MAY 2024

SCOPE 83

A MALAGHAN INSTITUTE PUBLICATION

MALAGHAN INSTITUTE OF MEDICAL RESEARCH

New clinical research aims to reduce stomach cancer rates and disparities in New Zealand

WHAT'S INSIDE

From the Director

As a charity, feedback from our community is so critical to achieving our goals.

I am privileged to regularly hear first-hand from many supporters representing the full spectrum of New Zealanders, the cares and concerns of those who are passionate about the future of health research in New Zealand. This feedback helps ensure we look outward and remain focused on the issues that matter to our community.

The Malaghan Institute has been going through a transformative phase over the past few years. While we share many of the challenges facing New Zealand right now, we are steadfast in our ambition to deliver solutions to address the health issues that actually matter to New Zealanders. We're confident in our ability to get the basics of medical research right, and we've gathered cutting-edge researchers and technology. Now, it's our responsibility to take all that we've learned, with the support of our community, and get on with the work.

Professor Graham Le Gros | Director

CNZM FRSNZ FRCPA (Hon)

New clinical research aims to reduce stomach cancer rates and disparities in New Zealand

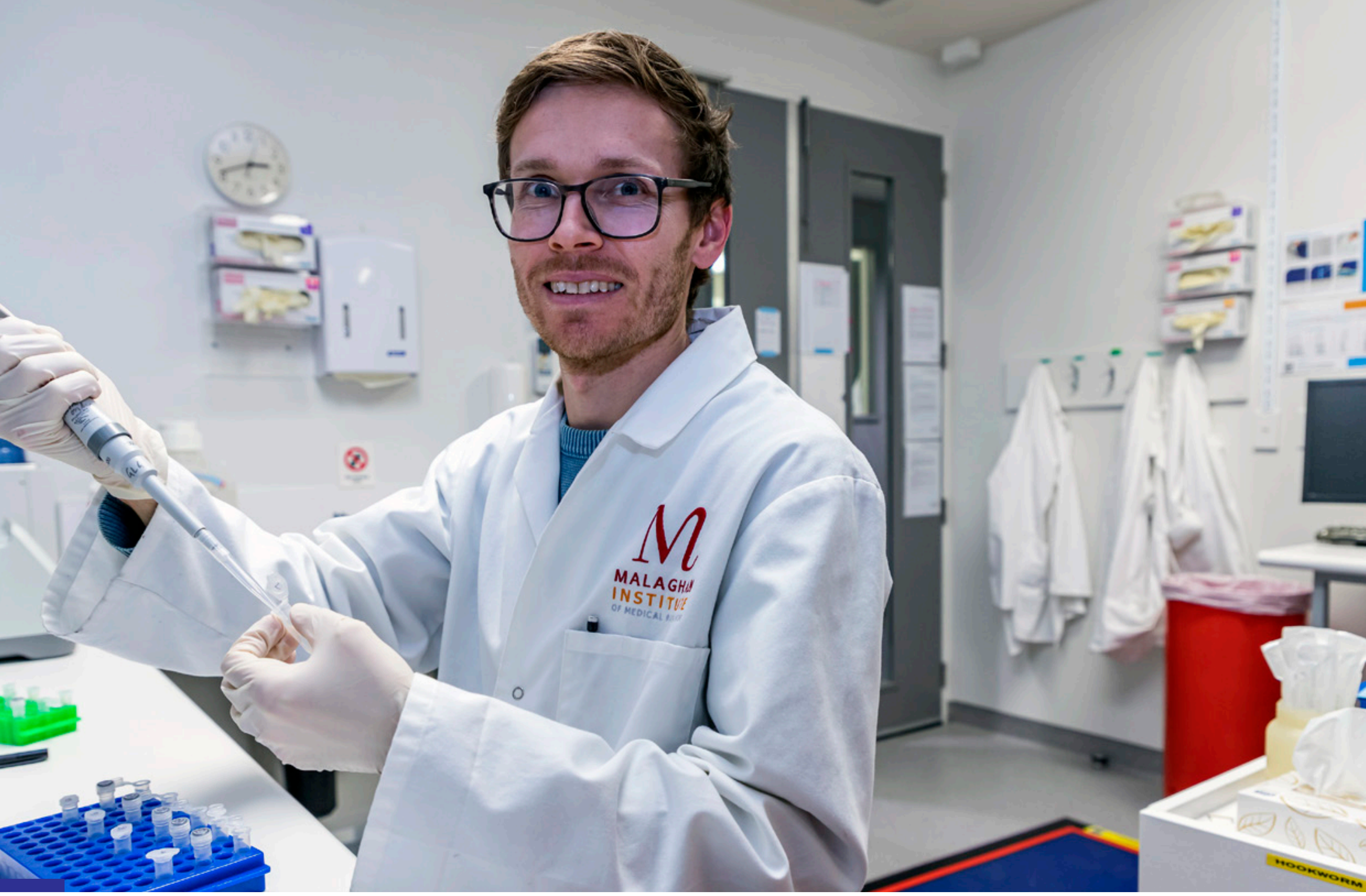
The Malaghan Institute has launched a new clinical research programme in collaboration with the University of Otago which aims to increase the successful eradication of *Helicobacter pylori (H. pylori)*, a bacterium that lives in the stomach and is the leading cause of stomach cancer.

H. pylori and stomach cancer disproportionately impact Māori and Pacific peoples in Aotearoa New Zealand. When *H. pylori* is identified and treated, stomach cancer can be prevented. However, the ability to successfully treat and eradicate *H. pylori* with commonly used antibiotics is declining due to increasing antibiotic resistance.

Dr Stephen Inns and Dr Tom Mules, gastroenterologists at Te Whatu Ora Hutt Valley and clinical researchers at the University of Otago and the Malaghan Institute respectively, are developing and validating new methods to test for antibiotic resistance in *H. pylori* to guide antibiotic prescribing.

H. pylori is responsible for most stomach cancers in New Zealand. Usually contracted in childhood, *H. pylori* infects the cells of the stomach, causing gastritis, or inflammation of the stomach lining. Left untreated, the inflammation can become chronic leading to tissue damage and ulcers and eventually, cancer.

"The best way to prevent stomach cancer is to eradicate *H. pylori*," says Dr Mules. "However, *H. pylori* is becoming more resistant to antibiotics, limiting our ability to treat infections."



▲ Dr Tom Mules. Cover: Research Officer Kate Maclean and Dr Tom Mules.

In New Zealand, the current practice is to prescribe everyone the same antibiotics to treat *H. pylori*, without knowing if it is the right antibiotic regimen for that individual.

“By determining the antibiotic resistance profile of H. pylori, we aim to individualise treatment regimens to increase eradication and decrease inappropriate antibiotic prescribing,” Dr Mules says.

> “The best way to prevent stomach cancer is to eradicate *H. pylori*. However, *H. pylori* is becoming more resistant to antibiotics, limiting our ability to treat infections.”

Significant disparities exist in the rates of stomach cancer among Māori and Pacific populations in Aotearoa, who have three to six times higher rates compared to New Zealand Europeans according to a University of Otago study.

“These ethnic inequalities in stomach cancer rates predominantly stem from the higher prevalence of *H. pylori* infection among Māori and Pasifika,” says Dr Mules. “Māori and Pasifika are also more likely to be infected with a more carcinogenic strain of *H. pylori*, further contributing to the heightened risk of stomach cancer.”

The research involves extracting *H. pylori* DNA from patient gastric tissue samples or stool samples taken as part of routine clinical testing for the presence of *H. pylori*, analysing these samples for the presence of antibiotic resistance genes, and tailoring antibiotic therapy based on this gene profile.

“Being able to individualise treatment so we can prescribe the right antibiotic for the right person is crucial to improve treatment success, while also reducing inappropriate antibiotic prescribing,” says Dr Mules.

Taking place at Hutt Hospital, the first phase of the research programme is already underway.

Dr Mules says the next phase is to perform a clinical trial to determine if routinely testing *H. pylori* for the presence of antibiotic resistance, and then individualising therapy based on this result, will increase the effectiveness of treatment in the clinical setting.

“This research has the potential to profoundly transform clinical practice, directly addressing and rectifying significant healthcare equity concerns in Aotearoa New Zealand.”

Significant milestone reached in first NZ CAR T-cell trial as preparations made for larger phase 2 registration trial

▲ Research Officer Felix O'Hagan with an automated CAR T-cell manufacturing Cocoon.

The goal of CAR T-cell cancer therapy becoming a standard of care in New Zealand is another step closer with patient enrolment completed and a total of 30 patients treated within the Malaghan Institute's ENABLE phase 1 safety trial, says Malaghan Institute Clinical Director Dr Robert Weinkove.

Preliminary results of the first 21 patients treated in the trial's dose escalation cohort, presented at the American Society of Hematology meeting in December 2023, suggested the new third-generation CAR T-cell therapy, developed in collaboration with Wellington Zhaotai Therapies Limited, is safer than leading commercial CAR T-cell products, while remaining highly effective for B-cell non-Hodgkin lymphomas.

Since then, a further nine patients have been treated at the optimal dose as part of a dose expansion cohort, with outpatient management and automated CAR T-cell manufacturing by New Zealand company BioOra Limited. Enrolment and treatment is now complete. Trial participants remain under follow-up, with a primary analysis of all 30 patients treated expected in June 2024, followed by publication of the results.

> "We are preparing a larger phase 2 trial to confirm effectiveness and safety of our CAR T-cell therapy – and to use it earlier in lymphoma treatment."

Dr Weinkove says the dose expansion cohort has established manufacture and delivery of CAR T-cells using cutting-edge automation technology, and has laid the groundwork for a phase 2 registration trial later in 2024.

"The most remarkable finding in the ENABLE trial is the low rate of two common side effects of CAR T-cell therapies: neurotoxicity and cytokine release syndrome. This has allowed us to treat patients without planned hospital admission, saving healthcare dollars. We are preparing a larger phase 2 trial to confirm effectiveness and safety of our CAR T-cell therapy – and to use it earlier in lymphoma treatment."

The Malaghan Institute is preparing for a phase 2 trial that it hopes will support registration in New Zealand and Australia. The multi-site trial, ENABLE-2, will treat 60 patients over two years.

"We have aligned ENABLE-2 with health service priorities and with a view to regulatory approval. We are actively discussing what it would take to make this treatment – and others like it – available for those who need it here in New Zealand," says Dr Weinkove.

"The main barriers to CAR T-cell therapy globally are the burden of managing side effects and the cost of the CAR T-cells themselves. By combining an improved safety profile with cost-effective manufacturing, we aim to address both issues."

BioOra, incubated within the Malaghan Institute, was established with Bridgewest Ventures in 2021 to optimise and scale-up CAR T-cell manufacturing in New Zealand, with a view to regulatory approval and reimbursement for CAR T-cell therapy. If the phase 2 clinical trial leads to successful registration, the Malaghan–BioOra partnership provides a pathway for the therapy to reach New Zealand and Australian patients rapidly and equitably.

BioOra CEO Andi Grant says overseas commercial CAR T-cell therapies are very expensive due to labour and capital intensive clinical and manufacturing models.

"Here in New Zealand, BioOra has partnered with the Malaghan Institute to develop a unique automated process for this personalised therapy that will enable us to manufacture CAR T-cells more consistently at lower cost, and to treat more patients. We have combined this technology with expertise in the delivery and reimbursement of therapeutic products to ensure both this, and other CAR T-cell therapies, can reach New Zealand and Australian patients, and beyond."

AWARD-WINNING COLLABORATION IDENTIFIES **INTERFERON-GAMMA AS POTENTIAL SARS-COV-2 ANTIVIRAL**

Conditioning the lungs with interferon-gamma, a natural immune system protein (cytokine) best known for fighting bacterial infections, appears to be a strong antiviral for SARS-CoV-2, the virus that causes Covid-19, according to National Institutes of Health scientists. The research, led by the Malaghan Institute's Dr Kerry Hilligan while on a postdoctoral fellowship at the National Institute of Allergy and Infectious Disease in Washington DC was awarded the 2023 CIG William E. Paul Award for Best Paper in Cytokine Research.

▲ Dr Kerry Hilligan

The researchers suggest testing interferon-gamma further, alone and in combination with other treatments, to limit early SARS-CoV-2 infection in people. They also hypothesise that people with prior bacterial infections that naturally release interferon-gamma in their lungs may be less susceptible to Covid-19.

Previously, the research team had observed that a vaccine for tuberculosis, known as BCG, given intravenously to establish a mild lung infection subsequently provided strong protection against SARS-CoV-2. The new study reveals that interferon-gamma, released by the immune system in response to BCG vaccine, is required for the observed SARS-CoV-2 antiviral immunity. The investigators also examined the mechanism by which interferon-gamma protects against SARS COV-2 and presented evidence that the cytokine targets lung epithelial cells, a major site of early viral replication, thus limiting its spread.

"IFN-gamma is currently used in the clinic for a variety of different things but rarely for viral infections and it is administered under the skin," says Dr Hilligan, who is now back at the Malaghan Institute. "Our study suggests that IFN-gamma could be used as a prophylactic option for limiting viral infections in highly susceptible populations, particularly if it is formulated as a nasal spray or similar.

"My current research programme at the Malaghan is further exploring the idea of 'infection interference' to understand how the lung adapts to protect itself from concurrent or sequential infections."

Since then, the research has been recognised for its important contribution in the understanding of cytokines. Named in honour of one of the most influential scientists in the field of immunology Professor William E Paul, the award also shares a special connection with the Malaghan Institute, with Professor Paul a mentor to the institute's director, Professor Graham Le Gros.

"To be awarded the William (Bill) Paul award is an incredible acknowledgement of Kerry and her scientific discoveries," says Prof Le Gros.

"Bill Paul is internationally acknowledged as one of the founders of our modern immunological understanding that is leading to so many amazing breakthroughs in health today. The award is given to those whose work continues that legacy. We are most proud that our homegrown New Zealand immunologist Kerry has been recognised in this way."

Study finds where MAIT cells live may determine their role in allergic disease

A clue about how we might target specific immune cells to prevent disease has been found in a recent study from the Malaghan Institute which investigated the role of MAIT cells in the development of allergies.

The research, published in *Allergy*, showed that MAIT cells could both help and hinder the development of allergies depending on where they were found in the body. While the findings further compound the complex relationship between immune cells and allergic disease, they shed some much-needed light on how researchers might develop future treatments for allergic disease by targeting key cells.

“We found that a specific subset of immune cells called MAIT cells plays an important role in the development of allergies,” says Dr Alissa Cait who led this Health Research Council of New Zealand-funded work. “Interestingly, we identified that this immune cell plays a different, and opposite, role in different tissues.”

MAIT cells are unique as they are associated with the mucosal areas in the body; the airway, gut and nasal passages. They’re one of the first immune cells to encounter potentially harmful organisms, including allergens, which makes them a key cell of interest for immunologists. They’re often associated with ‘homeostasis’; keeping the body on an even keel. Perhaps, then, it’s not surprising they can play both sides of the allergic disease field.

“It’s been previously discovered that MAIT cells in the lung can protect against allergy when exposure to allergens first happen in the airway. Our unexpected finding was that MAIT cells in the skin have the opposite effect: exposure to the same allergens promotes allergy development. This is really interesting in the context of the allergic march – the observation that infants with skin allergies, such as atopic dermatitis, progress over time to food allergies and then asthma ,” says Dr Cait.

“We’ve also known for a long time that introducing allergens via the gut – a mucosal site similar to the lung, protects against food allergies – what we call oral tolerance. But exposure to those same allergens in skin first is likely promoting food allergies.”

The results from this study closely mirror other findings from Malaghan scientists, eluding to the important role of the skin, and the immune cells that call them home, has in the initial development and possible prevention of allergic disease.

“These results are quite similar to findings from the Professor Ronchese Lab. They focused on other immune cells, in this case dendritic cells, which they found can behave different if found in the skin – where they can prime allergic responses.

“In our research, understanding the role of the MAIT cell in the skin and how they contribute to the development of systemic allergies like asthma and food allergies could allow us to develop novel interventions,” says Dr Cait. “There are some very effective topical inhibitors of MAIT cells in the works with our collaborators at the Ferrier Research Institute that could have potential in this context.”

These findings are yet to be tested in humans, but the researchers hope to continue to explore whether there could be a potential therapeutic benefit in blocking MAIT cells in the skin.

“We have lots of interesting MAIT cell research going on in the lab,” says Dr Cait. “There is lots to understand with those MAIT cells, how they might contribute to allergy and how we can intervene to prevent the development of potentially debilitating conditions.”

▲ Dr Alissa Cait

Celebrating 30 years at the Malaghan Institute

Thirty years ago in April, Graham Le Gros and Franca Ronchese joined the Malaghan Institute, fresh from research positions at Ciba-Geigy and the Basel Institute for Immunology (respectively) in Switzerland.

Moving to New Zealand with their young family, they brought with them a fresh new focus on immunology and how the immune system can be harnessed to prevent, treat and cure disease.

Malaghan Institute Chair Sir Paul Collins acknowledges their remarkable tenure. "While it's tempting to say we got '2 for the price of 1', I far prefer to say we got '3 for the price of 2'.

"By any measure their respective contributions are remarkable and without question underpin the Malaghan as an internationally recognised world-class independent medical research institute."

▲ Professors Franca Ronchese and Graham Le Gros

▲ Kylie Price

CAREER IN CYTOMETRY **RECOGNISED AT TOP LEVEL**

Malaghan Institute Chief Technology Officer and Hugh Green Cytometry Fellow Kylie Price has received the Australasian Cytometry Society's top honour – the Career Recognition Award – for her substantial contribution promoting research, developing capability and sharing knowledge of cytometry across Australia and New Zealand.

Kylie has been an integral part of the Malaghan Institute for more than 20 years, establishing and developing our Hugh Green Cytometry Centre into the international technology powerhouse it is today.

IN FOCUS

A gateway for toxic damage and immune health

A cellular receptor, once notorious for its interaction with environmental toxins is now being investigated for its potentially critical role in supporting immune health.

Dr Jeffry Tang is a senior research fellow working in the Gasser Laboratory at the Malaghan Institute. He specialises in nutritional immunology, studying how metabolites – molecules produced when food is broken down and absorbed by the body – affect our health. His research focuses on the aryl hydrocarbon receptor (AhR), a protein receptor found in a variety of cells across the body. A receptor is like a lock on the surface of or within a cell that can only be unlocked by specific molecules that fit into the receptor. When the right molecule binds to a receptor, it unlocks a particular action within the cell.

The discovery of the AhR was made through research looking into why a potent class of environmental pollutants called dioxins is so detrimental to health. Present in by-products of industrial processes as well as the infamous Agent Orange used to clear forests during the Vietnam War, dioxins can cause reproductive and developmental problems, damage the immune system, interfere with hormones, and cause cancer. The AhR was discovered to be a specific binding site for dioxins, providing insight into how dioxins interact with cellular components.

While the AhR was initially studied in the context of toxicology, over time, it has been found to bind to a variety of naturally occurring molecules, including some found in the human diet.

“The AhR was identified as a very important environmental sensor. This broadened the scope of research and interest in the AhR, shifting the focus from toxic responses to a wider understanding of its role,” says Dr Tang.

▲ Dr Jeffry Tang

Environmental toxins can disrupt immune homeostasis, and understanding the AhR’s role could provide a pathway to mitigating these effects.

“Research also suggests that certain dietary choices could potentially prime the AhR, preparing it to deal more effectively with pollutants. This could open up new dietary strategies for bolstering our body’s natural defences against environmental toxins, especially pertinent as pollution continues to be a growing problem globally.”

“A large part of the motivation for the research I do is to find lifestyle changes that individuals can adopt to help overcome the health effects of the circumstances that may be out of their control, such as living in a highly polluted city,” says Dr Tang.

“Everybody eats. So dietary recommendations based on new research can be more easily updated and adapted. If new findings emerge about a particular food or diet, clinicians can readily adjust their advice.”

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**

Thank you!

We had an amazing response to our annual appeal, raising more than **$430K** towards better, gentler treatments for diseases that affect all our lives.

We couldn't have done it without Kate who shared her own powerful story on why we need better, more effective ways to fight cancer. Thank you!

From all of us at the Malaghan, thank you for being part of our team. It takes everyone to translate cutting-edge science into life-saving treatments and cures.

IF THERE IS **ONE HOPE I HAVE** ABOVE ALL, IT IS THAT MY GIRLS AND MY LOVED ONES WHO MIGHT FACE CANCER IN THE FUTURE WILL NOT HAVE TO ENDURE THE SAME KIND OF SH** I HAD TO.

THAT HOPE CAN BE A REALITY, BUT WE NEED TO **WORK TOGETHER** AND WE ALL NEED TO **PLAY OUR PART IN SUPPORTING A BETTER FUTURE.**

I'M SHARING MY STORY TO ASK FOR YOUR SUPPORT **TO HELP FUND CUTTING-EDGE TREATMENTS** HAPPENING **AT THE MALAGHAN INSTITUTE** AND TO HELP MAKE THESE A STANDARD OF CARE IN NEW ZEALAND.

MEET LEGACY PARTNER **MIKE WINSBOROUGH**

Mike, a keen runner, actor and tennis player, 'stumbled' onto the Malaghan many years ago, and has been an active supporter ever since. Several years ago, Mike made the decision to leave a gift to the Malaghan in his will, to help ensure the institute remains at the forefront of research and technological development.

"I am incredibly supportive of their work trying to improve and prolong people's lives. I particularly support the development of new treatments for New Zealanders so they don't have to travel miles away."

Having lived in Wellington for many years, Mike now lives in New Plymouth but regularly returns to Wellington to visit his daughters and grandchildren. He believes that anyone can support medical research through gifts in wills, and encourages others to do the same.

▲ Mike Winsborough

"Just go for it. Unless you've had the privilege of living a very charmed life, we're all susceptible to disease, so it's important we support cutting-edge research where we can."

TO LEARN MORE ABOUT INCLUDING A GIFT IN YOUR WILL, PLEASE VISIT

donate.malaghan.org.nz/giftinyourwill

Chubb Life enters partnership to support the Malaghan's cutting-edge research

As part of a new partnership with the Malaghan Institute, Chubb Life Insurance New Zealand Limited has pledged $100,000 over three years to support the institute's research, advancing understanding of the immune system to improve human health.

To amplify the impact of the collaboration, Chubb Life, one of the country's leading providers of health insurance, supported our 2024 annual appeal by matching all donations received during the last week of March, to the total value of $100,000. We had an overwhelmingly positive response to the initiative and quickly reached the cap! Thank you!

"At Chubb Life we protect the life's work of New Zealanders with ours. We're committed to supporting the life-saving research happening at the Malaghan Institute," says Simon Tohill, Chubb Life General Manager Strategy and Marketing.

Malaghan Institute Director Professor Graham Le Gros says as an independent research organisation and charity, the Malaghan Institute relies on and is driven by support from the community.

"The generosity of organisations like Chubb Life allows us to accelerate our research into the immune system, across cancer, infectious disease, and allergic and inflammatory disorders, to ultimately save lives. We're excited to enter into this multi-year partnership that will provide a significant and vital boost to our research."

Team Malaghan at Round the Bays 2024

A massive thank you to all the runners, walkers and friends, including our partners from Jarden, who came along to support life-saving research by getting behind #TeamMalaghan at this year's Round the Bays.

Everyone at the Malaghan is hugely grateful for your generous contributions, raising more than $6,500!

Some very special acknowledgments go out to exceptional community fundraisers, Kevin Alkema and his family, and Katy Miller, whose efforts have made a significant difference to our cause.

We hope to see you there with us again next year!

▲ The many happy post-run faces from Round the Bays Wellington 2024!

ULTRA FOR LYMPHOMA

Thanks to Poppy Brinsley who raised close to $19,000 towards our CAR T-cell programme. Not only did Poppy gain support through completing the Scotland Ultra X Marathon earlier this month, she also donated 30cm of her hair! What an amazing effort!

"Last year, my dad was diagnosed with lymphoma, and managing his cancer is now a big part of his life. Many of us will know of someone affected by cancer, and the research that the team at the Malaghan Institute is undertaking is changing lives. The ground-breaking immunotherapy and CAR T-cell therapy treatments have the potential to make a real difference."

▲ Poppy Brinsley

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

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