MALAGHAN INSTITUTE OF MEDICAL RESEARCH | ANNUAL REPORT 07

The Malaghan Institute is New Zealand's only independent medical research institute and is a charitable trust.

Our scientists are dedicated to the prevention and treatment of cancer, asthma, arthritis, multiple sclerosis and infectious diseases.

At the Malaghan Institute we believe that the key to fighting illness lies in harnessing the immune system, the body's own natural defence against disease. Increasingly we are able to apply new insights into how immune reactions are triggered and controlled at a molecular level, including clues for how specific aspects of the immune response are governed by the genes within cells. As we increase the depth of our understanding of the immune system the potential benefits for New Zealanders are limitless. In addition to our drive for making discoveries, the Institute is committed to the development of New Zealand scientists and clinicians.

The Institute has an international reputation as a cutting-edge medical research and training facility, housing New Zealand's brightest and most creative scientists, doctoral students and post-doctoral fellows. To ensure that the vital research at the Institute persists, we rely on contestable grants, corporate sponsorship, trusts, bequests and donations.

Over the last 30 years, the Malaghan Institute has built an international network of collaborators and supporters who are helping us combat the diseases that affect New Zealanders. Working with these worldwide organisations ensures that our scientists keep abreast of the latest developments in the international arena, thus maintaining our research at a world class level. On a national scale, whilst still preserving our independent status, the Institute works closely with tertiary institutions, Crown Research Institutes, hospitals and clinics throughout New Zealand.

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CHAIRMAN'S REPORT

Each year I have to acknowledge the efforts of so many... they all continue to inspire me, and I believe themselves, on the journey that we are on.

The Malaghan Institute has grown to a stage where the Trustees recognise that the calibre and size of the staff, combined with their world class research, needs underpinning with a new and secure financial base.

In September the Institute was hosted at a function at Government House Wellington by Their Excellencies the Honourable Anand Satyanand, Governor General of New Zealand, and Mrs Susan Satyanand, at which time I was able to address some 300 supporters from around the country.

At that event I announced the Trustees intention to embark on a Capital raising mission and to seek greater security around our core funding, hence giving greater certainty to our research programmes.

Work on developing the ways we can proceed on that challenge has commenced, and we have established a new Trustee committee, chaired by Gary Quirke, resourced from the Director's staff.

We will look to the government to provide some capacity funding based on a similar model to the funding of independent research institutes in Australia, which are similar to ourselves. This will no doubt take some time, and the options as to how funding is provided will need to be carefully considered so that the independent approach to our research continues.

During the year we were made aware of several additional sources of future funding. Firstly we have been advised that the Taylor family have made available some $500,000 to support our cancer research. This is a fund to recognise that it is some ten years since the passing of Keith Taylor, a very able and energetic member of the Trust Board, and we are very appreciative of this philanthropic gesture.

Secondly, a sum of some $500,000 is being made available by an American citizen who graduated from Victoria University and is a strong supporter of cancer research. Much of the contact with this generous

CHAIRMAN'S REPORT

benefactor has been the work of trustee Bryan Johnson and the Victoria University Foundation, and we are very grateful for their efforts.

Late in the year our Director was invited to attend a conference on melanoma research in Washington DC. This was a very special invitation, as was discovered on attendance, in which we were part of a select group being asked as to what we could deliver from our research. We anticipate that this may well be another valuable opportunity to develop our research efforts in collaboration with others.

During the coming three years or so, we will be concentrating on growing the Capital Endowment Fund of the Institute. This fund captures gifts and bequests that are separately invested in income earning securities, under the watchful eyes of our advisor David Wale and our Investing subcommittee of the Trust Board chaired by Dan Williams. You may sight the details of this fund in this report.

This fund is the cornerstone of the Institute's independence and allows Trustees to ensure funding is available to the support functions of the Institute, and also to the Director, to allow the development of specific programmes and researchers.

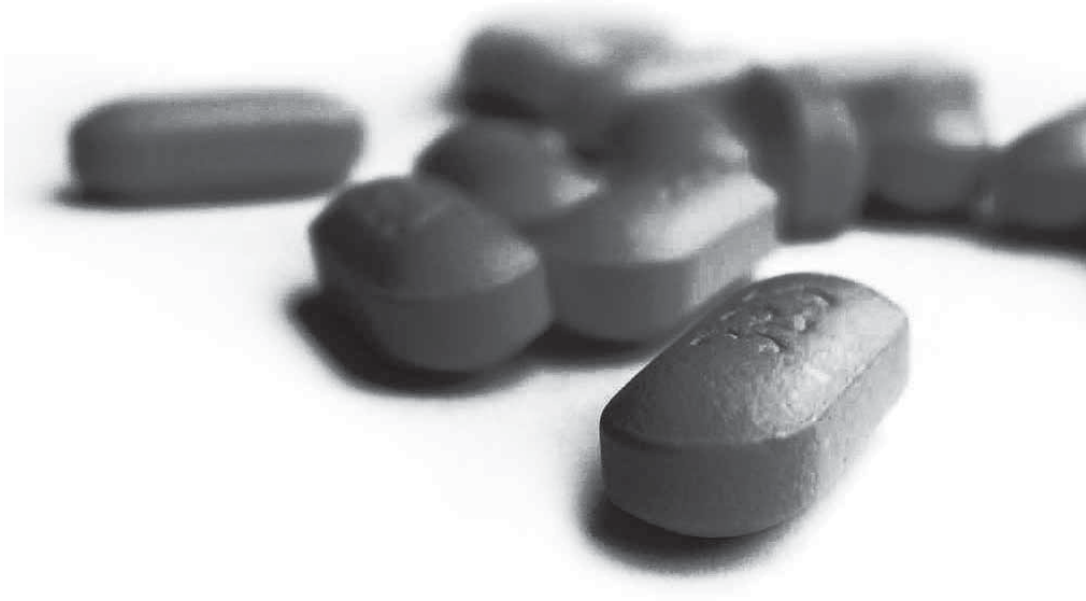
To be of real value we need to grow this fund from some $5 million to $20 million or more, so that our annual income is really able to achieve the goals stated above. Your willingness and ability to assist us in this effort would be greatly appreciated and I or any Trustee are available to meet with you to discuss this. Each and every contribution, no matter how large or small, will assist in achieving this goal.

The Malaghan family will be making its own contribution to this effort and will be donating $430,000 during 2008.

Each year I have to acknowledge the efforts of so many - our donors, members of Friends groups, researchers and their support teams, Trustees and the Director, they all continue to inspire me, and I believe themselves, on the journey that we are on.

Graham Malaghan

CHAIRMAN



...now more so than ever our groundbreaking work is being recognised by the international scientific community.

The past ten years have seen the medical research activities of the Malaghan Institute grow enormously, and with that growth has come new responsibilities and challenges. When we relocated to our new purpose-built facility on Victoria University's Kelburn campus in 2004 we had a staff of 50. Three years on we are again bursting at the seams with over 75 scientists and support staff dedicated to the prevention and treatment of cancer, asthma, arthritis, multiple sclerosis and infectious diseases. We take our reputation as New Zealand's leading independent biomedical research institute very seriously, and now more so than ever our groundbreaking work is being recognised by the international scientific community.

The Malaghan Institute has long held a commitment to educating, fostering and developing scientists, which we regard as essential to the continuing success of scientific research in New Zealand. Like many research facilities in this country however, we have struggled with finding the financial support necessary to halt the 'brain drain' of our talented young scientists to overseas institutes. One of the highlights of 2007 for me, therefore, was the award of ~$700,000 in NZ Lotteries grants to several of our young, early stage research scientists. This funding is a fantastic investment in our bright young stars, who bring an unparalleled level of energy and vitality to our scientific programmes and I am very happy that these individuals have been given the chance to start their careers.

I would also like to congratulate several of our up-and-coming young scientists on their individual successes in 2007. These include Willy-John Martin, who was awarded the Māori Education Trust Professions Scholarship; Kylie Quinn, who received the New Zealand Vice-Chancellors' Committee Todd Foundation Award for Excellence and was also joint winner alongside Lisa Goldsack of the 2007 Immunet Student Speakers Competition; and Clarissa Chandrahasen, for winning a New Zealand Microbiological Society oral presentation award. While research fellows Dr Patrizia Stoitzner and Dr

DIRECTOR'S REPORT

Nicholas van Panhuys were awarded the Austrian Society of Dermatology Auspitz and Otago Medical School Basic Research prizes respectively. Several other Malaghan students won travel scholarships to showcase their research talents on the international stage and I am very proud of the mature way in which they represented the Institute.

2007 has seen a lot of changes on the research front, with some projects coming to completion while others are just getting started. Our Immunoglycomics programme is now well underway, with new chemistry laboratories currently being built on site. This is a vast untapped area of drug discovery that impacts on our tuberculosis, asthma and cancer research programmes and is one of the new breakthrough fields of biomedical science in 2007.

The TerraMarine Pharmaceuticals venture comprising the Malaghan Institute, Crop and Food Research and NIWA, has now come to a close, with lead compounds currently being evaluated for use in preclinical studies of inflammatory conditions such as gouty arthritis.

I have written previously of the potential for using dendritic cells to treat cancer and indicated my excitement about our progression to conducting clinical trials with this approach. Unfortunately the rigours and difficulties of conducting large multi-centre clinical trials with patients in late stage disease were brought home to us this year, when we were forced to end our phase III melanoma trial. We are now in the process of reformulating the original vaccine protocol based on promising new data from our basic cancer immunotherapy research programmes and look forward to updating you on this work in the near future.

Our cancer stem cell research also looks to start providing valuable information in 2008 now that we have the systems in place to isolate and sort this rare population of cells, which appear to be an important source of cancer and a critical target for successful therapy.

The Infectious Diseases Group's three year study assessing risk factors for respiratory syncytial virus hospitalisation has now been published, revealing significant disparities in the health status of Māori and Pacific children compared to NZ European infants.

Finally, the Multiple Sclerosis Group has continued to make great strides in their development of immunotherapies for the treatment of autoimmune disorders and my own Asthma Group has significantly progressed our understanding of the allergic disease process.

It is said that it takes a village to raise a child; well it takes a team of dedicated support staff working behind the scenes to help nurture the development of our young scientists. Our Operations team has worked hard over the last couple of years to fine-tune the running of our world-class research facility. As a result, our scientists now have access to state-of-the-art research tools such as a Good Manufacturing Practice vaccine production laboratory, a Flow Cytometry Suite and an animal facility that is second to none, with specialist trained staff available on site to guide in their use. Each of these facilities represents the culmination of many years of study into the most effective way of doing things and are a truly unique resource for NZ. We also have the privilege of an enthusiastic Fundraising and Communications team working away in the background to ensure the future of our research funding, a talented Finance team that oversees the huge task of managing our funds and ever-patient Administration staff that manage the travel, security and day-to-day running of the Institute.

The Malaghan Institute Trust Board has been very active in the strategic development of the Institute in 2007, developing a capital base that will support our long-term research aims while enabling us to maintain our independent status. I feel very grateful to have such highly talented and successful individuals working alongside us to help raise our profile in the corporate sector, thus ensuring that we have access to all potential sources of research funding.

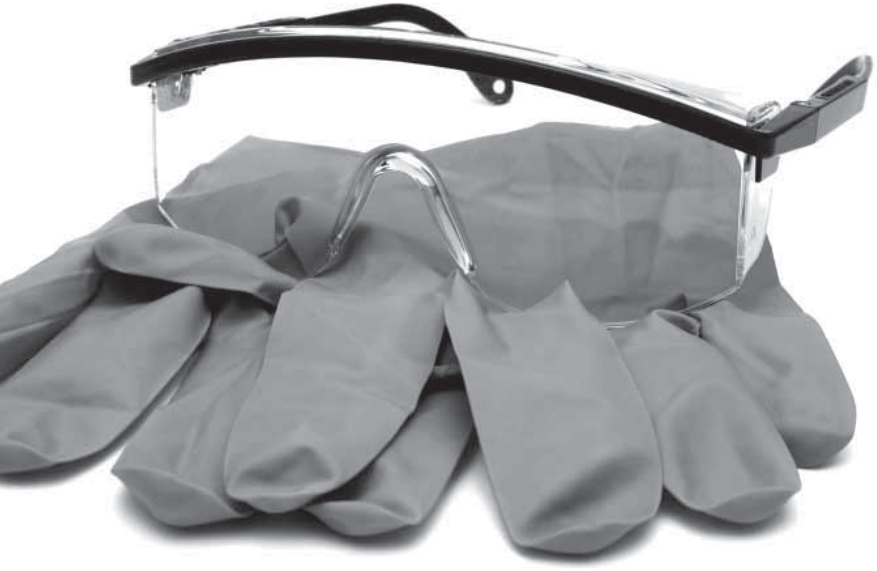
In November of this year I attended an international meeting in the United States of America focused on forming a global strategy against melanoma. The aim of this meeting was to find ways to fast track solutions for treating melanoma, and highlighted the importance of philanthropy in achieving this type of goal. This meeting got me thinking again about Len Malaghan and the role he and his family have played in bringing the Malaghan Institute to life. Inducted into the New Zealand Business Hall of Fame in 2007, Len was one of those rare individuals with an unfailing passion for fostering the development of medical research discoveries that provide tangible health benefits to all New Zealanders, and although he passed away forty years ago, the Malaghan Institute is proud to ensure that his legacy continues.

To our many supporters in the community, our hardworking Friends groups, our volunteers, our corporate sponsors, in particular AMI Insurance and Clemenger BBDO, and our research collaborators, I thank you for sharing in our vision of a disease-free future for all New Zealanders. I leave 2007 feeling more optimistic than ever before that we have the staff and infrastructure in place to secure our position as a world leader in biomedical research and look forward to seeing where that takes us in 2008.

Prof Graham Le Gros

DIRECTOR

THE MALAGHAN INSTITUTE TRUST BOARD



By supporting our scientists with quality resources and funding, the Malaghan Institute Trust Board plays a critical role in ensuring the future success of our world-class research programmes.

Graham Malaghan *FCILT (Chairman)*

In 1990, was appointed as the Chairman of the Malaghan Institute. He commenced employment at General Foods Corp in 1967, and was appointed General Manager of Refrigerated Freight Lines in 1970, acquiring the company in 1987. Was founding Chairman of Tasman Express Line and a Member of the LTSA for six years. Current directorships include several private companies.

John Beattie *LLB (VUW)*

Obtained a law degree from Victoria University and is a Fulbright Scholar from Cornell University (1979). Has been a Trustee of the Malaghan Institute since 1990 and is Director of Malcorp Biodiscoveries Limited, a subsidiary of the Malaghan Institute. He is also Chairman of the NZ Diabetes Foundation, NZ Sports Hall of Fame, and is a trustee for the Mt Aspiring College Foundation and the Life Education Trust, and an Executive Director of the Infinity Investment Group.

Prof David Bibby *DSc (Loughborough University)*

Was appointed to the Malaghan Institute Trust Board in December 2004. He is currently Pro Vice Chancellor (Science), Dean of Science and Dean of Architecture and Design at Victoria University of Wellington. He holds a PhD in nuclear chemistry and was awarded a DSc in 1995. He moved to the DSIR Chemistry Division in 1975 where he became Group Manager Research before joining Industrial Research Ltd in 1992, initially as General Manager Communications, Electronics and IT and then as General Manager Science Development. In 2003, he took his present position at Victoria University of Wellington.

THE MALAGHAN INSTITUTE TRUST BOARD

Assoc Prof John Carter *BMedSc, MBChB (Otago), FRACP, FRCPA*

Joined the Malaghan Board of Trustees in 2003. Did postgraduate work at the Fred Hutchinson Cancer Research Centre and the University of Washington. Clinically practices as a haematologist with a focus on stem cell transplantation. Is the immediate past Chair of the New Zealand Blood Service, and is currently Medical Leader of the Wellington Cancer Centre and the Chairman of Scots College.

Bryan Johnson *BCA (VUW)*

Obtained a commerce degree from Victoria University in 1963. Was a senior partner in the Stockbroking company Jarden & Co for 25 years and became chairman after the sale of the business to Credit Suisse First Boston in 1991. Retired from CSFB in December 2000 to further develop his Marlborough winery and vineyard, Spy Valley. Has been a director of various corporations, such as Brierley Investments, Royal Sun Alliance and recently retired as Chairman of the Duke of Edinburgh's Award and was a Trustee of the Wellington Stadium Trust.

Prof Graham Le Gros *BSc (Massey), Dip Immunol (Otago), MPHIL (Auck), PhD (Auck), FRSNZ*

Was awarded a Fogarty Fellowship at the NIH, Washington DC in 1987-1989, then took a scientist position with Ciba-Geigy in Basel Switzerland for five years before returning to New Zealand to take up the appointment as Research Director of the Malaghan Institute in 1994. He is a Professor of the Department of Biological Sciences, Victoria University, and has been elected as a Fellow of the Royal Society of New Zealand.

David H Mossman *BVSc, MRCVS, MNZIF*

Graduated from the University of Queensland in 1965 with a Veterinary Degree. Awarded the Australian College of Veterinary Scientists college prize in 1978, and the Coopers NZ Farm Management Award for significant innovative farm management concepts of great relevance to pastoral farming in New Zealand in 1984. A major involvement in Beef Cattle production research and delivered Scientific Papers to the New Zealand, Australian, and British Veterinary Associations, and Key note speaker at the World Angus and Hereford Conferences. A Member of the Lindisfarne College Board 1981-85. Managing Director of Farming, Forestry, Finance and Property Development Companies. Chairman of the Hawkes Bay Friends of the Malaghan Institute since 1999 and Retired Rural Veterinarian since 2001.

Prof John Nacey *MBChB, MBA, MD (Otago), FRACS*

Was appointed to the Malaghan Trust Board in 1998. Is currently the Dean of the Wellington School of Medicine & Health Sciences. He has clinical practice as a specialist Urologist and has long standing research interests in benign & malignant prostate disease.

Gary Quirke *BCA, CA, FCILT*

Was appointed to the Malaghan Institute Trust Board in 2001, when he was Managing Director of P&O Nedlloyd in New Zealand. Has an extensive background in the commercial sector and is a member of the Institute of Chartered Accountants and Fellow of the Chartered Institute of Logistics and Transport. Is currently involved in consultancy roles in service industries.

Dr Jim Watson *PhD (Auck)*

Was appointed to the Malaghan Institute Trust Board in 1993. Until recently has been the Chief Executive of Genesis Research & Development Corporation Limited, a company he co-founded in 1994. Has held Professorships at the University of California, Irvine (1976-81) and the University of Auckland (1981-93) serving as Head of the Department of Molecular Medicine (1983-93). He was a Director of the Foundation for Research, Science and Technology (1999-2002), President of the Australasian Society of Immunology (2001), the President of the Royal Society of New Zealand (2003-2006) and a Member of the Government's Growth and Innovation Advisory Board (2001-2004). Is currently Managing Director of BioJoule Limited, a renewable Energy Company.

C Dan Williams *CA*

Joined an antecedent firm of Deloitte in 1958 and following four years with the firm in London was admitted as a Partner in 1972, initially as the partner responsible for establishing the tax division and following that as a Business Advisory Partner. Retired in 2001 and is now a Consultant to the firm. Has a number of Private Company Directorships with emphasis on financial management.

CANCER IMMUNOTHERAPY

Prof Franca Ronchese

Group Leader

Prof Ronchese completed her studies at the University of Padova, Italy, and spent four years as a post-doctoral researcher at the NIH, USA. She then worked as an independent Scientific Member at the Basel Institute for Immunology, Switzerland, before being awarded a Malaghan Senior Research Fellowship. With support from the Wellington Medical Research Foundation, Prof Ronchese established the Cancer Immunotherapy group at the Malaghan Institute in 1994. Prof Ronchese's research centres on the dendritic cell, with a particular focus on the involvement of these cells in the early phases of an immune response, and how dendritic cells can be used to best advantage as carriers in cancer vaccines.

Clinical Perspective and Overview of Disease

With the exception of cardiovascular disease, more New Zealanders die from cancer than any other health condition (New Zealand Cancer Control Trust) and the need for more effective cancer treatments is higher than ever.

There is now considerable evidence that the abnormal proteins expressed in cancer cells can serve as targets for T cell-mediated immune responses that limit the growth of tumour tissue. Vaccination strategies that aim to induce the proliferation of tumour-specific T cells may therefore provide an effective therapy for cancer.

The establishment of T cell-mediated immunity, whether in response to disease or invoked by immunisation, is ultimately dictated by specialised antigen presenting cells called dendritic cells. Amazingly, only a few dendritic cells are necessary to initiate powerful immune responses.

We are using dendritic cells as the basis of cancer vaccines designed to instruct the immune system to selectively recognise and destroy cancer cells. We believe that a greater understanding of the basic biology of dendritic cells and how they initiate anti-tumour immune responses will help facilitate their use in cancer immunotherapy.

Project One: Regulation of the Immune Response by Perforin

One of the main obstacles to cancer immunotherapy is overcoming the mechanisms that limit current anti-tumour immune responses. We have observed that elimination of dendritic cells by the immune system prevents them from restimulating anti-tumour immune responses. Last year we determined that dendritic cell killing requires perforin, a protein produced and released by cytotoxic T lymphocytes (CTLs).

Early results indicate that while normal CTLs expand little after dendritic cell immunisation, do not increase their ability to secrete cytokines and inhibit the proliferation of other naïve $CD8^+$ T cells, the opposite is true for CTLs that cannot make perforin. This suggests that perforin plays an important role in regulating the outcome of immune responses.

However, we also find that dendritic cells can escape killing in some situations. Dendritic cells that are immature do not present antigen efficiently, and can not be recognised by CTLs and be eliminated.

We are currently examining whether natural killer T (NKT) cells, which are also able to kill cells although they do not require perforin in order to do so, can kill dendritic cells *in vivo*.

Project Two: Tumour Vaccination by Epicutaneous Immunisation

The cancer vaccines used in our clinical trials are tailor-made in the laboratory from samples of the patient's blood and tumour tissue and are injected into the patient. Epicutaneous immunisation is a simpler, more cost-effective approach to the treatment of skin cancers such as melanoma that involves the direct application of tumour antigen in a cream to the skin.

In collaboration with Dr Patrizia Stoitzner and colleagues, we have shown that immunisation strategies through the skin are feasible and induce the activation of tumour-specific T cells that acquire cytotoxic activity.

The skin is the site of an especially dense network of dendritic cells called Langerhans cells. In 2007 we used mice in which the Langerhans cells can be depleted *in vivo* to confirm that it is this population of cells, and not some other skin antigen presenting cell that must be present for this form of immunisation to work.

We also demonstrated that Langerhans cells are required to transport antigen to the lymph node, where they present it directly to the T cells to initiate an anti-tumour immune response.

Project Three: Intratumoural Antigen Presenting Cells

Last year we began a new project to identify the immune cells present inside a tumour following an anti-tumour immune response.

Using FACS analysis and staining of melanoma tumour sections we found that most of the tumour-infiltrating immune cells were macrophages with a few dendritic cells, B cells and T cells. Interestingly, although dendritic cells isolated from the tumours were shown to be functional in antigen uptake, they were not able to activate tumour-specific $CD4^+$ and $CD8^+$ T cells *in vitro*.

We have now extended this study by examining the role of T regulatory cells in modulating the function of the intratumoural dendritic cells. We find that the inability of the tumour-infiltrating dendritic cells to activate T cells does not appear to be due to the presence of high numbers of suppressive T regulatory cells in the tumours because depletion of the T regulatory cells did not reverse this effect.

This finding suggests that the function of intratumoural dendritic cells is defective and might explain why tumours activate immune responses so inefficiently.

Group Members

Prof Franca Ronchese, Haley Ataera, Dr Noriyuki Enomoto, Laura Green (to Apr), Markus Hoffmann (to Sep), Joel Zhi-Iong Ma, Rachel Perret, Jim Qin, Helen Simkins, Dr Patrizia Stoitzner (to Jun), Dr Robert Weinkove, Dr Sabine Witzel (to Mar), Dr Mark (Jianping) Yang

Collaborators

- Prof Vincenzo Cerundolo, University of Oxford, UK
- Dr Michelle Epstein, University of Vienna, Austria
- Dr Ian Hermans, Malaghan Institute of Medical Research
- Dr Bronwyn Kivell, Victoria University of Wellington, New Zealand
- Prof Bernard Malissen, Centre d' Immunologie Marseille-Luminy, France
- Prof Niki Romani, Innsbruck University, Austria

Funding

- Austrian Science Fund (FWF) • Cancer Society of New Zealand
- Genesis Oncology Trust • Harry & Beverly Romanes
- Health Research Council of New Zealand • New Zealand Lottery Health Research • The Royal Society of New Zealand Marsden Fund
- University of Otago • Wellington Medical Research Foundation

Cancer Immunotherapy Laboratory Supported by: HB Williams Turanga Trust

Dr Ian Hermans

Group Leader

Overseeing the Malaghan Institute's current involvement in the cancer vaccine trials is Dr Ian Hermans, Head of the Vaccine Research group. Dr Hermans studied dendritic cell vaccinations with Prof Ronchese at the Malaghan Institute between 1995 and 2001, before taking up a position at the Tumour Immunology Unit (Weatherall Institute of Molecular Medicine), at the University of Oxford, UK. In 2005 Dr Hermans returned to the Malaghan Institute and was awarded a Sir Charles Hercus Research Fellowship from the Health Research Council of New Zealand to pursue his research into improving the potency and efficacy of vaccines against cancer, asthma and infectious disease.

Clinical Perspective and Overview of Disease

The overall objective of the Vaccine Research group is to apply the basic principles of immune cell biology to the design of more effective vaccines against diseases such as cancer.

T cells with specificity for cancerous tissues need to be activated by dendritic cells in order to proliferate and migrate to the target tissue. The utility of using cultured dendritic cells loaded with tumour antigens to stimulate immune responses to cancer was first demonstrated in animal studies in the late 1990s and the first dendritic cell vaccination study in cancer patients was published in 1996. The development of reproducible protocols for culturing large numbers of dendritic cells for clinical application has facilitated further phase I and II studies designed to analyse the toxicity and clinical efficacy of this approach. These studies, including our own, have conclusively demonstrated the safety of dendritic cell vaccines. More importantly, some significant clinical responses have now been observed.

Invariant natural killer T (iNKT) cells are an excellent source of the signals required for optimal activation of dendritic cells and can thus influence the induction of anti-tumour T cell responses. We hope to improve T cell responses to tumours by exploiting the activity of these cells in our dendritic cell cancer vaccine design.

Project One: Improving Vaccines with Compounds that Stimulate iNKT Cells

There is very little information in the literature regarding the different subpopulations of iNKT cells and the role they play in mediating immunity. One subpopulation contains the CD4 marker, while the other doesn't. We have shown that following stimulation $CD4^+$ iNKT cells produce a significant quantity of IL-4 *in vivo*, which may influence the development of Th2 driven diseases such as asthma.

In 2007 we launched a new project in collaboration with Prof John Fraser from Auckland University, to exploit the potent immune-stimulating activity of superantigens to target tumour antigens to the dendritic cells. Preliminary findings suggest that this is a very effective way of getting the target antigen crosspresented to cells that mediate anti-tumour immunity. This approach generates much stronger anti-tumour immune responses with considerably less antigen.

It is now clear that the structure of the glycolipids presented to iNKT cells by dendritic cells can have a significant influence on their regulatory function. We are working with Dr Bridget Stocker, who heads the Immunoglycomics research at the Malaghan Institute, to investigate whether novel synthesised glycolipids can be used to promote iNKT cell activity and thus enhance immunity to tumours.

Project Two: Improving Dendritic Cell-based Vaccines for Cancer in a Laboratory Model

One of the main aims of our basic research programme is to increase the potency and efficacy of the dendritic cell-based vaccines so that we can stimulate strong, long-lasting anti-tumour immune responses. In 2007 we were successful in establishing an experimental model of the set-up used in our clinical trials, which will enable us to more directly test different ways of achieving this goal.

We have used this model to investigate whether Radiofrequency Ablation (RFA) treatment of tumours creates an environment that supports the generation of tumour-specific T cell responses. RFA is a novel technique that uses heat to destroy tumour cells *in situ*, while preserving surrounding tissue. We found that although RFA treatment was shown to delay tumour growth, a period of immunosuppression was observed immediately post RFA treatment and we are currently investigating this further.

In other work, we have now shown that we can generate very strong prophylactic anti-tumour immune responses when our standard dendritic cell vaccine is used in combination with αGalCer (stimulates iNKT cells) and the depletion of T regulatory cells. These results complement our discovery last year that certain combinations of Toll-like receptor ligands improve dendritic cell activity and will be taken into consideration when formulating our clinical vaccine protocols.

Project Three: Using Dendritic Cell-based Vaccines in the Clinic

Since 2004 the Malaghan Institute has been involved in a phase III trial of a dendritic cell-based melanoma vaccine with the Queensland Institute of Medical Research and the Wellington Cancer Centre. It was anticipated that the trial would involve 200 patients from across New Zealand and Australia, however, a mid-point review of trial outcomes by an independent statistician sadly led to closure of the trial in 2007. It is important to emphasise that the trial wasn't stopped because it hadn't worked but because the number of patients involved in the trial was too small to show a statistically significant improvement in the health of the individuals being treated. Despite closure of the trial, New Zealand patients involved in the study have opted to continue receiving the vaccine should their disease progress to stage IV.

We are now in the process of reformulating the original vaccine protocol based on promising new data from our basic research programme and are seeking approval to test this in a phase I trial for patients with stage IV melanoma.

In 2007 we also completed our protocol validation studies into the development of dendritic cell-based vaccines for the treatment of glioma (brain cancer) and are awaiting ethics approval to launch the trial proper.

Group Members

Dr Ian Hermans, Evelyn Bauer, Nina Dickgreber, Kathryn Farrand, Dr Scott Harding, Brigitta Mester, Dr Troels Petersen, Dr Anil Ranchord, Dianne Sika-Paotonu, Julie Walton (to Jul), Catherine Wood

Collaborators

- Prof Vincenzo Cerundolo, University of Oxford, UK
- Dr Sarah Hook, Department of Pharmacy, University of Otago, Dunedin, New Zealand
- Mr Martin Hunn, Neurosurgeon, Wellington Hospital, New Zealand
- Dr Gavin Painter, Industrial Research Limited, Wellington, New Zealand
- Dr Chris Schmidt, Queensland Institute of Medical Research, Australia

Funding

- Health Research Council of New Zealand • Milne Trust
- Mellor Trust • New Zealand Lottery Health Research
- University of Otago • Wellington Division of New Zealand Cancer Society

Clinical Human Immunology Laboratory Supported by: Lion Foundation

Prof Mike Berridge

Group Leader

Prof Berridge completed his postgraduate degree in Cell Biology at the University of Auckland in 1971. Following postdoctoral research at Purdue University, USA, and the National Institute for Medical Research, UK, Prof Berridge returned to Wellington in 1976 as the second Malaghan Fellow. He currently holds a Senior Research Fellowship with the Cancer Society of New Zealand, and recently held a James Cook Fellowship in the Health Sciences. Prof Berridge's current research concerns a stress adaptation and survival pathway in the cell membrane that has particular relevance to tumour cells, which is being targeted with small molecules designed to disrupt the pathway and eradicate cancer. Prof Berridge is also pursuing the elusive cancer stem cell, a minor population of quiescent, drug-resistant cancer cells that are thought to be responsible for the initiation of most cancers and their recurrence following treatment.

Clinical Perspective and Overview of Disease

It is a sobering fact that despite decades of research and billions of dollars of funding, cancer death rates have changed little over the past 50 years. What's more, cancer remissions are often transient, drug resistance a major problem and drug withdrawal can result in an aggressive return of the disease. New evidence suggests that part of the reason for this is that current cancer therapies are targeting the wrong cells.

The focus of most anticancer drug treatments is on killing the rapidly-dividing cells that form the bulk of a tumour. However, these treatments do not get rid of the 'cancer stem cells' that give rise to the disease, so the tumour is able to grow back. Like the stem cells that shape the development of the various tissues and organs in our body, cancer stem cells have the unique property of self-renewal and can divide indefinitely.

We have shown that cancer cells alter their metabolism to accommodate hypoxia and nutrient limitations, and use plasma membrane electron transport (PMET) to support these changes. Our research aims to understand the role of PMET in cancer stem cell survival and self-renewal, and to develop drugs that compromise this energy support system.

CANCER CELL AND MOLECULAR BIOLOGY

Project One: The Cancer Stem Cell as a Target for Cancer Treatment

Last year Dr Melanie McConnell initiated a research project to enrich and characterise stem cells from tumour tissue taken from patients with the aggressive primary brain cancer, glioblastoma multiforme (GBM).

One of the goals of this research is to establish cell lines that mimic the complex nature of cancer stem cells and can be used to screen for compounds that compromise their survival. In 2007 we successfully generated reproducible cultures of neurospheres from glioblastoma tissue. These neurospheres showed enhanced expression of self-renewal stem cell genes in comparison to the original primary tumour, suggesting the presence of cancer stem cells. In 2008 we will determine if the neurospheres have tumour-initiating capability using the NOD/SCID murine model.

We are also working with the Vaccine Research Group to establish methodologies for directing anti-tumour immune responses against cancer stem cells and are currently seeking funding with Wellington neurosurgeon Mr Martin Hunn to develop a model of cancer stem cells with more authentic tumour histology.

Project Two: Acute Responses to Reductive Stress and the Regulation of Gene Expression

One of the ways that cancer cells survive in the hypoxic environment of a rapidly growing tumour is by reverting to a predominantly glycolytic metabolism. As a consequence of this, cancer cells have an increased dependence on NAD^+, which is required for energy generation by glycolysis. We propose that an effective and specific method of killing cancer cells is to starve them of NAD^+ and plan to do this by simultaneously inhibiting two metabolic pathways that are highly active in cancer cells: NADH recycling via PMET (see Project Three), and NAD^+ salvage from nicotinamide, the by-product of NAD^+ - dependent enzymes.

SIRT1 is a member of the sirtuin family of NAD^+ - dependent deacetylases that plays a critical role in regulating a number of intracellular processes in response to changes in NAD^+ levels. We are currently exploring the interplay between SIRT1 and PMET in various cancer cell lines following knock-down of SIRT1 expression and have shown that loss of SIRT1 affects the cytotoxicity induced by inhibitors of PMET.

Dual inhibition of PMET and SIRT1 should provide a potent anti-tumour cocktail with the potential to eradicate quiescent cancer stem cells in addition to rapidly-dividing tumour cells.

Project Three: Development of Anti-Cancer Drugs that Inhibit Cell Membrane Transport Systems

We have identified and characterised a plasma membrane electron transport pathway that is essential for cancer cell proliferation and may be required for the survival of cancer stem cells that employ glycolytic metabolism. One of the main objectives of our research is to develop novel drugs that target the cell membrane and inhibit this pathway.

Several potential anti-cancer compounds that interfere with PMET and inhibit tumour cell growth have now been designed and synthesised by Prof Rob Smith and Dr Lesley Larsen from the University of Otago. In addition, the TerraMarine anti-inflammatory biodiscovery programme (see Arthritis Group report) has led to the identification of 15 compounds with significant anti-proliferative activity. Three of these compounds have since been shown to exhibit anti-tumour responses in murine cancer models.

Similar approaches with Novogen's pipeline of anticancer drugs, some of which are presently in advanced clinical trials for drug-resistant ovarian cancer, have established the cancer cell membrane as one site of action, but have also indicated effects on immune cells that warrant further investigation.

Group Members

Prof Mike Berridge, Nina Baker, Kate Broadley, Carole Grasso, Dr Patries Herst, Dr Melanie McConnell, Chakorn Rassameephauengphou, An Tan

Collaborators

- Prof Aldo Andreani, Prof Laura Landi and Dr Cecilia Prata, University of Bologna, Italy
- Dr David Brown, Novogen Inc, Sydney University, Australia
- Assoc Prof Brent Copp, Chemistry Dept, University of Auckland, New Zealand
- Prof Ian Dawes and Dr Gabriel Perrone, University of New South Wales, Australia
- Prof Alison Downard, Chemistry Dept, University of Canterbury, New Zealand
- Dr David Ritchie, Peter MacCallum Cancer Institute, Melbourne, Australia
- Prof Ann Smith, University of Missouri, Kansas City, USA
- Prof Robin Smith, Chemistry Dept, and Dr Lesley Larsen, Crop & Food Research, University of Otago, New Zealand

Funding

- Cancer Society of New Zealand • Genesis Oncology Trust
- Morris Cancer Research Foundation Trust • Novogen Inc • Roy McKenzie

Cancer Cell & Molecular Biology Laboratory Supported by: NZ Community Trust

Prof Graham Le Gros

Group Leader

Prof Le Gros was appointed Research Director of the Malaghan Institute in 1994, following a three year Fogarty Fellowship at the National Institutes of Health (NIH), Washington DC, and a five year scientist position with Ciba-Geigy in Basel, Switzerland. He is a member of the Cancer Society's Scientific Committee, Lotteries Health Committee, Wellington Medical Research Foundation Scientific Committee, various science advisory groups and is a Professor of the Department of Biological Sciences, Victoria University. In 2005 Prof Le Gros was elected as a Fellow of the Royal Society of New Zealand in recognition of his research contributions to the fields of immunology and asthma. Prof Le Gros' overall research interest lies in understanding the basic biology of Th2 immune responses, with a particular focus on the mechanisms and cell types involved in mediating allergic and asthmatic inflammation.

Clinical Perspective and Overview of Disease

Asthma is a chronic respiratory disease of major concern to our community, affecting one in four New Zealand children and one in six adults. It is characterised by recurrent attacks of breathlessness and wheezing, and varies in severity and frequency from person to person. During an asthma attack the lining of the bronchial tubes swells, causing the airways to narrow. This makes it hard to breathe in and even harder to breathe out.

It is now clear that the final symptoms of asthma are paradoxically due to our body's own immune system overreacting to quite harmless environmental triggers such as pollen or house dust mites. In fact it is only one part of the immune system that seems to be activated, the so-called Th2 immune response, which normally functions to protect us against parasitic worm infections.

Our research group is committed to unravelling the basic biology of the Th2 immune response that gives rise to asthma, so that we can apply this knowledge to the development of generally applicable vaccines and therapies for the treatment of individuals with established disease.

ASTHMA AND PARASITIC DISEASES

Project One: The Basic Biology of the Th2 Response

Our Asthma Research Group passionately believes that greater knowledge of the basic biology of the Th2 immune response is required before we can realistically start to provide practical advice on how best to avoid asthma and allergy.

The two immune cell types of particular interest to us are basophils and dendritic cells (DCs). We have shown that basophils are a principal source of IL-4 production and are currently examining the role they play in the induction of Th2 immunity *in vivo*. We are also investigating the contribution of DCs to the pathogenesis of allergic asthma using the drug FTY720, which blocks DC migration.

In 2007 we provoked much international discussion by demonstrating that IL-4 and STAT6 were not required for Th2 development in our asthma and allergy models. We have now extended this work by showing that IL-2 levels, which are thought to be responsible for activating and expanding T regulatory cells, increase in the absence of STAT6. The significance of this finding with respect to the development of a Th2 immune response is currently being investigated.

This groundbreaking work is providing new insight into the allergic disease process and we look forward to applying this information to the development of new diagnostic drugs and assays in the coming years.

Project Two: Bringing together, Parasites, Dust Mites and the Th2 Response

Two billion people worldwide are infected with intestinal nematodes such as hookworms, which can cause intestinal blood loss, protein malnutrition and anaemia.

Using the harmless laboratory-adapted rodent nematode *Nippostrongylus brasiliensis*, which has similarities to human hookworm and provokes immune responses reminiscent of asthma, we have shown that the lung is a central site for inducing protection against re-infection. In 2007 we discovered that the first point of contact of the worm to the host, the skin, is not as important as first thought. By tracking the different stages of the parasite as it migrates through the host, we have also been able to gain valuable insight into the location of the priming and cellular immune responses to the parasite allergens. This vital information will assist in the development of vaccination strategies against these parasites.

Last year we developed a novel Ear Model to measure the early induction of a Th2 immune response. In collaboration with Assoc Prof Jeroen Douwes and Prof Neil Pearce from Massey University, we are now using this model to measure the immune responses to environmental allergens known to trigger asthma such as house dust mites, pet dander and cockroaches. The results of this work will help us to identify the critical cells to target to halt an asthmatic reaction.

Project Three: A Sweet Solution to Asthma

While much is known about the causes of asthma, few studies have looked at the molecular structures of the allergens that trigger the disease and the role they play in influencing Th2 immune responses. In 2007 Dr Bridget Stocker, a resident synthetic chemist overseeing the Immunoglycomics research at the Malaghan Institute, was successful in securing funding that will enable us to address these key questions.

Upon close examination of the structural features of allergens such as pollen, food, and worms, we observed that particular structures (N-glycans) were conserved. Interestingly, antigens derived from bacteria and viruses neither possess these carbohydrate structures nor stimulate allergic immune responses, leading us to hypothesise that these unique structural motifs might be responsible for biasing the immune response towards Th2.

To investigate this hypothesis we will synthesise a library of N-glycans and test them in several Th2 immune response assays.

We hope that these studies will provide the first detailed insight into the relationship between N-glycan structure and Th2 bias and will lead to a better understanding of allergy and asthma.

Group Members

Prof Graham Le Gros, Mali Camberis, Peter Clark, Emma Dangerfield, Marina Harvie, Gregory Haslett, Jacqui Kane Barber, Melanie Prout, Stefanie Segers (to Dec), Dr Bridget Stocker, Shiau-Choot Tang, Dr Mattie Timmer, Dr Nicholas van Panhuys

Collaborators

- Prof Rick Maizels, University of Edinburgh, UK
- Dr Kathy McCoy, University of Zurich, Switzerland
- Dr Booki Min, Cleveland Clinic, USA
- Dr William Paul, NIAID, National Institutes of Health, Washington DC, USA
- Prof Neil Pearce and Assoc Prof Jeroen Douwes, Centre for Public Health Research, Massey University, Wellington, New Zealand
- Prof Murray Selkirk, University College London, UK

Funding

- AMI Insurance • Foundation for Research, Science & Technology (FRST)
- Health Research Council of New Zealand • Marjorie Barclay Trust
- New Zealand Lottery Health Research • Rex & Betty Coker Scholarship
- The Royal Society of New Zealand Marsden Fund

Asthma Laboratory Sponsored by: AMI Insurance
Parasitology Laboratory Sponsored by: NOW Couriers

Dr Joanna Kirman

Group Leader

After completing her postgraduate training in infectious disease-based immunology at the University of Otago and the Malaghan Institute, Dr Kirman was awarded a Fogarty Fellowship to pursue her work in vaccine development at the National Institute of Allergy and Infectious Diseases, USA. Dr Kirman returned to the Malaghan Institute in July 2002 to lead the Infectious Diseases group as a Sir Charles Hercus Research Fellow, supported by the Health Research Council of NZ. The overall aim of Dr Kirman's current research is to reduce the incidence of infectious disease in New Zealand through the development and implementation of vaccines.

Clinical Perspective and Overview of Disease

Reducing the incidence of infectious disease in New Zealand through vaccination is the ultimate goal of the research conducted by the Infectious Diseases Group.

Although it was once considered a problem of third world countries only, globalisation has meant that many New Zealanders are now exposed to, and contract Tuberculosis (Tb). Tuberculosis is the most lethal known bacteria, claiming 1.8 million lives and newly infecting >8 million people each year. It is estimated that one New Zealander a day is being newly diagnosed with Tb, a rate that is expected to rise unless preventative measures, such as new vaccines, are developed soon.

Respiratory syncytial virus (RSV) is one of the leading causes of infant hospitalisation, affecting more than 95% of children under the age of two. One of the aims of our research is to identify the factors that contribute to our high RSV hospitalisation rates so that we can start to look at possible interventions to reduce the rate of severe RSV infection in New Zealand.

Studies of these and other viruses of particular relevance to New Zealanders are crucial to determining appropriate vaccine design and administration.

Research Team

Dr Joanna Kirman, Clarissa Chandrahasen, Kasper Eckert, Lisa Goldsack, Rosemary Harty, Kylie Quinn, Natalie Redshaw (to Jun), Fenella Rich, Sophie Robinson (to Jan), Victoria Taylor, Catherine Wood

Collaborators

- Assoc Prof Glenn Buchan, Department of Microbiology and Immunology, University of Otago, New Zealand
- Drs Bryce Buddle, Geoff deLisle and Michel Denis, AgResearch, Wallaceville, New Zealand
- Dr Carlos Camargo, Massachusetts General Hospital, Boston,USA
- Dr Catherine Cohet, Dodet Bioscience, Lyon, France

Project One: Tuberculosis (Tb) Vaccine Development

The currently available vaccine against Tuberculosis, BCG, has been given to more than three billion people worldwide, yet it fails to consistently provide protection against the bacterium that causes the disease. In 2007 we looked at potential reasons for why the BCG vaccine fails, since these will need to be taken into account when designing new more effective Tb vaccines.

We have discovered that parasite infection impairs the ability of BCG to protect against Tb, a finding that is supported by the observation that countries in which BCG is least effective also have high parasitic worm burdens. We are investigating which aspects of the protective immune response are affected by worm infection. We have shown that regulatory T cells can suppress BCG-induced immune responses. While in otherwise healthy individuals this does not affect protection against Tb, in worm-infected individuals the regulatory T cells may affect protection.

Efforts to develop a new, more effective vaccine for Tb have been hampered by a lack of understanding of what constitutes a protective memory immune response. We are currently trying to understand which $CD4^+$ T cell subsets are important for mediating vaccine-induced protection against Tb. This information will be essential for the development of an effective vaccine.

Project Two: Multicentre Rotavirus Strain Surveillance

Rotavirus is a highly contagious virus that most commonly affects children under the age of two. It causes diarrhoea and vomiting, resulting in approximately 1000 hospitalisations in this country each year. In 2005 the Infectious Diseases Group established a multicentre rotavirus strain surveillance study to monitor New Zealand's rotavirus strains pre- and post-introduction of a commercial rotavirus vaccine. This information will be vital for predicting the potential effectiveness of the vaccines that will be introduced into New Zealand.

Early indications from this study are that the rotavirus strains prevalent in the South Island each winter differ to those prevalent in the North Island. Furthermore, while the predominant strain seen globally and in NZ is consistently G1, the strains making up the remaining 40-50 % change quite dramatically each season and no-one knows why. Data collection for this study will be completed in 2008.

A rotavirus vaccine has been recommended for inclusion in the national immunisation schedule but has yet to be approved. If the vaccine is approved, we will aim to re-establish strain surveillance to determine the effect of the introduced vaccine on circulating rotavirus strains.

Project Three: Paediatric Respiratory Viruses in New Zealand

We have led a prospective epidemiological study assessing the risk factors for RSV hospitalisation and disease severity in Wellington during the winter months of 2003-2005. This study, which revealed that Māori and Pacific infants have a higher risk of being hospitalised from RSV bronchiolitis than NZ European infants, has now come to a close and the results published in the international journal Epidemiology & Infection.

In 2008 we will initiate a collaborative pilot study with the Wellington Asthma Research Group to identify possible interventions to RSV-induced hospitalisation. This study will initially focus on determining whether vitamin D levels, which have been shown previously to play a role in respiratory health, correlate with the ability to protect against RSV infection and hence disease severity.

Over recent years bronchiolitis hospitalisation rates have been increasing in NZ. In 2007 we were the first to show that the recently discovered virus, human bocavirus, which is thought to cause severe respiratory illness in young children, is present in this country. Collectively this information is vital for understanding why NZ has such high hospitalisation rates for children with respiratory disease.

- Prof Julian Crane and Dr Tristram Ingham, Clinical Epidemiology, Wellington School of Medicine, University of Otago, New Zealand
- Prof Chris Cunningham, Research Centre for Māori Health and Development, Massey University, New Zealand
- Prof Brett Delahunt, Department of Pathology, Wellington School of Medicine, University of Otago, New Zealand
- Prof Keith Grimwood, Department of Paediatrics and Child Health, Wellington School of Medicine, University of Otago, New Zealand
- Dr Ronan O'Toole, School of Biological Sciences, Victoria University of Wellington, New Zealand
- Prof Neil Pearce, Centre for Public Health Research, Massey University, New Zealand

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- Aotea Pathology • Capital & Coast Health Laboratory
- Health Waikato • Hutt Hospital Laboratory • Medlab South
- Paediatric units and laboratories at Canterbury Health
- Starship Auckland Hospital • Southern Community Laboratories

Funding

- Health Research Council of New Zealand
- Merck, Sharp & Dohme NZ • New Economy Research Fund, Foundation for Research, Science & Technology (FRST) • New Zealand Lottery Health Research • University of Otago • Victoria University of Wellington • Wellington Medical Research Foundation

A/Prof Thomas Bäckström

Group Leader

Assoc Prof Thomas Bäckström, originally from Sweden, established the Multiple Sclerosis Basic Research group at the Malaghan Institute in 1997 following a one year Postdoctoral research position at the National Jewish Centre, USA, and five years as a member at the Basel Institute of Immunology, Switzerland. In 1999 Assoc Prof Bäckström was awarded a five year Wellcome Trust Senior Research Fellowship in Medical Science, and in 2005 he was the recipient of a Wellington Medical Research Foundation's Malaghan Senior Haematology Research Fellowship. Over recent years Assoc Prof Bäckström's research focus has been on identifying mechanisms that inhibit the development and activation of autoreactive T cells.

Clinical Perspective and Overview of Disease

Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) affecting 1:1,100 New Zealanders.

Surrounding and protecting the nerve fibres of the CNS is a fatty tissue called myelin, which helps nerve fibres conduct electrical impulses to and from the brain. In MS, myelin is lost in multiple areas leaving scar tissue, which disrupts the flow of messages controlling functions such as seeing, walking and talking.

Although the exact cause of MS is unknown, the damage to myelin is most likely the result of a malfunctioning immune system. Normally, the immune system protects us against harmful foreign invaders such as viruses or bacteria. In autoimmune diseases such as MS, the body attacks its own tissue.

The focus of our research is to better understand the cause of MS and to use that insight to develop therapeutic treatments that can be used to inhibit its progression.

Project One: Targeting Immune Suppressor Cells to fight Multiple Sclerosis

Previously we have shown that a modified superantigen (mSag) coupled to a myelin-derived peptide (MOG) alleviates the symptoms of disease in experimental autoimmune encephalomyelitis (EAE), a well-established murine model of MS. The mechanism of protection is unknown but we have proposed that it involves the expansion and/or activation of a population of MOG specific T regulatory cells (Tregs).

Tregs are a specialised immune cell type that suppress immune responses and therefore play a crucial role in preventing autoimmune disease. It has been shown that Tregs from the peripheral blood of MS patients have impaired suppressive function compared with healthy donors and it is thought that MS results from an inability of these cells to adequately turn off disease-causing self-reactive T cells. One of the goals of our research is to develop an immunotherapeutic agent that can be used to restore the suppressive function of Tregs in patients with MS.

It is known that antigen presenting cells (APCs) are important for Tregs to acquire their suppressive function. In 2007 we investigated the interactions between Tregs and APCs during immune suppression.

By labelling the mSag-peptide conjugate with a fluorescent dye, we were able to show that it bound to a distinct subpopulation of cells in the blood. The presence of MHC class II molecules was not necessary for binding of the mSag to this distinct newly identified cell subset, suggesting the presence of a second receptor for mSag binding to APCs. We also demonstrated that binding of control mSag-MOG to the blood-borne cells ameliorated symptoms and delayed the onset of disease in our EAE model.

We hypothesise that the mSag binds to and changes certain properties of the specific blood-borne cells identified in this study. Such changes endow these cells with the ability to suppress EAE.

Identification of the underlying mechanisms involved in this process is crucial for the development of an immunotherapy that can be used to treat and prevent MS and other autoimmune diseases. We are therefore very pleased to welcome Dr Elizabeth Forbes to our team, who brings with her the expertise required to study the cellular and molecular mechanisms involved in the mSag-peptide conjugate inhibition of autoimmunity.

Project Two: Understanding the Signalling Pathways involved in Multiple Sclerosis

Th1 cells producing cytokines are considered the predominant disease-causing cells in autoimmune disorders. However, the recent identification of a novel subset of autoimmune IL-17 producing $CD4^+$ T cells (Th17 cells) suggests other cells and signalling pathways may also play a critical role in inducing autoimmunity.

A key player in the IL-17 signalling pathway is Tyk2, an intracellular kinase that has previously been shown to be necessary for the generation of autoimmune arthritis. In 2007 we demonstrated that mice that are unable to produce the Tyk2 protein are resistant to the development of EAE. Although these mice did not develop disease, they did produce normal levels of IL-17. Our results indicate that signalling via Tyk2 is important in the induction phase of EAE and the generation of disease-causing autoimmune Th17 cells.

This is the first time a link has been demonstrated between Tyk2, IL-17 and EAE. We are currently investigating other pathways involving Tyk2 to determine its potential applicability as a drug target for the treatment of autoimmune disorders such as MS.

Group Members

Assoc Prof Thomas Bäckström, Clare Bai, Dr Elizabeth Forbes, Sara Mirmoeini (to Dec), Evelyn Spittle, Aras Toker

Collaborators

- Prof Claude Bernard, Monash University, Melbourne, Australia
- Prof John Fraser, Auckland University, New Zealand
- Dr Ian van Driel, University of Melbourne, Australia

Funding

- Health Research Council of New Zealand
- New Zealand Lottery Health Research
- Wellington Medical Research Foundation
- Wellington Region Foundation

Multiple Sclerosis Laboratory Sponsored by: The Wellington Company

Dr Jacquie Harper

Group Leader

Dr Harper obtained her PhD in Chemistry and Physiology from the University of Otago. After a post-doctoral position with the Physiology Department at Otago, Dr Harper took up a Fogarty Research Fellowship at the National Institutes of Health (USA) in the Laboratory of Biological Chemistry. As head of the Arthritis Group, Dr Harper's main research interests lie in the role of innate immune cells in driving arthritic diseases and the development of novel anti-inflammatory treatments for improved disease management.

Clinical Perspective and Overview of Disease

Arthritis literally means "inflammation of a joint" and it is the single greatest cause of disability in this country (Arthritis New Zealand).

There are more than 140 different types of arthritis affecting people of all ages - from babies and toddlers, through to teenagers and the elderly.

Gout is one of the most common forms of arthritis. It is caused by the build-up of uric acid crystals (MSU) in the joints, resulting in intense pain, swelling and reddening of the skin.

In New Zealand the prevalence of gout is twice that observed internationally and it is three times more prevalent in Māori and Pacific Island populations. Many individuals suffer from refractory disease or fail to respond to current therapies leading to high morbidity and poor disease management. Improved prognosis and alternative treatments are required to rectify this situation.

The main focus of the Arthritis & Inflammation Research Group is to advance our understanding of the cellular processes involved in MSU-induced inflammation with the goal of identifying therapeutic targets and new markers of disease progression for gouty arthritis.

ARTHRITIS AND INFLAMMATION

Project One: Role of Macrophages and Monocytes in Acute Gouty Arthritis

A key characteristic of the inflammatory response observed in a variety of arthritic diseases is the recruitment of immune cells called monocytes to the joints and connective tissues. These cells have the potential to develop into either proinflammatory or anti-inflammatory macrophages and might therefore either contribute to inflammation or shut it down respectively.

Last year we showed that monocytes entering the site of inflammation contributed little to the initiation and early progression of inflammation induced by MSU crystals. In 2007 we have gone on to successfully identify the resident macrophage as the key cell responsible for producing the initial inflammatory response to MSU, including the recruitment of damage-causing neutrophils that exacerbate the disease. We also found that whereas macrophages recruit neutrophils in response to MSU, epithelial cells recruit monocytes. The significance of this finding for disease therapy with respect to the potential to target different arms of inflammation in gout is the subject of current investigation.

We are also continuing to investigate the infiltrating monocyte populations in gouty arthritis to determine how their presence at the site of inflammation might be contributing to disease progression.

Project Two: A Clinical Study of Gouty Arthritis

Monocyte and neutrophil recruitment is a key characteristic of the inflammatory response to MSU in gout patients. For this reason they are the cellular targets of our clinical study into gouty arthritis.

Interestingly, only 20 % of people with elevated levels of uric acid in the blood develop gout, and it is unclear why the other 80 % remain asymptomatic.

The clinical study aims to determine whether immune cells isolated from the blood of healthy volunteers and gout patients respond differently to MSU and whether these responses correlate with susceptibility to or protection from developing gout.

The clinical study is now in year two and we have recruited half of the participants and some of our interim data has already revealed interesting differences between the inflammatory responses of different gout patient groups and healthy controls.

This work complements our basic research programme investigating the mechanisms of inflammation during the early onset of arthritis and will be presented at a major international clinical rheumatology conference in 2008.

Project Three: New Anti-inflammatory Treatments for Arthritis

TerraMarine Pharmaceuticals, a joint venture comprising the MIMR, Crop and Food Research (CFR) and the National Institute of Water and Atmospheric Research (NIWA), has now identified lead compounds from a New Zealand sponge that both inhibits neutrophil activation and suppresses neutrophil infiltration in gouty inflammation. These compounds have now undergone extensive structure-activity studies allowing us to identify the optimal structure(s) for specific anti-inflammatory activity and future drug development.

This work is underpinned by protection of the intellectual property around the structure and application of these compounds for the treatment of arthritis and other inflammatory diseases involving neutrophils.

In 2007 we also initiated a collaboration with HortResearch to develop anti-inflammatory neutraceuticals for improving management of inflammatory conditions.

Group Members

Dr Jacquie Harper, Elizabeth Chia (to Nov), Dr Rebecca Grainger, Tommy Liu, Willy-John Martin, Rene McLaughlin (to Dec), Dr Mischa Walton

Collaborators

- Assoc Prof Brent Copp, Auckland University, New Zealand
- Prof Carolyn Geczy, University of New South Wales, Sydney, Australia
- Dr Andrew Harrison, Wellington School of Medicine, New Zealand
- Dr Roger Hurst, HortResearch Ruakura, Hamilton, New Zealand
- Dr Keryn Johnson, Industrial Research Limited, Lower Hutt, New Zealand
- Dr Nigel Perry, Crop and Food Research, New Zealand
- Dr Vicky Webb, NIWA, New Zealand

Funding

- Arthritis New Zealand
- Foundation for Research, Science & Technology (FRST)
- Health Research Council of New Zealand
- New Zealand Lottery Health Research
- Wellington Medical Research Foundation
- Wellington Region Foundation

Arthritis Laboratory Sponsored by: Wellington Region Foundation

FLOW CYTOMETRY REPORT

Flow cytometry is the cornerstone technique for cell analysis at the Malaghan Institute and we are the busiest research-based flow suite in New Zealand. In simple terms, flow cytometry uses lasers to identify and/or purify specific cell types of interest that have been labelled with fluorescent dyes. Nearly of all the scientific staff at the Institute utilise flow cytometry as a research tool in their quest to develop immune-based therapies for the treatment of diseases such as cancer, asthma, multiple sclerosis, arthritis and infectious diseases.

To assist with meeting the increased demands for flow cytometry expertise at the Institute, we were very pleased to welcome Brigitta Mester to the team in 2007. Our role as flow cytometrists is to offer support and information to the scientists regarding new fluorophores, dyes or technologies that will benefit their research. We are also able to purify target cells of interest for them out of a mixed population of cells from any given tissue using a flow cytometer with cell-sorting capabilities called the BD FACSVantage DiVa.

My attendance at a laser safety course in Washington DC in April of this year followed by a visit to the prestigious flow cytometry suites at the National Institutes of Health (NIH) (generously sponsored by the Wellington Medical Research Foundation and the Wellington Division of the Cancer Society) enabled us to identify ways in which to improve possible laser hazards in our flow cytometry suite to the benefit of all our scientific staff. Meetings with flow cytometrists at the NIH also helped form our decision to purchase a Special Order Research Product (SORP) flow cytometer from Becton Dickinson. This machine (called an LSRII) will be built for us in February 2008 and will be the only one of its kind in the Southern Hemisphere. The SORP LSRII is capable of detecting 18 different colours and two physical characteristics. This means that a scientist could potentially design an experiment to look at 20 different parameters of a particular cell population and simultaneously get information on what types of cells are present, what cytokines are being produced and so on.

Research highlights for 2008 included isolating memory T cells that are reactive against tuberculosis, establishing procedures for sorting putative cancer stem cells, and simultaneously sorting three subsets of dendritic cells. Previously immunologists believed that only one particular subset of dendritic cells was capable of activating cytotoxic T cells, however the Vaccine Research Group was able to show that all three sorted dendritic cell subsets can cross-present. This information will facilitate the design of cancer vaccines that drive potent anti-tumour immune responses.

With staff numbers at an all-time high and research breakthroughs dependent more than ever on the scientific insight obtained using flow cytometry techniques, next year promises to be another bumper year for the flow cytometry suite and all its users.

Kylie Price (Manager), Brigitta Mester
FLOW CYTOMETRY

Flow Cytometry Laboratory Sponsored by: Becton Dickinson

OPERATIONS REPORT

2007 has not really been a year for milestones but for bedding down and preparing for the challenges ahead.

The overall goal of the Operations team in 2007 was to improve the efficiency of the running of the Institute wherever possible. Whether through addressing the energy efficiency of the building and its key equipment, by investing in new software to organise and automate many of our regular tasks, or simply by creating and revising procedural documentation, the aim has been to fine-tune the Institute's operations. In short – to get the place humming.

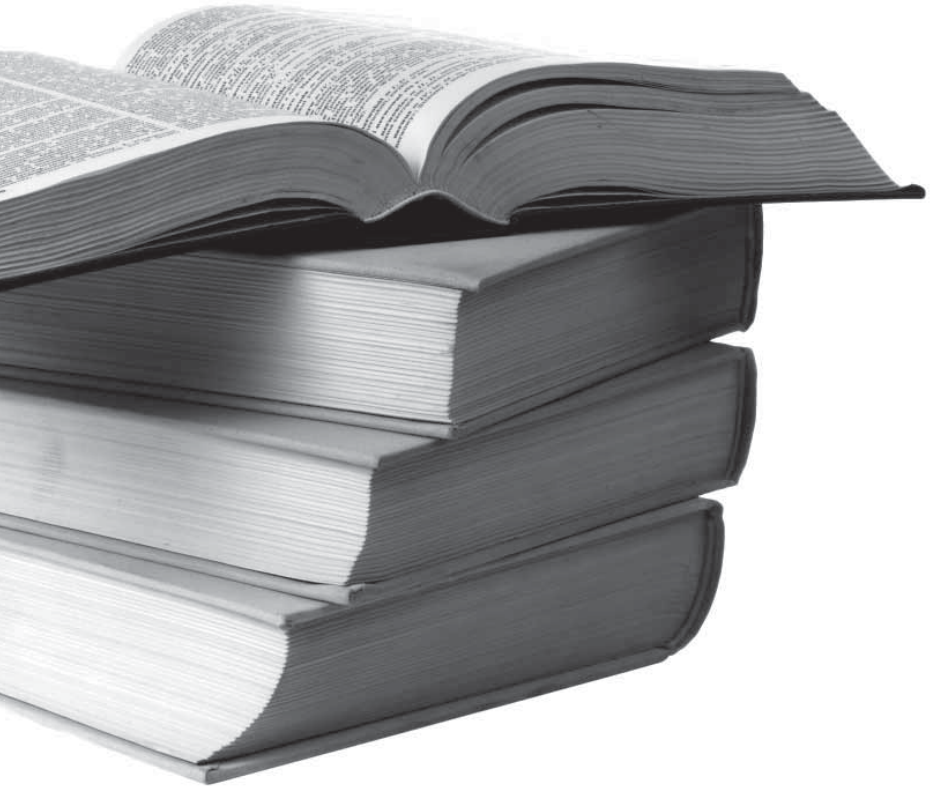
Notable milestones for the team this year included the uptake of a new application for asset management and maintenance scheduling, an increasingly vital tool as our size increases. We would like to acknowledge the support of the Victoria University Facilities Management team in helping to set this up. We also trained certain key staff in electrical compliance testing; an annual electrical health-check we are required to perform on all equipment and which we can now handle in-house. The re-configuration of our building plant, particularly heating and cooling, to run on-demand has allowed us to make considerable savings to our energy costs and therefore environmental impact. The work of Setpoint Solutions Ltd and Aquaheat Ltd were invaluable in achieving this. In March we welcomed Mark Williams to the Operations team as part-time IT Support. Mark's arrival enabled us to devote some time to improving our operational documentation, most importantly by creating an Emergency Response plan, which is vital for any Wellington-based enterprise.

From the perspective of the Operations team, 2007 has not really been a year for milestones but for bedding down and preparing for the challenges ahead. With a steady increase in staff numbers year after year, we are already challenging the limits of our existing facility. 2008 will see new equipment, new laboratories, and more new staff as our science programmes push on in their quest for discovery. Perhaps the most significant outcome of 2007 has been our ability to ensure that the day-to-day yet vital procedures underpinning the Institute research are running as efficiently as possible ahead of the changes to come.

Mike Zablocki, Laurence Fallon, Dominique Hawinkels, Darrell Smith, Mark Williams

OPERATIONS

PUBLICATIONS



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Full details of all 'in press' publications will appear in the 2008 Annual Report.

Each week both national and international scientists are invited to the Institute to present their research in a forum that promotes the active exchange of scientific ideas and insights.

February

Haley Ataera, Malaghan Institute of Medical Research. Designing strategies to improve the T cell mediated immunotherapy of mouse tumours.

Dr Melanie McConnell, Malaghan Institute of Medical Research. Manipulating transcription as a therapeutic approach to leukaemia.

Dr Gabrielle Belz, Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia. Antigen presentation: activating naïve and memory CD8+ T cells.

Dr Miles Davenport, Centre for Vascular Research, University of New South Wales, Kensington NSW, Australia. Understanding the kinetics of antigen presentation *in vivo*.

Prof Neil Pearce, Director, Centre of Public Health Research, Massey University, Wellington Campus, New Zealand. What causes asthma?

March

Catherine Wood, Malaghan Institute of Medical Research. Clinical trials story.

Prof Paul Atkinson, Professorial Fellow, Molecular Systematics Institute, School of Biological Sciences, Victoria University of Wellington, New Zealand. Chemical genetics, genetic networks & complex phenotypes.

Assoc Prof Jiri Neuzil, Apoptosis Research Group, School of Medical Science, Griffith University, Queensland, Australia. Role of ROS and BCL-2 family proteins in mitocan-induced apoptosis: a hypothesis.

Dr Rebecca Grainger, Malaghan Institute of Medical Research. Not mice but men; preparing observational study in human gout.

Stephanie Huck, Malaghan Institute of Medical Research. Containment facility refresher course.

SEMINARS

April

Prof Claude Bernard, Head Neuroimmunology Laboratory, Monash University, Australia. Understanding CNS autoimmunity: from animal models to MS patients.

Nicholas van Panhuys, Malaghan Institute of Medical Research. Mono-vs bi-allelism: Th2 modelling in *in vitro* and *in vivo* systems leads to differential expression patterns of IL-4.

Ron Germain MD, PhD, National Institute of Allergy and Infectious Diseases, National Institutes of Health, United States of America. A multiscale approach to understanding adaptive immunity: from molecules to models to movies.

Dr Wendy Williamson, Senior Scientist, ESR, Christchurch Science Centre, New Zealand. Environmental health: our pathogens, our environment, our health.

May

Prof Chris Cunningham, Massey University, New Zealand. Insulin resistance and Māori health.

Dr Patrizia Stoitzner, Malaghan Institute of Medical Research. Revisiting the role of Langerhans cells in skin immunity.

June

Nina Dickgreber, Malaghan Institute of Medical Research. Induction of potent T cell immunity to antigens conjugated to a modified superantigen construct.

Prof Chris Parish, Cancer & Vascular Biology Group, Division of Immunology & Genetics, John Curtin School of Medical Research, Australian National University, Canberra, Australia. Heparan sulfate: a key regulator of inflammatory responses; From sugar-based drugs to vaccines: a multifaceted approach to cancer control.

July

Dr Ben Marsland, Molecular Biomedicine, Institute of Integrative Biology, Zurich, Switzerland. Regulation of mucosal tissue integrity by pattern recognition receptors.

Prof Nicola Harris, Environmental Biomedicine, Institute of Integrative Biology, Zurich, Switzerland. Peace and war in the intestine.

Assoc Prof Catherine Bollard, MBChB, FRACP, RCPA, Baylor College of Medicine, Houston, Texas, United States of America. Cytotoxic T cell therapy for Lymphoma.

August

Helen Simkins, Malaghan Institute of Medical Research. Immune responses in perforin deficient mice after infection with influenza virus or immunisation with αGalCer.

Dr Troels Petersen, Malaghan Institute of Medical Research. How do regulatory T cells control anti-tumour CD8 T cell responses?

Prof Frank Carbone, University of Melbourne, Australia. The interplay between dendritic cells and T cells in control of herpes simplex virus infection.

Dr Patries Herst, Malaghan Institute of Medical Research. Plasma membrane: a novel target for anti-cancer strategies.

September

Prof Jonathan Cebon, Joint Laboratory Head, Cancer Vaccine Lab, Ludwig Institute for Cancer Research, Melbourne, Australia. Cancer immunotherapy directed against germ cell antigens.

Dr Bridget Stocker, Malaghan Institute of Medical Research. A cat among the pigeons: the story of what happens when a chemist arrives at an Immunology Institute.

Prof Ken McNatty, Victoria University of Wellington, New Zealand. From germ cells to ovarian follicle formation in the mammalian ovary.

Marina Harvie, Malaghan Institute of Medical Research Different roles of SIP in the effector and memory responses.

October

Willy-John Martin, Malaghan Institute of Medical Research. Neutrophil activation in acute gouty inflammation.

Prof Howard Evans, Wales Heart Research Institute, School of Medicine, Cardiff University, United Kingdom. How connexins provide highways for intercellular communication.

Prof Joe Trapani, Head, Cancer Immunology Programme, Peter MacCallum Cancer Centre, Melbourne, Australia. Structure and function of perforin: a key effector molecule of cytotoxic lymphocytes.

Aaron Hart, Application Scientist, Tree Star, Inc, Oregon, United States of America. Flow cytometry analysis seminar.

November

Darrell Smith and Thomas Bäckström, Malaghan Institute of Medical Research. Induction refresher.

Prof Hajime Karasuyama, Department of Immune Regulation, Tokyo Medical & Dental University Graduate School, Japan. Basophils play non-redundant roles *in vivo* that are distinct from those played by mast cells.

Rachel Perret, Malaghan Institute of Medical Research. CD8+ T cells activated *in vitro* establish a memory population *in vivo* and confer lasting tumour protection.

Kylie Quinn, Malaghan Institute of Medical Research. Do natural Tregs suppress the BCG vaccine against Tb?

Prof Booki Min, Cleveland Clinic, United States of America. T cell homeostasis: what are they competing for?

December

Dr Huib Ovaa, Division of Cellular Biochemistry, The Netherlands Cancer Institute, Amsterdam, The Netherlands. Conditional MHC ligands, chemical design and applications.

At the Malaghan Institute we know that our success is dependent on the calibre of the people who do their research here.

For New Zealand to remain at the forefront of scientific research we require a continuous flow of new, well-trained scientists. At the Malaghan Institute we know that our success is dependent on the calibre of the people who do their research here. For this reason, the mission of the Malaghan Institute has always included an active commitment to education. We wish to foster the development of new scientists and to expose students to the most recent advances in immunology and related topics. To that end, we actively sponsor programmes for doctoral candidates and also provide special opportunities for selected students early in their academic training. We are investing in improving human health by investing in our brightest people and giving them the opportunity to use their skills here in New Zealand.

Doctoral Candidates

In 2007, the Malaghan Institute supported the following PhD students by assigning them to a senior scientist to guide and advise their work. Their studies not only help them satisfy their thesis requirements but also contribute to the core research programmes of the Institute.

Haley Ataera *(BSc, MSc)* "Designing strategies to improve the T cell mediated immunotherapy of mouse tumours"

Clare Bai *(BSc, MSc(Hons))* "The role of T regulatory cells in autoimmunity"

Nina Dickgreber *(DipSci)* "Improving vaccines with adjuvants that stimulate NKT cells"

Lisa Goldsack *(BBmedSc(Hons))* "Dissecting the long-term memory response against Tuberculosis"

Marina Harvie *(BSc(Hons))* "Timing and tissue distribution of allergen specific Th2 cells"

Joel Zhi-Iong Ma *(BSc(Hons))* "Regulation of CD4+ T helper 2 cell responses by CD8+ T cells"

Willy-John Martin *(BSc, MSc(Hons))* "The role of macrophages in gouty arthritis"

Rachel Perret *(BSc(Hons))* "*In vitro* activated CD8+ memory T cells confer protective immunity against tumours"

Kylie Quinn *(BSc(Hons))* "Development of a novel DNA vaccine to prevent Tuberculosis disease"

Chakorn Rassameephauengphou *(BSc(Hons), MSc)* "Investigation of variant surface NADH-oxidoreductases on tumour and non-tumour cells"

Dianne Sika-Paotonu *(BSc, BBmedSc, MBmedSc(Hons))* "Increasing the potency of dendritic-cell based vaccines for the treatment of cancer"

Helen Simkins *(BSc(Hons))* "Immune responses in perforin deficient mice"

The Malaghan Institute is proud to support two Clinical Research Fellows in their PhD studies.

Dr Rebecca Grainger *(BMedSci(Distinc), MBChB(Distinc), FRACP)* "Immune inflammation in neutrophilic disease – a study of gouty arthritis"

Dr Robert Weinkove *(MA, MBBS, MRCPath)* "Invariant natural killer T cells in chronic lymphocytic leukaemia"

The following student had his thesis accepted and was awarded his Doctorate in 2007:

Nicholas van Panhuys *(BSc(Hons))* "Basic biology of the Th2 immune responses in protective immunity and allergic diseases"

Masters Students

In 2007 two international students undertook research towards their Masters degrees at the Malaghan Institute.

Kasper Eckert *(BSc)* "Worms and Germs: Do helminth infections impair the efficacy of the tuberculosis vaccine BCG?"

Aras Toker *(BSc)* "Targeting antigen presenting cells to treat autoimmune inflammation"

Honours Students

In continuing our relationship with Victoria University the Malaghan Institute hosted two Honours students in 2007. The research projects were tendered out by the Institute and undertaken by the following successful applicants as a contribution to their Honours study:

Rosemary Harty *(BBmedSc)* "Development of a virus neutralisation assay for respiratory syncytial virus"

Rene McLaughlin *(BBmedSc)* "Proteoglycans: Novel agents in the fight against cancer"

Visiting Students

The following two international students undertook research at the Malaghan Institute in 2007:

Markus Hoffmann *(BSc)* "Depletion of regulatory T cells *in vivo*"

Stefanie Segers *(MSc)* "Identifying pathways in the development of IL-2 producing T helper cells in an allergic response"

Summer Students

Each year, the Malaghan Institute hosts summer interns who have an interest in science, and are of the calibre to take on and benefit from an assigned research project at the Institute. Working with close direction from the Institute staff, they are able to conduct meaningful work and learn what a career in research offers. Over the summer of 2007/08, we fostered the following students:

Nina Baker *(BBmedSc, MBChB (3rd year))* "Characterisation of glioblastoma neurospheres using immunochemistry"

Peter Clark *(BBmedSc (2nd year))* "*Mycobacterial tuberculosis*: a greasy bug(ger)"

Rosemary Harty *(BBmedSc(Hons))* "Development of a virus neutralisation assay for respiratory syncytial virus"

Gregory Haslett *(BSc (3rd year))* "A sweet solution to asthma and aza sugars for treatment of Tb"

Jacqui Kane Barber *(BSc, BA)* "*Mycobacterial tuberculosis*: a greasy bug(ger)"

Tommy Liu *(BSc, Grad dip BBmedSc)* "Peritoneal responses to MSU"

Victoria Taylor *(MBChB (4th year))* "Characterising the phenotype of CD4+ T cell subsets in the protective immune response against Tuberculosis"

Community Education

At the Malaghan Institute, we are dedicated to disseminating the knowledge gained through our research to the community. In 2007, we had 12 community groups tour the Institute. The groups had the opportunity to meet the Malaghan's internationally acclaimed scientists, learn about the immune system and experience medical research in action. In addition our staff gave presentations to 10 clubs, community groups and schools offsite.

FUNDRAISING REPORT

Throughout the year of working together as a team we really developed a great understanding of one another and our individual strengths...

As the new Fundraising & Communications Manager, I am pleased to be a part of the exciting developments within the Malaghan Institute. 2007 was a year of change in the Fundraising Department with a farewell to Anthea Armstrong as Manager in March. Even though I had only been with the Malaghan Institute for a little over three months, Graham Le Gros had every confidence that I could rise to the challenge of the management position. It was a tremendous learning curve, but one that was made all the easier with the fantastic support of Communications Assistant, Dr Debbie Scarlett, and my two new part-time Fundraising Assistants, Ashley Hallsmith and Jacqui Whelan. Throughout the year of working together as a team we really developed a great understanding of one another and our individual strengths and talents have enabled the Fundraising Department to once again perform to a very high standard.

A significant achievement of the Fundraising team in 2007 was the launch of a new and improved Malaghan Institute website, see www.malaghan.org.nz. We would like to thank the innovative team at Cre@ive Design, Hawkes Bay for bringing the website to life and for providing us with a user-friendly platform in which to keep our supporters informed of upcoming events and research developments.

In terms of the fundraising activities in 2007, it was a great year with lots of exciting things happening. Over the course of the year we had 12 community groups visit the institute, and we also went out and spoke to another ten at their meetings; we had great success applying for external funding (eg private trusts and gaming trusts) with money being utilised for vital equipment purchases and support costs for our various research groups; and of course the success of our Friends of the Malaghan Institute groups in Wellington, Hawkes Bay and Auckland must be mentioned.

The Friends of the Malaghan Institute were again champions of our cause and collectively raised over $150,000 for our research programmes.

FUNDRAISING REPORT

The Lollipop Street Appeal Day, Sileni Vineyard Dinner, Rannoch House Art Exhibition and Golf Tournaments were extremely successful and well patronised. This not only helped us meet fundraising targets, but also enabled the promotion of the Malaghan Institute and our important work. We would like to take this opportunity to thank the hard working members of each committee and congratulate them on another successful fundraising year. All the scientists here at the Institute are truly grateful for your enthusiasm, passion and support for their work. We look forward to another year of working with you to achieve the same great results - thank you.

We would also like to thank our loyal donors, volunteers and supporters for another wonderful year of support and hope you all find it rewarding when you read our Scope Newsletters and hear of the progress in our research programmes. Part of the joy of our job is being able to show off our world-class research facilities and we invite each and every one of you to please contact us if you are in Wellington and would like to come and take a look around. It would truly be our pleasure.

Thank you all, once again, for your support of the worthwhile research programmes here at the Malaghan Institute. With such successes in 2007 it is exciting to look forward to what 2008 may bring.

Tanya Fulcher, Ashley Hallsmith, Dr Debbie Scarlett, Jacqui Whelan

FUNDRAISING AND COMMUNICATIONS

Wellington Friends

Robyn Vavasour (Chair)
Judy Blair
Adrienne Bushell
Maureen Cameron
Gaye Carroll
Penny Catley
Sylvia Goldman
Annemarie Janssen
Jill Kinloch
Susan Laurenson
Jill Strang

Wellington Fundraising Functions 2007

Lollipop Street Appeal
ING NZ Ltd Malaghan Golf Tournament

Hawkes Bay Friends

David Mossman (Co-Chair)
Denise Bull (Co-Chair)
Margie Dick
Caroline Green
Beth Kay
Angela Miller
Bry Mossman
Andy Neilson
Jan Patterson
Bruce Speedy
Lynn Spence
John Stovell
Terry Thornton

Hawkes Bay Fundraising Functions 2007

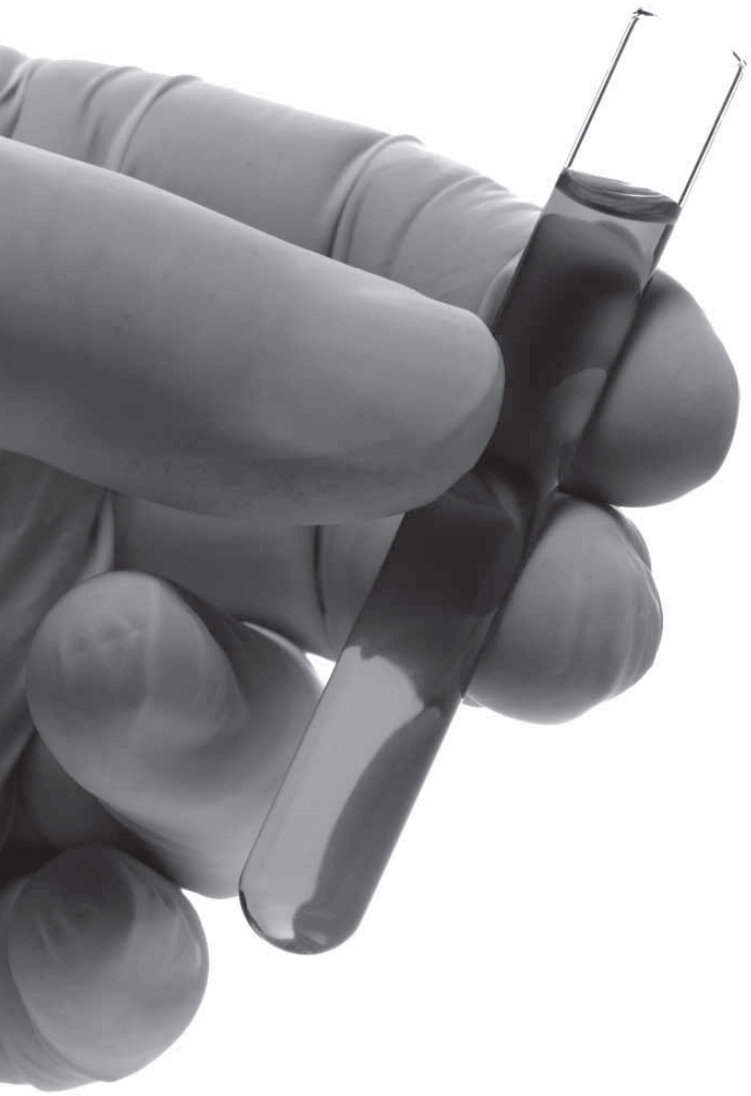
Sileni Dinner
Malaghan Institute Golf Tournament
Shoal Beach Ladies Morning Tea

Auckland Friends

Judy Jordan (Chair)
Mary Collow
Steve Culpan
MaryAnne Ellett
Nicholas Glanfield
Elaine Haggitt
Margaret Malaghan
Penny Rennell
Raewyn Roberts
Margaret Smith

Auckland Fundraising Functions 2007

Rannoch House Art Exhibition
AMI Insurance Malaghan Golf Tournament



The Malaghan Institute is at the forefront of international medical research. We have the most committed and qualified team of scientists working around the clock.

How can you help us lick cancer, asthma, arthritis, MS and infectious disease?

The Malaghan Institute is independent and receives no direct government funding. It is reliant on contestable research grants and contributions from corporate sponsors, trusts, bequests, individuals and fundraising initiatives.

The Malaghan Institute is at the forefront of international medical research. We have the most committed and qualified team of scientists working around the clock on the toughest, and most urgent, human diseases. We are making good progress toward the ultimate goal of developing effective treatments and vaccines for some of the world's most dangerous and debilitating diseases, but without funding the work will stop and the goal will be unattainable.

The Malaghan Institute is a registered charity and any support is gratefully received. Please support our vision by investing in health for the benefit of all New Zealanders.

The following are some options for supporting medical research at the Malaghan Institute of Medical Research.

Corporate Sponsorship

Corporate sponsorship enables the Institute to focus financial resources on core medical research and offers an opportunity to the corporate sector to enjoy the promotional benefits of being associated with the Malaghan Institute. We have several options for sponsorship including local and national events, laboratory naming rights and the procurement of specialist pieces of scientific equipment. We are happy to recognise support in a way that is appropriate to our sponsors.

We are making good progress toward the ultimate goal of developing effective treatments and vaccines for some of the world's most dangerous and debilitating diseases...

Donations

Donations from individuals and Trusts form a large part of our funding. The income is used to support the research programmes and are acknowledged by a personal letter and receipt.

All donations over $5 are tax-deductible.

Bequests

The research at the Malaghan Institute is very dependant on bequests. We have developed an endowment fund that will grow from major gifts and bequests, hence sustaining the future of the Institute.

Following is a suggested format for the wording of a bequest.

"I give a bequeath to The Malaghan Institute of Medical Research,

- A percentage (%) of my estate or
- The following property and assets or
- The residue of my estate or
- The amount of $ (in words) or

for its general purposes (or for the purpose of….) and I declare that the receipt of the chief executive or other proper officer shall be full and sufficient discharge to my trustees"

We would be delighted to discuss options for acknowledgement to suit your wishes.

Should you require any additional information about the above options or have any queries, please contact:

Fundraising and Communications Manager
Malaghan Institute of Medical Research,
PO Box 7060, Wellington, New Zealand
+64 4 499 9614

Please visit www.malaghan.org.nz for further information.

Thank you to the following individuals, organisations, businesses, Trusts and Foundations who helped support the Malaghan Institute in 2007:

Grants, Trusts and Foundations

AMI Insurance
Arthritis New Zealand
Austrian Science Fund (FWF)
Cancer Research Charitable Trust
Cancer Society Wellington Division
Canterbury University
Foundation for Research, Science & Technology
Genesis Oncology Trust
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H B Williams Turanga Trust
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First NZ Capital
Freyberg Pool

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I B Gough
J E Hetrick
I M Morgan
H Mossman
Dorothy Offenberger
Pittaway
Shirley Smith
B B Stoker
Raymond Weaver

The need for expanding the scope of the science projects has required us to take more space for laboratories, offices and storage.

The Institute has had another exciting and challenging year. We have again been fortunate to have the stunning support of our loyal donors who continue to excel themselves. Their money is vital to underpin the many under funded projects that the scientists pursue, as well as helping to provide those infrastructure costs that the grant funds often do not provide.

The need for expanding the scope of the science projects has required us to take more space for laboratories, offices and storage. This comes with a price tag that we are required to meet in order to keep up with the essential health research objectives of the Institute's science programmes.

Our cashflow has suffered this year as we have taken advantage of the current high interest rates. In order to maximise our returns we have locked in some of our funds for a longer term with the interest payable on maturity.

Depreciation for the year of $602k is the largest component of our operating deficit. Our funding for replacement assets has historically been funded by grantors.

Our Capital Endowment Fund has also been indispensable to underwrite our research. The growth in this fund is ensured by the people who have bequeathed us money. This year due to the dip in the sharemarket we have taken a loss, albeit an unrealised loss, on our investments. We did weight our portfolio more heavily into cash and more secure investments to ride out the downturn.

I am sure that 2008 will be just as exciting and it will again provide its own unique challenges. We will meet these headlong in order to continue to build an efficient and effective platform for our science activities to continue unimpeded and to facilitate those medical breakthroughs we need for our community.

Susie Whelan, Janine Gray
FINANCE

AUDIT REPORT

Deloitte.

TO THE TRUSTEES OF THE MALAGHAN INSTITUTE OF MEDICAL RESEARCH

We have audited the summary consolidated financial statements of the Malaghan Institute of Medical Research (the "Institute") for the year ended 31 December 2007.

Trustees' Responsibilities

The Trustees are responsible for the preparation of summary financial statements in accordance with New Zealand law and generally accepted accounting practice.

Auditors' Responsibilities

It is our responsibility to express to you an independent opinion on the summary financial statements presented by the Trustees.

Basis of Opinion

We conducted our audit in accordance with New Zealand Auditing Standards. We planned and performed procedures to ensure the summary financial statements are consistent with the full financial statements on which the summary report is based. We also evaluated the overall adequacy of the presentation of information in the summary financial statements against the requirements of FRS-43: *Summary Financial Reports.*

Other than in our capacity as auditor, we have no relationship with or interests in the Institute.

Opinion on the Summary Financial Statements

In common with organisations of a similar nature, control over the revenues from donations and bequests prior to being recorded is limited, and there are no practical audit procedures to determine the effect of this limited control. As a result, the Institute's full audited financial statements contained a qualified audit opinion.

In our opinion, the information reported in the summary financial statements complies with FRS-43: *Summary Financial Statements* and is consistent with the full financial statements from which it is derived. We expressed the qualified opinion referred to above in our report to the Trustees dated 12 March 2008.

For a better understanding of the scope of our audit for the Institute's consolidated financial statements and of the Institute's financial position, financial performance and cash flows for the year ended 31 December 2007, this report should be read in conjunction with the Institute's audited consolidated financial statements for that period.

Our examination of the summary consolidated financial statements was completed on 12 March 2008 and our opinion is expressed as at that date.

Deloitte

Chartered Accountants

WELLINGTON, NEW ZEALAND

This audit report relates to the summary financial statements of Malaghan Institute of Medical Research (the "Institute") for the year ended 31 December 2007 included on Malaghan Institute of Medical Research's website. The Board of Trustees is responsible for the maintenance and integrity of the Institute's website. We have not been engaged to report on the integrity of the Institute's website. We accept no responsibility for any changes that may have occurred to the summary financial statements since they were initially presented on the website. The audit report refers only to the summary financial statements named above. It does not provide an opinion on any other information which may have been hyperlinked to/from these summary financial statements. If readers of this report are concerned with the inherent risks arising from electronic data communication they should refer to the published hard copy of the audited summary financial statements and related audit report dated 12 March 2008 to confirm the information included in the audited summary financial statements presented on this website. Legislation in New Zealand governing the preparation and dissemination of financial statements and summary financial statements may differ from legislation in other jurisdictions.

Malaghan Institute of Medical Research - Abridged Accounts 2007

Consolidated Statement of Financial Performance For year ended 31 December	2007 Consolidated	2006 Consolidated
Income - Operating		
Income from Donations	755,894	503,420
Income from Scientific Grants	4,376,734	3,748,813
Interest and Income from Investments	133,873	178,124
	5,266,501	4,430,357
Expenses - Operating		
Salaries	2,585,693	2,319,049
Expenses (including depreciation)	3,379,728	2,933,826
	5,965,421	5,252,875
Operating (Deficit)	**(698,920)**	**(822,518)**
Plus Grant Income for Fixed Asset Purchases	115,324	438,934
Net (Deficit)	(583,596)	(383,584)
Capital Endowment Fund		
Income		
Investment Income	218,394	548,829
Bequests	312,731	260,934
Net Income	531,125	809,763

FINANCIAL ACCOUNTS

Consolidated Statement of Movements in Equity For year ended 31 December	2007 Consolidated	2006 Consolidated
Opening Balance	5,850,333	5,424,154
Net (deficit)/surplus for the year		
- Operating Income	(583,596)	(383,584)
- Capital Endowment Fund	531,125	809,763
Total recognised income and expenditures	(52,471)	426,179
Total Funds	5,797,862	5,850,333

Consolidated Statement of Financial Position As at 31 December	2007 Consolidated	2006 Consolidated
Current Assets	5,132,612	4,863,629
Less Current Liabilities	2,990,802	3,067,656
Plus Fixed Assets	1,326,027	1,525,228
Plus Investments	2,330,025	2,529,132
Total Equity	5,797,862	5,850,333

Consolidated Statement of Cash Flows For year ended 31 December	2007 Consolidated	2006 Consolidated
Net Cash Flow from Operating Activities	475,626	1,373,063
Net Cash Flow from Investing Activities	(717,880)	(851,310)
Net Cash Flow from Financing Activities	-	(2,374)
Net Increase in Cash Held	(242,254)	519,379
Cash at Beginning of the Year	2,562,517	2,043,138
Cash at End of the Year	2,320,263	2,562,517

These Summary Statements were authorised for issue by the Trust Board of the Malaghan Institute of Medical Research at a meeting held on 12 March 2008.

Financial information was extracted from the audited Financial Statements of the Malaghan Institute of Medical Research for the year ending 31 December 2007. The summary financial report cannot be expected to provide as complete an understanding as provided by the full financial report of the financial performance, financial position, and cash flows. A full copy of the Financial Statements including Notes can be obtained on request to the Financial Manager, Malaghan Institute of Medical Research, PO Box 7060, Wellington South, New Zealand.

BOARD OF TRUSTEES

Mr Graham Malaghan *FCILT (Chairman)*
Mr John Beattie *LLB(VUW)*
Prof David Bibby *DSc(Loughborough University)*
Assoc Prof John Carter *BMedSc, MBChB(Otago), FRACP, FRCPA*
Mr Bryan Johnson *BCA(VUW)*
Prof Graham Le Gros *BSc(Massey), Dip Immunol(Otago), MPHIL(Auck), PhD(Auck), FRSNZ*
Mr David Mossman *BVSc, MRCVS, MNZIF*
Prof John Nacey MBChB, MBA, MD(Otago), FRACS
Mr Gary Quirke *BCA, CA, FCILT*
Dr Jim Watson *PhD(Auck)*
Mr C Dan Williams *CA*

STAFF OF THE INSTITUTE 2007

Scientific

Director of Research

Prof Graham Le Gros *BSc(Massey), Dip Immunol(Otago), MPhil(Auck), PhD(Auck), FRSNZ*

Group Leaders

Assoc Prof Thomas Bäckström *BSc(Hons)(Stockholm), PhD(Auck) – Wellington Medical Research Foundation Malaghan Haematology Fellow*
Prof Mike Berridge *BSc, MSc(Hons), PhD(Auck) – Cancer Society Senior Fellow*
Dr Jacquie Harper *BSc(Hons), PhD(Otago)*
Dr Ian Hermans *BSc(Hons)(Otago), MSc(Distinc)(Otago), PhD(VUW) – Sir Charles Hercus Health Research Fellow*
Dr Joanna Kirman *BSc(Hons), PhD(Otago)*
Prof Franca Ronchese *PhD(Padua); Dip Microbiology*

Staff Scientists

Evelyn Bauer *NZCSc, Cert Animal Sci & Tech(Massey) – Clinical Trials Project Manager (from Apr)*
Stephanie Huck *BSc(Massey) – Manager BRU (on maternity leave)*
Nicola Kofoed *BSc, DipGrad(Otago) – Manager BRU*
Brigitta Mester *MSc(Hungary) - GMP Production/Flow Cytometry Technician (P/T) (from Nov)*
Kylie Price *BSc(Otago), MSc(Hons)(VUW) – Flow Cytometry Suite Manager*
Julie Walton *BSc(Massey) – Clinical Trials Project Manager (to Jul)*
Xiaodong Wang *Dip Med Tech, Dip Midwifery(Shanxi)*

Research Nurse

Catherine Wood *RN, BN, PGDipHealSci*

Visiting Researchers

Dr Scott Harding *MBChB(Otago), FRACP (P/T)*
Dr Patries Herst *BSc, MSc(Netherlands), MPhil(Waikato), PhD(Otago) (P/T)*
Dr Anil Ranchord *MBChB(Otago)*
Dr Sabine Witzel *MSc, PhD(Halle, Germany) (Jan-Mar)*

Senior Research Fellows

Dr Melanie McConnell *BSc(Hons), PhD(Otago)*
Dr Bridget Stocker *BSc(Hons), PhD(VUW)*
Dr Patrizia Stoitzner *MSc, PhD(Innsbruck) (to Jun)*
Dr Mattie Timmer *MSc, PhD (Leiden, Netherlands) (P/T) (from Sep)*

Research Fellows/

Post-doctoral Research Fellows

Dr Noriyuki Enomoto *MD, PhD(Japan) (from Nov)*
Dr Elizabeth Forbes *BSc(VUW), PhD(ANU) (from Sep)*
Dr Troels Petersen *MSc, PhD(Copenhagen)*
An Tan *BSc(VUW)*
Dr Nicholas van Panhuys *BSc(Hons)(VUW), PhD(Otago) (from Aug)*

Senior Research Officers

Mali Camberis *BSc(VUW)*
Elizabeth Chia *BSc(Burnaby) (to Nov)*
Kathryn Farrand *MSc(Massey)*
Melanie Prout *BSc(Hons)(VUW)*
Fenella Rich *BSc(Hons)(Otago)*
Evelyn Spittle *MSc(Distinc)(Otago)*
Dr Jianping Yang *MB(Shanxi Medical University)*

Research Officers

Kate Broadley *BSc(Massey) (from Mar)*
Clarissa Chandrahasen *BBmedSc(VUW) (from Jul)*
Emma Dangerfield *BBmedSc(Hons)(VUW) (from Mar)*
Carole Grasso *BSc(Hons)(West of England) (P/T)*
Laura Green *BS(Madison) (to Apr)*
Sara Mirmoeini *BBmedSc(Hons)(VUW) (to Dec)*
Jim Qin *BSc(Hons)(Auckland)*
Natalie Redshaw *BSc(Hons)(Bradford) (to Jun)*
Shiau-Choot Tang *Grad Dip Sci(VUW)*
Dr Mischa Walton *MSc(Friedrich-Schiller, Germany) PhD(Massey) (from Jan)*

Research Assistants

Sharon Brokenshire
Charlotte Cheriton *(from Apr)*
Kelly Locke
Katherine MacGregor *BSc(Massey)*
Rene McLaughlin *BBmedSc(VUW) (P/T) (to Feb)*
Amanda Payne *BSc(Otago) (from Mar)*

Clinical Research Fellows

Dr Rebecca Grainger *BMedSci(Distinc), MBChB(Distinc) (Otago), FRACP*
Dr Robert Weinkove *MA(Hons)(Cantab), MBBS(Hons) (London), MRCPath(UK) (from Dec)*

PhD Students

Haley Ataera *BSc, MSc(VUW)*
Clare Bai *BSc, MSc(Hons)(Auckland)*
Nina Dickgreber *DipSci(Kiel)*
Lisa Goldsack *BBmedSc(Hons)(VUW)*
Marina Harvie *BSc(Hons)(VUW)*
Joel Zhi-long Ma *BSc(Hons)(Singapore) (from Mar)*
Willy-John Martin *BSc, MSc(Hons)(Waikato)*
Rachel Perret *BSc(Hons)(Otago)*
Kylie Quinn *BSc(Hons)(Otago)*
Chakorn Rassameephauengphou *BSc(Hons)(Thornbury), MSc(Leicester) (from Mar)*
Dianne Sika-Paotonu *BSc, BBmedSc, MBmedSc(Hons)(VUW)*
Helen Simkins *BSc(Hons)(Otago)*
Nicholas van Panhuys *BSc(Hons)(VUW) (to Aug)*

Masters Students

Kasper Eckert *BSc(Copenhagen) (from Mar)*
Aras Toker *BSc(Germany) (from May)*

Honours Students

Rosemary Harty *BBmedSc(VUW) (Feb-Nov)*
Rene McLaughlin *BBmedSc(VUW) (Feb-Nov)*

Visiting Students

Markus Hoffmann *BSc(Hanover, Germany) (Aug-Sep)*
Stefanie Segers *MSc(Netherlands) (Jun-Dec)*

Summer Students 2007/2008 (Nov-Jan)

Nina Baker *BBmedSc(VUW), MBChB (3rd year)*
Peter Clark *BBmedSc (2nd year)*
Rosemary Harty *BBmedSc(Hons)(VUW)*
Gregory Haslett *BSc (3rd year)*
Jacqui Kane Barber *BSc(VUW), BA(VUW)*
Tommy Liu *BSc(Otago), Grad dip BBmedSc(VUW)*
Victoria Taylor *MBChB (4th year)*

Research Consultants

Assoc Prof John Carter, *Wellington Cancer Centre*
Prof Chris Cunningham, *Te Pümanawa Hauora, School of Māori Studies, Massey University*
Prof Brett Delahunt, *University of Otago*
Prof Keith Grimwood, *Dept of Paediatrics and Child Health, Wellington School of Medicine & Health Sciences*
Dr Andrew Harrison, *Dept of Medicine, Wellington School of Medicine & Health Sciences*
Dr Anne La Flamme, *Victoria University of Wellington*
Dr David Ritchie, *Peter MacCallum Institute, Melbourne, Australia*

Science Support and Administration

Administration

Gabrielle Dennis *RSA(English), Pitmans - PA to Director and Human Resources*
Carolyn Hallsmith - *Receptionist (P/T)*

Finance

Janine Gray *BCA(VUW) – Assistant Accountant (P/T)*
Susie Whelan *CA, NZIMDip – Finance Manager*

Fundraising

Anthea Armstrong *BBS(Massey) – Fundraising & Communications Manager (to Mar)*
Tanya Fulcher *BSc(VUW) – Fundraising & Communications Manager (from Mar)*
Ashley Hallsmith *BBmedSc(VUW) (2nd year) – Fundraising Assistant (P/T) (from Mar)*
Dr Debbie Scarlett *BSc(Hons), PhD(Otago) – Communications Assistant (P/T)*
Jacqui Whelan – *Fundraising Assistant (P/T) (from Mar)*

Operations

Laurence Fallon – *Lab Assistant/General Admin*
Dominique Hawinkels *NZCS, DipBusStudies(Massey) – Security and Reception Manager*
Darrell Smith *MSc(Hons)(VUW), (Dip A.T.)(Wgtn Polytech), BSA(Massey) – Facilities Manager*
Mark Williams – *Network Administrator (from Mar)*
Michal Zablocki *BA(Hons)(Bristol) – Operations/IT Manager*

ADVISORS

Auditors

Deloitte

Bankers

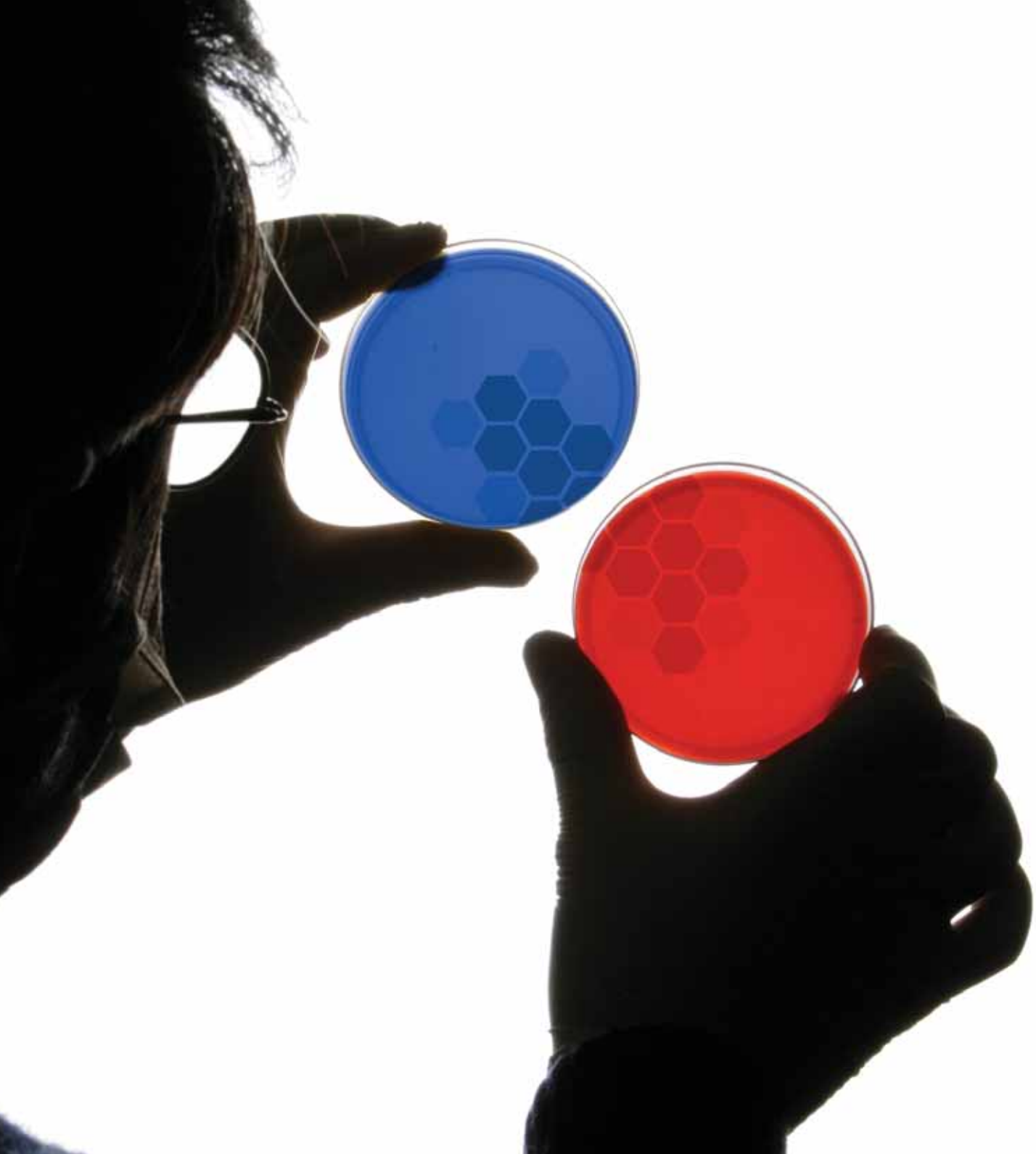
The National Bank

Investments

David Wale

Solicitors

Simpson Grierson



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