Annual Report

2014

MALAGHAN INSTITUTE
OF MEDICAL RESEARCH

This Annual Report covers the period 1 August 2013–31 July 2014.

Front Cover Image: Sotaro Ochiai, PhD Student.

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Malaghan Institute staff, 2014.

About Us

The Malaghan Institute is New Zealand's leading independent medical research institute, with a proud history spanning more than four decades. We are here to make a difference to people's lives, and our scientists believe that the key to making this difference lies in the immune system, the body's own natural defence against disease.

Our work is recognised internationally and our pioneering research programmes are focused on finding better treatments and cures for the diseases that affect many New Zealanders – allergy, cancer, asthma, multiple sclerosis (MS), arthritis and infectious diseases.

In addition to our drive for making medical discoveries that impact health, the Malaghan Institute is committed to the education and support of New Zealand scientists and clinicians. Our reputation as a leading-edge medical research and training facility sees us housing New Zealand's brightest and most creative scientists, doctoral students and post-doctoral fellows.

Our purpose-built facility on Victoria University of Wellington's vibrant Kelburn campus is home to around 80 researchers and support staff. We maintain close collaborative relationships with Victoria and other tertiary institutions, Crown Research Institutes, hospitals and clinics throughout New Zealand. Working with organisations worldwide also ensures our scientists keep abreast of the latest developments internationally and maintain our research at a world-class level.

We are a registered charity. To ensure that our vital research 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 make available, cures for cancer, asthma, allergy, arthritis, MS and infectious diseases.

The Malaghan Institute aims to make a difference in 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.

Chairman's Report

The theme of last year's Annual Report was change. Since progress without change is impossible, it is good to be able to report on the advances made this year.

We have now completed the first year of our five-year strategic plan, which reinvigorated and tightened our focus on immunology as the core of our research efforts. Our programmes, as the Director reports, have received international recognition this year.

After some seven years of effort by the Institute, the government recognised that New Zealand's independent research institutes were being handicapped from realising their value to the community by a focus on short term funding. While no new science funding was involved, the Malaghan Institute (and others including the Cawthron Institute) has secured seven-year funding certainty for its core research programmes.

We still need to finance these programmes with additional resources, support our other research endeavours and invest in our facilities to keep our teams at the top of their games. We are currently installing the latest cell sorter technology in a specialised laboratory – the most advanced in the Southern Hemisphere – funded by the Hugh Green Foundation. This, and other equipment funded by supporters this year, has seen our capacity to deliver research outcomes to patients significantly increased.

The current government has recently been returned and its focus on research can now be further advanced with confidence. We are up for that challenge.

Medical science is vital to meeting our country's health challenges, such as an aging population, but medical research can also be a driver of economic competitiveness, innovation and prosperity.

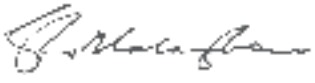
It is also imperative that New Zealand remains at the leading edge of medical science, where the Institute holds a unique position because of its global network of researchers and its ability to apply immunology to national health research priorities.

We have strong relationships in the wider New Zealand community, seen in our Friends groups and the recognition from the Wellington Gold Awards, as reported by the Director. This year Victoria University, our partner and landlord, appointed a new chief executive. We welcome Grant Guilford as Pro Vice-Chancellor, who has a background that is well aligned with our own.

During the year, three trustees stepped down after many years of wonderful service: Dr Jim Watson (22 years), Gary Quirke (13 years) and Professor David Bibby (10 years). Our sincere thanks go to each of them. We also welcomed Nicola Sladden to the Trust Board. Nicola brings a wealth of public health and legal experience to the talent around the table.

This year also saw Professor Graham Le Gros recognised by the Queen, with his appointment as a Companion of the New Zealand Order of Merit. We also marked Professor Le Gros' 20th year as Director, during which time he has crafted and built the Institute into New Zealand's most successful independent medical research institution.

I thank you all for being on this journey of change as we endeavour to find new solutions for the health demands of our community.



Mr Graham Malaghan ONZM FCILT Hon DSc
CHAIRMAN

Director's Report

This year, I am very pleased to report that the Malaghan Institute's pioneering cancer and allergic diseases research programmes have gained major national and international recognition. This firmly establishes the Institute and its scientists as New Zealand's leading independent biomedical research institute.

The Health Research Council of New Zealand (HRC) recognised the value of our research programmes to New Zealand through its internationally peer-reviewed contestable process and awarded $28 million of research contracts through its independent research funding and project schemes. These grants effectively consolidate the Institute's cancer and allergic diseases research projects into a seven-year programme of objectives and milestones to find better treatments for diseases like cancer and asthma, as well as many others that have an immunological, infectious or inflammatory basis.

Of course, this significant award carries with it an increased responsibility and an expectation that the Institute is in a position to deliver more tangible and beneficial outcomes, as well as the capability to translate its scientific discoveries into the clinic.

What I feel is most significant, is that this recognition will give the many donors, supporters, organisations and scientists working with the Institute, increased security and confidence that their efforts have a realistic chance of turning into tangible benefits, since the Institute has achieved a level of size, capability and longer-term funding that is internationally credible.

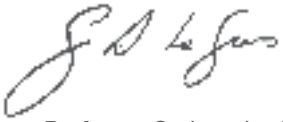
The importance of immunotherapy research and the opportunities it presents, was further endorsed when the editors of the prestigious international journal *Science* named cancer immunotherapy 'Breakthrough of the Year' for 2013. It does now seem that after many years of diligent effort and support, we have reached the point of being able to translate our knowledge of the immune system into significant new tangible outcomes for patients and society.

This excitement is shared in the progress we are making with our unique cancer immunotherapy approach against melanoma, using alpha-galactosylceramide as an adjuvant. The melanoma trial is underway and other related technologies are in development. Similar novel adjuvants, as well as adjuvants that are chemically linked to antigens, are being prepared by our chemistry partners at the newly established Ferrier Research Institute at Victoria University and are providing an exciting pipeline of compounds that will give us a much better chance of success.

As our collaboration with the Ferrier Research Institute demonstrates, we have a network of exceptional national and international partners. When it comes to the search for cures, no one can do it alone. Moving breakthroughs from discovery to patients requires all sectors – academia, government, clinical care and philanthropy – to work together throughout the research and development process.

The Institute's innovative capability was recognised at the Wellington Gold Awards this year. We were presented with the Cyber Gold Award and the Supreme Gold Award for our leadership in technology and for overall excellence.

Community support has played a fundamental role in catalysing innovation at the Institute. I thank all of our supporters for helping us advance medical research so that new treatments are truly within reach. With continued support from our community, we will continue to spearhead medical progress well into the future.



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 and logistics industries, and the community. Current directorships include several private companies.

MR JOHN BEATTIE

LLB

Appointed to the Malaghan Institute Trust Board in 1991 and is the Chairman of Malcorp Biodiscoveries Limited, a subsidiary of the Malaghan Institute. Obtained a law degree from Victoria University (1975) and was a Fulbright Scholar to Cornell University (1979). He is also Chairman of the New Zealand Diabetes Foundation and the New Zealand Sports Hall of Fame, Trustee of the Wanaka Festival of Colour and 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, FRACP, FRCPA

Appointed to the Malaghan Institute Trust Board in 2003. Did postgraduate work at the Fred Hutchinson Cancer Research Centre and the University of Washington. Clinically practises 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 Faculty of Medicine, for the University of Otago. 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.

DR ALLAN FREETH

PhD (ANU Canberra), MBA (Dist) BSc (1st Class Hons)

Appointed to the Malaghan Institute Trust Board in July 2013. Has extensive experience in management and board governance roles including as former CEO and Managing Director of TelstraClear and PGG Wrightson, senior executive roles in Trust Bank as well as a previous Chair/Director on the Boards of Genesis Research and Development Corporation, GNS Science, Treasury Advisory Board, Save the Children and Queen Margaret College. He is currently a trustee of Crimestoppers, Deputy Chair of FilmNZ, and Chairman of Downstage Theatre.

MR BRYAN JOHNSON

BCA

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 Award and was a Trustee of the Wellington Stadium Trust. Is also the Founder President of First NZ Capital.

PROFESSOR GRAHAM LE GROS

CNZM, FRSNZ, FRCPA (Hon), BSc, Dip Immunol, MPHIL, PhD

Appointed to the Malaghan Institute Trust Board in 1995. Was awarded a Fogarty Fellowship at the NIH, Washington DC in 1987-89, 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. A Fellow of the Royal Society of New Zealand, in 2014 was made a Companion of the New Zealand Order of Merit (CNZM) for his services to medical research.

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 New Zealand 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 Bachelor of Veterinary Science. 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 Hawke's Bay Friends of the Malaghan Institute and retired rural veterinarian since 2001.

MS NICOLA SLADDEN

LLB, MPH

Appointed to the Malaghan Institute Trust Board in July 2014. Currently the Deputy Banking Ombudsman at the Office of the Banking Ombudsman. Has more than 15 years' experience in dispute resolution. Has a Bachelor of Law degree from Victoria University and a Master of Public Health from Boston University. 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

Appointed to the Malaghan Institute Trust Board 2013. Professor Mike Wilson 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. Appointed as a Lecturer in Applied Mathematics and was subsequently promoted to Senior Lecturer, Reader and Professor of Applied Mathematics (1986). 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 staff of Victoria University of Wellington in 2013.

Professors Graham Le Gros and Franca Ronchese and Associate Professor Ian Hermans.

Research

The Malaghan Institute holds a unique place in the New Zealand health research sector.

Our scientists specialise in the fields of cellular immunology, haematology, cellular and molecular biology, immune models of human disease and the development of immunotherapies and vaccines.

Our goal is to deliver medical research discoveries that provide tangible health benefits to the community.

Cancer

The editors of *Science*, a prestigious academic journal, named cancer immunotherapy 'Breakthrough of the Year' for 2013.

Using a vaccine to wake up the body's own immune defences to kill tumour cells is the idea at the heart of cancer immunotherapy. The therapy is designed to target a patient's immune system, rather than a tumour.

Dubbed 'Breakthrough of the Year' for 2013 by the editors of *Science*, a prestigious academic journal, cancer immunotherapy now stands proudly alongside previous breakthroughs such as the first cloned mammal and the sequence of the human genome. According to *Science,* the accolade is well deserved since, "...this year, clinical trials have cemented its potential in patients and swayed even the sceptics."

The idea of enlisting the body's own defences to fight cancer is far from modern. The ancient Egyptian, Imhotep, described incising and dosing tumours with a poultice full of bacteria in a papyrus scroll dating from 2600BC, while American William Coley saw patients with a range of tumours recover after he inoculated them with a streptococcal infection in the late 1880s.

Overtaken by more direct methods of cancer treatment – surgery, radiation and chemotherapy – immunotherapy was almost forgotten until the 1980s. Now, its time may have come. Around the world, stories of remission and success in clinical trials are emerging, although clinical treatments remain many years away.

Immunotherapy promises fewer side effects and a permanent cure for cancer. Many cancers respond well to initial conventional treatments, but relapse months or years later. Vaccinating patients against their own cancer creates an immunological memory (in the same way that vaccination protects against a viral infection) so the body would automatically attack if the tumour began to regrow.

In New Zealand, Professor Franca Ronchese initiated research in cancer immunotherapy at the Malaghan Institute in the 1990s. She remains part of the team, now led by Associate Professor Ian Hermans, which is pioneering new approaches based on the use of chemical adjuvants – compounds that are administered alongside a vaccine to provoke a stronger immune response.

Research using alpha-galactosylceramide as an adjuvant is progressing well, with a melanoma trial underway and other related technologies in development. Similar novel adjuvants, as well as adjuvants that are chemically linked to antigens, are being prepared by our chemistry partners at the newly established Ferrier Research Institute at Victoria University of Wellington. This team of expert chemists was formerly part of Industrial Research Ltd, and we have maintained our successful collaboration with the team following their move to Victoria in January 2014.

Our cancer immunotherapy clinical and research programme is a New Zealand first. Within this country, collaborations with top scientists across disciplines such as immunology, biochemistry, molecular biology, chemistry and clinical research are providing all the components necessary to take our research from the laboratory through clinical trials and beyond.

PRINCIPAL INVESTIGATORS

Professor Mike Berridge
Associate Professor Ian Hermans
Dr Melanie McConnell
Dr Gavin Painter (collaborator)
Professor Franca Ronchese
Dr Robert Weinkove

Dr Robert Weinkove, Dr Gavin Painter, Associate Professor Ian Hermans.

RESEARCH HIGHLIGHT

$3.6 MILLION INVESTMENT IN CANCER IMMUNOTHERAPY

The Health Research Council (HRC) of New Zealand has supported the Malaghan Institute's cancer immunotherapy research programme with an investment of $3.6 million over three years. Three projects each received funding of $1.2 million.

Associate Professor Ian Hermans received funding to develop cancer vaccines that use new adjuvants to activate innate-like T cells (a type of white blood cell). The new vaccines are comprised of adjuvants that are chemically linked to fragments of proteins displayed by tumours.

"First, we will check that the vaccines invoke an immune response using cells from human blood. If they do, we will test their ability to prevent tumour growth in cancer models," he says.

Assoc Prof Hermans' project to trial the use of immune-active drugs with a cancer vaccine was also funded. "We believe our cancer vaccines will be most effective when they are used in combination with new drugs called immunomodulators. These drugs prevent the body damping down its immune response, which could help in cancer treatment where we want to induce a strong immune response."

The funding will enable a suite of drugs to be trialled in order to select the most effective candidate.

Professor Franca Ronchese received funding to study a class of dendritic cell that is involved in delaying the growth of tumours after immunotherapy. "The involvement of these cells in anti-tumour immune responses has not been reported before. So, to harness their potential in cancer therapies, we need a better understanding of what they do and how they are different to other dendritic cells."

CLINICAL HIGHLIGHT

TOWARDS A SYNTHETIC CANCER VACCINE

Dr Robert Weinkove, a haematologist at Wellington Hospital and Clinical Research Fellow at the Malaghan Institute, provides clinical support for our cancer immunotherapy programme alongside his work treating patients with blood cancer. He is integral to one of the Health Research Council-funded projects extending the dendritic cell vaccine research programme.

"Going forward, we want to simplify the vaccine. At the moment it requires growing dendritic cells from rare precursor cells in the blood of individual patients, which is quite complex and resource-intensive. This could limit the widespread adoption of our vaccine approach," he says.

Associate Professor Ian Hermans and Dr Weinkove have found that a chemically-linked antigen and adjuvant vaccine may find its way to patients' own dendritic cells and eliminate the need to grow the cells in a laboratory.

"It might it be possible to give the vaccine directly to a patient to induce a similar immune response. This type of synthetic vaccine would be simpler, cheaper and more feasible to use in clinical practice. It could also be patentable."

Alongside development of the synthetic vaccine in tumour models, Dr Weinkove is researching its effects in humans using blood from volunteers and patients with cancer. "We are using blood samples to see if the synthetic vaccine is effective in humans. It is quite exciting – we have some very good preliminary results."

He also plans to test a range of other adjuvants that are linked to an antigen using the same linking technology as the synthetic vaccine.

Evelyn Bauer, Clinical Trials Manager.

"Some immune cells are much more common in humans than in animals. To get the best possible response to vaccination, we want to trial a range of compounds using human blood cells, so we can pick the best candidates to take further."

RESEARCH HIGHLIGHT

MAKING 'BAD' CELLS WORK FOR GOOD

Monocytes are white blood cells that the body can change into different types of cells to fight inflammation and infection. They are also acquired by tumours to help grow new blood vessels or to turn off an immune response towards them. Because of these properties, new anti-cancer therapies are proposed to deplete monocytes and prevent their accumulation in tumours.

In work supported by a Health Research Council (HRC) grant, Professor Franca Ronchese has shown that a more effective approach is to divert these cells into performing a useful function in the body.

"We have found that in some forms of immunotherapy, monocytes can turn into dendritic cells or monocyte-derived dendritic cells (moDCs). The moDCs were able to delay the growth of tumours. This anti-tumour immune response had not been reported before, so we are keen to explore it, as well as find out more about the basic properties of these cells," she says.

The HRC grant will also enable her team, along with Dr Jacquie Harper, to investigate how metabolic syndrome affects the immune system's ability to respond to tumours.

RESEARCH HIGHLIGHT

CANCER VACCINE TECHNOLOGY APPLIED TO ASTHMA

Recently published work in a high-impact journal, *Nature Chemical Biology*, has described a successful trial of a vaccine targeting asthma. The research is an extension of work done by Associate Professor Ian Hermans' team, which is developing vaccines for cancer.

"Cancer and asthma both involve the immune system, but in cancer we are trying to get the body to take notice of foreign proteins, while in asthma, we want to stop it overreacting to an allergen," he says.

The vaccine has been developed in conjunction with the Ferrier Research Institute and required some "pretty clever chemistry". While most vaccines comprise an adjuvant and an antigen mixed together, the new vaccine chemically links the two components.

"By linking them, we make sure they are both delivered to the right place in the body. Once there, they are cleaved and presented to the immune system to initiate a response. We worked with the chemists to design and make a molecule that would come apart cleanly. This was challenging, but Dr Gavin Painter and his team came up with some novel concepts that were ultimately successful."

Although the linked vaccine concept was developed with cancer in mind, Professor Franca Ronchese thought it could also be used to modify an immune response to allergens. "Allergy is the wrong sort of immune response. Using the vaccine, we appear to have initiated a more appropriate immune response and prevented allergy from taking hold."

Patent protection for the linked vaccine has been obtained and opportunities to commercialise the technology will be sought as the research progresses.

Anderson RJ, Tang C, Daniels NJ, Compton BJ, Hayman CM, Johnston KA, Knight DA, Gasser O, Poyntz HC, Ferguson PM, Larsen DS, Ronchese F, Painter GF, Hermans IF (2014). A novel synthetic self-adjuvanting lipopeptide vaccine to induce cytotoxic T lymphocytes that suppress allergic disease. Nature Chemical Biology (accepted).

Ching-Wen Tang was a key part of the synthetic vaccine research programme.

RESEARCH HIGHLIGHT

VITAMIN C AND RADIATION THERAPY

High-dose vitamin C (ascorbate), taken intravenously, is a popular alternative cancer treatment. It is believed to reduce the side effects and enhance the effectiveness of cancer therapy, but is clinically unproven.

Dr Melanie McConnell, Malaghan Institute Research Associate and Senior Lecturer at Victoria University, is researching the effects of ascorbate and radiation on cancer cells *in vitro* and in a mouse tumour model, in collaboration with the University of Otago. Her goal is to improve the evidence base for cancer patients and their doctors.

"Our first study simply compared a brain cancer cell line with a normal brain cell line and we saw a clear difference. With ascorbate, the cancer cells sustained more damage during radiation and were less able to repair the damage," she says.

In a second cellular study, a larger panel of brain cancer and normal cells were treated and the damage sustained was fully characterised.

"We are now very sure of ascorbate's mechanism *in vitro*. It is converted to hydrogen peroxide outside the cell, then the peroxide enters the cell and damages its DNA. Adding this effect to radiation therapy augments the damage and significantly increases the number of cells that are killed."

This year, the ascorbate-radiation treatment was trialled in a mouse brain tumour model. "We expected to get the same result. Surprisingly, we found the opposite – ascorbate in combination with radiation almost totally reversed the effect of the radiation."

Dr Melanie McConnell.

Dr McConnell believes the tumour cells take up ascorbate too readily and leave none for conversion to peroxide outside the cells. She is planning further research to confirm these initial results.

Castro LM, McConnell MJ, Herst PM (2014) Radiosensitisation by pharmacological ascorbate in glioblastoma multiforme cells, human glial cells, and HUVECs depends on their antioxidant and DNA repair capabilities and is not cancer specific. Free Radical Biology and Medicine (Epub ahead of print).
Free Radic Biol Med, 74:200-9 Frontiers in Oncology (in revision).

RESEARCH HIGHLIGHT

THE ROLE OF MITOCHONDRIAL DNA IN CANCER

In work under revision for publication in leading biological journal, *Cell Metabolism*, Professor Mike Berridge and his team explored the role of mitochondrial DNA in the formation and metastasis of tumours.

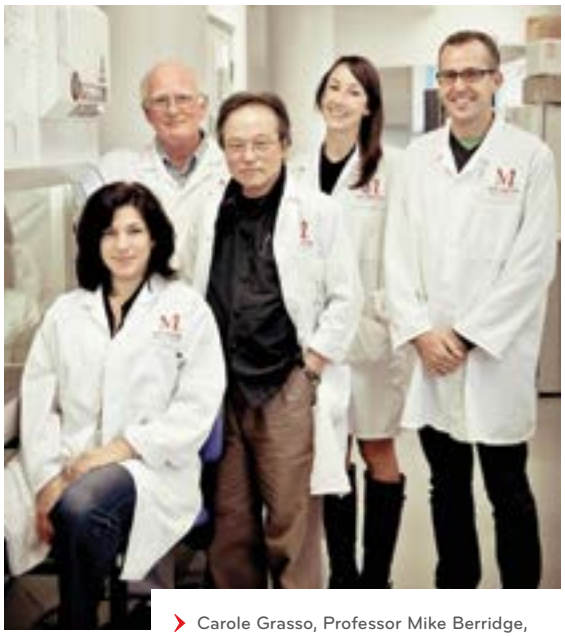
"We are the first and senior authors on the paper, but to publish at this level requires a level of skill and a range of science that is very difficult to achieve without significant collaborations. In this case, Professor Jiri Neuzil and his teams from Griffith University in Australia and the Institutes of Biotechnology and Molecular Genetics, Academy of Sciences of the Czech Republic, provided large amounts of supporting data to meet publication requirements," he says.

Inside cells, mitochondria convert energy from food into a form that can be used by the body. Mitochondria have their own DNA, or genome, which is distinct from the nuclear genome. In their experiments, Prof Berridge's team removed the mitochondrial DNA from breast cancer and melanoma cells and investigated their ability to grow as primary tumours and metastasize.

"We found that although these cells will grow in culture, they will not produce tumours in animals until they have acquired mitochondrial DNA from surrounding normal cells."

Although other groups had seen mitochondrial movement between cells in culture, the Malaghan Institute team was the first to demonstrate the DNA transfer in a tumour model.

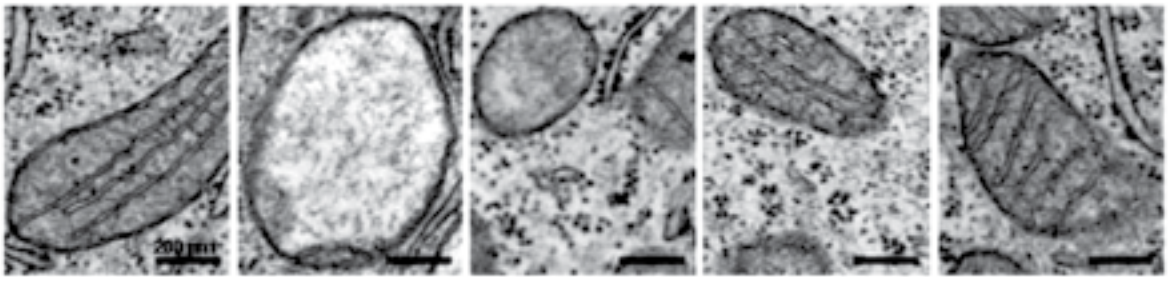
"This is a basic physiological mechanism in the body that no one has seen before because they lacked the tools we have developed. Whether this new phenomenon is important in tumour formation is still unclear, but we are interested in pursuing the research to see if the transfer occurs more widely in the body."



Carole Grasso, Professor Mike Berridge, An Tan, Alanna Cameron, Dr James Baty.

The research lays important groundwork for understanding other human diseases that are underpinned by altered energy metabolism. It could also usher in a new field where synthetic mitochondrial DNA is custom-designed to replace defective genes. M

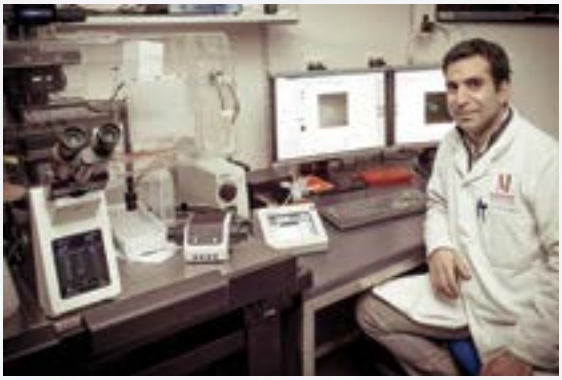
Tan AS, Baty JW, Dong L-F, Bezawork-Geleta A, Endaya B, Goodwin J, Bajzikova M, Kovarova J, Peterka M, Yan B, Pesdar EA, Sobol M, Filimonenko A, Vondrusova M, Kluckova K, Sachaphibulkij K, Rohlena J, Hozak P, Truksa J, Neuzil J, Berridge MV (2014) Mitochondrial genome acquisition restores respiratory function and tumorigenic potential of cancer cells depleted of mitochondrial DNA. Cell Metabolism (manuscript under revision).



Electron microscope images showing cells that have acquired mitochondria from surrounding normal cells. From left: mitochondria of a metastatic breast cancer cell; mitochondria of a breast cancer cell with mitochondrial DNA removed; a primary tumour cell with abnormal mitochondria; a circulating tumour cell and a cell from lung metastasis after having acquired normal mitochondria.

Dr Olivier Gasser is a Senior Research Fellow working in the vaccine therapy programme. His work includes optimising the vaccine production process, checking the quality of the vaccine and analysing samples from patients to determine their response to the vaccine.

LASER CONFOCAL MICROSCOPE



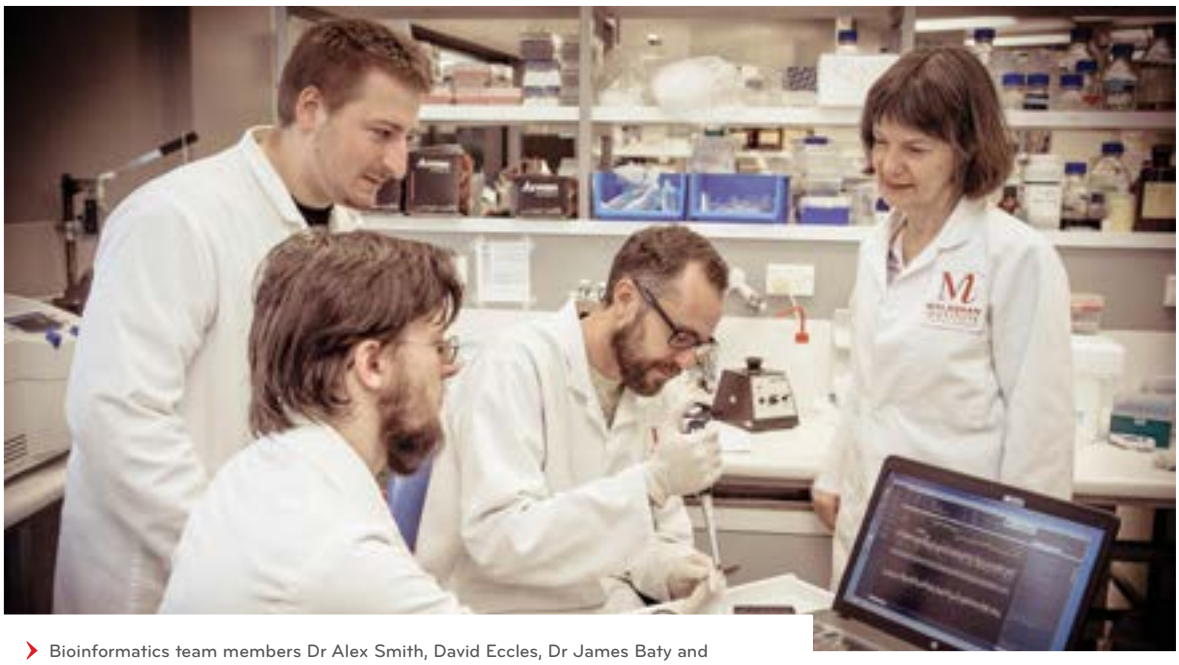
This powerful new instrument is enabling researchers to study the details of cell interactions in the skin in real time. Virtual slices of skin are visualised and recombined into a three dimensional image that can be rotated and examined from any direction.

"We can actually see changes on the surface of the dendritic cells in the skin," says Research Assistant Alfonso Schmidt, pictured in the Cell Technology Suite with the new laser confocal microscope.

"Also, we know that the cells move around, so by observing how all the different types of cell contact and communicate with each other, we can learn a lot about the processes that are going on."

The purchase of the microscope was made possible with the support of our Hawke's Bay Friends and a generous donor. M

A fluorescent microscope image showing the dense network of immune cells in the skin. The outermost layer of the skin (epidermis) is populated by specialised populations of dendritic cells (green) and T cells (red). These cells have very similar shapes, but are easily distinguishable thanks to the power of the microscope.



Bioinformatics team members Dr Alex Smith, David Eccles, Dr James Baty and Professor Franca Ronchese preparing to analyse DNA with a new miniature sequencer.

Asthma & Allergy

The long-term goal of this research programme, led by Professor Graham Le Gros, is to develop vaccines against asthma, allergy and human hookworm.

Tracking back to the very beginning of an allergic response may open new ways to prevent allergies rather than relying on therapies to treat established allergic disease.

At the moment of birth, a baby's inexperienced immune system is confronted with a host of foreign organisms such as pollen, bacteria and viruses. If the response it makes to them is correct, harmless pollen is ignored and a defence is mounted towards the pathogenic microorganisms. An inappropriate response to pollen, however, is sensitisation and the genesis of a lifelong allergy that can have significant effects on a person's quality of life.

Little is known about how allergies start, despite the growing number of people with environmental and food allergies in the Western world. Our recent research in asthma and allergy has sought to better understand the very early stages of an allergy, in order to inform prevention strategies rather than treatments.

This challenging work requires an investigation of cell processes well before any symptoms of disease are visible, because it is the events in these early phases that determine whether disease is likely to develop or not.

Professor Franca Ronchese and her team recently focussed on a rare type of skin cell that represents only one percent of all skin cells, but was found to carry over an allergy from an allergic to a non-allergic mouse.

They also identified a new type of skin-based dendritic cell, which they believe is implicated in the allergic reaction that leads to skin sensitisation and eczema. Previously ignored by other researchers, the cells are now being researched to gain insights into their role in allergy.

These new cell types are being investigated further using a whole genome approach, which builds on previous antibody and molecular biology research.

The transcriptome (all the molecules of RNA rather than DNA) of the dendritic cells in allergic and non-allergic mice are sequenced and compared to find the subtle genetic changes that account for the observed allergic response.

PRINCIPAL INVESTIGATORS

Dr Elizabeth Forbes-Blom

Dr Jacquie Harper

Professor Graham Le Gros

Professor Franca Ronchese

RESEARCH HIGHLIGHT

INVESTIGATING A LESSER-KNOWN ROLE OF THE PROTEIN PERFORIN

Perforin is a protein that kills compromised target cells by perforating their plasma membrane. It is normally used as a weapon by the immune system to eliminate body cells that have been invaded and taken over by infection.

Professor Franca Ronchese has recently published research into a less well-understood role that perforin has in the immune response.

"It has been known for a while that if you don't have perforin, your immune system goes crazy. There are a number of theories about why this is, but we wanted to look at its connection to regulatory cells, which are known to turn off immune responses," she says.

In several experiments that compared perforin-deficient mice with control mice, no significant difference in their immune regulation was found. This result suggests that there is a connection between our immune system's ability to clear infection and maintain a healthy balance.

"Our journal article has been downloaded quite often since it was published, so other groups working in this field internationally are clearly interested in our result." M

Ataera H, Simkins HMA, Hyde E, Yang J, Hermans IF, Petersen TR, Ronchese F (2013) The control of $CD8^+$ T cell responses is preserved in perforin-deficient mice and released by depletion of $CD4^+CD25^+$ regulatory T cells. Journal of Leukocyte Biology 94:825–833.

RESEARCH HIGHLIGHT

DUE DILIGENCE ON A HORMONE'S FUNCTION

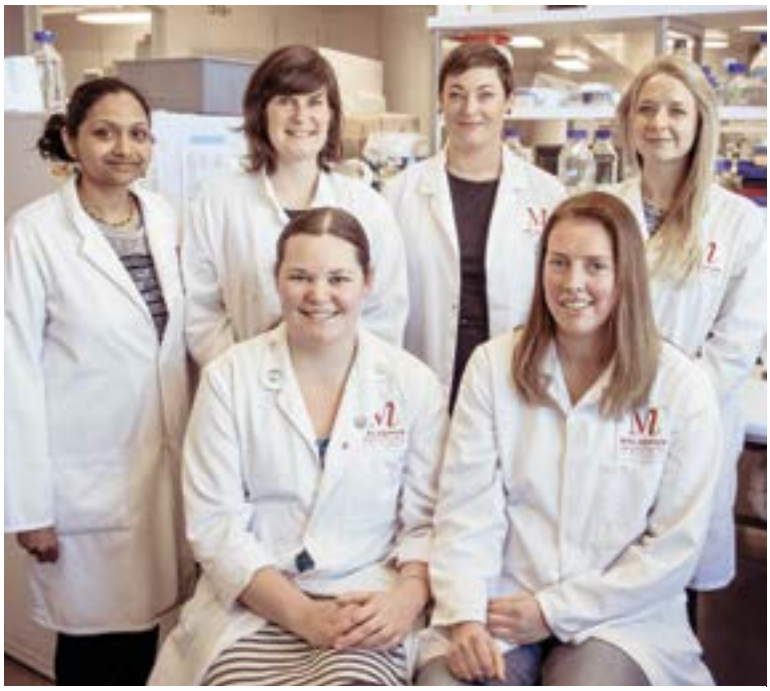
A new assay has enabled a team of Malaghan researchers to determine if the hormone IL-25 has a critical role in making T helper 2 cells, which have been proposed as targets for asthma therapies.

"Everyone believed that IL-25 was an important hormone in driving allergic disease – drug companies were developing therapies based on that assumption and trying to target the gene that expresses it. We wanted to test that hypothesis," says Professor Graham Le Gros, who led the research.

The assay was developed using mice missing the IL-25 gene (generously provided by Merck Research Laboratories) crossed with mice where the gene responsible for triggering an allergic response has been replaced with a jellyfish gene. In the new assay, when a mouse tries to mount an allergic response, its ears fluoresce green in UV light.

"Merck didn't have the skills to do this research so they gave us the mice, but they were also interested in whether IL-25 was implicated in allergy and asthma. We got a negative result – IL-25 is not essential for an allergic response – so we now think the hormone probably has a more fundamental role in the immune system." M

Mearns H, Forbes-Blom EE, Camberis M, Tang S-C, Kyle R, Harvie M, Kleinschek MA, Le Gros G (2014) IL-25 exhibits disparate roles during Th2-cell differentiation versus effector function. European Journal of Immunology 00:1–5.



Karmella Naidoo, Dr Lieke van den Elsen, Catherine Plunkett, Dr Elizabeth Forbes-Blom, Angela Jones, Dr Hazel Poyntz.

Gut Inflammation

Overwhelming evidence points to an important relationship between diet and the immune system. We have begun to understand the 'jungle' of microorganisms that live in the human gut – collectively called the gut microbiota – which are likely to be the connection between diet and immunity.

Poor nutrition strongly influences the ability of the immune system to prevent infection and disease. Malnutrition is the most common cause of immunodeficiency in the world, while overnutrition, or obesity, is known to drive disease-promoting chronic inflammation. We now recognise that diet plays a dominant role in shaping the composition and function of the gut microbiota – and the impact of nutrition on the gut microbiota could be the pivotal link between diet and immunity.

Dr Elizabeth Forbes-Blom's research aims to understand how diet and nutritional status can influence the composition and dynamic operations of the gut microbiota and the immune system. Her team is focussing on an emerging hypothesis that this is profoundly consequential in early life, when the relationship between the gut microbiota and the host's immune system is just being established.

Microbiota discoveries are opening up new territory in 21st century medicine.

RESEARCH HIGHLIGHT

HOST-MICROBIOTA INTERACTIONS SHAPE IMMUNE RESPONSES IN THE GUT

Previous research has shown that production of the hormone IL-25 is reduced in the inflamed gut of patients with inflammatory bowel disease (IBD). After successful treatment IL-25 production is enhanced, which suggests that IL-25 may play a role in limiting gut inflammation.

"We have discovered that IL-25 controls appropriate immune education in the gut. Mice lacking IL-25 have several immune deficiencies that lead to a disturbance in their gut microbiota. Together these effects result in a greater susceptibility to gut inflammation," says Dr Elizabeth Forbes-Blom.

Her group's latest findings support the current rationale that IBD may require multiple abnormalities that affect several overlapping layers of immune regulation of immune balance in the intestine. "We now have a pre-clinical model of these converging factors that will allow us to examine new approaches for the potential treatment and prevention of IBD."

PRINCIPAL INVESTIGATORS

Dr Elizabeth Forbes-Blom

Professor Graham Le Gros

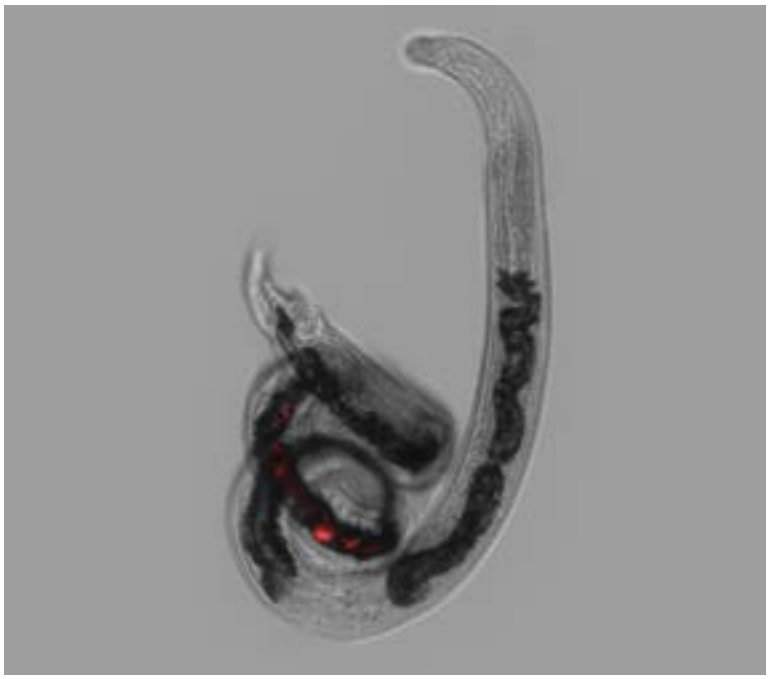
Parasitic Diseases

Parasitic worms have evolved to coexist with their human hosts in a complex relationship that verges on mutualism. While other microbes cause a vigorous and immediate immune response, parasites elicit a different immune response that enables them to survive inside a host.

This ability to damp down an immune response could help in the treatment of allergic disease (where the immune system is overstimulated), since both processes use the same immune pathway. In what is now a mature research programme, Professor Graham Le Gros and his team are studying the mechanisms involved in an immune response to a parasite infection, which primarily controls the damage caused by the parasites in the various tissues it infects.

Human hookworm infects more than one billion people in the developing world. Its larvae enter through the skin, travel through tissue to the lungs and are then coughed up and swallowed to reach the gut. The disease causes nausea, diarrhoea and anaemia, and a vaccine is sought to prevent ongoing cycles of reinfection after treatment.

The microscopic rodent parasite, *Nippostrongylus brasiliensis*, models human hookworm. In the rodent, however, immunity develops after a first exposure. Recent research at the Malaghan Institute has highlighted the importance of the lung as a site where this immune response against the worm is made and is informing the development of future therapies for hookworm. M



Female *Nippostrongylus* worm at the L4 larval stage, 1mm long. Inside the worms are natural black pigments and the fluorescent-dyed red blood cells they have ingested.

RESEARCH HIGHLIGHT

PARASITIC WORM *IN VITRO* ASSAYS

New *in vitro* assays developed at the Malaghan Institute are helping researchers understand the life cycles of parasitic worms and the mechanisms they use to evade a host's immune system.

"We are learning more about the worms themselves and how they progress through their different life stages, particularly the lung stage," says Professor Graham Le Gros.

Secreted and excreted products from the worms are collected and then trialled in an allergic mouse model. "We know that the whole parasite suppresses an allergic response in the lung, but we now want to see if the worm products will have the same effect. We're also interested to see if they can suppress other forms of allergy, such as a skin allergy."

The research could lead to new treatments for allergic disease. "If we understand how the products that rodent worms have made over millions of years affect the immune system, we can design and make new chemical targets to reproduce the effect in humans." M

PRINCIPAL INVESTIGATOR

Professor Graham Le Gros

Parasitology has a natural link with allergic diseases because they both use the same immune response pathways.

Arthritis & Inflammation

Gout is a type of arthritis caused by the formation of uric acid crystals in a sufferer's joints (most often the big toe), which triggers extreme inflammation, swelling and debilitating pain.

One of the known risk factors for gout is hyperuricaemia, a high level of soluble uric acid in the blood. Recent research also links hyperuricaemia with obesity-related diseases, including heart disease and diabetes, and implicates it as a driver of inflammatory disease.

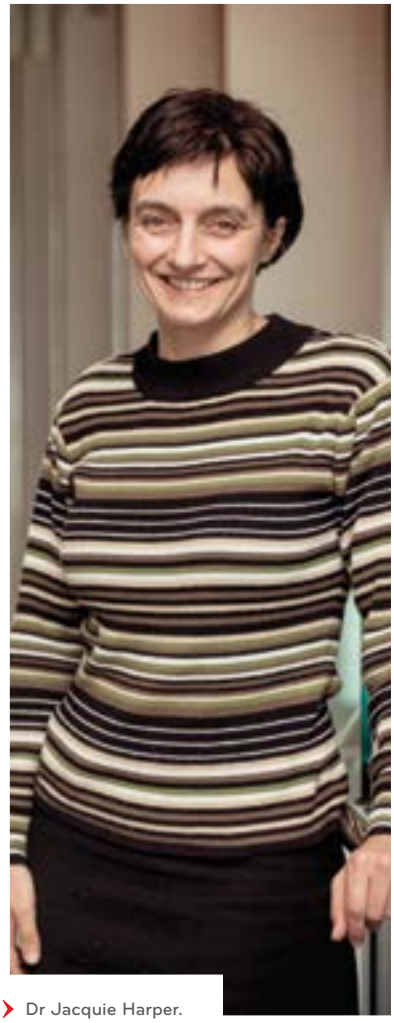
In other diseases, however, hyperuricaemia could have beneficial effects. For people with inflammatory autoimmune conditions such as multiple sclerosis and Parkinson's disease, hyperuricaemia appears to downregulate the immune inflammation and decrease the severity of patients' symptoms.

Ongoing research by Dr Jacquie Harper is aimed at investigating the effects of soluble and crystalline uric acid on inflammation in the body, to gain a better understanding of its potential benefits as well as its role in obesity-related diseases.

Her research, highlighting the link between gout and obesity, was featured on Māori Television in May. Almost half of all Māori are obese and approximately fifteen percent of Māori men and six percent of Māori women suffer from gout. These levels of gout are approximately two and a half times higher than in European New Zealanders.

Dr Harper's studies are providing insights that will enable the different forms of uric acid to be targeted separately in therapeutic approaches, to better manage gout and other inflammatory conditions.

Our research provides important insights into new potential therapeutic options for the improved management of inflammatory diseases.



Dr Jacquie Harper.

PRINCIPAL INVESTIGATOR
Dr Jacquie Harper

RESEARCH HIGHLIGHT

OBESITY, GOUT AND THE IMMUNE SYSTEM

Obesity-related diseases are often associated with an over-stimulated immune system, dysregulation of normal immune function and chronic inflammation. Using a mouse model of obesity, Dr Jacquie Harper, Dr Odette Shaw and a rheumatology collaborator, Associate Professor Nicola Dalbeth from the University of Auckland, set out to determine if being obese would increase the severity of a gout attack.

"Our result was totally unexpected. We went in with the hypothesis that excess weight gain would make a gout attack worse. Instead, we found that despite a high background of inflammatory markers in obese mice, the response made to the gout-causing uric acid crystals was no more severe in obese mice than normal mice."

Dr Harper believes this research demonstrates the complex interactions of uric acid with the immune system and that further work is necessary to determine the broader impact of weight gain and dietary fat on the ability of the immune system to respond to inflammatory challenge.

Shaw OM, Pool B, Dalbeth N, Harper JL (2014) The effect of diet-induced obesity on the inflammatory phenotype of non-adipose-resident macrophages in an in vivo model of gout. Rheumatology (in press).

CLINICAL HIGHLIGHT

ELEVATED BLOOD URATE AND IMMUNE SUPPRESSION

The effect of hyperuricaemia on the function of immune cells was investigated by examining the inflammatory responses of monocytes, a type of immune cell, from the blood of patients with the condition.

In this study, Dr Jacquie Harper's team and her research collaborators first profiled the inflammatory responses of monocytes from patients with hyperuricaemia and compared them with the monocyte responses from healthy volunteers.

"When monocytes from patients with hyperuricaemia were activated with an inflammatory stimulus, we discovered that the cells were less inflammatory than monocytes from healthy people. A similar pattern of suppressed inflammatory responses was also observed if healthy cells were exposed to uric acid prior to immune stimulation."

When the isolated monocytes from patients with hyperuricaemia were tested again after urate-lowering therapy, they showed an increased inflammatory response. These results clearly illustrate an inverse relationship between blood uric acid levels and the inflammatory response of blood monocytes.

"Our findings indicate that the elevation of blood urate may act as a mechanism to limit inappropriate hyper-inflammatory responses in the blood. This mechanism would prevent the development of life-threatening inflammation associated with conditions such as septicaemia."

This work was carried out in collaboration with Professors Tony Kettle and Lisa Stamp, at the University of Otago, Christchurch.

Associate Professor Anne La Flamme.

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic autoimmune disease that is thought to be the primary cause of neurological disability in young New Zealanders. The disease causes nerve degeneration via a process of demyelination – damage to the myelin sheath around the nerves – and results in a gradual loss of feeling and movement.

At any given time, about half of New Zealand's MS patients have the relapsing-remitting form of the disease and the others have one of two progressive forms. Current therapies treat only the relapsing-remitting stage. There is no cure for MS.

Associate Professor Anne La Flamme from Victoria University of Wellington's School of Biological Sciences, leads the Malaghan Institute's MS research programme. Her work is investigating the underlying mechanisms of the disease, particularly the process of demyelination, and the remyelination that occurs in periods of remission. She is also researching a new therapy, MIS416, developed by the New Zealand biotechnology company, Innate Immunotherapeutics. This work is done in collaboration with Dr Gill Webster of Innate Immunotherapeutics.

Although MIS416 is known to alter the immune system, exactly how it can reduce progressive MS is not well understood. Assoc Prof La Flamme's work has helped clarify the mechanism and brought insights into how to treat patients and predict who will do well on this type of medication. The drug has now been trialled by a small group of patients with progressive disease, who provided anecdotal evidence of the improvements it offers and reassurance about its safety and acceptability.

Assoc Prof La Flamme is also using a newly established experimental model to study the immunological mechanism of progressive disease, which is believed to be very different from that of relapsing-remitting disease. This model has become a valuable tool to help in understanding the pathways that are driving disease and the development of new treatments for progressive MS. M

PRINCIPAL INVESTIGATOR
Associate Professor Anne La Flamme

New Zealand has a high prevalence of multiple sclerosis. Worldwide, the prevalence of MS appears to be increasing.

REPURPOSING AN OLD DRUG TO TREAT MS

The antipsychotic drug clozapine was first released in the 1970s and along with risperidone, is used internationally to treat schizophrenia and bipolar disorder.

A serendipitous discussion with Associate Professor Bronwen Connor, a neuroscientist at the University of Auckland, who mentioned the anti-inflammatory properties of risperidone, led to Associate Professor Anne La Flamme investigating the potential of these drugs for multiple sclerosis.

"We looked at their mechanism in an animal model and found that they seem to work in a different way to how they treat psychosis. Our studies showed positive changes in the central nervous system, particularly with clozapine in the relapsing-remitting disease," she says. The next stage is to trial the drug in the progressive disease model.

Since clozapine has been widely used for decades, its adverse effects (that can be serious for a very small percentage of patients) are well characterised.

"We want to make sure that any MS patient who takes it will not suffer significant side effects, so identifying the lowest effective dose is important. But when you have progressive, accumulating disability, the benefits may well outweigh the drawbacks."

Assoc Prof La Flamme has taken out a method of use patent for clozapine in MS and is now preparing for a small trial to look at safety and acceptability for patients with progressive MS.

"Realistically, we are hoping that it will stop the disease progressing. If it can actually reverse it, that would be beautiful." M

O'Sullivan D, Green L, Stone S, Zareie P, Kharkrang M, Fong D, Connor B, La Flamme AC (2014) Treatment with the antipsychotic agent, risperidone, reduces disease severity in experimental autoimmune encephalomyelitis. PLoS ONE 9(8): e104430.

THE GREAT NEW ZEALAND TREK

Horse riders, walkers and mountain bikers travel a portion of New Zealand each year to support multiple sclerosis research at the Malaghan Institute. The Great New Zealand Trek started in Cape Reinga in 2006 and is set to finish in Bluff in 2020. In March 2014, more than 300 participants and support crew journeyed over the course of a week in Marlborough, from Wairau Valley to Clarence.

Since 2009, the group has contributed more than $173,000 to the Malaghan Institute, which is used in seed funding for novel MS projects. "I've always used this money for projects that will be of interest to the Trek and to support emerging researchers in MS," says Associate Professor Anne La Flamme. "It's an absolutely fantastic resource that enables us to do so much. We are incredibly grateful for their support and we deeply value our ongoing relationship."

Assoc Prof La Flamme spent time walking with the group last March and during previous Treks. "During the journey I make personal connections with people whose lives are affected by a disease I am trying to cure. There can be no greater motivation for a scientist than that." M

Associate Professor Anne La Flamme (centre, standing) with other participants in the Great New Zealand Trek.

Next year's Trek will travel through Molesworth Station to Rangiora. See *greatnewzealandtrek.org.nz* for more information.

Publications

2013

Ataera H, Simkins HM, Hyde E, Yang J, Hermans IF, Petersen TR, Ronchese F (2013) The control of CD8+ T cell responses is preserved in perforin-deficient mice and released by depletion of CD4+ CD25+ regulatory T cells. **J Leukoc Biol**, 94:825-33

Benton MC, Lea RA, Macartney-Coxson D, Carless MA, Goring HH, Bellis C, Hanna M, Eccles D, Chambers GK, Curran JE, Harper JL, Blangero J, Griffiths LR (2013) Mapping eQTLs in the Norfolk Island genetic isolate identifies candidate genes for CVD risk traits. **Am J Hum Genet**, 93:1087-99

Kim S, Karasuyama H, Lopez AF, Ouyang W, Li X, Le Gros G, Min B (2013) IL-4 derived from non-T cells induces basophil- and IL-3-independent Th2 immune responses. **Immune Netw**, 13:249-56

Kuhn S, Hyde EJ, Yang J, Rich FJ, Harper JL, Kirman JR, Ronchese F (2013) Increased numbers of monocyte-derived dendritic cells during successful tumor immunotherapy with immune-activating agents. **J Immunol**, 191:1984-92

Kuhn S, Ronchese F (2013) Monocyte-derived dendritic cells: Emerging players in the antitumor immune response. **Oncoimmunology**, 2:e26443

O'Sullivan D, Miller JH, Northcote PT, La Flamme AC (2013) Microtubule-stabilizing agents delay the onset of EAE through inhibition of migration. **Immunol Cell Biol**, 91:583-92

Roohullah A, Moniwa A, Wood C, Humble M, Balm M, Carter J, Weinkove R (2013) Imipenem versus piperacillin/tazobactam for empiric treatment of febrile neutropenia in adults. **Intern Med J**, 43:1151-4

Shaw OM, Harper JL (2013) An efficient single prime protocol for the induction of antigen-induced airways inflammation. **J Immunol Methods**, 395:79-82

Weinkove R, Brooks C, Carter J, Hermans I, Ronchese F (2013) Efficient depletion of chronic lymphocytic leukemia B cells using serial rounds of immunomagnetic depletion. **J Immunol Methods**, 396:152-6

Weinkove R, Dickson M, Eliadou E, Stace NH, Goossens L, Ferguson P (2013) Fever and pancytopenia in a patient with Crohn's disease. **Gut**, 62:1327

PATENTS FILED 2013–14

Anderson RJ, Compton BJ, Hayman CM, Hermans IF, Johnston KA, Painter GF.

Amino Sphingoglycolipid Analogues.

New Zealand Provisional Application NZ625895.

2014

Anderson RJ, Tang C, Daniels NJ, Compton BJ, Hayman CM, Johnston KA, Knight DA, Gasser O, Poyntz HC, Ferguson PM, Larsen DS, Ronchese F, Painter GF, Hermans IF (2014) A novel synthetic self-adjuvanting lipopeptide vaccine to induce cytotoxic T lymphocytes that suppress allergic disease. **Nature Chemical Biology**, (accepted)

Castro LM, McConnell MJ, Herst PM (2014) Radiosensitisation by pharmacological ascorbate in glioblastoma multiforme cells, human glial cells, and HUVECs depends on their antioxidant and DNA repair capabilities and is not cancer specific. **Free Radic Biol Med**, 74:200-9. **Frontiers in Oncology**, (in revision)

Chuluundorj D, Harding SA, Abernethy D, La Flamme AC (2014) Expansion and preferential activation of the CD14+CD16+ monocyte subset during multiple sclerosis. **Immunol Cell Biol**, (in press)

Connor LM, Tang SC, Camberis M, Le Gros G, Ronchese F (2014) Helminth–conditioned dendritic cells prime CD4+ T cells to IL-4 production in vivo. **J Immunol**, (accepted)

Mearns H, Forbes-Blom EE, Camberis M, Tang SC, Kyle R, Harvie M, Kleinschek MA, Le Gros G IL-25 exhibits disparate roles during Th2-cell differentiation versus effector function. **Eur J Immunol**, (in press)

McConnell MJ, Herst PM (2014) Ascorbate combination therapy: new tool in the anticancer toolbox? **Sci Transl Med**, 6:222fs6

Nyanhanda T, Gould EM, McGhie T, Shaw OM, Harper JL, Hurst RD (2014) Blackcurrant cultivar polyphenolic extracts suppress CCL26 secretion from alveolar epithelial cells. **Food Funct**, 5:671-7

Ochiai S, Roediger B, Abtin A, Shklovskaya E, Fazekas de St Groth B, Yamane H, Weninger W, Le Gros G, Ronchese F (2014) CD326loCD103loCD11blo dermal dendritic cells are activated by Thymic Stromal Lymphopoietin during contact sensitization in mice. **J Immunol**, (accepted)

Prendergast KA, Osmond TL, Ochiai S, Hermans IF, Kirman JR (2014) Sustained in vivo depletion of splenic langerin(+) CD8α(+) dendritic cells is well-tolerated by lang-DTREGFP mice. **J Immunol Methods**, 406:104-9

Shaw OM, Pool B, Dalbeth N, Harper JL The effect of diet-induced obesity on the inflammatory phenotype of non-adipose-resident macrophages in an in vivo model of gout. **Rheumatology (Oxford)**, (in press)

Shaw OM, Steiger S, Liu X, Hamilton JA, Harper JL GM-CSF drives MSU crystal-induced inflammatory macrophage differentiation and NLRP3 inflammasome upregulation in vivo. **Arthritis Rheumatol**, (in press)

Steiger S, Harper JL (2014) Mechanisms of spontaneous resolution of acute gouty inflammation. **Curr Rheumatol Rep**, 16:392

Tan AS, Baty JW, Berridge MV (2014) The role of mitochondrial electron transport in tumorigenesis and metastasis. **Biochim Biophys Acta**, 1840:1454-63

White M, Webster G, O'Sullivan D, Stone S, La Flamme AC (2014) Targeting innate receptors with MIS416 reshapes Th responses and suppresses CNS disease in a mouse model of multiple sclerosis. **PLoS One**, 9:e87712

Full details of all 'in press' publications will appear in the 2014/2015 Annual Report.

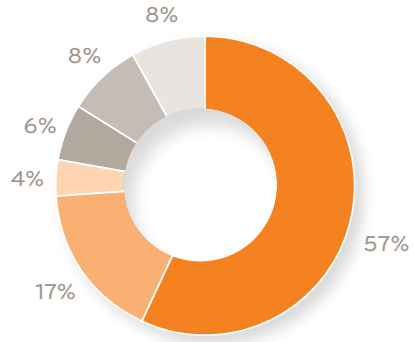
Financial Report

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.

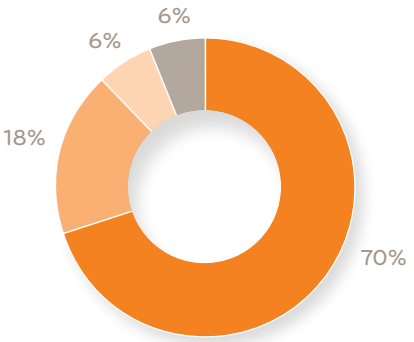
The Trust Board provides the Institute with strategic guidance and oversight, while the management of the Institute is overseen by Director Professor Graham Le Gros.

Financial Overview



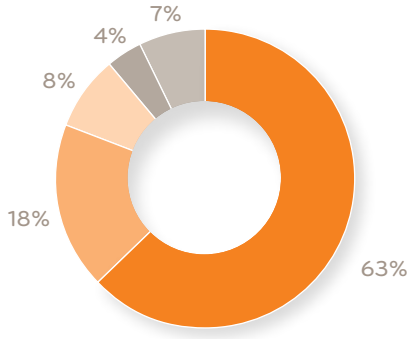
INCOME

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



EXPENDITURE

	Science
	Laboratory Support
	Communications/Development
	Administration



STAFF NUMBERS – HEADCOUNT

	Science
	Science Students
	Laboratory Support
	Communications/Development
	Administration

Financial Overview
For the Year ended 31 July

	2014 CONSOLIDATED	2013 CONSOLIDATED
Income – Operating		
Donations	541,369	596,657
Scientific Grants	6,857,821	6,945,144
Sundry	280,914	302,585
	7,680,104	**7,844,386**
Expenses – Operating		
Salaries	4,539,199	4,062,725
Science & Laboratory Support	3,321,744	3,420,956
Other		200,891
	7,860,943	**7,684,572**
Operating Surplus (Deficit)	**(180,839)**	**159,814**
Depreciation	(410,293)	(449,804)
Grant Income	482,459	133,008
Net (Deficit)	**(108,673)**	**(156,982)**
Income – Other		
Capital Endowment Fund – Investment Income	667,755	626,368
Capital Endowment Fund – Bequests	750,001	1,557,675
Net Income Capital Endowment Fund	**1,417,756**	**2,186,043**

Financial Overview
As at 31 July

	2014 CONSOLIDATED	2013 CONSOLIDATED
Current Assets	3,198,219	3,739,274
Current Liabilities	(3,126,982)	(3,712,321)
Working Capital	**71,237**	**26,953**
Fixed Assets	1,537,244	1,329,117
Investments	8,088,184	7,260,468
Total Equity	**$ 9,696,665**	**$ 8,616,538**

Run for Research participants 2014.

Community Engagement

Support from the community underpins the Malaghan Institute of Medical Research. We are extremely grateful to have a wonderful network of donors, supporters, sponsors and volunteers who work tirelessly to ensure our research can continue.

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.

[COMMUNITY ENGAGEMENT]

Her Worship the Mayor of Wellington Celia Wade-Brown presents the Supreme Dominion Post Wellington Gold Award to Professor Graham Le Gros.

Wellington Gold Awards – two wins recognise our team

THE MALAGHAN INSTITUTE OF MEDICAL RESEARCH WON THE CYBER GOLD AWARD AND THE SUPREME DOMINION POST WELLINGTON GOLD AWARD IN 2014.

The Cyber Gold Award recognises innovation, leadership and sustained growth in the information sector. The Supreme Gold Award recognises overall excellence, and the Malaghan Institute is the first charity to win this award.

These awards celebrate the dedication and commitment of all our supporters and staff who have made significant contributions over many years. They are the culmination of the efforts of thousands of people throughout New Zealand.

Philanthropic support for our medical research is ideally positioned to significantly move this field of research forward and increase the likelihood that other parties will also invest. Although private philanthropy is only a small share of overall spending on medical research in New Zealand, its flexibility and focus on outcomes has an outsized impact on the medical research sector.

We are delighted to be recognised by the Wellington Gold Awards as it helps us demonstrate to our thousands of supporters throughout New Zealand that their generosity will help us beat diseases. Medical research is challenging, but thanks to the support of people and organisations throughout New Zealand, this is an era of great promise for immunotherapy. M

Fundraising Highlights

EACH STEP IN THE RIGHT DIRECTION DESERVES A CELEBRATION!

While many were enjoying a Sunday sleep-in, a record 14,000 people turned out at Wellington's waterfront on Sunday 23 February to take part in the iconic AMI Round the Bays.

This year marked the Malaghan Institute's third year as the Official Charity Partner of this much-loved community event. We were proud to see more than 300 people band together to get behind our cause and Run for Research.

The energy and excitement at the Institute was higher than ever before as we celebrated our most successful run to date. People of all ages (3 to 83), from all walks of life and all fitness levels, took part in the Run for Research, united by their motivation to raise awareness and accelerate the pace of medical research in New Zealand.

Thanks to the incredible efforts of our Run for Research fundraisers, over $49,000 was raised! Every dollar moves us one step closer to pioneering medical research discoveries and immune-based therapies that will provide tangible health benefits to the community.

The Institute enjoyed widespread awareness through various channels including the use of a sleek Run for Research branded Lexus IS 250, thanks to Lexus of Wellington and Z Energy. The remarkable Malaghan Ambassadors, world-renowned runner Melissa Moon and Newstalk ZB radio DJ Jason Pine also spread the word, using their influence to reach out, inspire, educate and engage our community.

It is thanks to our partnership with AMI Insurance and Sport Wellington that we had this valuable opportunity to connect with the community and raise awareness of the Malaghan Institute. The Run for Research gives people from all walks of life a platform to make a difference by fundraising in support of our research programmes. We hope to continue this partnership in the future.

Congratulations and thank you to everyone involved in making the 2014 Run for Research the most successful ever!

- Brooklyn Fire Station staff were keen Run for Research supporters this year.

Every step brings us closer to a cure

- As the Official Charity Partner of AMI Round the Bays, we raised almost $50,000 to accelerate our medical research.
- Thanks to more than 300 wonderful people who ran or walked as part of the Run for Research, their friends, family and sponsors.
- Malaghan Ambassadors included Radio DJ Jason Pine and world-renowned runner Melissa Moon.

Every step is a gift

"Why do I run? Because I can where others can't. Even when it's hard and it hurts, I'm thankful I can do it. Every step is a gift." This was Darci Thompson's philosophy as she supported the Malaghan Institute through her 2014 Run for Research.

"Why do I fundraise? Because it makes an immense impact in people's lives and I've lost too many people I love to illnesses that I would love researchers to find cures or treatments for in my lifetime." Darci's positive message is inspiring and we are grateful for her boundless energy and initiative. Join us in our journey to fight back and find better treatments for the diseases that affect our loved ones.

JOIN US IN 2015!

There are many ways that you can support the Malaghan Institute:

- participate and fundraise as an individual, family, group of friends or corporate team in any sporting event
- sponsor someone taking part
- hold your own community fundraising event (quiz night, sausage sizzle or raffle)
- volunteer your time and skills.

For more information please contact: Shannon Eydt, Database and Administration Adviser, 04 4996914 ext. 895 / seydt@malaghan.org.nz

Darci Thompson.

A STORY OF COURAGE

"Live every day like it is your last!" These inspirational words come from Louise Curtis as she passionately strives to send a message to others with terminal illnesses to make the most of the time they have and "live like there's no tomorrow".

Louise, 43, is a Wellingtonian mother of two. Last December she was diagnosed with a brain lesion which was later found to be cancerous. Louise did not take this diagnosis lying down, but gave herself the challenge to overcome, stay active and continue cycling, which is one of her passions and most important outlets.

Louise has been actively raising awareness and funds through her activities involving cycling fundraising events, which she has dubbed 'a year on the bike,' successfully tackling four major cycling events in the name of charity and support of the Malaghan Institute. She has already completed the iconic 101 km Forrest GrapeRide through Marlborough and organised two marathon RPM fundraising sessions at Les Mills. Louise has taken every opportunity to share her story and instil hope in others affected, while promoting medical research in New Zealand.

Her zest for life has never faltered through her ordeal and her message has been received loud and clear, "You can battle through it, just try and live every day like it is your last."

Louise Curtis.

Friends of the Malaghan Institute

The Malaghan Institute is very fortunate to have the support of four regional volunteer Friends committees. These wonderful people work extremely hard on our behalf, not only to raise funds for our work, but also to raise overall awareness of the Malaghan Institute. Our sincere thanks go to these amazing people who give their time to our cause.

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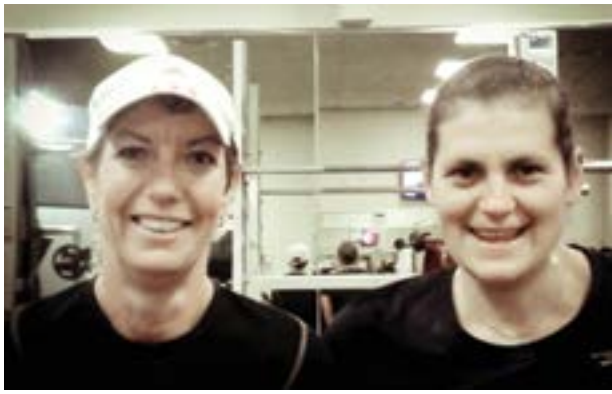


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Thank you to the following individuals, organisations, businesses, trusts and foundations who helped support the Malaghan Institute from 1 August 2013–31 July 2014.

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The following people generously left bequests to the Institute:

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In Memoriam

Donations were received in memory of the following people:

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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 focussed on finding better treatments and cures for diseases affecting New Zealanders – cancer, asthma, & allergy, arthritis, & inflammation, multiple sclerosis and infectious disease.

The Malaghan Institute is a registered charity and you can support our vision by investing in health for the benefit of all New Zealanders. Some options of how you can become involved follow:

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, and secure the future of the Malaghan 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."

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

If you would like any additional information about these options or if you have any queries, please contact:

James Araci
National Development Manager

Malaghan Institute of
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Wellington 6242
New Zealand

P: +64 4 499 6914 ext. 855
E: jaraci@malaghan.org.nz

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

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