SCOPE 81

A MALAGHAN INSTITUTE PUBLICATION

MALAGHAN INSTITUTE OF MEDICAL RESEARCH

Cracking the code on the ageing immune system

WHAT'S INSIDE

From the Director

International connections and collaborations are key to our progress as a small but influential research institute positioned at the far end of the world. Indeed international collaborations are the lifeblood of all science. The exchange of ideas, technology and ways of thinking that comes from such cross-border partnerships have helped humankind progress throughout the ages and improved the situation for people across the planet.

In this issue of Scope we highlight some of our international collaborations that aim to improve health outcomes across a range of diseases. Our cover story showcases a recent collaboration with the Babraham Institute in Cambridge, UK, looking at answering the fundamental questions behind why ageing immune systems respond less effectively to vaccines and other therapies than their younger counterparts.

We also highlight a trans-Tasman collaboration designing a world-first mRNA malaria vaccine that targets immune cells in the liver against the malaria-causing parasite. This ground-breaking advancement would not have been possible without strong links with local and Australian colleagues, bringing unique research and expertise together.

Thank you for your support,

Professor Graham Le Gros | Director
CNZM FRSNZ FRCPA (Hon)

International collaboration to crack the code on the ageing immune system

Our immune system protects us from infection and disease throughout our life. Like us, it grows and evolves as we encounter new and familiar infectious organisms. In a similar vein, as we age, the immune system also ages, becoming less efficient and effective.

One of the most significant changes is that the older immune system responds less effectively to vaccines, producing fewer protective antibodies, offering less protection from disease. Why this happens is only just starting to be understood, with Cambridge's Babraham Institute leading global research into the fundamental biological changes of an ageing immune system. And in a new research collaboration with the Malaghan Institute, funded by the Biotechnology and Biological Sciences Research Council – part of UK Research and Innovation – there is hope that the ageing immune system can be revitalised. The partnership aims to hone in on 'germinal centres', a unique immunological structure that forms in response to an infectious organism, and use RNA technology to improve its performance.

"This collaboration brings together the fundamental biology of the germinal centre response in ageing that we've developed at the Babraham Institute, with the Malaghan Institute's mRNA vaccine development platform," says Dr Michelle Linterman, who heads the Linterman Laboratory at the Babraham Institute. "Our combined expertise puts us in a unique position to make and test new mRNA vaccines that we hope will rejuvenate the ageing immune system and promote health in the later years of life."

WHAT ARE GERMINAL CENTRES AND WHY ARE THEY IMPORTANT FOR FIGHTING INFECTIONS?

Germinal centres are immunological structures made up of immune cells that form in lymph nodes or the spleen during infection or following vaccination. The germinal centre is where weakened or deactivated infectious agents are presented, analysed and countered. These temporary structures, which last only a few weeks, are where high-quality and long-lived antibody-secreting cells are produced – cells that enable robust, enduring protection from infectious disease.

Part antibody factory, part art studio, germinal centres are immunological laboratories where antibodies get made, tested and prepared for distribution. Inside a single germinal centre millions of antibodies are created, all with slight variations. These antibodies get tested against the infection until a perfect match is found. Once the match is made, germinal centres also produce long-lived memory B-cells that can respond to any future infection of the same kind.

> "Our combined expertise puts us in a unique position to make and test new mRNA vaccines that we hope will rejuvenate the ageing immune system and promote health in the later years of life."

For germinal centres to function optimally, multiple immune cell types must come together, congregating in the right place at the right time to help make protective antibodies. This includes B-cells (that produce antibodies) and T follicular helper cells (a type of T- cell that helps the B-cell make antibodies).

With millions of cells working in sync, germinal centres are key to effective, long-lived protection from infectious disease. If something were to go wrong, or perhaps become less efficient, it results in a lower-quality protective immune response. This is what happens with ageing immune systems – with the germinal centres' response declining with age. This is one of the reasons why older people need more frequent vaccination, to compensate for their germinal centre's declining performance.

"We saw plenty of evidence of this during the COVID-19 vaccine rollout (including the Vaccine Alliance Aotearoa New Zealand's Ka Mātau Ka Ora study) where it became a priority for older people to receive boosters to enhance their levels of protective antibodies," says the Malaghan Institute's Dr Theresa Pankhurst, who is currently seconded to the Babraham Institute as part of Te Urungi Churchill College By-Fellowship.

USING RNA TECH TO TARGET IMMUNE CELLS IN GERMINAL CENTRES

RNA technology, the ability to package cellular instructions – such as a vaccine or therapeutic agent – in microscopic bubbles and deliver them to cells like a courier service, is revolutionising biomedicine. It may also be the key to boosting ailing germinal centres by targeting the immune cells inside them.

"The COVID-19 pandemic propelled mRNA vaccines into the spotlight and highlighted their potential across many applications," says Dr Linterman. "Although there is plenty of evidence demonstrating how the immune system responds to mRNA vaccination, very little of this has taken age into account or how mRNA vaccines can be improved to be more effective for older people."

By assisting waning immune cells through targeted RNA technology, it may be possible to artificially sustain germinal centre efficiency – offering the same protection of a younger, stronger immune system.

"Through this partnership we aim to investigate the germinal centre response to mRNA vaccination and how this changes with age. Furthermore, we can encode our mRNA vaccines with specific ingredients we have hypothesised might improve the age-related decline of the germinal centre, and then test these in aged mice."

Professor Graham Le Gros says the collaboration is a fantastic opportunity to combine world-class expertise and leaders in the fields of immunology to tackle a key health issue which is ageing immune systems. "Through this partnership we will gain access to cutting-edge genetic and molecular immunology tools we don't have access to in New Zealand. This really will be a step up in what we can do for improving vaccinations for some of our most vulnerable people."

▲ Dr Michelle Linterman

Malaghan Institute and BioOra **deliver automated manufacturing to scale up CAR T-cell cancer therapy in NZ**

▲ A Lonza Cocoon in action

In a significant milestone for New Zealand's first CAR T-cell clinical trial, partners at the Malaghan Institute and BioOra have started the clinical production of CAR T-cells using a new automated process – a shift that is key to scaling up this ground-breaking cancer therapy in New Zealand and "taking it to the people," says Malaghan Institute Director Professor Graham Le Gros.

"This isn't just a process change, this is a step change, it's about democratising a cutting-edge cancer therapy that New Zealanders deserve to have access to, and reducing inequities in cancer outcomes.".

Malaghan Institute Clinical Director Dr Robert Weinkove says moving manufacture from a time-intensive, manual process to an automated one will allow the team to manufacture CAR T-cells more consistently and at scale.

"This automation is critical to enable us to treat more patients – within our clinical trial programme at first and, we hope, as a future standard of care. This a huge milestone for our CAR T-cell programme, and demonstrating that this can be done here will put New Zealand among leaders internationally in this field."

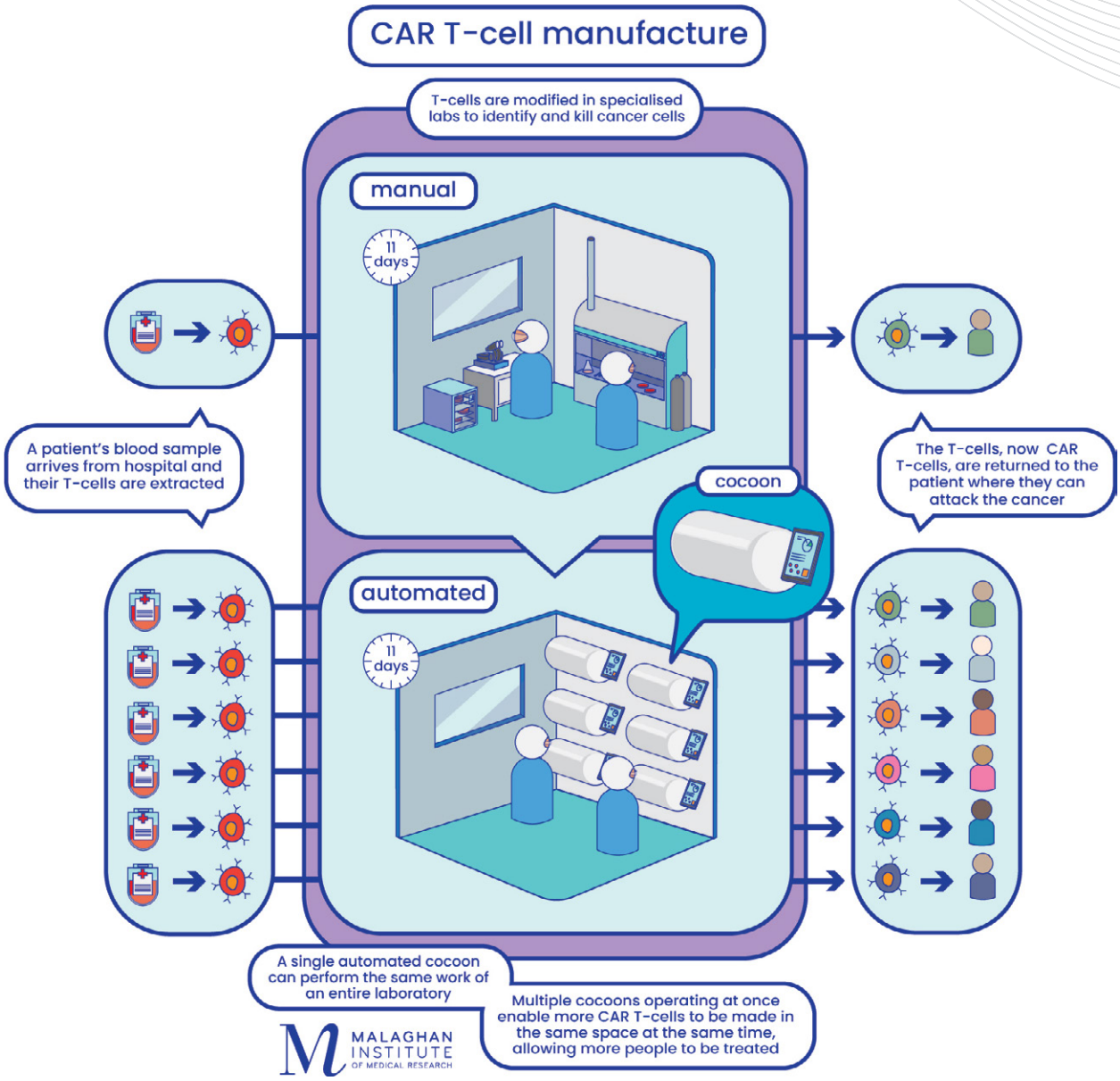
CAR (chimeric antigen receptor) T-cells are patients' own immune cells that have been gene-engineered to redirect them against their cancer. CAR T-cells have become a standard of care for certain blood cancers overseas, but are not yet funded in New Zealand.

Dr Weinkove says until recently, the Malaghan Institute has manufactured patients' CAR T-cells manually, a time-intensive process requiring over 40 hours of skilled operator time inside a specialised clean room for each patient's dose.

> "This a huge milestone for our CAR T-cell programme, and demonstrating that this can be done here will put New Zealand among leaders internationally in this field."

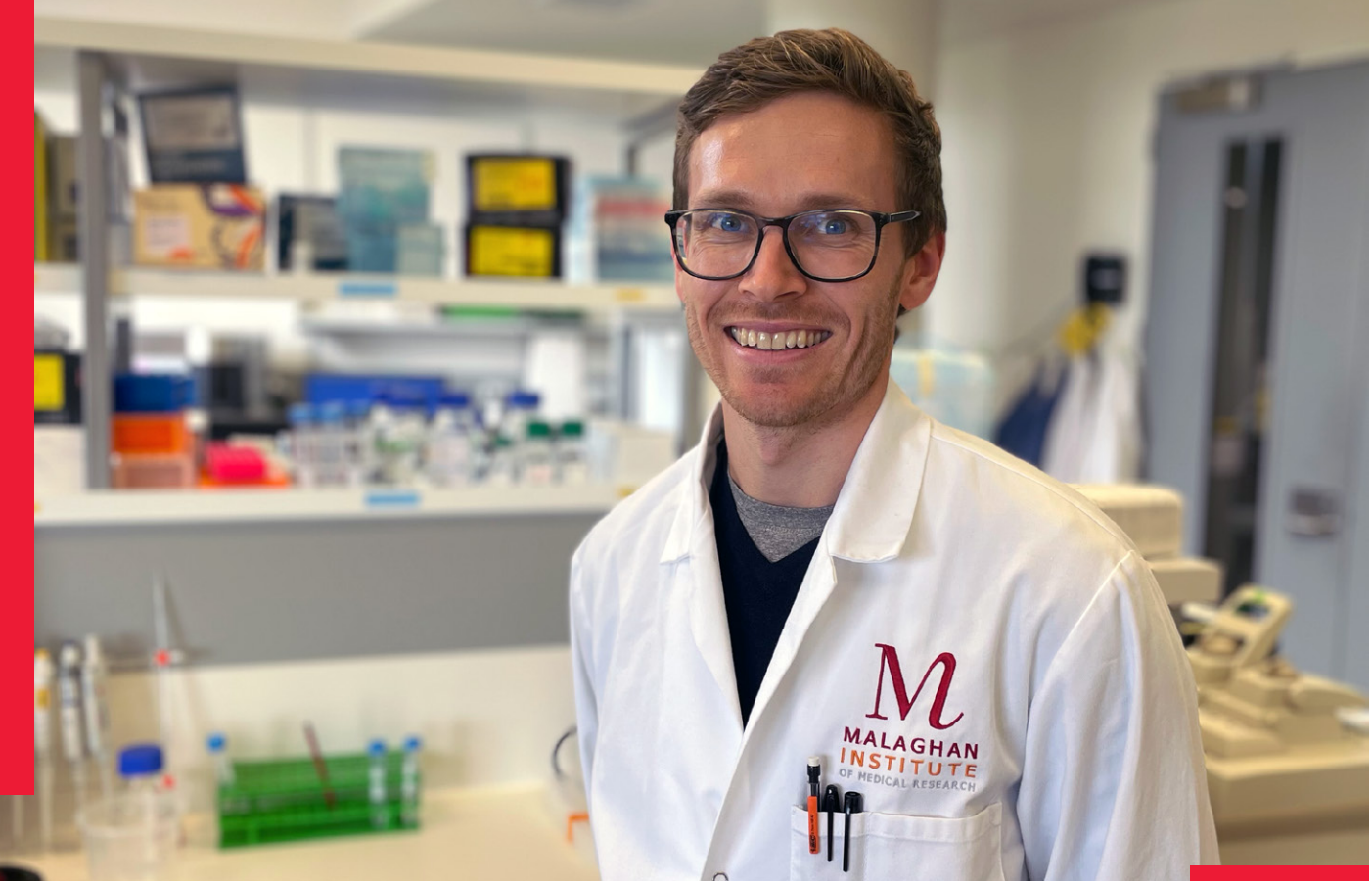
"Working with BioOra, this process has now been largely automated with manufacture of patient CAR T-cells taking place in a closed system – Lonza's Cocoon Cell Therapy Manufacturing Platform. Automating the manufacture provides significant advantages including increased throughput and lower costs, while maintaining quality."

The production of CAR T-cells is complex, involving multiple steps, so automation demanded careful optimisation and validation, says Dr Weinkove. "Teams at the Malaghan Institute and BioOra worked closely with New Zealand regulators to develop a world-leading process for manufacture of CAR T-cell products here in Aotearoa."



In 2019, the Malaghan Institute began enrolling patients to ENABLE, a phase 1 safety trial of a novel 'third generation' CAR T-cell construct for relapsed and refractory B-cell non-Hodgkin lymphoma, developed in partnership with Wellington Zhaotai Therapies. More than 20 patients have been treated in the trial, with the final patient in the 'dose escalation cohort' treated in January 2023. The phase 1 trial has been extended to add a 'dose expansion cohort', in which patients are receiving CAR T-cells manufactured using the new automated process. The Malaghan Institute, BioOra and Wellington Zhaotai Therapies are planning a larger phase 2 trial from 2024, to establish the effectiveness of these CAR T-cells.

In 2021, the Malaghan Institute formed a new company with Bridgewest Ventures – BioOra – to automate the manufacture of CAR T-cell therapy with a vision of delivering this new type of therapy locally, and at lower cost. The Malaghan Institute and BioOra will work together to complete the phase 1 trial using the automated manufacturing process and during the planned phase 2 trial.



▲ Dr Tom Mules

'INFECT AND FORGET': HOOKWORM STUDY SETS GROUNDWORK FOR MEDICATION-FREE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE

Could a dose of hookworms provide a medication-free alternative to people with inflammatory bowel disease? The Malaghan Institute's Hookworm Therapy team, who recently published the results from their year-long clinical study, think it's possible. Published in *Inflammatory Bowel Diseases*, the feasibility study found that hookworms were safe and long-lasting for participants with ulcerative colitis – paving the way for wider clinical studies.

The Malaghan Institute has been exploring the potential therapeutic benefits of human hookworms for patients suffering allergic and inflammatory disease for a number of years. Funded by the Health Research Council of New Zealand, this current study was the first of its kind to investigate whether hookworms could offer a medication-free alternative for patients living with ulcerative colitis to manage their disease.

"This pilot study is the first controlled evidence in the use of hookworm as a therapy in ulcerative colitis," says Malaghan Institute clinician and gastroenterologist Dr Tom Mules who led the study alongside Rutherford Clinic gastroenterologist Dr Stephen Inns. "Our study has shown this kind of therapy is well-tolerated, safe and feasible to take into a full-scale trial."

In this pilot randomised controlled trial, patients currently in remission from ulcerative colitis were infected with a controlled dose of hookworm larvae or given placebo, and followed up over twelve months. Patients would provide regular feedback on any changes to their gut health or discomfort. Samples were collected throughout the year-long infection to test a range of scientific parameters such as gut inflammation, microbiome and immune cell composition.

"We deliberately chose to target patients with ulcerative colitis in remission," says Dr Mules. "We believe that the effect of hookworms may not be strong enough to push someone from an active disease state into disease

remission. However, once someone is in remission hookworm could keep them there, prevent them from having disease flares and reduce the need to take medication, such as steroids, which supresses the immune system and has adverse effects."

Living in remission from an inflammatory disease typically means that patients experience less pain and discomfort associated with active disease. In order to stay in remission patients generally have to take daily medications to prevent flare ups. However, Dr Mules explains that there are significant barriers to taking daily medication, particularly when you do not have active symptoms to remind you to take pills morning and night. Importantly, not taking the medication increases the risk of having a flare. Disease flares impact quality of life, can lead to disease complications and need strong medications to bring under control.

"One of the key findings from this study was that a single dose of hookworm can reside in the body for several years, if not longer," says Dr Mules. "This means that if hookworm is effective at preventing disease flares you can get infected and potentially no longer have to daily medicate. 'Infect and forget'. The worms just sit there in the background and do their thing. I think that's where the power of this therapy lies."

"This means that if hookworm is effective at preventing disease flares you can get infected and potentially no longer have to daily medicate. 'Infect and forget'. The worms just sit there in the background and do their thing. I think that's where the power of this therapy lies."

However, before the team could truly test this 'infect and forget' theory in a full-scale trial, they had to confirm its safety.

"We did see that around the 6-8 week mark participants reported mild tummy symptoms, but those had all resolved by week 10-12," says Dr Mules. "Otherwise, compared to the placebo group there was no significant differences in adverse events.

"The fact that these worms are well tolerated and safe to give to people with inflammatory disease is really important. One of the big safety questions was if the immune response triggered by the hookworm in the early stages of the infection could trigger a flare of ulcerative colitis. We did not see this, again highlighting that this therapy is safe in these patients."

With no effective cure for severe inflammatory and allergic diseases the idea of using hookworms to manage harmful and aggressive symptoms is something many people have latched onto. There exists a thriving 'underground' market of people self-medicating with hookworms, and significant anecdotal evidence indicating they are helpful in treating disease and managing symptoms, says Dr Mules.

"We know that people with inflammatory bowel disease, including ulcerative colitis, already use medically unsupervised hookworms to manage their symptoms and regain some semblance of quality of life, however the evidence needed to support this is lacking. The aim of this study was to provide some solid scientific groundwork, to hopefully one day make this a real, legitimate therapy to help people living with debilitating disease."

Moving forward, the team plans to progress to larger clinical trials and to apply their findings to other diseases.

"The power of our study's findings is that we can apply them to other diseases as well," says Dr Mules. "We are in the process of deciding what the best disease target is. It could be ulcerative colitis but there are also early findings demonstrating hookworm therapy could be beneficial to a wide-range of autoimmune, allergic and metabolic diseases.

"We're extremely grateful to the participants for taking part in this important study which will let us apply hookworm therapy where it will have the biggest impact."

Scientific breakthrough harnesses mRNA technology to develop powerful malaria vaccine

A new mRNA vaccine targeting immune cells in the liver could be the key to tackling malaria, a disease that causes over half a million deaths each year according to the World Health Organization, yet has no effective long-lasting vaccine.

Trans-Tasman research collaborators from Te Herenga Waka— Victoria University of Wellington's Ferrier Research Institute and the Malaghan Institute of Medical Research in New Zealand, and the Peter Doherty Institute for Infection and Immunity in Australia have developed an mRNA-based vaccine that can effectively target and stimulate protective immune cell responses against the malaria-causing parasite Plasmodium in preclinical models.

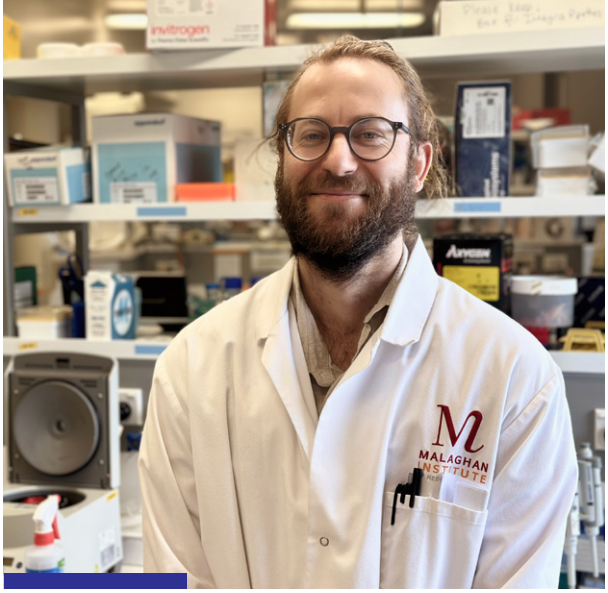
Ferrier Research Institute's Professor Gavin Painter says the approach is distinctive, as the team leveraged years of prior research from the University of Melbourne's Professor Bill Heath at the Doherty Institute and Professor Ian Hermans from the Malaghan Institute.

"Thanks to this synergy, we were able to design and validate an example of an mRNA vaccine that works by generating resident memory cells in the liver in a malaria model," says Prof Painter.

"It demonstrates the huge potential of RNA technology in solving some of the world's biggest health problems and the growing capability and expertise in mRNA vaccine development here in New Zealand and Australia."

Published in *Nature Immunology,* the focus of the collaborative research investigating a novel target for malaria was originally on peptide-based vaccines. However, in 2018, the team shifted their approach and started investigating RNA-based vaccines – a decision that, so far, seems to have paid off with the recent success of RNA technology in vaccine development.

"While our successful peptide-based vaccines targeting malaria only contain small protein fragments of a malaria protein, mRNA vaccines encode an entire malaria protein," says the University of Melbourne's Dr Lauren Holz, Research Officer at the Doherty Institute and co-author of the paper.



▲ Dr Mitch Ganley

"This is a real strength because it means we can generate a broader and hopefully more protective immune response."

To pack an extra protective punch, the mRNA vaccine has been combined with an adjuvant – originally developed at the Malaghan and Ferrier Institutes for cancer immunotherapies – which targets and stimulates liver-specific immune cells. This additional ingredient helps localise the RNA vaccine response to the liver, a key site in preventing the parasite from developing and maturing in the body.

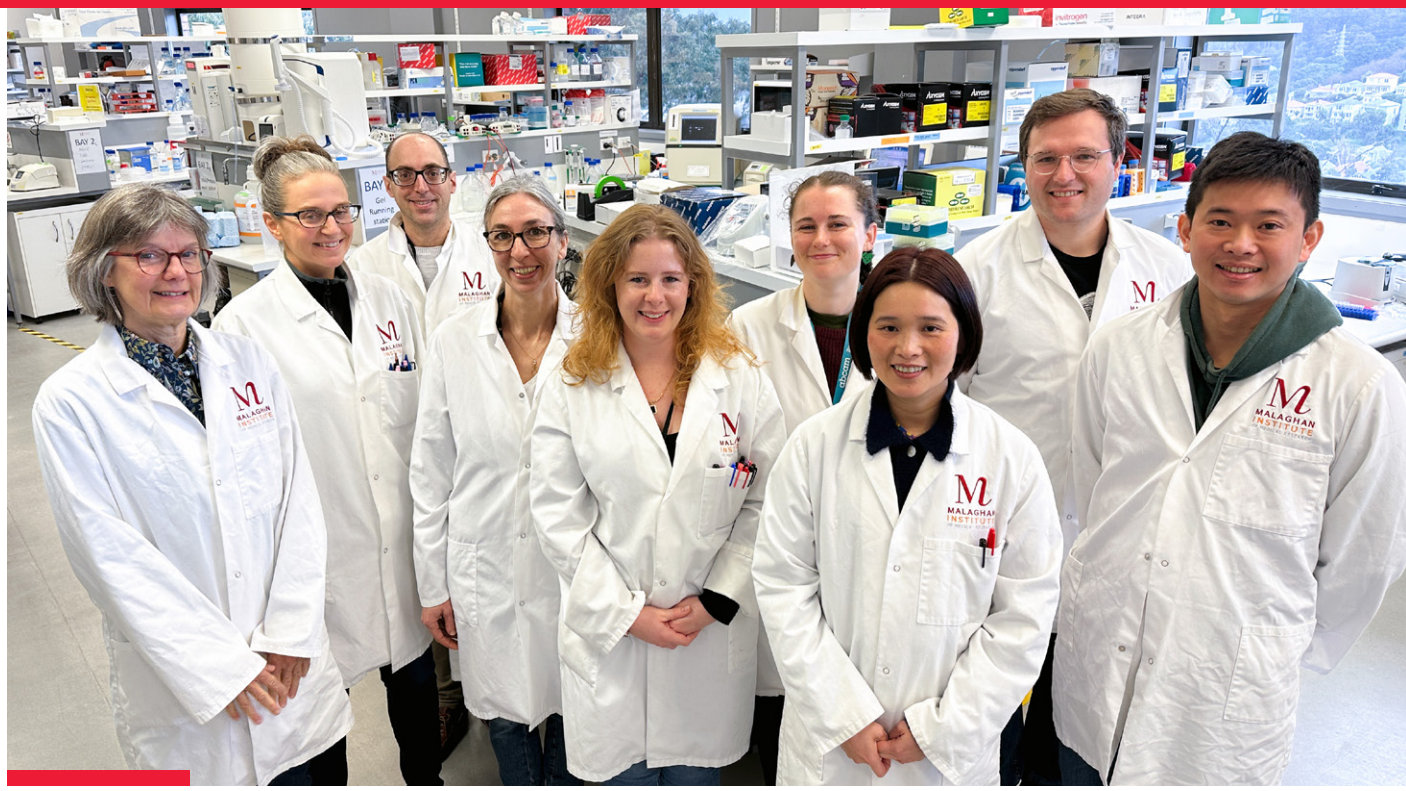
"When the parasite first enters the bloodstream, it travels to the liver where it develops and matures before going on to infect blood cells, which is when disease symptoms occur," says Dr Mitch Ganley, Postdoctoral Research Fellow at the Ferrier Research Institute, and co-author of the study.

"Unlike the COVID-19 vaccine that works by neutralising antibodies, our unique approach relies on T-cells which play a critical role in immunity. Specifically, a type of T-cell called a tissue-resident memory T-cell, that halts malaria infection in the liver to completely stop the spread of infection."

Dr Holz says the key advantage of this vaccine is that it isn't affected by previous exposure to malaria.

"A lot of malaria vaccines undergoing trials have worked really well in animal models or when they're given to people who haven't had malaria before, but they don't work well when given to people living in malaria-endemic regions. In contrast, our vaccine is still capable of generating protective liver-specific immune cells and providing protection even when the animal models have been pre-exposed to the disease," says Dr Holz.

The research team is now working towards taking the vaccine into human clinical trials, which they expect to take several years.



▲ The Ronchese Laboratory

Health Research Council to fund clinical study investigating the skin's role in initiating allergic disease

The Health Research Council of New Zealand has granted the Malaghan Institute's Ronchese Laboratory $1.2 million to better understand the crucial role immune cells in the skin play in initiating allergic diseases.

The project, 'Plasticity of the skin IL-13+ innate lymphoid cell niche,' comes off the back of earlier Health Research Council-funded research in which the Ronchese lab made the ground-breaking discovery that the skin is constantly prepared to trigger allergic responses – marking it as 'ground zero' for allergic disease.

"The aim of this project is to study the impact of immune responses on a specific type of immune cells called type 2 innate lymphoid cells, in both mouse and human skin," says Malaghan Research Fellow Dr Sotaro Ochiai. "Under normal conditions, these cells produce a chemical signal called interleukin-13. Our recent research has shown that IL-13 plays a crucial role in the development of pro-allergic skin dendritic cells."

"Our recent research has shown that IL-13 plays a crucial role in the development of pro-allergic skin dendritic cells."

Over the next three years, the lab will investigate whether their previous findings into the role of skin immune cells carry over into human studies. Working alongside clinical immunologist Dr Maia Brewerton, they will be investigating the composition and function of immune cells found naturally in the skin for both healthy individuals and those living with allergic disease, in order to gain a deeper understanding what drives this phenomenon.

Professor Franca Ronchese says the grant will help the lab understand whether this population of innate immune cells which are specific to the skin, and which are programmed to initiate allergic responses are a fixed property of the skin or can be changed or replaced.

"If they are 'fixed' – as in they are needed for normal skin functions – we can develop ways to manage them for people with allergic disease. Alternatively, if they can be replaced, we can look at ways to remove them to prevent the skin programming allergic responses throughout the body," say Prof Ronchese.

"I think it is very exciting that the Health Research Council is further supporting our research, and we look forward to using this support for the benefit of all New Zealanders. The Health Research Council is the only New Zealand organisation that funds research into allergies and inflammatory diseases which affect more than 20 to 30 percent of our population, sometimes severely."

IN FOCUS

Using state-of-the-art technology to probe the immune system's role in health and disease.

Sam Small is a senior staff scientist working in the Hugh Green Cytometry Centre, the hub of cutting-edge technologies and experts that underpin the research conducted at the Malaghan Institute. At the heart of these technologies lies flow cytometry, a powerful tool which allows researchers to understand the complexities of cells and interrogate their role in the context of disease.

"Flow cytometry provides valuable insights into cellular functions and characteristics, paving the way for ground-breaking discoveries," says Sam.

"It allows us to characterise individual cells in a sample of many cells, meaning we can answer a wide range of questions such as what surface molecules are present on an immune cell that enable it to target and destroy cancer?"

Flow cytometry quietly underpins most experimental work across all research groups at the Malaghan. This technology plays a pivotal role in offering deep insights into cellular dynamics and behaviours, shaping scientific progress across disciplines.

In the vaccine space, flow cytometry provides a window into the strength of the immune response following vaccination. By comparing vaccinated and non-vaccinated individuals, researchers can gain insight into the effectiveness of a vaccine.

In allergy research, flow cytometry sheds light on the behaviour of immune cells during allergic response, potentially guiding future treatments.

Within cancer biology at the Malaghan, flow cytometry helps us assess the results of cancer treatments such as CAR-T cell therapy. It allows researchers to monitor shifts in cell populations and track changes within tumours, informing therapeutic strategies.

Sam's expertise in the intricacies of flow cytometry makes her a valuable ally that researchers rely on to uncover the hidden details of cellular behaviour.

"The process begins by labelling a sample of cells with tags specific to unique identifiers such as proteins. This enables scientists to distinguish between different cell types and gain valuable insights into their functions and behaviours."

Once the cells are prepared, they are introduced into the flow cytometer, which reads the tagged cells as they pass through a laser in single file. This results in a range of properties being identified per cell.

"The data obtained from this process plots each cell as a unique data point, providing a visual representation of the cell population that researchers can go and analyse," says Sam.

Sam's role enables other researchers to use this technology effectively and correctly. She prepares the flow cytometer for use and runs experiments while monitoring its performance to ensure optimal results.

"I've learned everything I know about flow cytometry during my time at the Malaghan. Flow cytometry is something you can't learn entirely by reading books. Mostly it comes from hands-on experience, guided by knowledgeable experts in the field," says Sam.

"My favourite part of my role is that I can help researchers carry out this technique and in doing so, take part in a wide range of projects. My main motivation for going into science in the first place was so I can help people."

▲ Sam Small

In Focus is a monthly e-update taking a close up look at our research and the scientists behind it. If you're not already subscribed, you can sign up on our website **malaghan.org.nz**

Malaghan in the community: Science Talks

I want to say a personal thank you to our long term supporters, Jarden, who generously hosted the first of our new 'Malaghan Science Talks' in Auckland in June.

A panel of our scientists discussed some of the work underway at the Malaghan Institute to advance and apply understanding of the immune system to tackle diseases that affect all our lives, including CAR T-cell therapy and allergic disease. The audience put our scientists to the test with an in-depth Q&A session and everyone involved from the institute enjoyed the opportunity to reconnect with supporters.

Being able to show the work that you make possible is a privilege for me and the team, and our scientists really enjoy getting out into the community to share their research. We look forward to getting similar events out across the country in the near future. Thank you again to the team at Jarden for your support over the years. We couldn't do what we do without you.

LAURA GOLLAND
Head of Fundraising

▲ **Thank you Lexus:** The installation of a new EV charger at the Malaghan Institute is the perfect excuse to celebrate our long-standing relationship with Lexus New Zealand!

Lexus has long supported the spirit and ambition of the Malaghan Institute, sharing a commitment to pioneering, reimagining and delivering innovation and excellence for the benefit of New Zealand.

▲ **Thank you Harvey House:** On 18 June the boys at Whanganui Collegiate School's Harvey House held a remarkable Dusk to Dawn 'rowathon', rowing non-stop for 12 hours, raising funds to support the Malaghan Institute. What absolute champions!

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

People we love are suffering and dying from diseases we don't know enough about. But we do know the immune system holds the key to prevention, treatment and cures. By supporting the Malaghan Institute you are providing hope to those living with disease now and in the future.

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.

TO DONATE, SIMPLY SCAN THE QR CODE, OR VISIT

donate.malaghan.org.nz

You can also give our friendly fundraising team a call on 04 499 6914

If you would prefer, you can also donate via direct deposit in to our bank account.

If you donate via direct deposit, please email us with your details so we can make sure to send you a receipt.

ACCOUNT NAME: **The Malaghan Institute of Medical Research**

ACCOUNT NUMBER: **06-0507-0052635-30**

YOUR REFERENCE: **First name & Last name**

THANK YOU TO OUR PARTNERS

LEXUS

hrc Health Research Council of New Zealand

KINETICS GROUP making IT work for you

HUGH GREEN FOUNDATION

SPY VALLEY WINES

JUST PATERSON

FREEMASONS New Zealand

JARDEN

MALAGHAN INSTITUTE

P +64 4 499 6914 **E** info@malaghan.org.nz
PO Box 7060, Wellington 6242, New Zealand
malaghan.org.nz