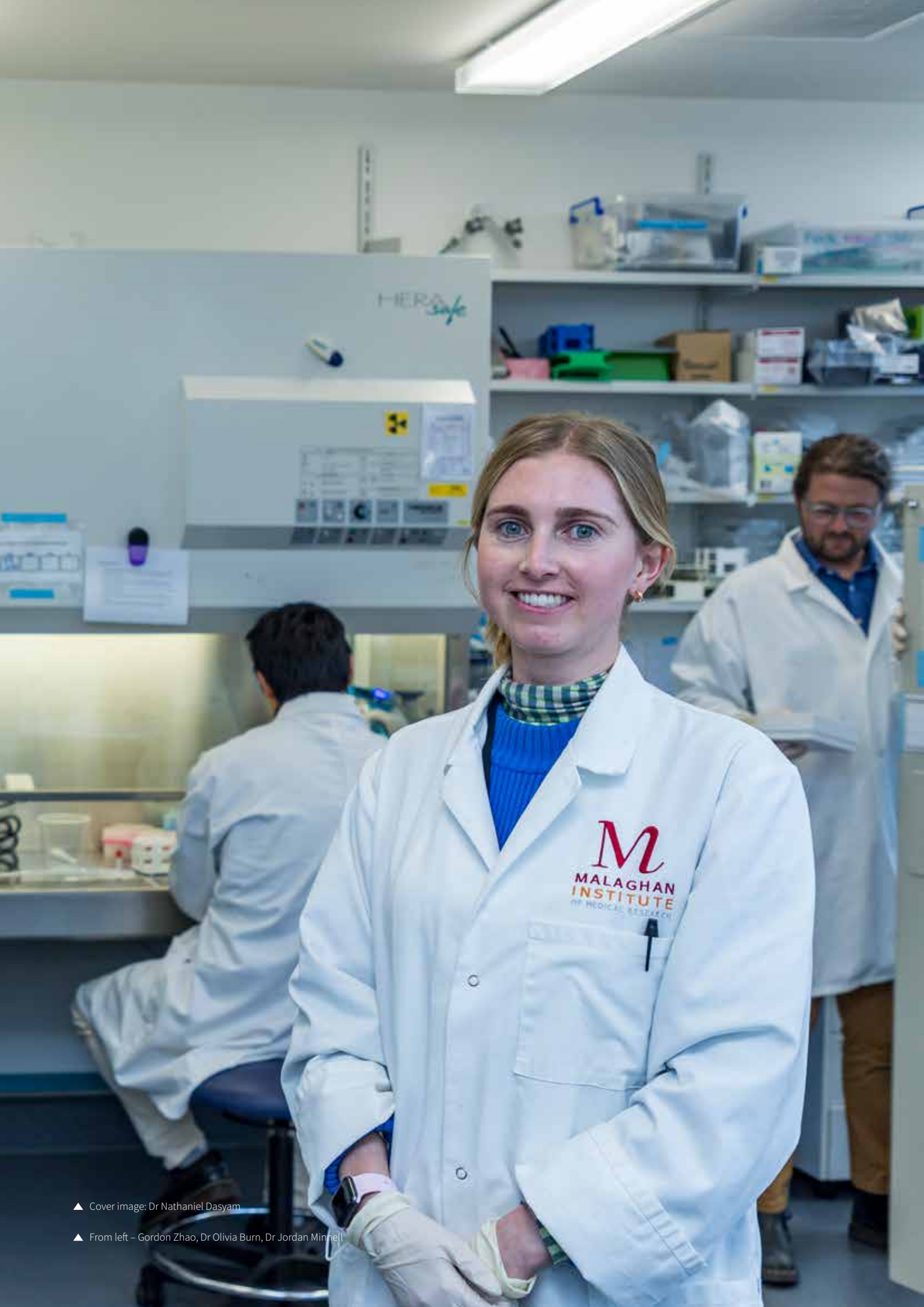
MALAGHAN INSTITUTE OF MEDICAL RESEARCH

ANNUAL REPORT

2022



▲ Cover image: Dr Nathaniel Dasyam

▲ From left – Gordon Zhao, Dr Olivia Burn, Dr Jordan Minnell

Contents

Year in review

OUR PEOPLE

127 STAFF

12% GROWTH FROM 2020-21

64% RESEARCH STAFF

11 PHD + MASTER'S STUDENTS

18 POSTDOCTORAL RESEARCH FELLOWS

PROFESSOR MIKE BERRIDGE

SHORLAND MEDAL

Awarded by the New Zealand Association of Scientists

OUR COMMUNITY

$8.6 MILLION

RAISED IN PHILANTHROPIC SUPPORT

37% OF TOTAL FUNDING

300+ MEDIA ARTICLES

Jodi Butler's March for the Malaghan

RAISED OVER **$19K**

Colin MacDonald's March for Myeloma

RAISED OVER **$35K**

OUR RESEARCH

KEY AREAS OF RESEARCH AND DISCOVERY

CANCER

INFECTIOUS DISEASE

ALLERGIC + INFLAMMATORY DISEASE

IMMUNE HEALTH

KEY COLLABORATORS

VACCINE RESEARCH + DEVELOPMENT

University of Otago
Victoria University of Wellington – Te Herenga Waka
South Pacific Sera
Avalia Immunotherapies
University of Melbourne

CAR T-CELL THERAPY

Guangzhou Institutes of Biomedicine & Health
Wellington Zhaotai Therapies
BioOra

HOOKWORM THERAPY

James Cook University

ALLERGIC + INFLAMMATORY DISEASE

National Institutes of Health
Weizmann Institute of Science

40
PAPERS PUBLISHED

7
CLINICAL TRIALS + STUDIES

LE GROS LABORATORY

Allergy and parasitic disease. Hookworm therapy.

BERRIDGE LABORATORY

Brain health. Neurodegenerative disease.

HERMANS LABORATORY

Cancer immunotherapy. Infectious disease. Vaccines.

GASSER LABORATORY

Immune health. Gut microbiome.

RONCHESE LABORATORY

Allergic and inflammatory disease.

WEINKOVE LABORATORY

Cancer immunotherapy. CAR T-cell therapy.

About the Malaghan Institute of Medical Research

Too many of our loved ones are dying and suffering from diseases we don't know enough about. But we do know the immune system holds the key to prevention, treatment and cures.

Deeper understanding

We research to understand how to use the immune system to fight disease.

Better treatments

We develop new immunotherapies to more effectively treat disease.

Fairer access

We are committed to taking our research into the community to provide treatment options for all.

Together, we can harness the power of the immune system and save lives.

The Malaghan Institute is New Zealand's world-class independent biomedical research institute with a focus on breakthrough discoveries in immunology and immunotherapy.

Our journey started more than 50 years ago with a vision to improve the lives of all New Zealanders through advancements in medical research. In 1966, a group of far-sighted New Zealanders set a course for high-quality independent medical research to be carried out in Wellington. In 1986 the organisation, then the Wellington Cancer and Medical Research Institute, was renamed the Malaghan Institute of Medical Research, in recognition of the generosity of Tip Top founder Len Malaghan and his wife Ann.

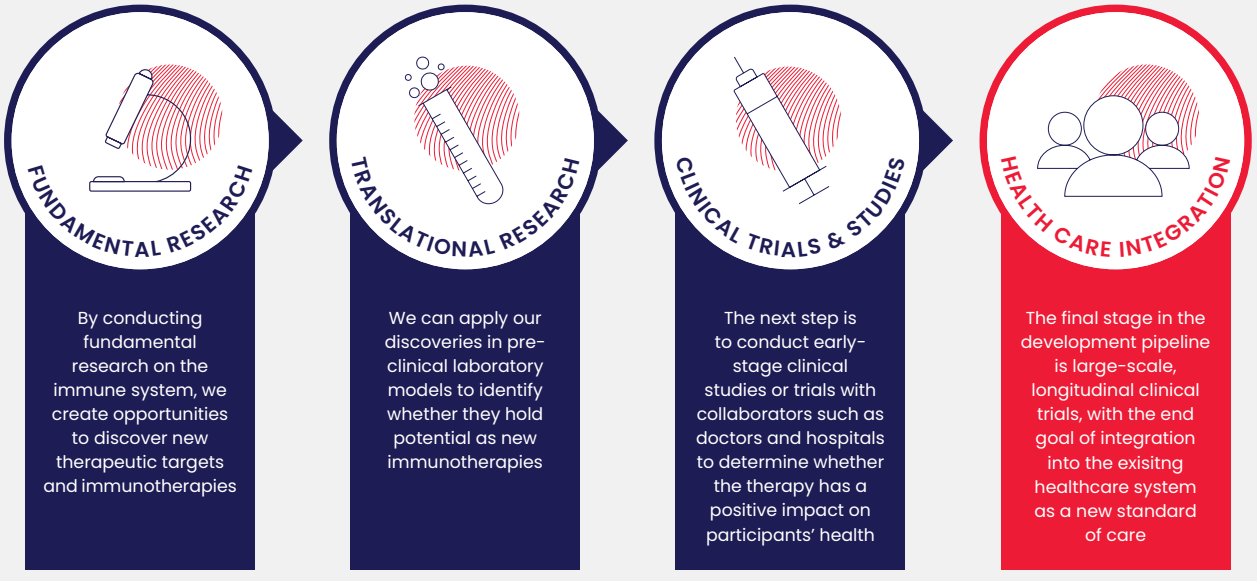
From benchtop to bedside

Fundamental research meets clinical development at a single site at the Malaghan Institute. By bringing together world-class immunological research with clinical expertise, and cutting-edge technology platforms within the Hugh Green Cytometry Centre, we are uniquely positioned to translate new discoveries into new therapies to prevent, treat and cure disease.

Owned by New Zealand, for all New Zealanders

Our value to New Zealand lies in our independent status as a research organisation, backed by the community. As a registered charity, we are owned by New Zealand, for the benefit of all. Through a range of funding sources, including philanthropic, government and corporate, the Malaghan Institute has developed the capability and expertise to deliver significant health and economic benefits to New Zealand, while retaining the freedom, flexibility and spirit to make breakthrough discoveries.

At the current pace of advances and discoveries in immunotherapy, we see a future where diseases can be prevented and cured through an immune-based approach and treatment is accessible and affordable for all.



Chairman's report

Science requires a consistent and confident source of funding to achieve outcomes that will have a lasting benefit on our communities.

We at the Malaghan Institute are extremely appreciative of the many New Zealanders who support our research with their donations. This enduring support has been critical to our work, for not just months and years, but decades. We cannot express how grateful our science leaders and staff are for this support.

"New Zealand is embarking on significant health delivery reforms, and cutting-edge science has a key role to play..."

It should be noted that our benefactors now come from both New Zealand and offshore. While they prefer to remain out of the spotlight, they are hugely supportive of our research, and their contribution is making a real difference. I look forward to sharing some more news in the philanthropy space in the coming year.

The Health Research Council renewed our Independent Research Organisation funding for a further two-year period, when it will come under the jurisdiction of the Ministry of Business, Innovation and Employment. This long-term commitment of government funding to our core programme of activity has proven to be a significant enabler for the most cutting-edge research programmes that seeds innovation in health research.

With our continued growth, a significant challenge the institute now faces is how to accommodate and fulfill all the various laboratory and facility needs of New Zealand's independent biomedical research organisation. A special sub-committee of the Board has been formed to develop plans to see the institute through this next phase of its growth. This sub-committee is chaired by our recently-confirmed Deputy Board Chair Sir Paul Collins. I have every confidence that his insight and expertise will ensure we have a steady and guiding hand throughout this period of development. Trustees and senior staff have also been engrossed in the planning of our long-term strategy, with expert input from external specialists bringing insight and assistance to these deliberations.

As usual, the activities across our various science groups will be covered in the director's report. All I can say is that it has been an extremely exciting period for research at the Malaghan Institute, with developments both at the fundamental and clinical level giving us all a strong sense of purpose and achievement. The director's profile across national media throughout the pandemic has certainly raised awareness of the work, goals and values of the institute as well as providing a reassuring expert voice at a time when the public has needed to trust science more than ever.

New Zealand is embarking on significant health delivery reforms, and cutting-edge science has a key role to play in delivering the breakthroughs that can meet the needs and challenges the country faces. New Zealanders for Health Research, of which the institute is a member, is helping ensure research is embedded in these reforms.

No organisation can progress without the efforts of many people. Despite the challenges we have all faced over the past two years, through lockdowns and restrictions, we have got through. So my own and trustees' appreciation of staff, supporters and the public in general is never far from our minds.

MR GRAHAM MALAGHAN | CHAIRMAN
ONZM, Hon DSc, FCILT

Director's report

The achievements and impact of our organisation on the health innovation sector this past year have been profound. I attribute these important developments to the passion, intelligence and tenacity of the many people who make up the Malaghan Institute's science, technology and support staff. It is also enabled by the shared vision of our supporters and collaborators who back us and work with us to come up with solutions to some of the most pressing health issues of our time.

Across the research pipeline – from fundamental research to clinical studies – our scientists are geared towards harnessing the power of the immune system to develop safer and more effective treatment options for diseases that touch all our lives.

As an independent New Zealand organisation with global impact, we are committed to accelerating New Zealand's access to emerging global standards of healthcare. Our clinical programmes in cancer immunotherapy – including our ENABLE CAR T-cell clinical trial – are a big part of this, helping give New Zealanders access to the latest and most advanced treatment options the world has to offer.

In terms of having impact in New Zealand it is clear that our ambition has to be matched by size and access to fit-for-purpose infrastructure and to this end we are also focused on building essential capability to respond to global health threats. The pandemic has not only highlighted just how important it is for New Zealand to stand on its own two feet but it has presented a significant opportunity for the future of healthcare in RNA nanotechnology. We have shown that we have the expertise here in New Zealand to develop our own COVID vaccines – with a homegrown booster vaccine candidate nearly ready for clinical trial that has the potential to protect against a broader range of COVID-19 escape variants. What's more, as we start to build a national RNA platform, with significant Government investment in the 2022 Budget, New Zealand has the opportunity to become a leader in the development of novel RNA therapeutics and provide vaccine security in the face of future pandemics.

The immune system can be our greatest ally in the fight against disease, but for some people it is the very thing that makes us sick. Yet the reasons for this remain shrouded in mystery. So this will always be a focus for us – understanding the fundamentals of allergic and inflammatory diseases. Over recent years our scientists have made significant headway in answering some of the fundamental questions of why allergies begin – discoveries that will shape research at the institute for years to come. Our research is also focused on what constitutes a healthy immune system, and the mechanisms that drive the cells that make it. The immune system does not exist in isolation – and so we must understand the factors that influence it such as our diet, our environment and our microbiome.

"We are ambitious for New Zealand, but we are also realistic that we can't do this alone."

As we continue our focus on better understanding the immune system to provide better treatments, we must also lift our heads to determine who benefits from our research. As an independent community-backed New Zealand institute, it is on us to develop real-world solutions for New Zealand specific problems, including diseases that disproportionately affect our Māori and Pasifika populations. We are ambitious for New Zealand, but we are also realistic that we can't do this alone – it is only through partnerships, collaborations and deep funding into breakthrough science and innovation that as a nation we will be able to deliver real health benefits and security for our people.

As always, we are grateful for the generous support and shared vision and ambition of our many backers. We couldn't do it without you, thank you.

PROFESSOR GRAHAM LE GROS | DIRECTOR
CNZM, FRSNZ, FRCPA (Hon), BSc, Dip Immunol, MPHIL, PhD

CANCER

We can harness the power of the immune system to create highly-effective, highly-personalised treatments to fight cancer. Our cancer immunotherapy research aims to find new and better ways to stimulate the immune system against a person's cancer, and to help boost the overall effectiveness of therapy.

CAR T-CELL THERAPY: TRANSFORMING CANCER TREATMENT

CAR T-cells are changing the game in how we fight previously untreatable blood cancers. For the past several years, the Malaghan Institute has been running New Zealand's first and only CAR T-cell clinical trial in parallel with our Freemasons CAR T-cell Research Programme.

ENABLE clinical trial

The ENABLE clinical trial is a phase I dose escalation and safety trial of our new third-generation CAR T-cell construct, treating patients around New Zealand for certain types of relapsed or refractory B-cell non-Hodgkin lymphoma. The trial got underway in 2019 and was extended in 2022 to provide additional data critical to phase 2 trial design, including validating automated manufacturing technology and adopting outpatient CAR T-cell delivery. We hope to release preliminary results from our phase I trial in late 2022.

"Having the opportunity to apply my lab skills to such an exciting and innovative project has been very rewarding," says Senior Production Technician Kirsty Wakelin, who has been involved in manufacturing several patients' CAR T-cells. "I love knowing that the work I do has the potential to drastically change someone's life.

"Every patient's cells pose a different challenge, and not every manufacturing batch is smooth sailing, so it is always such a great feeling when we are successful at treating a patient with CAR T-cells. We can often work long hours in the facility to grow the cells, but the feeling of pride and excitement we get when delivering the cells to the clinical team at the hospital makes it worth it. I feel extremely fortunate to get to work on this groundbreaking research and cannot wait to grow our team and treat more patients in the future."

"I love knowing that the work I do has the potential to drastically change someone's life."

As the ENABLE trial progresses, the CAR T-cell team have set their sights on automating CAR T-cell manufacture. Currently, the number of patients we can treat is limited due to the time and resources it takes to safely manufacture and deliver a single dose of CAR T-cells. In September 2021, BioOra, a new company formed between the Malaghan Institute and Bridgewest Ventures NZ, was established to scale up CAR T-cell manufacture through the use of automated cell therapy manufacturing technology. Using an automated, close-system method, LONZA Cocoon technology will enable the Malaghan Institute to shorten manufacturing times and increase the number of trial participants. The Cocoon is being validated at the Malaghan Institute and is expected to begin manufacturing patients' CAR T-cells in the near future. As BioOra grows, it will provide contract manufacturing services to the institute for future CAR T-cell clinical trials.

"We now have an opportunity to scale up CAR T-cell manufacture, with the goal of improving both affordability and availability of this potentially life-saving therapy in New Zealand," says Clinical Director Dr Rob Weinkove.

Another focus for the ENABLE trial team is ensuring equity of access to CAR T-cell therapy, and reducing the burden of treatment on patients and their whānau. Clinician Dr Robbie Fyfe has been working closely with patients, and with Te Aho o Te Kahu, the New Zealand Cancer Control Agency, to inform design of our clinical programme and refine and improve patient care.

"RE-TELL is a qualitative study of the experiences of New Zealanders with CAR T-cell therapy," says Dr Fyfe. "We have interviewed 19 patients and their support people, alongside clinicians and administrators. We are looking forward to a future national CAR T-cell service, and want to hear from those involved on how this should be designed, particularly to ensure Māori have a voice in the future of this service."

Dr Fyfe says the study has yielded important insights, some of which are seen internationally, while some are unique to Aotearoa New Zealand. "These include the imperative to develop multiple centres for patients to access care closer to home, the ease of treatment compared to other treatments for blood cancers, and the importance of respect for indigenous data and cell sovereignty."

Freemasons CAR T-cell Research Programme

CAR T-cell therapy still has some way to go to become a first line treatment option for different cancers. Understanding exactly how CAR T-cells operate within the body, and how they impact the rest of the immune system, is an important area of research. Currently, CAR T-cell therapies are most effective against blood cancers where CAR T-cells have ready access to cancerous cells. Solid tumours, such as lung or breast cancers, pose a challenge for a patient's modified CAR T-cells to effectively penetrate and kill.

"Current CAR T-cell technology is proving extremely promising for treating certain blood cancers," says Dr Rachel Perret. "However, some blood cancer patients still relapse after therapy, and there are many patients with solid tumours in organs such as the lungs, pancreas and brain that still lack any form of effective treatment. So there is always room for improvement, and our work will not be done until there are safe and curative therapies available for all cancer patients."

Dr Perret leads the Malaghan Institute's Freemasons CAR T-cell Research Programme in the Weinkove Laboratory and works alongside Dr Weinkove to improve CAR T-cells' ability to find and target cancer.

"We're trying to design a dual CAR system where we'll make T-cells that can target two different cancer proteins instead of one," says Dr Perret. "That way, we can guard against cancers losing a single protein and becoming 'invisible' to the immune response."

Current CAR T-cells can only recognise a limited range of proteins – one CAR can only target one cancer protein. Using dual CARs, the resulting CAR T-cells are more likely to respond to more cancer cells within a tumour. The team are currently investigating whether dual CAR T-cells are effective in patients with different forms of blood cancer, with the hope to broaden their work to target solid cancers.

"There is always room for improvement, and our work will not be done until there are safe and curative therapies available for all cancer patients."

"Solid tumours typically express their proteins 'heterogeneously' – as in not every cell expresses the same target," says Dr Perret. "By applying dual CARs to our CAR T-cells, we increase the chances that the therapy will recognise all the cells in a tumour and so more effectively remove it from the body."

However, even with dual CAR T-cells recognising up to two different proteins on a cancer cell, when it comes to solid tumours, it's unlikely that current CAR T-cells will correctly identify every cell in a tumour as cancerous. This is simply because of how cancer cells in a solid tumour vary in their expression.

Rather than relying on CAR T-cells to correctly identify every single possible variation of a cancer cell in a solid tumour, Professor Ian Hermans' laboratory is investigating ways to get around this limitation by creating CAR T-cells that work in combination with chemotherapy.

The research involves arming the CAR T-cells with an enzyme that activates a chemotherapeutic drug once it binds to a cancer cell. Once this chemotherapy drug is activated, it destroys the surrounding cells, including the parts of the tumour the CAR T-cells could not target.

The added benefit of this method is that it allows very direct and targeted chemotherapy application without the negative side-effects that chemotherapy injected into the bloodstream can bring.

Both these research projects represent the wide range of approaches under investigation that may lead to the development of CAR T-cells that are more durable and effective at targeting different types of tumours for destruction.

OTHER RESEARCH HIGHLIGHTS

Professor Mike Berridge awarded Shorland Medal

Prof Berridge's decades-long scientific career spans the globe and several fields from plant biology to cancer metabolism, where his discoveries have challenged paradigms of molecular biology. In November 2021 the New Zealand Association of Scientists recognised his significant and continued contribution to research, awarding him the prestigious Shorland Medal.

Prostate cancer study opens doors for immunotherapies

Research funded by the Prostate Cancer Foundation and published in *Frontiers in Immunology* has found that immune cells that can reside in prostate tissue, called MAIT cells, function abnormally and have an abundance of a molecule called PD-1 on their surface. When these MAIT cells were activated using a vitamin B variant and the PD-1 molecule was blocked, it resulted in anti-tumour activity that destroyed the cancer cells, an insight that holds potential for cancer therapy.

Breast cancer research shows promise for future vaccine development

A unique vaccine targeting specific breast cancer antigens has been shown to delay tumour growth and prevent breast cancer metastasis in preclinical models. The research, published in *Clinical & Translational Immunology*, shows promise for future development of an effective therapeutic vaccine against high-risk breast cancer.

Dr Nathaniel Dasyam named KiwiNet Emerging Innovator

Dr Dasyam has been exploring ways to better understand how CAR T-cell technology can be applied to other forms of disease. As a KiwiNet Emerging Innovator, he was awarded mentoring and initial funding to test and validate a concept he has been working on, and help build his capabilities in translating his research to relevant clinical settings.

Bioenergetic and metabolic adaptation in tumour progression and metastasis

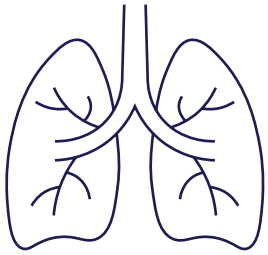
The Berridge Laboratory has published research in *Frontiers in Oncology* on the unique metabolic adaptations of cancer cells in tumour progression and metastasis. The paper highlights altered energy metabolism of cancer cells that involves mitochondria rather than non-mitochondrial pathways, which could lead to new ways of controlling metastatic disease and reducing cancer mortality by restricting their ability to produce chemical energy in their mitochondria.

Intratumoral injections to stimulate immune cells effective at shrinking tumours

Recent research by the Malaghan Institute has found that intratumoral injections to activate natural killer T-cells are effective at shrinking tumours in preclinical studies. The study also found the treatment is effective at shrinking untreated tumours elsewhere in the body, suggesting it has the potential to prevent metastases.

Blake Malley

ALLERGIC & INFLAMMATORY DISEASE



Fundamental research is helping reveal the genetic and environmental triggers that cause chronic, dangerous inflammation in the body. By better understanding these triggers, which often occur years or decades before disease symptoms present, we can design therapies to intervene at key developmental points or molecular pathways to prevent allergies and inflammatory conditions from starting or progressing.

▲ Katie Gell

DISCOVERY IN FUNDAMENTAL IMMUNOLOGY GOES MORE THAN SKIN-DEEP

A groundbreaking discovery from the Ronchese Laboratory has shone a light on immune cells in the skin, suggesting they play a much larger role in the onset of allergies than first thought.

Published in *Nature Immunology* in November 2021, and supported by funding from the Health Research Council of New Zealand, the paper provides novel insights into why the skin is often the starting point for many allergic diseases.

The research found that a key molecule associated with allergic responses, IL-13, is always made in the skin regardless of exposure to allergens, and skews the differentiation and function of skin dendritic cells so they become better able to start allergic responses. Importantly, in healthy individuals not exposed to allergens, IL-13 is only made in the skin, indicating not only that the development of allergies is favoured there, but that dendritic cells behave differently depending on where they're found in the body.

"Historically, we've assumed that a dendritic cell in the skin is virtually identical in form and function as a dendritic cell in the lung," says Professor Franca Ronchese. "We're only just realising that's not the case, so in many ways we're playing catch-up in terms of our understanding and implications in disease."

These new findings provide a mechanism for earlier observations linking the role of the skin in allergy development. This includes epidemiological studies showing an association between early peanut exposure via the skin and development of food allergy to peanuts, the genetic association between defective skin barrier and incidence of food allergies, and the allergic march where babies who develop skin allergies are more likely to develop other allergies, including food allergy and asthma, later in life.

"This is the most important immunological discovery to come out of New Zealand in the past twenty years."

In New Zealand, where the prevalence of these conditions – particularly in Māori – is among the highest in the world and contributes to a large proportion of direct and indirect health spending, these findings are a meaningful contribution to future health advancement.

"This is the most important immunological discovery to come out of New Zealand in the past twenty years," says Professor Graham Le Gros. "It marks a milestone in fundamental immunology which will have far-reaching impacts in the design and development of immunotherapies that target allergic and inflammatory conditions."

OTHER RESEARCH HIGHLIGHTS

Hookworm therapy

Our programme exploring the therapeutic potential of human hookworms has continued to make significant progress. We have extended our healthy volunteer study to include new participants, incorporating a novel production method of sourcing juvenile 'cryoworms' for infection. These cryoworms, which are stored frozen, can be thawed and reanimated safely and reliably for use in research or clinical studies. The Le Gros Laboratory is the only laboratory in the world producing therapeutic worms using this cutting-edge method, of which the Hugh Green Cytometry Centre's Influx cell sorter is key to isolating the hookworm eggs needed.

HRC fellowship for hookworm research

Dr Thomas Mules received a Health Research Council of New Zealand (HRC) Clinical Research Training Fellowship to investigate the effect of chronic hookworm infection on intestinal barrier function. The funding is helping Dr Mules gain a better understanding of intestinal barrier function immunology to find potential targets to treat a range of inflammatory, allergic, metabolic and neoplastic diseases.

Dr Kerry Hilligan awarded Royal Society and Health Research Council grants

Returning researcher Dr Kerry Hilligan has been awarded two significant grants to kick-start her research back at the Malaghan Institute. The first, a Royal Society Te Apārangi Fellowship, is to investigate the relationship between germs and the development of allergies. The project will explore how different microbes prime our immune system to recognise and effectively respond to threats, while limiting the development of allergic disease and autoimmune disorders. Dr Hilligan was also awarded an HRC Emerging Researcher First Grant for her project, 'Improving population health through education of the innate immune system,' which will build on expertise gained at the National Institute of Allergy and Infectious Diseases over the last four years.

How IL-13 shapes skin-resident dendritic cells

Following their research published in *Nature Immunology* on dendritic cells in the skin, the Ronchese Laboratory has published a review in the *European Journal of Immunology*. The review expands on the findings on the molecule IL-13 in the skin, looking at the wider context of available clinical and human-studies data which aid in contextualising how different therapeutics that block IL-13 signalling might affect dendritic cells in the skin.

Tissue-specific immunity in helminth infections

A review by the Le Gros Laboratory published in *Mucosal Immunology* took a closer look at how helminth infections influence the development of key immune response pathways. The review focuses on the new discoveries of the cells and cytokines involved in tissue-specific immune responses to helminths and how these contribute to host immunity against helminth infection and allow the host to accommodate the presence of parasites when they cannot be eliminated.

▲ Brittany Lavender

▲ Shiau-Choot Tang

INFECTIOUS DISEASE

Understanding how our immune system fights and responds to the many pathogenic and infectious organisms that threaten our health is key to designing better strategies to boost the immune system's protective response.

CLINICAL STUDY SHOWS STRONG IMMUNE RESPONSE TO PFIZER VACCINE ACROSS NEW ZEALANDERS

In 2021, the Malaghan Institute, as part of Vaccine Alliance Aotearoa New Zealand – Ohu Kaupare Huaketo (VAANZ), launched a clinical study to better understand how the New Zealand population has responded to the Pfizer-BioNTech COVID-19 vaccine, tracking and monitoring participants' immune responses to the vaccine over 18 months.

The initial results of the study, Ka Mātau, Ka Ora (from knowledge comes wellbeing) – the largest evaluation of COVID-19 vaccine immune responses in Māori and Pasifika – showed near universal strong immune responses in vaccine recipients, after two doses.

Clinical Immunologist Dr Maia Brewerton says ongoing research has been monitoring the difference seen in the immune response in our population following a booster dose, which is important to understand as more New Zealanders develop infection-induced or 'hybrid' immunity and as new variants arise.

"It's great to be part of a study that's so pertinent to society. Rather than something that might be relevant in 10 years' time, these results are relevant now."

"Driving up vaccination rates and correcting health and social inequities to reduce the burden of disease amongst Māori and Pasifika remains critical," says Dr Brewerton.

Running a nationwide clinical study during the height of a pandemic was no small task. The team had to navigate lockdowns, coordinating facilities remotely as well as collecting and analysing results coming in from across the country.

"It's great to be part of a study that's so pertinent to society. Rather than something that might be relevant in 10 years' time, these results are relevant now," says Clinical Programme Manager Brittany Lavender.

RNA TECHNOLOGY: CHANGING HOW WE FIGHT INFECTIOUS DISEASE

The COVID-19 pandemic brought the growing field of RNA technology to the forefront of infectious disease research. While using RNA to help the immune system fight infectious disease has been researched for several decades, it was the leap in nanolipid technology and the hyperfocus of a global pandemic that finally made RNA vaccines a reality.

"Lipid nanoparticles have been proven to provide a safe and stable way to deliver the encapsulation of mRNA for SARS-CoV-2 vaccines. The implications of that success are huge and open an entirely new frontier for the development of novel medicines – nanomedicines," says Chief Technology Officer Kylie Price.

RNA nanotechnology presents a significant opportunity for New Zealand to supercharge its biotech sector.

Thanks to donor funding, over the last year, the Malaghan Institute has secured key technology platforms to bridge the gap between lab research and clinical development of RNA nanomedicines. These are first being put to use on a pilot mRNA COVID-19 vaccine VAANZ has under development.

RNA nanotechnology presents a significant opportunity for New Zealand to supercharge its biotech sector, become a leader in the development of novel RNA therapeutics and provide vaccine security in the face of future pandemics. It offers the potential to develop real-world solutions for New Zealand specific problems, including diseases that disproportionately affect our Māori and Pasifika populations.

The Government's May 2022 budget allocation of $40m over four years towards an RNA research and development platform demonstrated it shares the Malaghan Institute's commitment to building a New Zealand platform and pipeline for RNA nanomedicine. The institute is continuing to work closely with Government and local and international partners to continue to build this capability.

▲ Bibek Yumnam

OTHER RESEARCH HIGHLIGHTS

Developing a homegrown COVID-19 vaccine

While effective COVID-19 vaccines were produced in record time, saving many lives, what has become clear as the pandemic continues is the need for better vaccines. This has been the focus of VAANZ, established in 2020 as part of the Government's vaccine strategy, which has pivoted to address two key concerns in the evolving pandemic – a booster vaccine for variants of concern and vaccines to protect broadly against future coronaviruses. VAANZ's protein-based vaccine has been developed in a similar way to many traditional vaccines, using genetic information from the virus's distinct spikes to replicate and manufacture a spike protein in the lab. It has undergone a range of preclinical trials both in New Zealand and at the National Institutes of Health in Washington DC, demonstrating 100% protection from disease, and cross-protection against other variants. The next stage will involve establishing the safety and appropriate dosage of the vaccine in humans in a small clinical trial, planned for 2023.

Preclinical study finds TB vaccine prevents serious COVID-19 illness

A collaborative study between the Malaghan Institute and the National Institutes of Health has found that a vaccine commonly used to treat tuberculosis is also effective at preventing lethal infection from COVID-19 in mice when administered intravenously. The study, published in the *Journal of Experimental Medicine*, highlights the potential for novel methods for fighting respiratory viruses such as COVID-19 by increasing immune protection in the lungs.

▲ Jonason Francisco (left) and Sventja von Daake

▲ Sophie Faulkner (left) and Katie Gell

COVID-19 researcher awarded Te Urungi Churchill College By-Fellowship

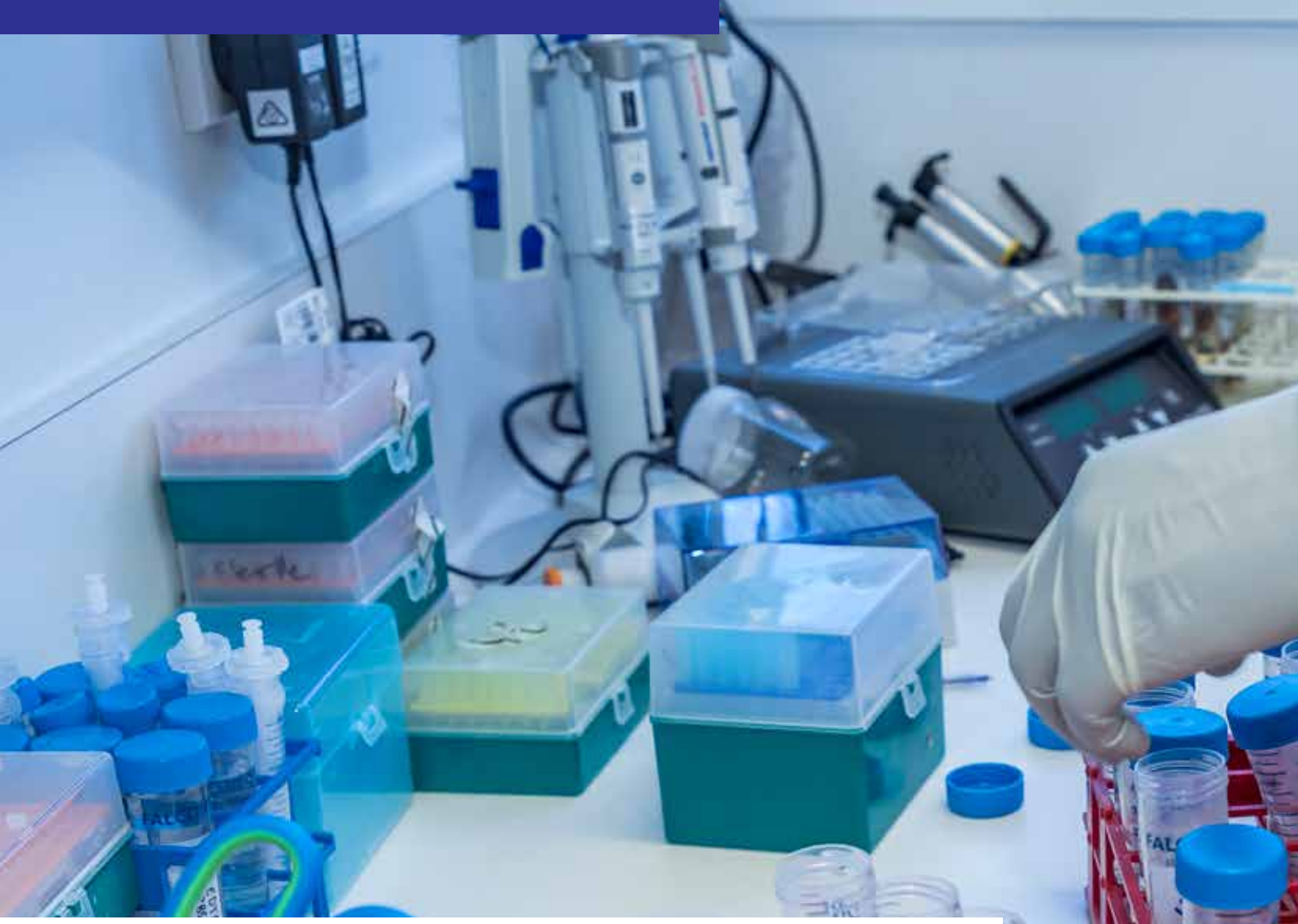
A new fellowship to strengthen relationships with Māori communities and ultimately improve Māori health outcomes has been awarded to Malaghan Institute postdoctoral researcher Dr Theresa Pankhurst (Ngāi Tahu, Ngāti Kahungunu, Ngāti Porou) who will be seconded to the Babraham Institute at the University of Cambridge to work with Dr Michelle Linterman. The three-year fellowship is supported by the institute's Māori advisory group, Te Urungi and joint funded by the Malaghan and Babraham Institutes.

Developing COVID-19 nasal boosters

The Berridge Laboratory have been working in collaboration with Professor Richard Beasley from the Medical Research Institute of New Zealand, and with the Oxford Clinical Trials Unit and AstraZeneca, to develop an intranasal booster for COVID-19 with the adenovirus-based vaccine, ChAdOx1-S. This resulted in a small 12-patient pilot group being added to an ongoing phase I clinical trial in the United Kingdom. Preliminary unpublished results were positive but insufficient to support a larger Wellington-based trial.

Developing vaccines to protect against liver-stage malaria

A collaboration between the Malaghan Institute, Ferrier Research Institute, the University of Melbourne and Avalia Immunotherapies recently published a paper in *RSC Chemical Biology*, screening candidates for a novel malaria vaccine. The project is now incorporating RNA technology to produce the immunostimulatory proteins needed to develop this vaccine.



IMMUNE HEALTH

Fundamental understanding of the unique metabolic and energetic needs of our immune cells is key to designing effective immunotherapies, and no place is more involved in the relationship between the immune system and metabolism than the gut.

The gut holds a unique position in the body, serving as the interchange between our external environment (via the food we eat), the billions of microbes that call it home, and our immune system. More than 70% of our immune system is located in the gut, but we are only just beginning to understand the depth of its influence and its potential as a mechanism for improved immune health and ability to protect us from disease.

FIBRE IS KEY TO IMMUNE HEALTH

Dietary fibre is one of the most important molecular influencers of how well our immune cells function, whether responding to a threat like a virus or a cancer cell, regulating dangerous inflammation, or responding to a vaccine.

The Gasser Laboratory is investigating how fibre impacts the immune system, and whether the amount of fibre we eat can make a tangible impact on preventing or managing disease and improving health.

It's not fibre itself that fuels our immune system – it is the products it is broken down into as it is digested by the bacteria that live in our gut, known as short-chain fatty acids. These molecules then pass through the lining of the gut to be taken up by waiting immune cells.

"Increased dietary fibre and the subsequent production of short-chain fatty acids by gut microbiota is known to influence immune cell function and metabolic activity," says Dr David O'Sullivan, Postdoctoral Research Fellow. "High fibre diets correlate to a decrease in inflammatory markers and we've seen in preclinical models that dietary fibre can modulate immune cell metabolism, leading to a rebalancing away from pro-inflammatory phenotypes."

UNDERSTANDING THE RELATIONSHIP BETWEEN GUT BACTERIA AND FIBRE

Despite its widespread benefits, our body can't digest fibre – at least not on its own. Instead, we enlist bacteria that live in our gut to perform this vital and necessary function. But not every bacterium in the gut microbiota digests fibre, and not all do so equally. We're interested in understanding which bugs are best at aiding digestion of fibre, and whether by influencing the gut microbiome, we can influence this relationship.

"Dietary fibre consumption is the best tool we have to manipulate our microbiome in a beneficial way," says Postdoctoral Research Fellow Dr Alissa Cait.

The research comes off the back of the High-Value Nutrition Ko Ngā Kai Whai Painga National Science Challenge, looking at immune responses to the influenza vaccine. Participants were asked to report on their diets, with samples of their gut microbiome tested to understand which types of bacteria were prevalent prior to vaccination. After being given the influenza vaccine, participants' blood was then analysed to assess the resulting antibodies they produced and determine how responsive their immune system was to the vaccine.

"Dietary fibre consumption is the best tool we have to manipulate our microbiome in a beneficial way."

"Initially, our goal was to see if there were any specific types of bacteria that could predict the immune response to the vaccine," says Dr Cait. "Interestingly, we found that for participants who were receiving their influenza vaccine for the first time, those who had the best immune responses had a prevalence of fibre-specific bacteria in their gut.

"These results suggest that those who consume a diet rich in fibre from foods such as fruits, vegetables and grains seem to produce a better immune response to the first dose of a vaccine due to specific colonies of bacteria that are cultivated in their guts."

OTHER RESEARCH HIGHLIGHTS

Link between prenatal antibiotic exposure and allergic disease

A review of data from various clinical studies has found that children born to mothers who take antibiotics during pregnancy are at higher risk of developing asthma and other inflammatory or allergic diseases. The findings, published in *Allergy*, highlight the need to better understand what's behind this relationship, and the importance of responsible antibiotic stewardship throughout the prenatal period.

Marsden Fund for research on the impact of fever on immune cell function

Dr David O'Sullivan received a Marsden Fund Fast-Start grant to investigate the impact of fever on our immune response. His project is exploring how the increase in physiological temperature during fever impacts the function of T-cells that are crucial in mounting an appropriate immune response against infectious diseases.

Preclinical study finds goat milk protective against atopic dermatitis

A preclinical finding that lipids in goat's milk can suppress the development of inflammation in the skin has provided a clue about the role of a key immune cell – natural killer T-cells – in allergic disease, opening doors for future research and treatment options. The research, undertaken by the Gasser Laboratory and funded by Dairy Goat Co-operative (NZ) Ltd, was based on anecdotal evidence from parents who switched from cow's milk to goat's milk infant formula and saw a decrease in atopic dermatitis, otherwise known as eczema, in their children.

Brain energetics an early detection mechanism for neurodegenerative diseases

Progressive neurological diseases such as Parkinson's and Alzheimer's disease are often characterised by loss of sense of smell and taste. In collaboration with Darren Day and Bart Ellenbroek at Victoria University of Wellington, the Berridge Laboratory is investigating whether the loss of these senses is linked directly or indirectly to loss of neuronal sensory function in the nasal cavity. The team has developed a digital droplet qPCR for use in comparing the expression of mitochondrial and nuclear genes that constitute respiratory complexes and mitochondrial protein synthetic machinery. It is proposed that differential loss of expression of a small panel of mitochondrial genes will predict early onset of dementia.

Impact of traditional Chinese herbal medicine on immune cells

A clinical study by the Gasser Laboratory investigating the impact the traditional Chinese herbal medicine indigo naturalis – also known as Qing-Dai – has on the immune system has concluded and the team are analysing samples with initial results expected within the next year.

Dietary fibre intervention study investigating impact on type 2 diabetes

A clinical study by the Gasser Laboratory seeks to understand the impact of dietary fibre on blood glucose levels of people living with type 2 diabetes. This intervention study, which includes incorporating a daily fibre supplement into participants' diets, seeks to better understand the impact fibre has on changes to immune cell populations and metabolites in the gut and in blood plasma.

Study investigating impact on fibre in breast milk and infant microbiome

A collaboration with the University of Auckland is investigating the relationship between infant microbiome and dietary fibre for infants who are still breastfeeding. The SUN (Seeding throUgh feediNg) study aims to compare the impact of mothers consuming kūmara powder on infant gut bacteria and how this supports infant immune health.

▲ Dr Jordan Minnell

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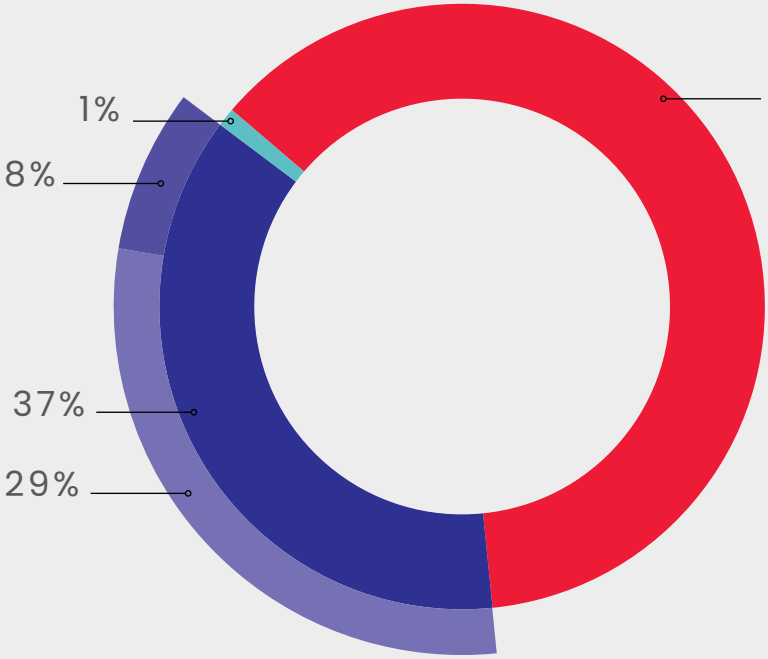
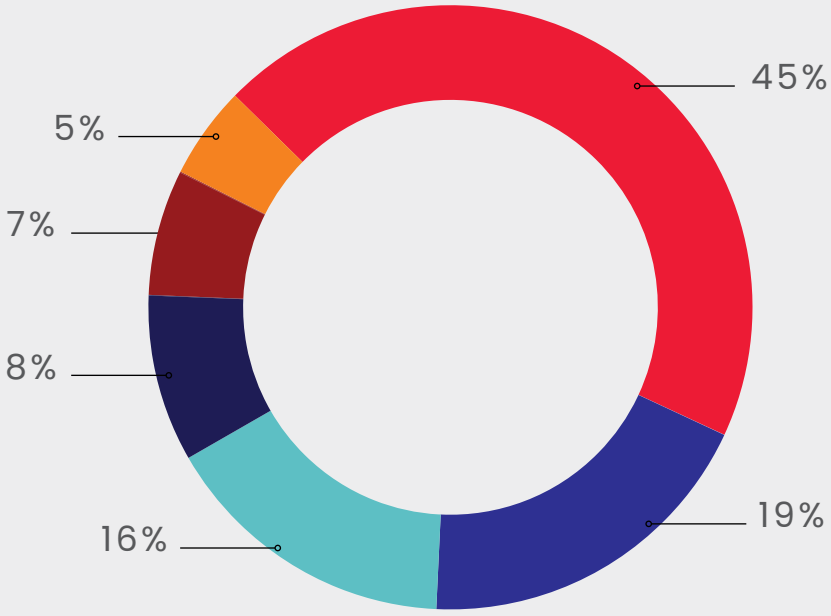
Financial Performance



REVENUE

- Grants revenue
- Philanthropic revenue
  - Donations
  - Bequests
- Other revenue



EXPENSES

- People costs
- External research
- Lab costs
- Facilities costs
- Depreciation
- Other costs

FINANCIAL PERFORMANCE

For the year ended 31 July 2022	2022	2021
Revenue		
Grants revenue	14,667,206	12,676,033
Philanthropic revenue	8,635,354	6,186,344
Investment revenue	(251,627)	1,731,318
Other revenue	256,886	161,719
	23,307,819	20,755,414
Expenses		
Depreciation	1,428,436	1,093,807
Facilities costs	1,831,445	1,573,029
Lab costs	3,399,294	2,905,594
Other costs*	5,108,673	5,217,401
People costs	9,549,561	8,335,315
	21,317,409	19,125,146
Surplus / (Deficit)	1,990,409	1,630,268
Share of surplus/(deficit) of associates	(200,000)	–
Total comprehensive revenue and expenses	1,790,409	1,630,268

FINANCIAL POSITION

As at 31 July	2022	2021
	Consolidated	Consolidated
Assets		
Current assets	28,107,530	23,358,238
Non-current assets	12,288,444	8,719,667
	40,395,974	32,077,905
Liabilities		
Current liabilities	13,662,115	7,134,456
	13,662,115	7,134,456
Net assets	26,733,859	24,943,449

* In 2022 Other costs have been split into External research ($4,128,491) and Other costs ($980,182).

Thank you for your support

Thank you to all our supporters, big and small. As a charitable organisation, we are owned by New Zealand for the benefit of all, which is why your support means so much to us.

We would also like to thank our Friends groups and individual community supporters for sharing your journeys and stories this year, helping raise awareness of the Malaghan Institute and highlighting the importance of medical research in New Zealand.

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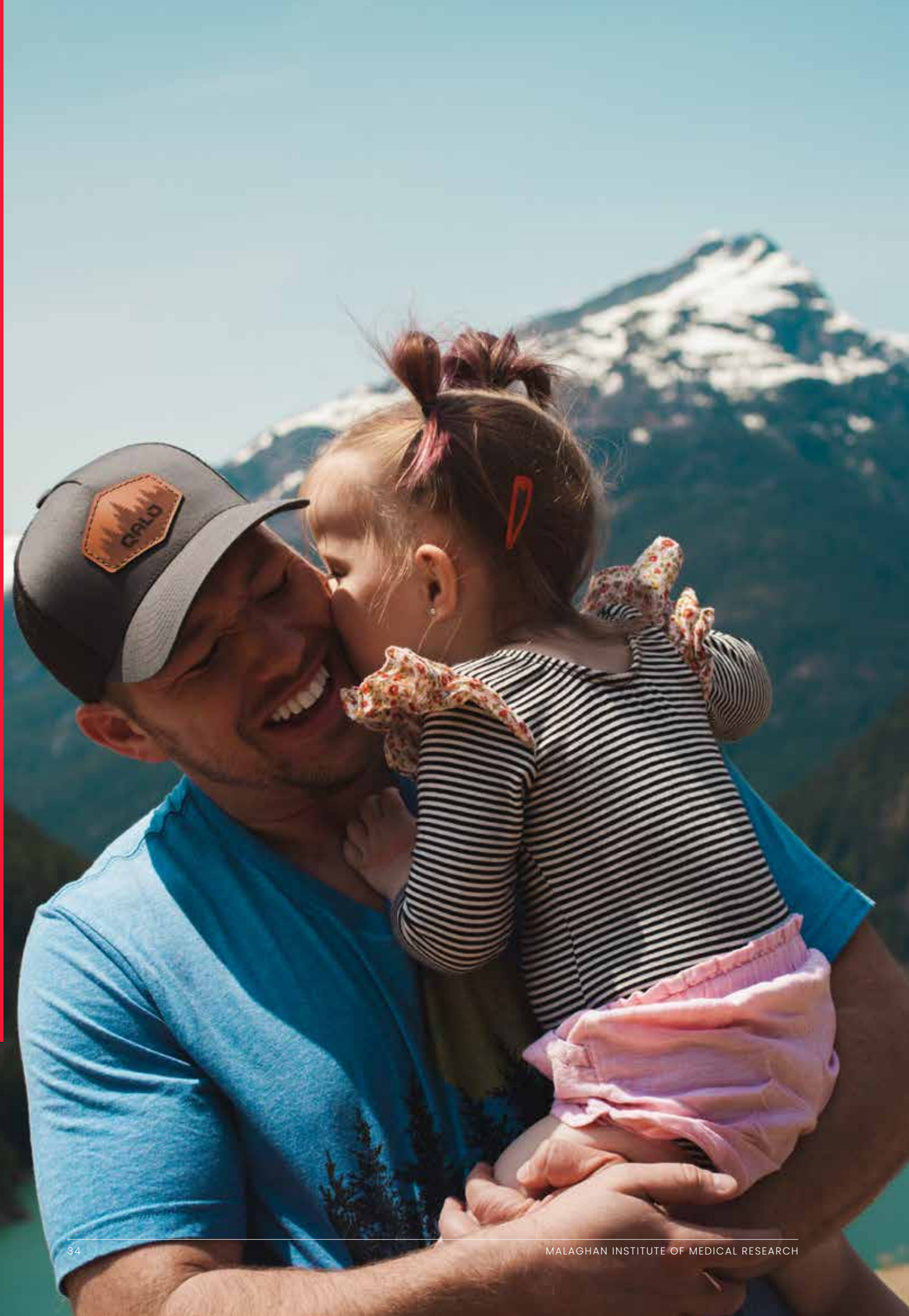

Te Urungi Māori

Te Urungi: the steering paddle of the waka which supports the work of the kaihoe by guiding the course.

Te Urungi Māori is an integral yet independent group at the Malaghan Institute, providing advice to the leadership team, with an overall approach of equitable health outcomes for Māori as a result of our research and clinical activity. Te Urungi Māori provides guidance on engagement with and implementation of the articles of Te Tiriti o Waitangi and Vision Mātauranga.

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