France, Germany, New Zealand, Switzerland, United Kingdom, United States, Japan</td>
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<tr>
<td>Application No.</td>
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<td>Filing Date</td>
<td>Countries</td>
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<td>PCT/AU01/00930</td>
<td>Mucin</td>
<td>27/07/2001</td>
<td>United States</td>
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<td>PCT/NZ97/00133</td>
<td>Enzyme having S-adenosyl-L-homocysteine hydrolase (AHCY) type activity</td>
<td>4/10/1997</td>
<td>Australia, Europe, France, Germany, Japan, New Zealand, United Kingdom, United States</td>
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<td>PCT/NZ97/00134</td>
<td>Dendritic cell-specific antibodies</td>
<td>9/10/1997</td>
<td>Australia, Europe, France, Germany, Italy, Japan, New Zealand, Sweden, Switzerland, United Kingdom, United States</td>
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<td>PCT/AU00/01486</td>
<td>Dendritic cell-specific antibodies</td>
<td>1/12/2000</td>
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<td>PCT/AU02/01512</td>
<td>A method of treatment and agents useful for same</td>
<td>24/10/2002</td>
<td>Australia, Canada, Europe, Hong Kong, Japan, New Zealand, United States</td>
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<td>PCT/AU02/01761</td>
<td>Novel polynucleotides and uses</td>
<td>24/12/2002</td>
<td>United States</td>
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<td>PCT/AU02/01610</td>
<td>Method for culturing dendritic cells</td>
<td>26/11/2002</td>
<td>Australia, New Zealand, United States</td>
<td>Under Examination, Pending, Pending</td>
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<td>PCT/AU05/001864</td>
<td>Binding partners of antibodies specific for dendritic cell antigens</td>
<td>9/12/2005</td>
<td>International</td>
<td>Pending</td>
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</table>
Publications

Journal Articles 2006


Tait DM and Hardy J. Consent for investigating and treating adults with cancer. *Clinical oncology (Royal College of Radiologists (Great Britain))*. (2006) **18**: 23-29.


**Book Chapters**


**In Press**


## Grants

### External Research Grant Funding 2006

<table>
<thead>
<tr>
<th>Funding Body</th>
<th>Chief Investigators</th>
<th>Title</th>
<th>Years</th>
<th>Total Funding Amount</th>
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<tbody>
<tr>
<td>Australian Red Cross Blood Service</td>
<td>Ms Melinda Dean</td>
<td>How Mannose Binding Lectin interacts with and affects the function of antigen presenting cells</td>
<td>2004-2006</td>
<td>$30,000.00</td>
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<tr>
<td>Australian Stem Cell Centre</td>
<td>Professor Kerry Atkinson</td>
<td>Determination of molecular homing mechanisms of mesenchymal stem cells to infected myocardium and assessment of impact on cardiac function</td>
<td>2006-2008</td>
<td>$738,444.00</td>
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<td>Golden Casket Foundation</td>
<td>Dr Steven McTaggart</td>
<td>The role of HLA-G in dendritic cell-mediated production of regulatory T cells</td>
<td>2005-2006</td>
<td>$22,000.00</td>
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<td>Inner Wheel Australia</td>
<td>Professor Kerry Atkinson Professor Derek Hart</td>
<td>Co-transplantation of umbilical cord blood cells with human mesenchymal stem cells in order to accelerate platelet and neutrophil recovery posttransplant</td>
<td>2006</td>
<td>$65,000.00</td>
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<tr>
<td>John P Kelly Foundation</td>
<td>Dr Janet Hardy</td>
<td>The Efficacy of Haloperidol in the Management of Nausea and Vomiting in Patients with Advanced Cancer</td>
<td>2006</td>
<td>$15,000.00</td>
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<tr>
<td>Kidney Health Australia</td>
<td>Dr Steven McTaggart Dr Christopher Tracey</td>
<td>Induction of Renal Allograft Tolerance via Administration of Tolerogenic Dendritic Cells</td>
<td>2006</td>
<td>$15,000.00</td>
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<td>National Health and Medical Research Council</td>
<td>Professor Derek Hart Dr David Munster Dr Alison Rice Professor Kenneth Bradstock</td>
<td>Activated Dendritic Cell Monoclonal Antibodies as Therapeutics to Prevent Graft Versus Host Disease</td>
<td>2004-2006</td>
<td>$432,750.00</td>
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<td>National Health and Medical Research Council</td>
<td>A/Professor Jean-Pierre Levesque</td>
<td>Role of neutrophil proteases and their inhibitors in haemotopoietic stem cell mobilisation</td>
<td>2004-2006</td>
<td>$472,750.00</td>
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<td>National Health and Medical Research Council</td>
<td>Professor Derek Hart Dr Kristen Radford</td>
<td>Cytokine production by human dendritic cells - Is less more?</td>
<td>2006-2008</td>
<td>$369,936.00</td>
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<td>National Health and Medical Research Council</td>
<td>Dr Masato Kato Professor Derek Hart</td>
<td>Biology of the novel C-Type lectin receptor DCL-1 in innate and adaptive immune response</td>
<td>2005-2007</td>
<td>$431,550.00</td>
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<td>National Health and Medical Research Council</td>
<td>Dr Ingrid Winkler A/Professor Jean-Pierre Levesque</td>
<td>Role of selectins and their receptors in the regulations of the haemopoietic system</td>
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<td>National Health and Medical Research Council</td>
<td>A/Professor Michael McGuckin Phillip Sutton Victoria Korolik A/Professor Timothy Florin Dr Sara Linden</td>
<td>Mucins in Gastrointestinal Barrier Function</td>
<td>2006-2008</td>
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<td>National Institutes of Health (USA)</td>
<td>Dr Eric Gowans Professor Derek Hart</td>
<td>Immunotherapy of Hepatitis C Virus Infection</td>
<td>2003-2006</td>
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<td>Perpetual Charitable Planning Services</td>
<td>Dr Alison Rice</td>
<td>Immunotherapy to treat children who relapse with leukaemia after transplantation</td>
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<td>Queensland Cancer Fund</td>
<td>Professor Derek Hart Dr Frank Var</td>
<td>A clinical trial of a biological treatment for multiple myeloma</td>
<td>2006</td>
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<td>Queensland Cancer Fund</td>
<td>Dr Kristen Radford Dr Ray Wilkinson Dr Peter Swindle</td>
<td>Selection of prostate-derived kallikriens for dendritic cell immunotherapy</td>
<td>2005-2006</td>
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<td>Queensland Cancer Fund</td>
<td>Dr Alison Rice Professor Ross Pinkerton Beverley Kerr</td>
<td>Fanning the fire: combination immunotherapy to treat relapsed leukaemia post transplant</td>
<td>2006-2007</td>
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<td>Queensland State Government - Growing the Smart State PhD Funding</td>
<td>Mr Ben Jones</td>
<td>The Role of Mesenchymal Stem Cells in Attenuation of Solid Organ Allograft Rejection</td>
<td>2006-2008</td>
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<td>Susan G. Komen Breast Cancer Foundation (USA)</td>
<td>Professor Derek Kennedy, Professor Derek Hart</td>
<td>Developing anti-breast cancer therapies based on G3BP</td>
<td>2006-2008</td>
<td>$247,478 (USD)</td>
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<td>United States Army (USA)</td>
<td>Professor Derek Hart, Dr Rebecca Prue</td>
<td>A Phase I Clinical Trial of a CMRF-56+ Blood Dendritic Cell Preparation for the Immunotherapy of Metastatic Hormone Refractory Prostate Cancer</td>
<td>2005-2006</td>
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**PhD Scholarship**

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<tr>
<td>Leukaemia Foundation of Australia</td>
<td>Ms Jennifer Freeman</td>
<td>Further definition of the tumour antigen targets for DC based immunotherapy in multiple myeloma</td>
<td>2005-2007</td>
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<td>Leukaemia Foundation of Australia</td>
<td>Mr Andy Hsu</td>
<td>Proof of Principle for the use of CTL induced by RNA loaded CD34+ stem cell derived DC to eradicate leukemia post transplantation</td>
<td>2005-2007</td>
<td>$120,000.00</td>
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<tr>
<td>Leukaemia Foundation of Australia</td>
<td>Ms Courtney Modra</td>
<td>Potential new target molecules for AML treatment: the role of the 35-L5 molecule</td>
<td>2005-2009</td>
<td>$120,000.00</td>
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<td>National Health and Medical Research Council (Dora Lush)</td>
<td>Mr Ben Jones</td>
<td>Mechanisms of Indoleamine 2,3-deosygenase mediated immunosuppression by mature Dendritic Cells</td>
<td>2006-2007</td>
<td>$42,462.00</td>
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<td>ANZ Trustees</td>
<td>Mr Chad Heazlewood</td>
<td>Biochemical and Physiological Characterisation of Muc2 mutant mice</td>
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**Fellowship**

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<td>Leukaemia Foundation (UK) Marie Curie</td>
<td>Dr Hannah Cullup</td>
<td>An investigation of host and donor DC modulation in GVHD through the use of comparative in vitro (human) and in vivo (chimeric human/murine) models</td>
<td>2005-2006</td>
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<td>Leukaemia Research Foundation (UK)</td>
<td>Dr Lisa Freeman</td>
<td>Priming and enhancement of immunity to tumours using in vivo strategies</td>
<td>2006-2008</td>
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<td>National Health and Medical Research Council (Peter Doherty)</td>
<td>Dr Penny Jeffery</td>
<td>Cell Surface Mucins modulate epithelial cell growth and apoptosis of normal mucosal wound repair and epithelial cancers</td>
<td>2006-2009</td>
<td>$264,000.00</td>
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<td>Queensland Cancer Fund</td>
<td>A/Professor Jean-Pierre Levesque</td>
<td>Basic Biology of the haematopoietic system and therapeutic applications for the treatment of cancers</td>
<td>2006-2010</td>
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<td>Queensland Cancer Fund</td>
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<td>Cell Surface Mucins in Adenocarcinomas</td>
<td>2003-2007</td>
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