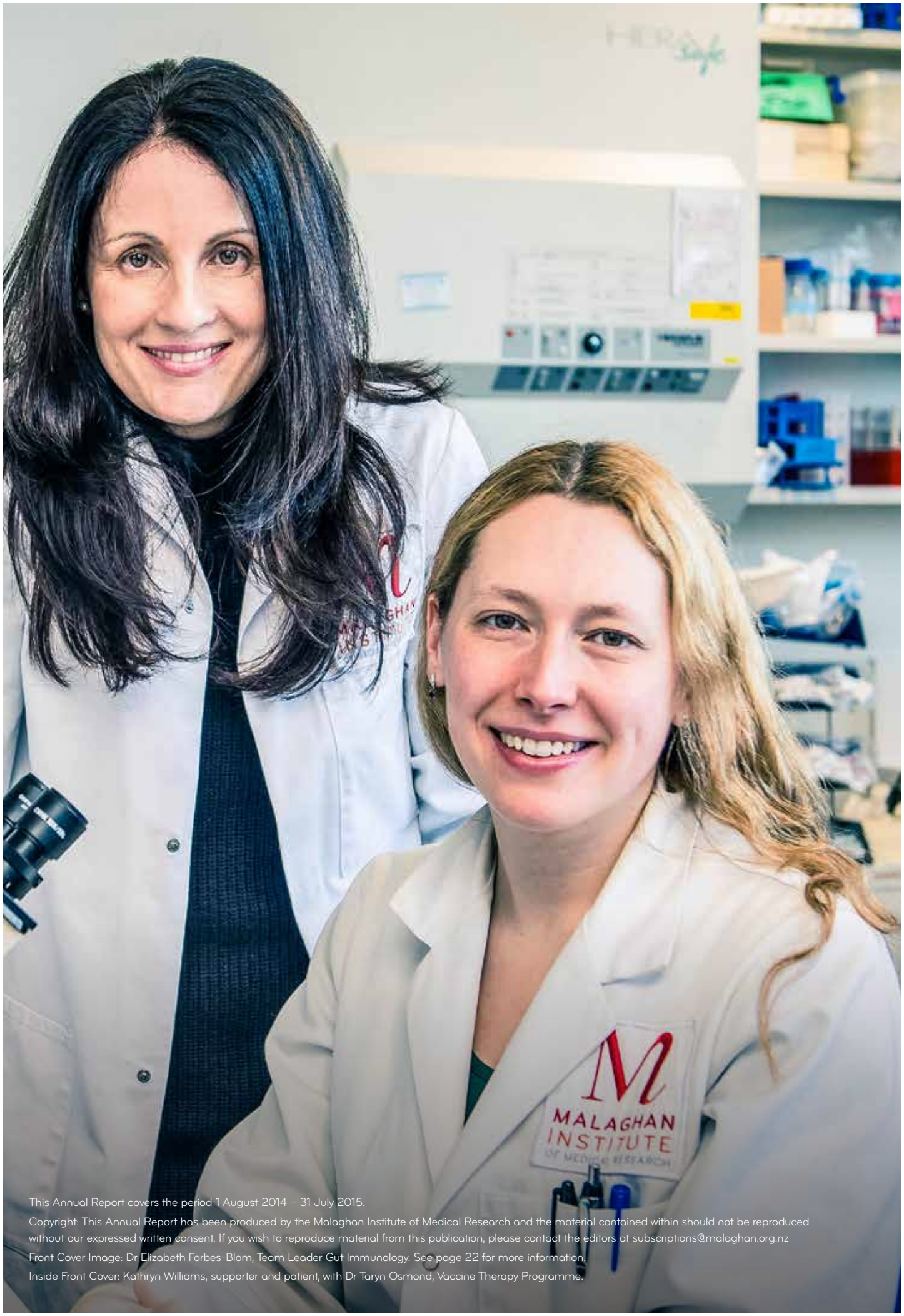
Annual Report

2015

MALAGHAN INSTITUTE
OF MEDICAL RESEARCH



This Annual Report covers the period 1 August 2014 – 31 July 2015.

Front Cover Image: Dr Elizabeth Forbes-Blom, Team Leader Gut Immunology. See page 22 for more information.

Inside Front Cover: Kathryn Williams, supporter and patient, with Dr Taryn Osmond, Vaccine Therapy Programme.

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Malaghan Institute staff, 2015.

About Us

The Malaghan Institute aims to make a difference to people's lives. Our scientists believe that the key to making this difference lies in harnessing the immune system, the body's own natural defence against disease.

The Malaghan Institute is New Zealand's leading independent medical research institute, and celebrates its 50 year anniversary in 2016. Our scientists believe the key to fighting illness lies in harnessing the immune system, the body's own natural defence against disease.

Our work is recognised internationally and our pioneering research programmes focus on immunology, gut immunology and cell biology to seek better treatments and cures for diseases affecting New Zealanders – including cancer, asthma and allergy, Multiple Sclerosis (MS) and infectious disease.

Our reputation as a cutting-edge medical research and training facility sees us house New Zealand's brightest and most creative scientists, doctoral students and post-doctoral fellows. This drive to make a difference to New Zealand's health and wealth means we attract and train the best, which strengths the educational and career pathways for future New Zealand scientists and clinicians.

Our purpose-built facility on the Kelburn campus of Victoria University of Wellington is home to over 85 researchers and support staff. We also maintain close collaborative relationships with tertiary institutions, Crown Research Institutes, hospitals and clinics throughout New Zealand and overseas. Working with 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.

We are a registered charity and to ensure that the vital research at the Institute continues, we rely on contestable grants, corporate sponsorship, trusts, bequests and donations. All funding contributes to the world-changing potential we strive for, and the belief that we will find, and actually make available, cures for the diseases that affect us most in the 21st century.

Chairman's Report

In the last twelve months, we have, I believe witnessed the Malaghan Institute of Medical Research transition into a significant third phase of its journey as an organisation; a period marked by greater self-determination and independence. It is with pleasure that I report on progress this year.

Our growing independence represents an evolution from the early days of individual research in Wellington in the 1960s, through the decades when researchers worked on projects, together or alone; in a rather stop-start fashion, dependent on the vagaries of funding, to the strategic and more cohesive approach the Malaghan Institute is able to adopt today.

This evolution has seen us consolidate according to our strengths; focussing on immunology and immunotherapies. This cohesion, enabled to a large extent by longer term Government funding for our core programmes, is creating a noticeable acceleration in our research.

Two years into our five-year Strategic Plan, a novel way of treating cancer using a chemical specifically designed to stimulate the immune response against cancer has been developed by a joint research venture between the Ferrier Institute and the Malaghan Institute. The technology has been patented and a company called Avalia Immunotherapies has been formed to progress it to clinical trials. It is a significant step, moving discovery from bench to bedside, taking years and considerable investment, but we mark this beginning of the journey with pride and optimism. The ability to continuously feed a discovery pipeline will support and sustain ourselves and our emerging biotech sector, while contributing greatly to the health and wealth of New Zealanders.

As the Director describes in his report, this is only one exciting new breakthrough from our research teams. The board of Trustees, in recognition of the rapidly increasing demands of undertaking research at the cutting edge, decided to invest in two underpinning technologies to build on this momentum.

The first is the upgrade of the technology platform. This suite of specialist equipment has been made possible due to the generosity of the Hugh Green Foundation and our Hawke's Bay Friends.

The other significant upgrade to facilities this year has been the expansion of our Biomedical Research Unit. The $2m planned investment, in partnership with our colleagues at Victoria University of Wellington, future-proofs what is a vital part of medical research: in vivo testing prior to human clinical trials.

The gains made during the last year could not have been made without the support of my talented Trust Board. This year we bid farewell to Dr Allan Freeth and thank him for his contribution during the previous financial year. Joining us is Dr Dianne McCarthy who brings a broad range of skills; from oversight of the Royal Society, involvement in the Government's National Science Challenges, to directorships involved in translating research into economic gain.

Lastly, we congratulate Bryan Johnson who was made an Officer of the New Zealand Order of Merit (ONZM) for his services to business and philanthropy in the New Year's Honours List.

As always we as Trustees are indebted to you, our supporters and providers, for our ability to continue and expand our research, led so ably by our Director, Professor Graham Le Gros, and his Deputy Director Associate Professor Ian Hermans.

Thank you all for joining us on this next stage of the Institute's journey.

Mr Graham Malaghan
ONZM FCILT
Hon DSc
CHAIRMAN

Director's Report

The word 'breakthrough' may now be at risk of over-use syndrome as a descriptor for the new cancer drugs. The tipping point I spoke of last year, with respect to cancer immunotherapy, has seen various international magazines such as *Time* and *Newsweek*, and New Zealand's *North & South* and *The Listener*, each detail startling results in cancer patients with advanced stage disease, for whom there had been no previous hope.

But these new drugs – mostly checkpoint inhibitors which derail cancer cells' ability to turn off immune cell's attack – are not available here yet, are priced at around $200,000 per patient and still do not work in all patients. The future of cancer as a treatable chronic disease may have begun, but it has not yet arrived. Our approach, using a vaccine-based therapy could work alongside the checkpoint inhibitors, helping the immune system to recognise the tumours and destroy them. As our Chairman reports, we have patented this technology and a company called Avalia Immunotherapies has been formed to progress it to clinical trials.

Gaining a deeper understanding of the body's immune responses holds therapeutic promise for many other disease states. Work in our Allergic and Parasitic Diseases Programme has brought us closer to finding a way to cure one billion of the world's poorest citizens of the scourge of hookworm. We created an immune response in the lungs of mice that made it hard for the parasite to live – and, therefore, break its lifecycle. Research to translate these hopeful findings into a practical treatment continues.

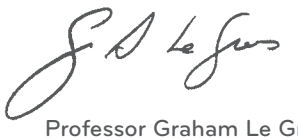
Gut immunology is a rising star in medical research. There is growing consensus that our gut microbiome – the billions of bacteria resident in our intestines – plays a vital part in regulating our health: how we process our food, how we deal with infections, how our immune system develops from birth, and how it responds throughout our lives. In the coming year our work will form part of New Zealand's High Value Nutrition National Science Challenge, investigating links between microbiome and immunity to disease, and how this can be positively influenced by diet.

We started the calendar year with a major discovery in cellular biology; a team jointly led by ourselves and Griffith University in Queensland became the first in the world to demonstrate mitochondrial DNA movement between cells in an animal tumour. A finding like this creates its own energy, and new research possibilities, as we assess the potential for supporting mitochondria in fatigued or dying cells, such as in neurodegenerative diseases or after radiation treatments in cancer.

Our Allergy and Asthma Programme has made new inroads during the year as they investigate which 'culprit' cells initiate an allergic response and validated the mode of action described in our novel asthma vaccine published last year.

We have enjoyed more visibility than ever during the last year. The growing interest in us is a natural result of the enthusiasm around our advances and a symbol of our maturation as an organisation.

I would like to thank everyone who makes our work possible; our Trust Board, our staff, our funders, and our loyal Friends and supporters. I thank you all.



Professor Graham Le Gros
CNZM FRSNZ FRCPA (Hon)
BSc, Dip Immunol, MPhil, PhD
DIRECTOR

Trust Board Profiles

MR GRAHAM MALAGHAN

ONZM, FCILT, Hon. DSc (VUW) (Chairman)

Appointed Chairman of the Malaghan Institute Trust Board in 1990. 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. In 2009 was awarded an Honorary Doctor of Science from Victoria University of Wellington for his key role in rebuilding the Malaghan Institute into the largest independent medical research organisation in New Zealand. Received the Sir Bob Owens award in 2010 for contributions to the transport, logistics industries and the community. Made an Officer of the Order of Merit for his services to medical research and philanthropy in 2012. Current directorships include several private companies.

MR JOHN BEATTIE

LLB (VUW)

Obtained a law degree from Victoria University (1975) and was a Fulbright Scholar to Cornell University (1979). Has been a Trustee of the Malaghan Institute since 1991 and is the Chairman of Malcorp Biodiscoveries Limited, a subsidiary of the Malaghan Institute. He is also Chairman the NZ Sports Hall of Fame. He is a Trustee of the Wanaka Festival of Colour, has been a partner in national law firm Kensington Swan, General Manager of Brierley Investments Limited and was the co-founder of Genesis Research & Development Limited with Professor Jim Watson, a former Trustee of the Malaghan Institute.

ASSOCIATE PROFESSOR 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 both the New Zealand Blood Service and Scots College, and is currently Medical Leader of the Wellington Blood and Cancer Centre and an Associate Professor of the University of Otago.

PROFESSOR PETER CRAMPTON

MBChB, PhD, FAFPHM, MRNZCGP

Appointed to the Malaghan Institute Trust Board in 2008. Is Pro-Vice-Chancellor of the Division of Health Sciences and Dean of the University of Otago Medical School. Is a specialist in public health medicine, with his research focused on social indicators and social epidemiology, health care policy and health care organisation and funding.

MR BRYAN JOHNSON

ONZM, BCA (VUW)

Appointed to the Malaghan Institute Trust Board in 1998. Obtained a commerce degree from Victoria University of Wellington 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 as Chairman of the Duke of Edinburgh's Award and was a Trustee of the Wellington Stadium Trust. Bryan is also the Founder President of First NZ Capital. In 2015 was made Officer of the New Zealand Order of Merit (ONZM) for his services to business and philanthropy.

PROFESSOR GRAHAM LE GROS

CNZM, FRSNZ, FRCPA (Hon)

Appointed to the Malaghan Institute Trust Board in 1995. 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. Is a Professor of the Department of Biological Sciences, Victoria University of Wellington. Made a Fellow of the Royal Society of New Zealand, and a Companion of the New Zealand Order of Merit (CNZM) for his services to medical research, in 2014.

DR DIANNE MCCARTHY
ONZM, CRSNZ, PHD MSC (Hons) BA BSC

Appointed to the Malaghan Institute Trust Board in 2015. Was Chief Executive of the Royal Society of New Zealand (2007-2014) and has over 20 years' experience in various management and governance roles in the tertiary education, science and health sectors. Currently sits on the Council of the University of Auckland and the Advisory Board of its Centre for Brain Research. Is a Director of Powerhouse Ventures Ltd, the Cawthron Institute, and a member of the governance groups of the Dodd-Walls Centre for Photonic and Quantum Technologies, and two National Science Challenges, Ageing Well and Healthier Lives. Is a Trustee of the Deafness Research Foundation (NZ). Made an Officer of the New Zealand Order of Merit in 2008, for services to education, and a Companion of the Royal Society of New Zealand in 2015, for services to science.

MR MATTHEW MALAGHAN
BCom

Appointed to the Malaghan Institute Trust Board in August 2008. Graduated from Otago University in 1994 with a Commerce degree. Subsequent employment with Refrigerated Freight Lines in Auckland and Melbourne, and Sea Containers Group in London, Madrid and Buenos Aires. Owns and operates property and mineral processing businesses in New Zealand and Australia. A Director of the Perlite Institute (USA). Member of the NZ Institute of Directors.

DR DAVID MOSSMAN
QSM, BVSc, MRCVS, MNZIF

Appointed to the Malaghan Institute Trust Board in 2005. Attended Lincoln College and then graduated from the University of Queensland in 1965 with a Veterinary Degree. Awarded the Australian College of Veterinary Scientists college prize in 1978 and in 1984 the Coopers NZ Farm Management Award for significant innovative farm management in New Zealand. Keynote speaker at the World Angus and Hereford Conferences. A member of the Lindisfarne College Board 1981-85. Managing Director of private farming, forestry, finance and property companies. President of the Hawkes Bay Friends of the Malaghan Institute and retired rural veterinarian since 2001. Awarded The Queen's Service Medal for services to veterinary science in 2012.

MS NICOLA SLADDEN
LLB, MPH

Appointed to the Malaghan Institute Trust Board in July 2014. Appointed Banking Ombudsman at the Office of the Banking Ombudsman in August 2015 after four and a half years as Deputy Banking Ombudsman. Has at least 15 years' experience in dispute resolution, a law degree from Victoria University and a Masters of Public Health from Boston University. Was previously the Chief Legal Advisor at the Office of the Health and Disability Commissioner and has worked in private practice. Has published and presented on dispute resolution in New Zealand and abroad.

MR C DAN WILLIAMS
CA

Appointed to the Malaghan Institute Trust Board in 2005. 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.

PROFESSOR MIKE WILSON
MA PHD CANTAB

Appointed to the Malaghan Institute Trust Board 2013. Is Pro Vice Chancellor for the Faculties of Science, Engineering, Architecture and Design at the Victoria University of Wellington. Obtained a 1st class degree in Natural Science from Cambridge University (1980), then obtained a PhD in Physics (1984) after carrying out research with the Radio Astronomy Group at the Cavendish Laboratory. Was appointed as a Lecturer in Applied Mathematics and was subsequently promoted to Senior Lecturer, Reader and Professor of Applied Mathematics (1986) and was appointed as Head of the School of Mathematics at the University of Leeds (2001). In 2005, was appointed as Dean for the Faculty of Mathematics and Physical Sciences at the University of Leeds before joining the Victoria University of Wellington in 2013.

A Pillar of the Malaghan Institute Dr William E Paul (1936 – 2015)

Dr William E (Bill) Paul who passed away in September 2015 can be viewed as an unseen pillar of the Malaghan Institute and I would like to honour him for his vital contribution. He was my mentor when I first met him in 1987 at NIH Washington DC, and remained so. The role he played in helping establish my career in New Zealand, securing major grants, and creating the momentum that the Malaghan Institute now enjoys is considerable.

Twenty years ago he supported my Wellcome Trust International Senior Research Fellowship, an international grant of $1.5 million which enabled me to build and develop our research programme here. It was a companion to the Malaghan Haematology Fellowship which supported Professor Franca Ronchese at the time. The research landscape then, was as it is now, competitive and challenging but we did not have a body of local research to showcase. That someone like Bill Paul, a person who lent his leadership to NIH-sponsored AIDS scientific activities in the 1990s, when prior to that there had been neither a comprehensive plan nor a unified budget to steer America's approach to the disease, gave us backing, bred confidence. He believed, as I did, that we could achieve world-class investigations here in New Zealand.

Bill spoke at New Zealand conferences which empowered our scientific community. He enabled Professor Franca Ronchese and my sabbaticals at the NIH Laboratory for Immunology, which further strengthened international networks, and then in 2001 he supported the allergic diseases research programme. The momentum this generated enabled me to make a series of successful HRC funding proposals and put our research at the cutting-edge internationally.

Bill allowed Cindy Watson, his staff member at NIH, to take a couple of year's absence to work at the Malaghan Institute. Her husband Steve Watson, a professional strategic consultant, helped us to structure and develop the Institute's internal processes, and negotiate the stunning premises we now occupy on the Kelburn campus.

Dr Willian E (Bill) Paul.

Over subsequent years his collaboration and support for our scientific research helped shape New Zealand immunology.

Now this vital pillar is gone but his confidence and support, his mentorship and friendship, have created a strong and enduring legacy. We are now on an established journey with medical research in New Zealand but it could never have happened without Bill Paul.

Professor Graham Le Gros
CNZM FRSNZ FRCPA (Hon)
BSc, Dip Immunol, MPhil, PhD
DIRECTOR

Research

For five decades the Malaghan Institute has built and sustained a completely independent approach to medical research in New Zealand.

Today our scientists are recognised internationally for their leading research into the development of more effective immunotherapies and treatments for cancer, asthma and allergy, Multiple Sclerosis and infectious disease; and for gut immunology.

Our goal is to deliver medical research discoveries that provide tangible health benefits to our nation.

Cancer

With the first cancer immunotherapy drugs becoming available for patients – and producing some spectacular early results – the long-heralded era of immunotherapy has finally become a reality.

The antibody-based drugs (also known as checkpoint inhibitors), anti-PD-1 (pembrolizumab, Keytruda) and anti-CTLA-4 (ipilimumab, Yervoy) are very expensive and are neither approved nor available in New Zealand at this time. But overseas, both are significantly increasing the survival rates of people with advanced melanoma, for whom there was previously no effective treatment.

Researchers at the Malaghan Institute have anticipated this moment for a number of years. In fact, the new therapies exploit knowledge that was first gained in the 1990s, when Professor Graham Le Gros' group carried out some early studies in this area.

At the beginning of an immune response, T cells are deployed to fight a cancer cell or virus. As the natural healing processes take place, molecular mechanisms in the body turn down and eventually switch off T cell activity. Although the new antibody-based drugs and the vaccine therapies in development at the Institute both create the elevated levels of T cells required to kill cancer cells, they act on this process in quite different ways.

The antibody-based drugs prevent cancer cells from switching off T cell activity. Vaccine therapy, however, works by creating a stronger initial immune response by stimulating the body to produce more T cells to fight the tumour.

Associate Professor Ian Hermans sees the two approaches as complementary. He believes that being able to use vaccines to initiate immune responses and antibody-based drugs to maintain their activity will be of particular benefit to the large group of patients whose immune systems do not respond to either therapy alone.

A number of laboratory studies at the Institute support this theory, with the combination working well to prolong immune responses to cancer cells in preclinical models. The focus now is to continue improving the vaccines, ensuring these observations translate to better outcomes for cancer patients. M

Associate Professor Ian Hermans.

Vaccine therapy works by creating a stronger initial immune response by stimulating the body to produce more T cells to fight the tumour.

RESEARCH TEAM

Associate Professor Ian Hermans

Professor Gavin Painter (Ferrier Research Institute)

Professor Franca Ronchese

Dr Robert Weinkove

Dr Lindsay Ancelet, Astrid Authier-Hall, Dr Camille Baey, Evelyn Bauer, Dr Collin Brooks, Kathryn Farrand, Cameron Field, Dr Olivier Gasser, Connie Gilfillan, Dr Martin Hunn, Dr Sabine Kuhn, Dr Brigitta Mester, Dr Taryn Osmond, Emma Petley, Amy Shepherd, Gene Swinerd, Ching-Wen Tang, Dr Jianping Yang.

Vaccine Therapy Programme Group 2015: Dr Robert Weinkove, Astrid Authier-Hall, Emma Petley, Dr Olivier Gasser, Kathryn Farrand, Ching Wen Tang, Dr Taryn Osmond, Dr Lindsay Ancelet, Associate Professor Ian Hermans.

MAURICE WILKINS CENTRE PROJECTS

The Maurice Wilkins Centre, a New Zealand centre of research excellence, is supporting a range of projects at the Malaghan Institute under its *Harnessing the immune system to treat cancer programme*.

Patients with glioblastoma multiforme, a severe and incurable type of brain cancer, are being studied in one project led by Associate Professor Ian Hermans. These patients typically relapse within months of current treatment, so new therapies are desperately needed.

"We are monitoring various immune cells in these patients over the course of treatment, to try and find a window where vaccination to the cancer may be most effective. We believe that glioblastoma cells are very good at supressing any immune responses made towards them, so if we see a decrease in the number of cells that suppress the activity of T cells during treatment, this could be the best time to give a vaccine," he says.

Other projects include the discovery and further development of new vaccines, and drugs that limit the ability of tumours to suppress immune responses. This ongoing research is in collaboration with Maurice Wilkins Centre researchers at the University of Auckland and chemists at the Ferrier Research Institute.

Associate Professor Hermans is one of eight current principal investigators at the Centre, charged with refining research themes and distributing funds to Maurice Wilkins Centre investigators throughout New Zealand.

"We are pleased that the ongoing relationship between the Malaghan Institute and the Maurice Wilkins Centre enables us to continue working with the best researchers across the country to progress our discoveries to viable drug candidates." M

TRANSLATING DISCOVERIES

AVALIA IMMUNOTHERAPIES

A new company, Avalia Immunotherapies Ltd, has been formed to commercialise the novel synthetic vaccine technology created by the long-term collaboration between the Malaghan and Ferrier Research Institutes.

The vaccine technology is the product of a ten-year research and development collaboration between immunologists at the Malaghan Institute, led by Associate Professor Ian Hermans, and chemists at the Ferrier Research Institute, led by Professor Gavin Painter.

Associate Professor Hermans believes the creation of the company recognises that the synthetic vaccine project has progressed beyond the discovery phase and now needs a defined structure and different expertise as it moves into commercialisation and Phase I clinical trials.

The company's Chief Executive Officer, Dr Shivali Gulab, Victoria Link Ltd, says significant investment for pre-clinical evaluation and refinement of the product is now needed.

"To get our vaccine through the 'valley of death' from academic discovery to the market via human clinical trials, we need specialised acumen and expertise. Avalia provides a vehicle for us to package and develop the technology and to attract private and public investment," she says.

The vaccine technology has been fully developed in New Zealand, meshing existing chemistry, immunology, drug manufacture and clinical trial expertise from throughout the country.

"We've made the original discovery and developed the intellectual property in New Zealand, but to license it offshore at this stage would mean the loss of potential major economic benefits. Of course we have to take on more risk, but there is a significant opportunity to build our biotechnology expertise locally. This base would then be available to help develop other technologies and potentially support the creation of a new biotechnology hub here in the future," she says.

Associate Professor Hermans believes the creation of the company recognises that the synthetic vaccine project has progressed beyond the discovery phase and now needs a defined structure and different expertise as it moves into commercialisation and Phase I clinical trials.

The new vaccine technology has been patented in four separate intellectual property filings or patent families. Although the vaccines have been developed to target cancer, the technology is also applicable to any disease where a strong T cell response is beneficial.

"The most effective way – perhaps the only way – for us to have an impact on health is to have a pharmaceutical company partner with us to progress the vaccine concept through later stage clinical trials. If we can undertake more of the development here, such as Phase I trials, then New Zealand will gain greater benefit from the significant investment we've already made."

Avalia was founded by the Malaghan and Ferrier Research Institutes in combination with Powerhouse and the New Zealand Venture Investment Fund.

TRANSLATING DISCOVERIES

DEMONSTRATING THE VACCINE'S MODE OF ACTION

Vaccines traditionally have two separate components: an antigen (such as a protein fragment) that stimulates an immune response, and an adjuvant, a chemical that magnifies the body's response to the protein fragment.

The vaccines being developed for commercialisation by Avalia are delivered with these two components physically linked together, which makes them extremely effective. Once they reach the right location in the body the components separate and initiate an immune response.

"Some modes of activity are quite standard in the pharmaceutical industry," says Associate Professor Ian Hermans, "so you can make a lot of assumptions about how your drug is working at a cellular level."

This vaccine, however, has a completely new mode of activity. If it were successfully commercialised, it would be the first of its kind.

"It's unusual in that it relies on a series of molecular and cellular interactions that happen one after the other. Once delivered to key cells in the lymph nodes, the vaccine triggers activity from a second cell type. This cell then oversees the activation of a third, the T cell, which is sent to kill the tumour."

Although the vaccine's action is well understood in animals, it must be shown to work in the same way in humans before being allowed to progress to a clinical trial.

"There is no precedent for what we are doing with this vaccine – it's completely new. Although all the cell types involved are found in humans, their distribution and number is different to the animals we have been studying. Our first goal therefore is to collect evidence that the concept will work in patients, and the next step is to find out which patients would benefit the most from it." M

RESEARCH HIGHLIGHT

WAKING UP TUMOUR DENDRITIC CELLS

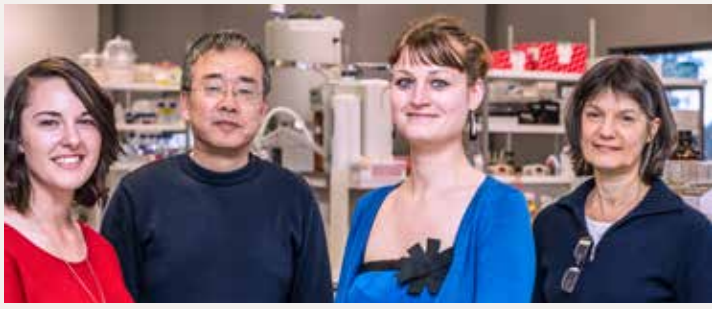
In a tumour, dendritic cells that would normally instruct the immune system to make a response to invading cancer cells are disempowered. This research investigated if tumour dendritic cells could be 'awakened' by two immune-activating stimuli – mycobacteria, a type of bacteria that model infection and monosodium urate crystals that cause gout and model inflammation without infection.

Professor Franca Ronchese says that although mycobacteria have been used historically in immunotherapy, they are poorly understood. "Because the way they work and how best to use them wasn't clear, they fell out of favour. But if we could understand them better and use them in combination with another immune stimulant, they could be useful."

The study found that after the stimuli were given, the protein Interleukin 1-beta was produced. This activated two types of T-cells to make a response to the tumour: CD4 cells as well as cytotoxic T-lymphocytes. It appears that the CD4 cells help the lymphocytes work for longer.

"As we often find in the immune system, a network of cells is helping each other. When we took out the interleukin 1-beta, we blocked the activity of CD4 and got a poorer immune response. By changing one factor we were able to study the relationships between these different types of cells."

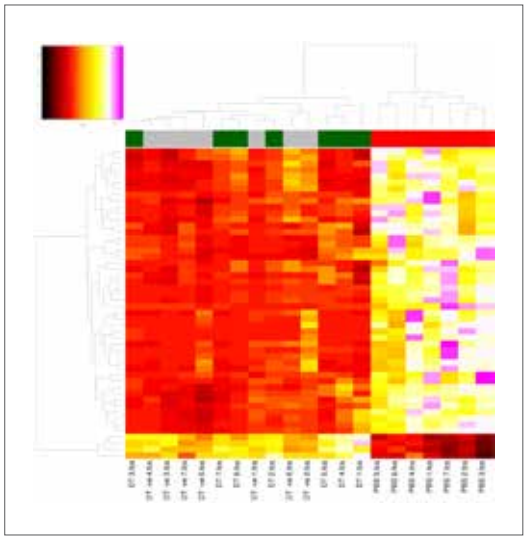
Kuhn S, Yang J, Hyde E, Harper J, Kirman J, Ronchese F (2015) L-1beta receptor-dependent priming of anti-tumor CD4 T cells and sustained anti-tumor immunity after peri-tumoral treatment with MSU and mycobacteria. OncoImmunology (in press).



Connie Gilfillan, Dr Jianping Yang, Dr Camille Baey, Professor Franca Ronchese.

Asthma & Allergy

Harnessing the power of bioinformatics, a technology that makes use of computer software and analysis methods to probe biological systems, requires large-scale data processing capability, a knowledge of statistics and a good deal of bravery on the part of the researcher.



Heatmap showing the results from a bioinformatic analysis of flow cytometry data.

Instead of making a hypothesis based on detailed cellular interactions, the technology forces a scientist to stand back and take a landscape-scale look at the cascade of changes that might result from a single perturbation to a biological system. Ideally, the experiment throws up some (but not too many) new leads.

Professor Franca Ronchese is using bioinformatics to investigate the processes that begin an allergic reaction. Focussing on the immune system's dendritic cells, she is investigating the similarities between various types of cells rather than the differences.

After inducing allergy in two different ways in a mouse model, genetic changes in the transcriptome (all the molecules of RNA rather than DNA) of dendritic cells were compared with a control group. The vast amount of data created was then filtered to home in on the relevant changes.

The hunt eventually led Professor Ronchese to several interesting molecules whose identities could not have been predicted from previous research. Her team is now characterising the role of these molecules and preparing the research for publication.

Bioinformatics can be applied to any field where a large amount of data is generated. One example is flow cytometry, a well-established cell identification and counting method. Fluorescent probes are attached to specific molecules on the surface of cells, which allows the cells to be separated and counted when irradiated with laser light of different colours.

As this technology has matured, the number of probes has grown to 12 or more which, although more powerful, results in thousands of possible combinations and generates huge amounts of data. Bioinformatics enables researchers to look at the combination of probes attached to the cells of interest – dendritic cells in this case – and also highlights other interactions that may not have been anticipated.

Studying the molecules on the surface of a cell enables researchers to discover more about the processes going on inside a cell, as well as highlighting unexpected relationships between different types of cells. These relationships can then be explored in further experiments.

The Malaghan Institute gratefully acknowledges the ongoing support of the Hugh Green Foundation in the Cell Technology Suite.

RESEARCH TEAM

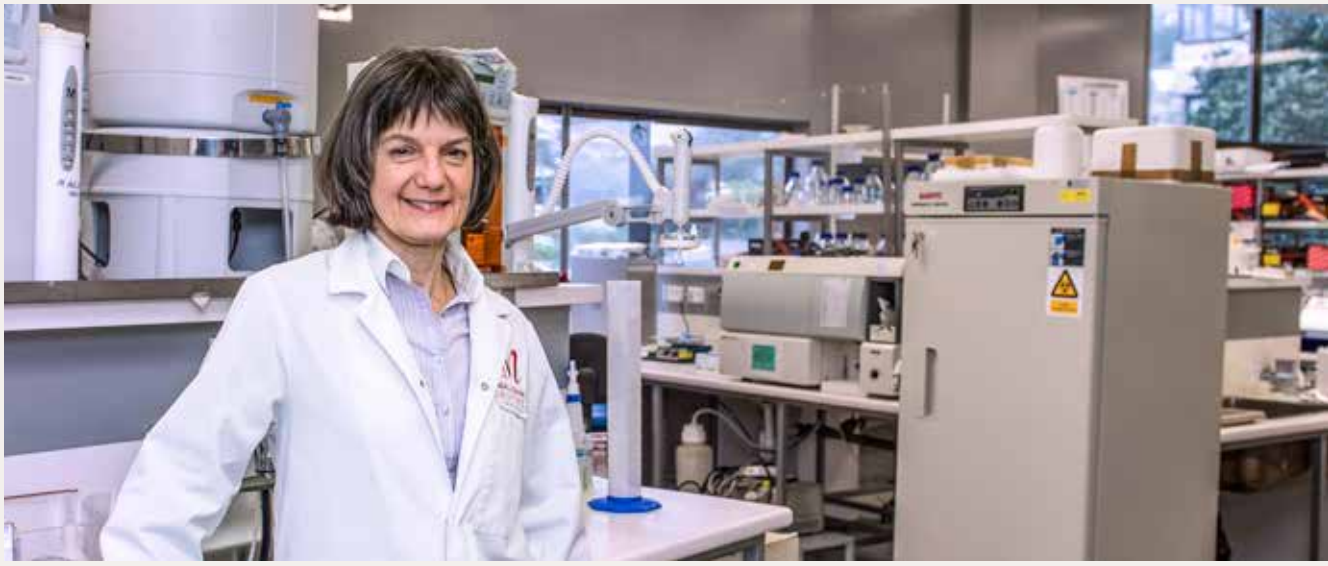
Professor Franca Ronchese

Dr Melanie McConnell (Research Associate)

Dr Lisa Connor, Dr Emmanuelle Cognard, Dr David Eccles, Connie Gilfillan, Kerry Hilligan, Sotaro Ochiai, Sam Old, Dr Alex Smith, Shiau-Choot Tang.

RESEARCH HIGHLIGHT

CELLULAR ACTION OF ASTHMA VACCINE CONFIRMED



Professor Franca Ronchese.

Following on from research published in Nature Chemical Biology in 2014 describing a successful trial of a vaccine targeting asthma, Professor Franca Ronchese's team have fully described the vaccine's mode of action.

"Although we suspected what was going on, we didn't know for sure. This research used three different methods to prove that our initial results showing a suppression of the allergic response were correct," she says.

The research demonstrated that asthma-causing dendritic cells are attacked by cytotoxic T-lymphocytes (CTL, a type of immune cell) that are produced by the immune system after exposure to the vaccine.

Using a mouse model, treatment with CTL caused the dendritic cells to express suicide molecules (that result in their death) and the number of dendritic cells also declined. In addition, observations of cells in the lungs found CTL in close proximity to the dendritic cells.

"Understanding how this vaccine works is very important – you cannot make a drug better until you understand exactly how it works. We now know that the vaccine is going to the right cells and why it induces such a good immune response." *M*

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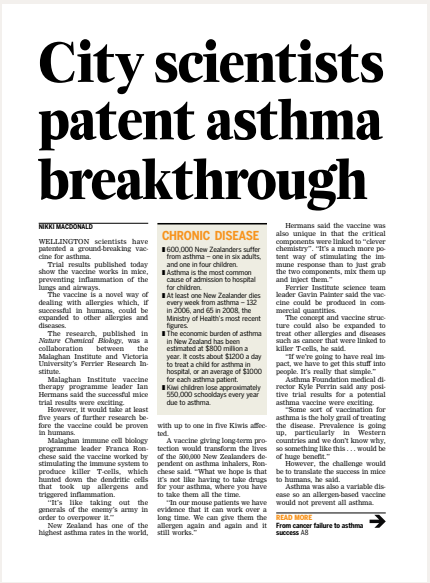


City scientists patent asthma breakthrough

NIKKI MACDONALD

WELLINGTON scientists have patented a ground-breaking vaccine for asthma.

Trial results published today show the vaccine works in mice, preventing inflammation of the lungs and airways.

The vaccine is a novel way of dealing with allergies which, if successful in humans, could be expanded to other allergies and diseases.

The research, published in *Nature Chemical Biology*, was a collaboration between the Malaghan Institute and Victoria University's Ferrier Research Institute.

Malaghan Institute vaccine therapy programme leader Ian Hermans said the successful mice trial results were exciting.

However, it would take at least five years of further research before the vaccine could be proven in humans.

Malaghan immune cell biology programme leader Franca Ronchese said the vaccine worked by stimulating the immune system to produce killer T-cells, which hunted down the dendritic cells that took up allergens and triggered inflammation.

"It's like taking out the generals of the enemy's army in order to overpower it."

New Zealand has one of the highest asthma rates in the world, with up to one in five Kiwis affected.

A vaccine giving long-term protection would transform the lives of the 500,000 New Zealanders dependent on asthma inhalers, Ronchese said. "What we hope is that it's not like having to take drugs for your asthma, where you have to take them all the time.

"In our mouse patients we have evidence that it can work over a long time. We can give them the allergen again and again and it still works."

Hermans said the vaccine was also unique in that the critical components were linked to "clever chemistry". "It's a much more potent way of stimulating the immune response than to just grab the two components, mix them up and inject them."

Ferrier Institute science team leader Gavin Painter said the vaccine could be produced in commercial quantities.

The concept and vaccine structure could also be expanded to treat other allergies and diseases such as cancer that were linked to killer T-cells, he said.

"If we're going to have real impact, we have to get this stuff into people. It's really that simple."

Asthma Foundation medical director Kyle Perrin said any positive trial results for a potential asthma vaccine were exciting.

"Some sort of vaccination for asthma is the holy grail of treating the disease. Prevalence is going up, particularly in Western countries and we don't know why, so something like this . . would be of huge benefit."

However, the challenge would be to translate the success in mice to humans, he said.

Asthma was also a variable disease so an allergen-based vaccine would not prevent all asthma.

CHRONIC DISEASE

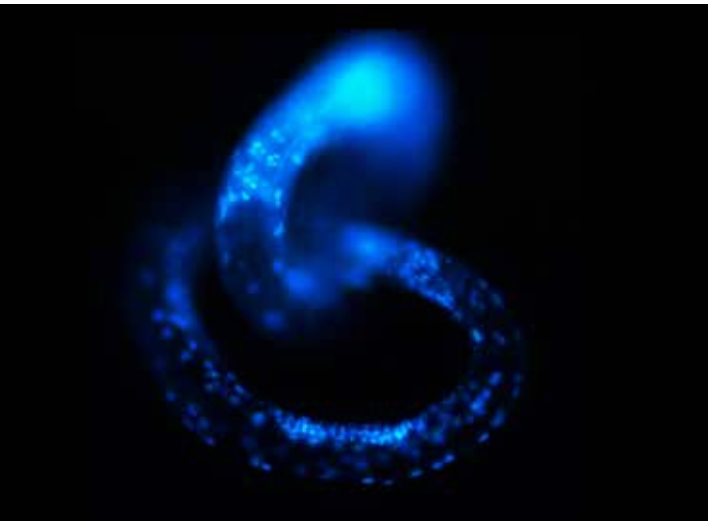
- 600,000 New Zealanders suffer from asthma – one in six adults, and one in four children.
- Asthma is the most common cause of admission to hospital for children.
- At least one New Zealander dies every week from asthma – 132 in 2006, and 65 in 2008, the Ministry of Health's most recent figures.
- The economic burden of asthma in New Zealand has been estimated at $800 million a year. It costs about $1200 a day to treat a child for asthma in hospital, or an average of $1000 for each asthma patient.
- Kiwi children lose approximately 950,000 schooldays every year due to asthma.

READ MORE

From cancer failure to asthma success A8

Dominion Post front page 6 October 2014.

Parasitic Diseases



A microscopic image of the parasite Nippostrongulus brasilenisis. DNA staining reveals the brighter blue of the cells' nuclei.

The mechanisms by which parasitic worms subdue the immune system have been studied at the Malaghan Institute for many years because of their potential to dampen harmful inflammatory immune responses, such as those made in asthma and allergy.

Over millions of years, parasitic worms have evolved complex mechanisms that enable them to survive and reproduce inside a host species by hiding from or manipulating their host's immune system. The mechanisms by which these organisms subdue the immune system have been studied at the Malaghan Institute for many years because of their potential to dampen harmful inflammatory immune responses, such as those made in asthma and allergy.

The rodent gut worm Heligmosomoides polygyrus is known to have a strong effect on its host's immune system, inducing the production of chemicals and regulatory cells that dampen down responses towards it. Nippostrongylus brasiliensis, another rodent worm, is used in laboratory studies to model infection with human hookworm. It migrates through the skin to the bloodstream and lungs and then enters the gut, causing anaemia and tissue damage.

In new research, N. brasiliensis was given to mice already infected with H. polygyrus. (Infection with more than one worm models real world scenarios where people in Asia and Africa live with a number of parasitic worms in their bodies.) Because of the immune dampening effect of H.polygyrus, it was expected that N. brasiliensis would flourish in the mice.

Surprisingly, the exact opposite occurred and one of the most robust and repeatable protective immune responses against this worm to date was observed. Within 24 hours, N. brasiliensis parasites in the lung (a crucial and very damaging part of its life cycle) were being attacked and killed by the immune system to a much greater extent than in the mice without H. polygyrus infection.

Work to solve this mysterious result is now underway, with researchers exploring how a worm restricted to the gut (H. polygyrus) could affect immunity in distant organs like the lung. One focus is the damaging effect that H. polygyrus has on a mouse gut. During larval development, the parasites burrow into the gut lining and puncture it, allowing metabolic products and gut bacteria to leak into the bloodstream. Protein-containing secretions from the worm that modify the immune system could also be involved. M

RESEARCH HIGHLIGHT

THREE IMMUNE CELLS WORK TOGETHER

Professor Graham Le Gros and Dr Tiffany Bouchery-Smith.

> "This new knowledge sheds light on how cells in the lung can set up the chronic inflammatory process that leads to emphysema, chronic obstructive pulmonary disease and chronic allergic diseases, if unchecked."

Research published in the prestigious journal *Nature Communications* sets out the cellular mechanisms in the lung that are involved in protecting mice against infection with the parasitic worm Nippostrongylus brasiliensis.

Three types of immune cell were found to be involved: lung CD4(+) T cells, group 2 innate lymphoid cells and macrophages. The study showed a new connection between innate lymphoid cells and T cells during the immune response made to the worms.

"Other groups have studied the interaction of the parasite with the immune system in detail when it was living in the rodent's gut, but we were interested in researching the immune response made towards the earlier lung stage," says Professor Graham Le Gros. "We already knew that there are significant protective mechanisms in the lung and also, as a model for human hookworm, knowing how to target the worm as it arrives in the lung could reduce the significant damage it causes there."

Microscope images of the parasites after attack by immune cells (presumably macrophages) were included in the publication, showing first a bubble then a rupture in the outer membranes of their larval stage – a novel and exciting finding.

"Understanding how and where the worms are being attacked is an important step. It allows us to target research towards a future vaccine at the site where they are naturally most vulnerable."

Professor Le Gros says that although the immune cells in the lungs check parasite infections, they also drive the lung damage seen in conditions such as allergy and asthma. So, as well as investigating parasitic diseases in their own right, these experiments could help better understand the immune responses involved in allergy and other inflammatory diseases. M

Bouchery T, Kyle R, Camberis M, Shepherd A, Filbey K, Smith A, Harvie M, Painter G, Johnston K, Ferguson P, Jain R, Roediger B, Delahunt B, Weninger W, Forbes-Blom E, Le Gros G (2015) ILC2s and T cells cooperate to ensure maintenance of M2 macrophages for lung immunity against hookworms. Nature Communications 6:6970.

RESEARCH TEAM

Professor Graham Le Gros

Dr Tiffany Bouchery-Smith

Dr Mali Camberis

Dr Kara Filbey

Professor Mike Berridge.

Mitochondrial transfer between cells

Research published in a leading biological journal earlier this year by Professors Mike Berridge and Jiri Neuzil (Griffith University) and their teams described a previously unreported biological phenomenon – the transfer of mitochondrial DNA between cells.

In their experiments, Professor Berridge's team used a drug to remove mitochondrial DNA from breast cancer and melanoma cells. Several weeks later after injecting these cells into mice, they were observed to have regained mitochondrial DNA, which was identified as coming from surrounding tissue rather than the tumour cells. After acquiring these replacement mitochondria (which provide energy for the cell and contain mitochondrial DNA), the cancer cells were once again able to grow and metastasize.

Although other groups had seen mitochondria move between cells in culture, the Malaghan Institute team and its collaborators were the first to demonstrate the transfer in a mouse tumour model.

News of the discovery, which according to Professor Berridge flies in the face of everything that was previously believed about mitochondrial dynamics, created a wave of reaction in the biological research community as well as traditional and social media internationally. Its consequences have also spawned several new areas of research at the Institute.

Research funding is now being sought to explore the fundamental mechanisms of the transfer process.

RESEARCH HIGHLIGHT

SCIENTIFIC REVIEW OF MITOCHONDRIAL TRANSFER

Professor Mike Berridge and his Griffith University collaborators recently published a review of the field of mitochondrial transfer between cells, which he says puts the Malaghan Institute's work into the context of other research internationally.

"This invitation to review the field was made on the back of the major contribution we've made, showing that mitochondrial DNA was transferred between cells in animal tumour models."

The original paper was reviewed in *Nature Reviews Cancer*, the world's top cancer journal, and been highly cited and downloaded several hundred times in its first six months.

Professor Berridge believes the mitochondrial transfer process is novel and fascinating from an academic perspective, but also has relevance to understanding the physiology and pathology of a raft of different diseases.

"It's a real opportunity for the Institute to become involved as pioneers in a new research area that relates to brain function, the development of cancer, aging, degenerative diseases and aspects of early life and development."

Berridge MV, Dong L, Neuzil J (2015) Mitochondrial DNA in tumour initiation, progression and metastasis: role of horizontal mtDNA transfer. Cancer Research 75: 3203–3208.

RESEARCH HIGHLIGHT

MITOCHONDRIAL TRANSFER AFTER BONE MARROW TRANSPLANTATION

Proving that the mitochondrial transfer observed in mice also happens in humans is a challenge. Dr Robert Weinkove, a Consultant Haematologist at Wellington Blood and Cancer Centre and Clinical Research Fellow at the Malaghan Institute, believes that people who have undergone a certain type of bone marrow transplant may provide the ideal opportunity to find out.

Bone marrow transplantation is sometimes used to treat patients whose bone marrow is not working properly or to try to cure aggressive types of leukaemia. Patients receive chemotherapy or radiotherapy to suppress their own bone marrow and are then given an infusion of bone marrow stem cells from a matched donor.

"We know that successful transplants often result in a mixture of donor and recipient cells in a patient's bone marrow, so by looking very closely at the patient's cells, we might be able to detect donor mitochondria in patient cells, and vice versa", says Dr Weinkove.

Previous research has found that approximately two percent of immature red blood cells inside the bone marrow are connected to each other by tiny bridges.

"We are interested in finding out if these bridges are part of a mechanism that allows mitochondria to move between cells. They could be irrelevant, or they could be important evidence of cells communicating with each other – we just don't know yet."

This research also has implications for people with rare disorders caused by the failure of their mitochondria to work properly.

"If we can show that healthy mitochondria are able move from donor cells into patient cells then we could potentially use bone marrow transplantation to treat these devastating conditions."

RESEARCH HIGHLIGHT

HRC GRANT FOR BRAIN RESEARCH

Dr Melanie McConnell, Malaghan Institute Research Associate and Senior Lecturer at Victoria University of Wellington, received funding of more than $1 million from the Health Research Council in 2015 to research the transfer of mitochondria between cells in the brain.

The project will look at the transfer mechanism in healthy and injured brain cells, as well as in cancerous glioblastoma multiforme cells.

"We've discovered this process of mitochondrial transfer and now we want to find out if it's a normal process that occurs in response to damage and stress", she says. "There's a growing recognition that the way cells handle stress might be more sophisticated that we thought."

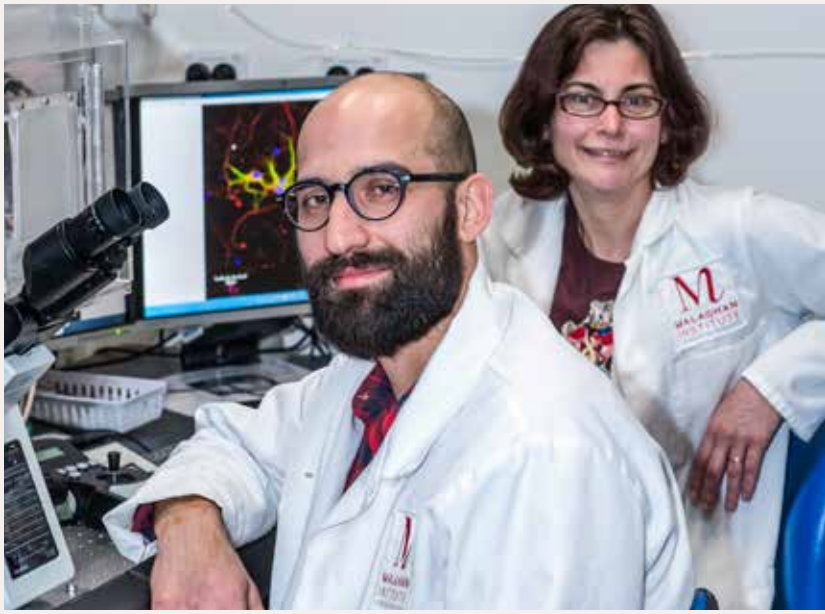
In the brain, neurons (nerve cells that transmit information through the body by chemical and physical messages) are surrounded and supported by star-shaped brain cells called astrocytes. Dr McConnell believes that astrocytes may donate their mitochondria as part of this support.

"We think the process may be important in helping neurons survive stress, with mitochondria from the astrocytes moving in to restore mitochondrial function in the vulnerable nerve cells."

To model this process in the laboratory, brain cells are deliberately injured then tracked to study the effect on mitochondrial transfer and the consequence for the cell. Early results show much higher rates of transfer into an injured cell than an uninjured one.

Dr McConnell's brain injury research models the effects of diseases such as Alzheimer's and Parkinson's. "We're looking at the chronic injury caused by genetic mutations associated with Alzheimer's and other degenerative brain diseases. Understanding the processes that go on could be useful for developing new therapies for brain disease."

The project is also studying the relationship between cancer cells and normal cells. In glioblastoma, a highly treatment-resistant brain cancer, the cancer cells may be using the same mitochondrial transfer mechanism to their advantage.



Remy Schneider and Dr Melanie McConnell.

"Unlike the normal brain cells, these cancer cells are invulnerable. We are studying the mitochondrial transfer process to see if it has been changed in some way to give them this ability to resist treatment."

In the experiment, glioblastoma cells were injured in the same way as normal brain cells, and mitochondrial transfer of the two types of cell was compared.

"We hypothesise that mitochondrial transfer increases cell survival. Obviously we want to encourage survival of a damaged normal cell, and to prevent survival after injuring a cancer cell. If we understand the process and work out how to manipulate it, we could change the balance between life and death for injured cells."

RESEARCH TEAM

Professor Mike Berridge, Dr Melanie McConnell (Research Associate), Dr Robert Weinkove, Jodi Chandler, Carole Grasso, Remy Schneider.

Kylie Price.

Hugh Green Cytometry Core

During the past year our researchers have uncovered more information at a cellular level, faster and more accurately, in their work to develop immune-based therapies for the treatment of diseases such as cancer, asthma and allergy, multiple sclerosis and parasitic infection. We are so grateful for this support.

This suite of specialist equipment including flow cytometry and confocal microscopy is proudly called the Hugh Green Cytometry Core. It is used by researchers at the Malaghan Institute and hired out to external investigators.

In simple terms, flow cytometry works by utilising lasers to stimulate fluorescent dyes that are attached to a cell type of interest via an antibody specific for that cell. This enables recognition, characterisation and subsequent sorting of cells of interest.

The generosity of the Hugh Green Foundation enabled the Malaghan Institute of Medical Research to upgrade its technology platform in August 2014.

Gut Immunology

EARLY LIFE DIET-GUT MICROBIOTA-IMMUNE INTERACTIONS

From the moment we are born our bodies begin to be colonised by trillions of non-human organisms: bacteria, fungi, and viruses collectively known as microbiota. In parallel, our immune system is developing. The infant gut is simply not just a tube for processing food and eliminating waste; it is the site of a dynamic cross-talk between the developing immune system and the trillions of resident and transitory cells of the microbiota.

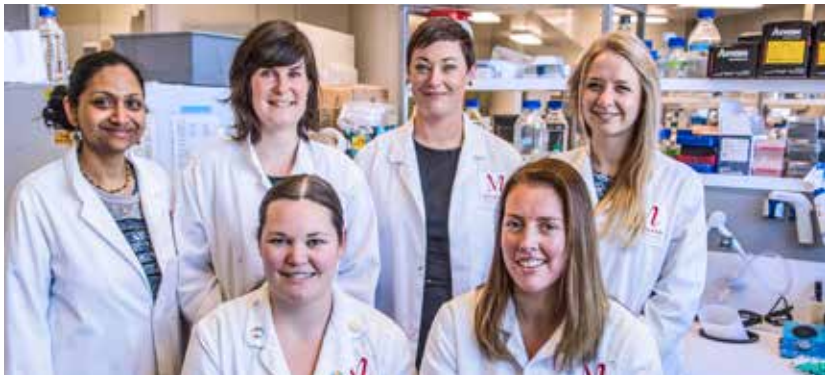
Once we achieve adulthood, 70 to 80 percent of our immune cells reside in the gut. How this vital and interactive environment, the diet-microbiota-immune axis, develops during the first years of life and how this impacts on long-term health is under investigation by Dr Elizabeth Forbes-Blom and her Gut Immunology team. They hope to identify specific milestones which influence the development of an optimal immune system and identify linkages with non-communicable diseases such as asthma, allergy, obesity, cardiovascular disease and cancer.

One of the first exposures to microbes from the outside world happens during birth. Early colonisation of gut microbiota happens via the mouth and nose as the baby travels down the birth canal. Emerging evidence points to this as a significant step in the development of the immune system, with babies born by Caesarean section procedures having different communities of microbes to babies born vaginally. This is of paramount interest, as babies who enter the world through Caesarean delivery face much greater risks of developing a range of chronic immune disorders caused by defects in the immune system, compared to those delivered naturally.

The Gut Immunology team aims to discover whether poor or defective immune maturation in early life, following altered gut microbiota colonisation, leads to increased rates of allergy, colitis, obesity or cancer over a lifetime. Earlier investigations using completely germ-free mice, bred without any micro-organisms but colonised with gut microbiota after birth, confirm poor immune development.

There is growing research consensus that our gut microbiota plays a vital part in regulating our health. A better knowledge of how our early life diet-gut microbiota-immune interactions lead to health into adulthood would open a range of new opportunities for intervention.

In more recent work Dr Forbes-Blom's team has used two strains of mice, bred separately, born by Caesarean (BALB/c C) or vaginally (BALB/c V) as a starting point to pose questions of the relationship between diet, microbes and immune development and responses to models which mimic human disease.



The Gut Immunology Team: Karmella Naidoo, Dr Lieke van den Elsen, Catherine Plunkett, Dr Elizabeth Forbes-Blom, Angela Jones, Dr Hazel Poyntz.

NATIONAL SCIENCE CHALLENGE

The first of the Government's 11 National Science Challenges was launched in April 2014. Research into high-value foods with validated health benefits, or 'High Value Nutrition' forms another work stream for the Gut Immunology team. Investigations underway now, into possible links between gut microbiota signature and immune response to vaccination, could to lead to improved health in our communities and, through commercialisation, drive New Zealand's economic growth.

There is a great deal of variation in how well people respond to an influenza vaccine. Ideally, the adaptive immune system responds, or gears up so it can prepare itself to fight a disease it has not yet met, in the future. Some people are high responders, developing good levels of protective antibodies and others less so. Whether there is a connection between gut microbiota and this immune response has not yet been clearly established, but by studying the gut microbiota signatures of high responder vaccinated individuals and that of low responders, Dr Forbes-Blom's team hope to establish those links.

The research team will then investigate the ability of foods that influence the gut microbiota to beneficially modulate immune defence against influenza.

Gene sequencing analysis is also being used to establish the genetic profile of vaccine responders. Typically a month after vaccination the body has (or has not) developed good levels of protective antibodies, but after only one week blood samples may reveal the so called 'early genes' that are up regulated or down regulated.

This blood work has two crucial benefits to the research team; it forms a back-up if associations between gut microbiota signature and adaptive immune response are not clear, identifying responders via their genetic signatures. It also lays important exploratory and feasibility groundwork to distinguish low vaccine responders for future human nutritional intervention trials with industry partners, to establish food-health claims for immune defence against respiratory infection.

RESEARCH HIGHLIGHT

EARLY LIFE IL-25

A growing consensus indicates strong links between our microbial signature and our immune response but does our microbial signature in early life and adulthood relate to that of our mothers, and how does this relate to health, disease and the immune system?

Catherine Plunkett has investigated the development of our gut microbiota and the cross-talk with the immune system from early life. She used two different mouse models: normal wild type mice and the other deficient in an important hormone IL-25. This hormone is known to drive the (unhelpful) T helper cell 2 (Th 2) pathway in allergy, while it paradoxically seems to play a helpful role in limiting gut inflammation. Mice that cannot produce IL-25 develop severe gut inflammation as well as having very different microbiota as compared to 'normal' mice.

To isolate how genetic and microbial-driven effects contribute to gut health, pups from these mice were cross-fostered twenty-four hours after birth by adoptive mothers with the different genetic makeup. As most gut microbiota are acquired after birth, cross-fostering allows the acquisition of the foster mother's gut microbiota. While Catherine found the pups tended to adopt the profile of the foster mother, she has now found exciting new roles for both microbes and IL-25 itself in maintaining healthy gut function.

PhD student Catherine Plunkett.

PRINCIPAL INVESTIGATORS

Dr Elizabeth Forbes-Blom, Catherine Plunket

Multiple Sclerosis

Associate Professor Anne La Flamme.

Although different drugs are now available to treat the relapsing-remitting form of MS, there is no treatment for people with progressive disease.

The chronic autoimmune disease multiple sclerosis (MS) causes nerve degeneration via a process of demyelination – damage to the myelin sheath around the nerves – and results in a gradual loss of feeling, movement, vision and cognition.

MS is a complicated disease. Not only do the symptoms vary from one person to another, but the disease has three distinct forms: a relapsing-remitting form and two progressive forms. Although different drugs are now available to treat the relapsing-remitting form, there is no treatment for people with progressive disease.

The Malaghan Institute's MS research programme is led by Associate Professor Anne La Flamme from Victoria University of Wellington's School of Biological Sciences. Her work is investigating the underlying mechanisms of the disease and working to develop new drugs for progressive disease. A new mouse model of progressive disease is now established at the Institute and is proving to be a valuable tool in understanding demyelination.

In work with Innate Immunotherapeutics developing a new immune-based therapy for secondary progressive MS (MIS416), Associate Professor La Flamme and her team are investigating the major biological pathways that are critical for the drug to work. They are also looking for biomarkers that may link a beneficial response in a patient to a change in their immune system. By tracking these changes, valuable information about which therapies would benefit particular groups of patients can be gained.

MIS416 is currently in a Phase 2B clinical trial in Australia and New Zealand.

CLINICAL TRIAL PREPARATIONS IN PROGRESS

A donation of $35,000 from the 2015 Great New Zealand Trek is helping with preparations for a safety trial of the antipsychotic drugs clozapine and risperidone that are being repurposed to treat MS.

Each year the Trek brings together sponsored horse riders, walkers and mountain bikers who travel a portion of New Zealand together over a week. The Trek began in Cape Reinga in 2006 and is due to finish in Bluff in 2020. During this time, the Trek has contributed more than $200,000 for MS research.

Clozapine and risperidone have been used since the 1970s to treat bipolar disorder and schizophrenia. Research in 2014 by Associate Professor Anne La Flamme showed they could also be useful in treating the damage caused by the immune system during MS.

"We need to find out which drug will work better and to check its safety for people with MS. We are now applying for ethics approval, then once we have the remainder of the funding, we can start the trial."

Being part of the Trek is always a special experience for Associate Professor La Flamme, who travelled through Canterbury with the group this year.

"I like to walk along with people so I can answer their questions about the research we're doing, one on one. The Trek has supported our MS research directly since 2009 and maintains a real interest in what we do. We are so grateful to everyone involved. Their support has made a very significant contribution to our research programme over the years and enabled us to do things we couldn't have dreamed of doing otherwise."

The Malaghan Institute would like to pay special tribute to the contribution of Great New Zealand Trek Trustee Bo Patel, who sadly passed away during the 2015 Trek.

In February 2016 the Trek will begin in Springfield and travel south to the Fairlie area. See greatnewzealandtrek.org.nz for more information.

The Great New Zealand Trek 2015.

"We worked hard to rid ourselves of parasites during the 19th and 20th centuries with drugs and public health strategies to prevent transmission," says Associate Professor La Flamme, "but now we're finding that they may bring real benefits for people with multiple sclerosis, type 1 diabetes, Crohn's disease and ulcerative colitis, for example."

RESEARCH HIGHLIGHT

THE HEALTH BENEFITS OF HOSTING A PARASITE

A special edition of the journal *Parasite Immunology*, edited by Associate Professor Anne La Flamme, explores the ways in which parasites modify the human immune system and reduce the incidence or severity of some chronic immune-related diseases, including MS.

To survive in a human host, parasitic worms (such as hookworms) modify the immune system and dampen down its responses towards them. This modification also dampens the incorrect immune responses that result in autoimmune diseases and asthma. The interactions between parasite infection and the immune system have been studied at the Malaghan Institute by Associate Professor La Flamme's and Professor Le Gros' teams for many years.

"The next challenge is to understand how the parasites are modifying the immune system, with the aim of developing new therapeutic agents or products to treat these disorders," she says.

The journal issue presents an update of current research across a range of diseases and ends with a caveat that not all parasites have protective benefits.

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Full details of all 'in press' publications will appear in the 2016 Annual Report.


Science
AAAS
FRONTIERS IN LIGHT MICROSCOPY
CANCER


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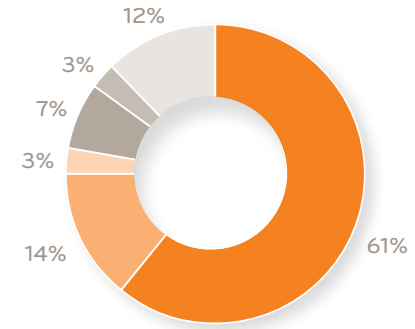
Financial Report

The Malaghan Institute is an independent charitable trust with tax-exempt status.

With no host organisation or direct government funding, we rely on fully-costed grants and public donations to support our research programmes.

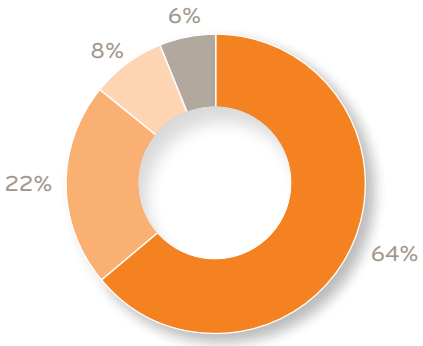
The Trust Board provides the Institute with strategic guidance and oversight, while the management of the Institute is overseen by Director Professor Graham Le Gros.

Financial Overview



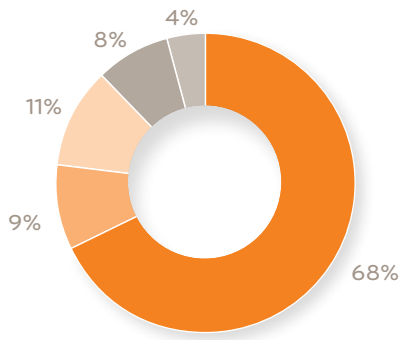
INCOME

	Contestable Grants – Government
	Contestable Grants – Non-Government
	Other Funding
	Donations
	Bequests
	Investment Income



EXPENDITURE

	Science
	Laboratory Support
	Communications/Development
	Administration



STAFF

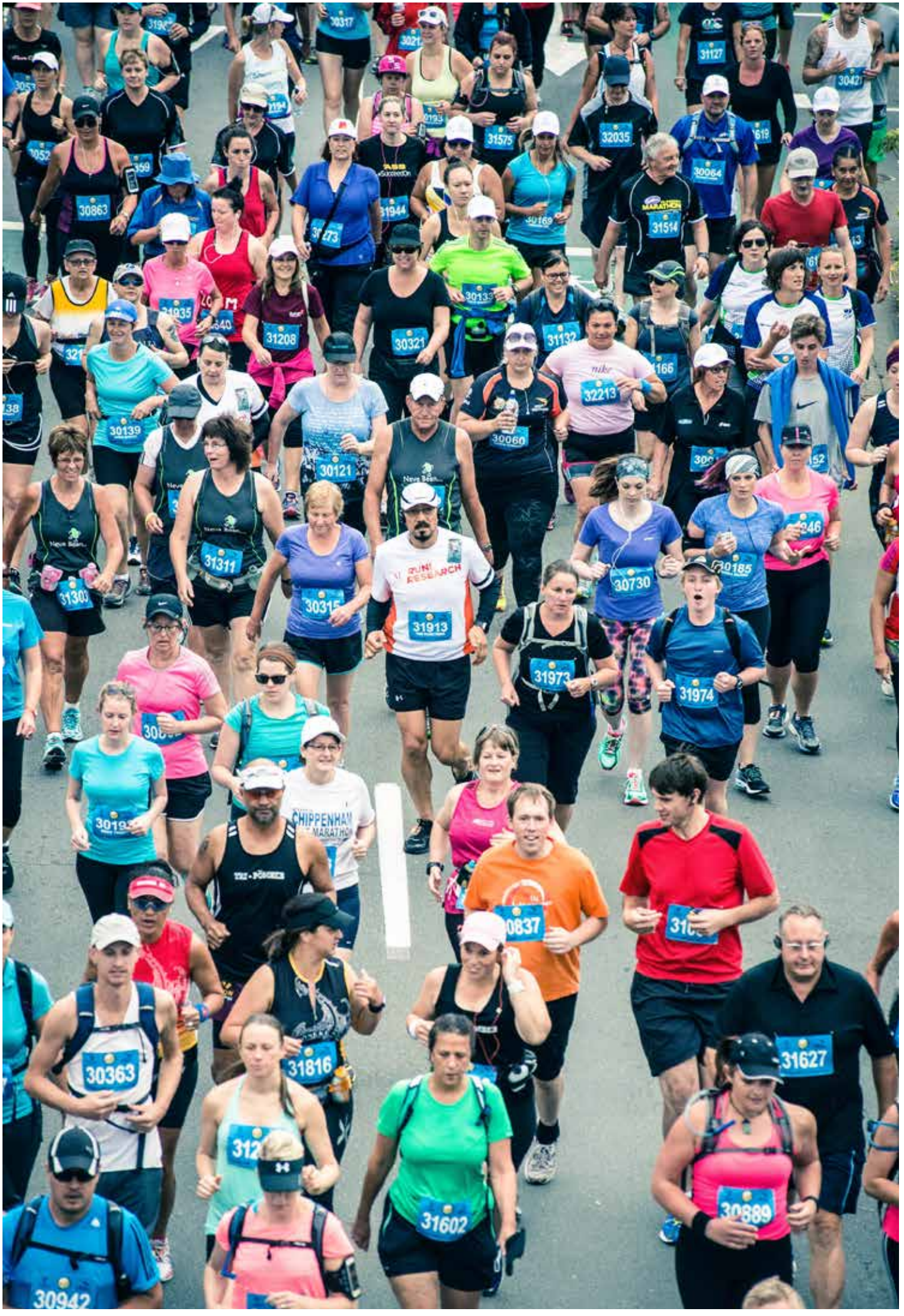
	Science
	Science Students
	Laboratory Support
	Communications/Development
	Administration

Financial Performance
For the Year ended 31 July 2015

	2015 CONSOLIDATED	2014 CONSOLIDATED
Income – Operating		
Donations	732,467	541,369
Grant Income	7,156,477	6,857,824
Interest Received	105,204	109,858
Sundry Income	184,514	171,056
	8,178,663	**7,680,106**
Expenses – Operating		
Researchers' Salaries	3,201,125	3,282,715
Research Operating Expenses	3,625,988	3,823,826
Administration	1,148,804	983,356
	7,975,916	**8,089,897**
Operating Surplus (Deficit)	**202,747**	**(409,791)**
Depreciation	460,002	410,293
Grant Income for Fixed Assets	438,032	482,460
Net (Deficit)	**180,777**	**(337,625)**
Income – Other		
Capital Endowment Fund – Investment Income	1,127,600	667,754
Capital Endowment Fund – Bequests	263,011	750,001
Net Income Capital Endowment Fund	**1,390,611**	**1,417,755**

Financial Position
As at 31 July 2015

	2015 CONSOLIDATED	2014 CONSOLIDATED
Current Assets	2,709,445	3,198,221
Current Liabilities	2,338,753	3,126,879
Working Capital	**370,693**	**71,342**
Fixed Assets	2,094,421	1,537,245
Investments	8,803,042	8,088,181
Total Equity	**$11,268,156**	**$9,696,768**



Run for Research participants 2015.

Community Engagement

The Malaghan Institute of Medical Research has enjoyed more visibility than ever during the last year.

Our enthusiasm to share research developments is more than reciprocated by the interest from our supporters, our Friends, our donors and our volunteers. This network of individuals, clubs and corporate partners gains more energy and more momentum each year. We are extremely grateful.

This support enables us to remain independent and allows us to follow a journey of discovery that is dictated by research and hope, a hope that all our supporters share in.

Fundraising Highlights

People from all walks of life support the Malaghan Institute. Our staff shares a common goal with those who want to make a difference to the lives of other New Zealanders. Together we have built important relationships that have lasted for many years. These bonds cross clubs, community groups, corporate groups, individuals, people who enjoy good health, and those for whom the search for new cures and treatments has direct importance.
We sincerely thank them all.

SUPPORT FROM ROTARY AND LIONS CLUBS

The enduring and generous community work of the Rotary and Lions Clubs of New Zealand translates into valuable support for Malaghan Institute research programmes.

These two organisations have donated over $350,000 to the Institute over the years. Contact between us has strengthened during this period with many visits and meetings hosted at our Wellington site. Like their members, we too are neighbours, community leaders and global citizens uniting for the common good and to make a difference to the lives of others.

We wish to convey a heartfelt thank you to these clubs and their members throughout New Zealand for their direct support to progress New Zealand-led medical research.

For several years members of the Rotary Club of Port Nicholson have been outstanding supporters through quiz nights, auctions and dinners. Their dedication and enthusiasm was evidenced once again by their fundraising dinner and auction at the Intercontinental Hotel in May 2015. We are hugely appreciative of the efforts made by Rotary to support their research and education.

Over a weekend in April 2015 the Island Bay and Eastern Suburbs Lions Clubs held a book fair in support of our scientists and their research. Their time and efforts directly contributed to the purchase of vital equipment. Their fundraising helps to bring our discoveries from bench to bedside and closes the divide between theory and care for our friends and families.

Thank you to all the members of these clubs who so selflessly dedicate their time to make our communities better.

TRADE ME

For the first time Trade Me joined the Run for Research at Wellington Round the Bays 2015.

Thanks to the dedication and enthusiasm of their charities coordinator Catherine Smith, 13 of their staff ran Round the Bays to help raise over $4,800 through our online Run for Research fundraising website and also sold some unique auction prizes on Trade Me. The team were so dedicated that eight of them auctioned themselves off for a half-day's labour to the highest bidder. Incredibly someone paid them $455 to clean up their garden and contribute towards our world-class research.

Thanks to the Hurricanes, Jason Pine, Park Road Post Production, Ormelie Lodge and Lexus and our scientists at the Institute they helped raise an additional $4,500 for the Run for Research through auctioning five unique prizes on the Trade Me website, with Trade Me forgoing all listing and success fees so that 100 percent went directly to our research.

The winning bidders were able to join the Hurricanes for a training session, the captain's run and watch a game from the corporate box; to sit with Jason Pine as he commentated during a Phoenix match and see the behind the scenes at the game; see the inner workings of the sound mixing facilities, picture grading suites, client cinema and meet a senior member of staff from Weta Digital at Park Road Post Productions; drive a Lexus for a Hawke's Bay getaway; and experience a day in the life of a scientist at the Malaghan Institute. A massive thank you to everyone that made these prizes possible and those that bid on them.

Not only were Trade Me fantastic fundraisers and supporters, they continue to be great ambassadors for our work and firm believers that the key to better treatments lies within our own immune system. We are proud to announce that Trade Me will expand the Run for Research to their Auckland office in 2016 and are our official Run for Research Partner.

CORPORATE SUPPORT

Since our inception we have always enjoyed a strong relationship with the New Zealand business community through their financial support, starting with Tip Top Ice Cream through the generosity of Ann and Len Malaghan. This year we introduced a new business sponsorship programme for businesses that want to support the Institute.

We would like to recognise the generosity of our first Lab Partners in 2015: Just Paterson Real Estate, Thermo Fisher Scientific, Nichecom, CQ Hotels, Kinetics Group, and Dave Clark Design.

Our Lab Partner package makes it easy for businesses to strengthen their community relations. At the same time as supporting ground-breaking research into cancer, asthma and allergies and immunology, Lab Partners receive several benefits to help promote your support to your customers, clients, staff and the community.

Astrid Authier-Hall and Corporate supporter Ian Paterson.

nichecom Thermo SCIENTIFIC KINETICS GROUP CQ Hotels Wellington JUST PATERSON Dave Clark DESIGN ASSOCIATES

Friends of the Malaghan Institute

The Malaghan Institute is very fortunate to have the support of four regional volunteer Friends committees. Many of our Friends, and their families, have been touched by diseases, which we work hard to find new treatments and cures. It is a tribute to them that they are steadfast in their support and the generous gift of their time. They work extremely hard on our behalf, not only to raise funds for our work but also to raise awareness and relevance of the Malaghan Institute's work in their respective communities.

Charity Golf Events – about to enter the 18th year – is evidence of our Friends' longstanding commitment and support. During this time they have raised over $1.7 million dollars towards our research; providing sizeable and very welcome funding to our research programme. This year we welcome Rick Hart as the new Chair of the Taupo Friends. Taupo was the first of the four very successful Research Updates hosted by each of our Friends' groups this year, where Professor Le Gros delivered an update on the work of the Institute and its future direction to over 300 people. We celebrate these great Friends:

WELLINGTON COMMITTEE

Fiona Matthews (Chair)
Susan Laurenson
Adrienne Bushell
Maureen Cameron
Kelly Falconer
Jill Kinloch
Lizzie Quinn
Denise Udy

HAWKE'S BAY COMMITTEE

David Mossman (President)
Denise Bull (Chair)
Andrew Blair
Margie Dick
Beth Kay
Andy Neilson
Bry Mossman
Rosemary O'Connor
Jan Paterson
Kathy Rittson – Thomas
Bruce Speedy
Lynn Spence
John Stovell
Terry Thornton
Graeme Wedd

AUCKLAND COMMITTEE

Greg Shepherd (Chair)
Jo Flemming
Julie Sobiecki
Deborah Malaghan
Matthew Malaghan
John Lister
Raewyn Roberts
Jacque Lethbridge
Rebecca Gadson-Green
Trudi Gardner

TAUPO COMMITTEE

Rick Hart
Sarah Hart
Judy Kirk
Anne Velvin


MALAGHAN
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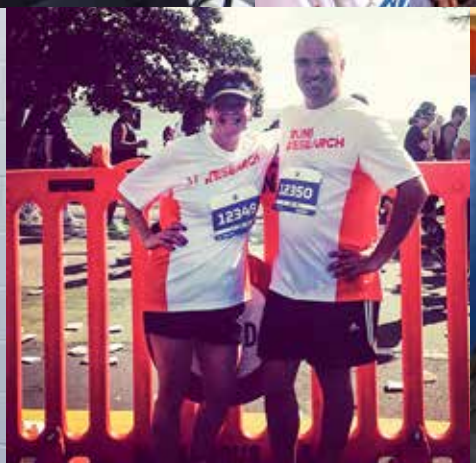

Funding Sources

Thank you to the following individuals, organisations, businesses, Trusts and Foundations who helped support the Malaghan Institute from 1 August 2014 – 31 July 2015.

Grants, Trusts and Foundations

Grants, Trusts and Foundations
Arthur N Button Charitable Trust
Auckland Uniservices
BEA Trust
Cancer Society (Wellington)
Cancer Society of New Zealand
Carol Tse (No 2) Family Trust
Cawthron Institute
EM Pharazyn Charitable Trust
FH Muter Charitable Trust
Fonterra
Genesis Oncology Trust
Glenpark Foundation
Health Research Council of New Zealand
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Humphry Bayly Charitable Trust
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Margaret Russell Charitable Trust
Massey University
Maurice Wilkins Trust
Michael Williams Family Trust
Ministry of Business, Innovation and Employment (MBIE)
Ministry of Scientific Research and Technology
New Zealand Community Trust
New Zealand Lotteries Grants Board - Health Research
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NZ Cancer Society
NZ Guardian Trust
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The Paddy Brow Charitable Trust
The Pegasus Sports Foundation
The Southern Trust
University of Otago
Victoria University of Wellington
Wellington Medical Research Foundation

In Memoriam

Donations were received in memory of the following people:
Erica Bridgman
Mike Carter
Adam Chisholm
Carol Cooper
John Craig
Allan Criglington
Peter Farrington
B.M Forbes
J M Greenhalgh
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Joyce Hogg
Warwick Isaac
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Ian Montgomerie
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Jessie Laing Parker
Bo Patel
Joan Plant
Dennis Rastrick
Denise Reeve
Murray Owen Smith
Clive Stephens
George Edwin Tanner
Lynnette Webb
Frederick Wheeler

Bequests

The following people generously left bequests to the Institute:
Valerie D Aplin
Beryl J Baker
Estate of Walter Arthur Clark
Carol Cooper
Henry W Dangerfield
Jean Dougall
Joyce M Fountain
Ethel R Hitchen
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Royston Hospital
Sacred Hill Wines
Sally Bush
Sam & Mary Orton
Saunders Unsworth
SBM Legal
Selby J Palmer
SenateSHJ
Shed 5 Restaurant and Bar
Silver Fern Farms
Simpson Grierson
Spark New Zealand
Spicers
Spy Valley Wines
Squawking Magpie Wines
Steph Pinel
Steve & Laura Smith
Strawberry Fare Restaurant
Strawberry Patch
Sudhindra Rao
Sue Train
Suncourt Hotel Taupo
Systems Advisory Services Ltd
The Kelliher Charitable Trust
The Hawkes Bay Club Inc
Thomson's Suits
Thorndon Caci Clinic
Tiki Winery
Tim & Elaine Olphert
Todd Corporation Ltd
Toms Cottage
Trevor Melville
Trinity Hill
Trois on Allen
Tunanui Farm Cottages
Unichem Broadway Pharmacy
Urban Retreat of Hastings
Urban Sanctuary Beauty Therapy Clinic
Veterinary Associates Hastings Ltd
Veterinary Enterprises - Te Awamutu
Veterinary Services HB Ltd - Hastings
Village Press
Vista Café
Wairoa Warrant of Fitness Centre
Wayne & Bev Larsen
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Zephyr Consulting Ltd
Zibibbo Restaurant & Bar
Zoar Trust

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Clemenger BBDO
Earthquake Commission
Abigail Higgins

How You Can Help

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.

We are at the forefront of international medical research, and our scientists believe that the key to fighting illness lies in the immune system. Our research programmes are focused on finding better treatments and cures for diseases affecting New Zealanders – cancer, asthma & allergy, inflammation, Multiple Sclerosis and infectious disease.

The Malaghan Institute is a registered charity. The funds we receive support our research programmes, enabling our scientists to bring new treatments or cures that much closer; for the benefit of all New Zealanders. These are the many ways our supporters help us:

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.

Donations

Donations from individuals and trusts form a large part of our funding. The income is used to support the research programmes. Donations over $5 may be eligible for a tax credit.

In Celebration Donations

Instead of receiving presents for your celebration, please consider asking people to donate to the Malaghan Institute in your name instead.

In Memory

Your gift is a way to express your sympathy and remembrance while at the same time making a real difference to medical research. Gifts can be small or large, in lieu of flowers at a funeral, or as a tribute to a life well lived.

Bequests

The research at the Malaghan Institute is very dependent 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 and 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) 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."

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

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