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MALAGHAN INSTITUTE OF MEDICAL RESEARCH

New Zealand to New York and back again: Malaghan researcher tackling liver cancer

WHAT'S INSIDE

From the Director

One of our most important assets in the fight against disease is our young scientists. Nurturing these young, bright minds is key to us continuing to make a difference to the health of all New Zealanders.

Our young scientists are the engine room of the institute, bringing fresh perspectives and drive to our work. Their innovation and exploration of new avenues of research is vital to making ground-breaking discoveries. But, to retain the brightest of minds and support our scientists long term, we must provide them with sustainable funding, giving them the flexibility to succeed and the freedom to pursue breakthroughs.

Nurturing these talented individuals is perhaps our best investment for ensuring New Zealand's access to future technologies, discoveries and treatments.

Thank you for taking the time to read this issue of Scope and for being part of the future of medical research.

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

New Zealand to New York and back again: Malaghan researcher tackling liver cancer

Bright lights, big city, cutting-edge cancer research. Dr Olivia Burn has spent the past twelve months working as a Malaghan International Research Fellow on a collaborative liver cancer programme at the Icahn School of Medicine at Mount Sinai Hospital in New York. Now, armed with new skills, connections and expertise, she's back at the Malaghan Institute, keen to apply what she's learned to make a difference for the many Kiwis living with liver cancer.

According to the Ministry of Health, liver cancer rates in New Zealand have been steadily climbing since the 1980s. Today, around 400 New Zealanders are diagnosed with this disease each year, with rates higher in Māori than non-Māori – a disparity influenced by complex social, environmental and health factors. Known risks for developing liver cancer include fatty liver disease, hepatitis B, obesity and alcohol consumption.

What's more, survival rates for liver cancer globally are poor, partly due to the genetic diversity of the disease and lack of effective treatments available. For most cancers, the more genetically-diverse cancer cells are within tumours and between individuals, the less likely a given therapy will work for everyone.

"Liver cancer patients often have fewer treatment options compared to other liver diseases and cancers," says Dr Burn. "And those that do exist are not hugely effective in the long term. Immunotherapies like immune checkpoint inhibitors are making strides, but they're still a long way off compared to treatments for other kinds of cancers."

The collaboration between the Malaghan and Mount Sinai aims to lay the groundwork to challenge this status quo, bringing together world-leading expertise from opposite sides of the globe to tackle liver cancer and develop better solutions for patients in need. The partnership leverages expertise and cutting-edge liver cancer models

from Associate Professor Amaia Lujambio's laboratory at Mount Sinai Hospital with Professor Ian Herman's Laboratory at the Malaghan Institute, and their patented vaccine technology that specialises in stimulating strong, lasting immune responses in the liver. It's a winning combination the team believe will one day lead to new kinds of immune treatments for liver cancer.

"The liver is a fascinating organ that carefully balances its role in recognising and destroying harmful pathogens while not overreacting to the toxins and waste it filters from the blood. How it manages this complex task is not yet fully understood," says Dr Burn, whose international fellowship was supported by the Cancer Society of New Zealand and the Dines Family Foundation.

"That complexity extends to liver cancer, too. For any immune therapy to be effective, we need to know which features of the cancer – which antigens – we can target to trigger the body's defence system. This is a challenge when you have an extremely diverse cancer like liver cancer."

Dr Burn says this is one of the main reasons she went to Mount Sinai. "The Lujambo lab has developed these impressive preclinical models for liver cancer where we can switch on and off different genetic drivers of the disease that closely mimic what we see in human liver cancers, and test the vaccine we've developed at the Malaghan Institute against these."

Assoc Prof Lujambio, whose lab focuses on the mechanisms of liver cancer and the genetic changes that give rise to the formation of liver tumours, says that while Dr Burn's time at Mount Sinai was brief, it was impactful.

"Having Olivia in our laboratory at Mount Sinai was a real treat," says Assoc Prof Lujambio. "Olivia came to our lab with lots of ambitious goals and not that much time, but somehow she was able to be incredibly productive and generate high-quality data in record time. She fitted perfectly in the lab from the first day and became a key member of the team.

"It's been amazing to see how her vaccine strategy has significant therapeutic effects in hepatocellular carcinoma – liver cancer – a tumour type that is really hard to treat. Given her enthusiasm for science and her unique vision, I am sure she will keep contributing enormously to the liver cancer field in the years to come."

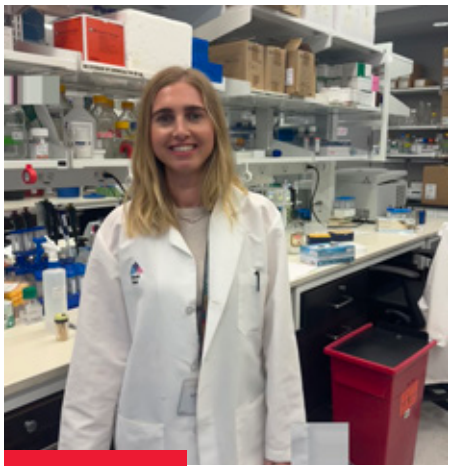
Dr Burn, who hails from the Bay of Plenty, says she found working across the road from Manhattan's Central Park a hugely exciting and eye-opening experience.

"New York was such a vibrant and diverse place to live and work. One day, you're wondering why you're struggling to get home from work, only to realise it's because of the Met Gala; the next, you're enjoying lunch in Central Park while trying to catch the April solar eclipse with half of New York. Above all, I'm just very thankful I got the opportunity to be part of some really advanced research in a world-leading lab."

Having settled back into her life and routine at the Malaghan Institute, Dr Burn is passionate about ensuring the gains made in New York continue to advance liver cancer research in New Zealand.

"If we want to bring this sort of therapy to the clinic in New Zealand, we really need to make sure we have the right support to get it there," says Dr Burn. "We're looking at immune responses to genetically diverse liver cancers in a new way, but if we want to build up enough evidence to suggest it's worth designing new treatments for clinical trials we need to do a lot more groundwork to make that happen.

"That means more fundamental research, more data, and – crucially – more financial support to really prove we are on to something."



▲ Dr Burn in the lab at Mount Sinai

▲ Times Square, New York

▲ Assoc Prof Lujambio and Dr Burn

Five areas of research advancing CAR T-cell therapy

Chimeric Antigen Receptor (CAR) T-cell therapy has been transformative in the treatment of certain blood cancers, offering hope where conventional treatments have been unsuccessful.

This cutting-edge approach involves engineering a patient's T-cells to recognise and attack cancer cells. However, while CAR T-cell therapy has shown remarkable success, it is still in its infancy as a treatment. Malaghan Institute scientists Danielle Blud, Dr Patricia Rubio-Reyes, Dr Rachel Perret and Clinical Director Dr Robert Weinkove recently published a review article in *Seminars in Hematology* which outlined various strategies being implemented both here at the Malaghan and internationally to improve CAR T-cells to enhance therapeutic efficacy while minimising adverse effects.

1

OVERCOMING ANTIGEN ESCAPE

Cancer cells can evade CAR T-cell therapy over time by losing the antigens (proteins) that CAR T-cells are designed to target. This is known as antigen escape. This means that although CAR T-cells may be effective initially, the cancer can evolve to escape targeting by CAR T-cells, leading to relapse in some patients.

RESEARCH APPROACHES:

- **Dual or multi-antigen targeting CARs:** By engineering CAR T-cells to target multiple antigens simultaneously, the chances of cancer cells evading detection can be reduced. This means even if the cancer evolves to lose one antigen that is targeted by the CAR T-cells, there is still another antigen that can be used to recognise and destroy the cancer cell. The Malaghan Institute is currently working on developing dual CAR T-cells to target multiple myeloma, a cancer that has been shown to be particularly susceptible to antigen escape.

2

TARGETING SOLID TUMOURS

CAR T-cell therapy has been most effective in treating blood cancers like leukaemia and lymphoma, where the cancer cells are relatively easy to identify and access. However, solid tumours, such as lung, breast or colon cancer, present a more complex challenge. In solid tumours, cancerous cells are clumped together, often creating a hostile environment with limited resources for immune cells like CAR T-cells. This can suppress immune responses, making it difficult for CAR T-cells to infiltrate and attack the cancer effectively.

RESEARCH APPROACHES:

- **Cytotoxic pro-drugs:** Researchers are investigating methods to enhance CAR T-cell activity by incorporating additional molecules to amplify the cancer-killing activity of CAR T-cells. These molecules activate only when the CAR T-cells bind to tumour cells, allowing the cell-killing activity to be concentrated around the tumour. This approach may provide the potency of treatment required to destroy solid tumours.

3 ENHANCING SAFETY

While the CAR T-cells used in the Malaghan Institute's clinical trial have so far shown to have a good safety profile, one of the risks of CAR T-cell therapy is our immune system reacting adversely to CAR T-cells. CAR T-cells can sometimes generate a very strong immune response or may attack healthy cells that express proteins like those on cancer cells, leading to unintended side effects.

RESEARCH APPROACHES:

- **CAR design:** By tweaking the different structural components of the CAR T-cell to optimise for safety, it is possible to reduce the rate of adverse side effects. This is one of the approaches used in the Malaghan Institute's CAR T-cell construct.
- **Quality control:** Researchers have developed methods to ensure that the CAR gene is inserted into a safe location within the T-cell genome during CAR T-cell production, reducing the risk of potential side effects. At the Malaghan Institute, researchers are refining and implementing further safety checks to CAR T-cells to incorporate into wider scale CAR T-cell production.
- **Safety switches:** To address the risks of severe side effects, scientists are integrating 'safety switches' or 'suicide genes' into CAR T-cells. These switches can be activated to quickly eliminate the CAR T-cells from the body if dangerous side effects begin to occur. The Malaghan Institute has created its own safety switch which could be used in future CAR T-cell constructs and other cell therapies.

4 EXPANDING ACCESS: OFF-THE-SHELF CAR T-CELLS

Currently, CAR T-cell therapy is a personalised treatment, requiring the modification of a patient's own T-cells. This process is time-consuming and expensive, limiting the therapy's availability.

RESEARCH APPROACHES:

- **Pre-produced CAR T-cells:** Scientists are exploring the development of CAR T-cells derived from healthy donors rather than from the patient. These CAR T-cells could be mass produced and stored, making the therapy more accessible and affordable.
- **Gene editing:** Techniques like CRISPR are being used to edit the genes of donor T-cells to reduce the risk of rejection and improve their safety and effectiveness in a broader range of patients.

5 IMPROVING PERSISTENCE AND DURABILITY

For CAR T-cell therapy to be effective in the long term, the engineered T-cells need to persist in the patient's body and continue to fight any remaining or recurring cancer cells. However, in many cases, CAR T-cells lose their effectiveness over time which can lead to relapse.

RESEARCH APPROACHES:

- **Memory CAR T-cells:** CAR T-cell therapy is usually a mixture of cytotoxic T-cells, which kill cancer cells, and memory T-cells which remain in the body after the cancer has initially been cleared, waiting for any reoccurrence of cells with the target protein. If the cancer cells resurface, these memory cells will convert to cytotoxic T-cells and rapidly proliferate to destroy the cancer cells. Part of optimising CAR T-cell therapy is determining the ideal proportion of cytotoxic and memory CAR T-cells to have the most effective outcome in patients.
- **Enhanced metabolic programming:** Scientists are identifying specific targets in the energy regulation pathways of CAR T-cells that reduce CAR T-cell effectiveness over time. After identifying these pathways, they can alter them to increase CAR T-cell longevity and efficacy within the body.

RNA researcher named KiwiNet Emerging Innovator

▲ Dr Rebecca McKenzie

Dr Rebecca McKenzie has been selected as a 2024 KiwiNet Emerging Innovator for her research developing novel RNA therapeutics.

Dr McKenzie, who is a project leader in the Malaghan Institute's RNA technology development facility and one of seven pillar leads in the national RNA development platform, has been developing research-grade RNA products for use in research projects across New Zealand.

"I'm very excited to be selected to join the programme and am looking forward to developing my commercialisation skills which I believe will be essential to support translational science coming out of the RNA platform," says Dr McKenzie.

"The programme will help me on my current journey with the central RNA production facility where we are working to find our market and develop a service model to bring RNA technology to New Zealand."

Community partnerships: Zephyr Consulting empowering emerging scientific talent

The Malaghan Institute recently partnered with Zephyr Consulting Limited to help support future leaders in ground-breaking cancer therapies.

Inspired by our ground-breaking cancer research and its potential to enhance the health and wellbeing of our community, Zephyr are passionate about supporting emerging scientific talent. As a result, they have generously committed to fund Malaghan PhD student Paul Owaci's tuition for three years.

Paul is working within the CAR T team investigating 'exhaustion' of CAR T-cells – a phenomena that could be why some people's lymphomas do not respond to, or relapse after, CAR T-cell therapy. He is exploring alternative CAR T-cell manufacturing processes that could help reduce exhaustion, and to re-engineer CAR T-cells to knock down genes linked to this exhaustion.

At the Malaghan, we recruit top PhD students from New Zealand and abroad, whose passion, skill and international connections fuel scientific discovery.

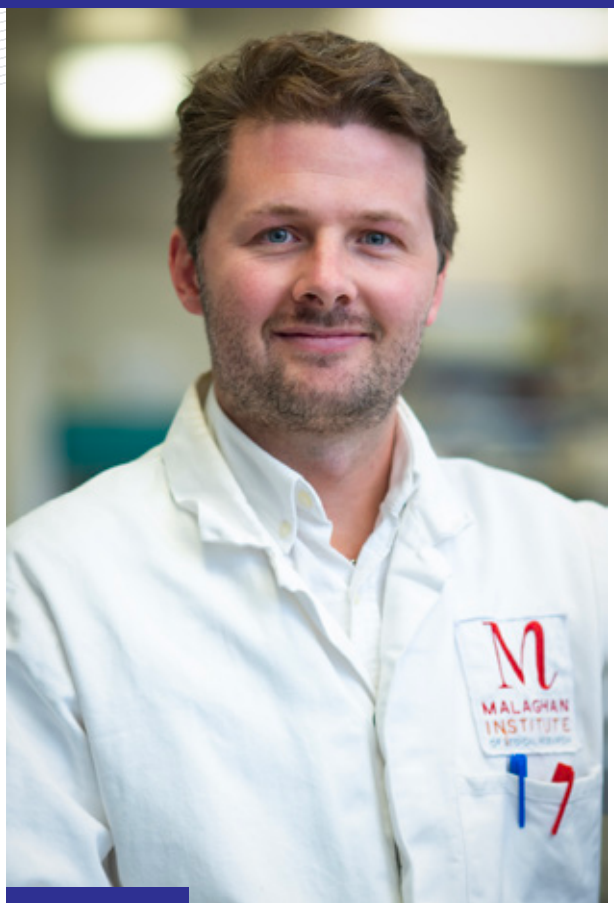
▲ PhD student Paul Owaci

As a charity, the support of these individuals comes largely through university scholarships – often needing additional funds from the community to cover things like living expenses. Through support like Zephyr's, these future scientific world-leaders have the right support and tools needed to make the most out of their doctoral studies, setting them on the best path for a long and fruitful scientific career.

We are immensely grateful to Zephyr for their valued partnership and their commitment to empowering the next generation of scientific leaders. **If you would like to learn more about how you can drive impact by supporting life-changing medical research with the Malaghan, please email us at fundraise@malaghan.org.nz to discuss ways to partner with us.**

Fast Start grant to explore and establish next generation RNA technology

Malaghan Institute postdoctoral researcher Dr Jordan Minnell's research into self-amplifying RNA is one of eight nationwide projects recently awarded a Fast Start Project Grant worth $250,000 from New Zealand's RNA Development Platform.



▲ Dr Jordan Minnell

RNA Development Platform Co-Director and Deputy Director of the Malaghan Institute Professor Kjesten Wiig says the Fast Start Projects are about getting some quick wins for RNA technology to build capability across New Zealand.

"RNA technology marks a step change in medicine, as disruptive and revolutionary as penicillin and computers," she says. "These Fast Start Projects encompass a diverse range of areas within RNA research, including the development of messenger RNA (mRNA) vaccines, exploration of disease drivers, formulation of RNA therapeutics and the synthesis of critical reagents for the RNA Platform."

> "RNA technology marks a step change in medicine, as disruptive and revolutionary as penicillin and computers."

Dr Minnell's project, which he is co-leading with Sarah Draper from the Ferrier Research Institute, is about setting up the RNA Platform to leverage self-amplifying RNA (saRNA), which has the potential to further improve RNA-based therapies and vaccines.

The project will involve exploring the use of saRNA technology in the Malaghan Institute's existing research programme investigating a malaria vaccine candidate. Prior research conducted in the Hermans Laboratory established an mRNA vaccine candidate which has shown to protect against malaria in pre-clinical mouse models. Dr Minnell and his team will be using the Fast Start grant to determine if they can carry over the principals from the mRNA vaccine to an saRNA setting to see how well the perform in fighting malaria infection.

Self-amplifying RNA (saRNA) is the next generation of RNA technology. Rather than just a list of instructions to make a protein (like with mRNA), saRNA also comes with instructions to make itself – a leap forward in the technology's ability to fight disease.

"Self-amplifying RNA has several key advantages over traditional RNA-based treatments," says Dr Minnell. "I believe it's the future of RNA technology, which has already shown such huge potential."

"In the process of amplifying or replicating itself inside a cell, the saRNA also sets off cascades of cellular reactions and promotes interactions which more closely mimic the biological conditions of a cell encountering a foe. This helps mount a more effective immune response with all of the appropriate biochemical signals."

"One of the huge advantages of this technology is that it's dose sparing – needing smaller doses for the same effect," says Dr Minnell. "One molecule of saRNA can do the job of ten regular RNA molecules, so the transformative potential of this technology as a way to quickly and efficiently fight infectious and other diseases is huge."

▲ Dame Patsy Reddy

▲ Sir Ashley Bloomfield

▲ David Downs

New trustees appointed to Malaghan Institute trust board

Dame Patsy Reddy, Sir Ashley Bloomfield and David Downs will join the Malaghan Institute of Medical Research's trust board at its AGM this December.

Chair Sir Paul Collins announced the appointments in the institute's 2023/24 annual report, acknowledging recent changes and future-proofing of the institute had necessitated a careful review of the skills required to strengthen and sustain its governance team.

"I am delighted Dame Patsy, Sir Ashley and David will be joining the Malaghan – it is a privilege to have people of this calibre become part of our team. Their collective knowledge and expertise will undoubtedly enhance our efforts to make a meaningful impact on healthcare in New Zealand and beyond," he says.

"As a charity, we rely on the generosity of our trustees to give their time and expertise voluntarily. Their decision to join us speaks volumes to the strength of our organisation, our track record and vision."

Dame Patsy Reddy served as the Governor-General of New Zealand from 2016–2021. Trained as a lawyer, she has had extensive experience in non-executive governance and business consulting roles in both the public and private sector, and with creative and charitable organisations.

She says she is honoured to join the board of an organisation that is at the forefront of biomedical research. "The work being done at the Malaghan Institute has the potential to transform lives, and I look forward to contributing to its continued success and growth."

Sir Ashley Bloomfield says he is looking forward to contributing to the continued success of "one of New Zealand's leading health research organisations."

He brings 25 years' experience in public health, policy and health leadership, including as Director-General of Health during the Covid-19 pandemic. He is now a professor at the University of Auckland's School of Population Health and Interim Chief Executive at the Institute of Environmental Science and Research.

David Downs has a longstanding relationship with the Malaghan Institute as a living example of the effectiveness of CAR T-cell cancer immunotherapy, which saved his life in Boston in 2017. He has had a successful career in the private and public sector and is currently CEO of the New Zealand Story Group. He also acts as a consultant and is a director on several boards and published author.

As someone who has benefited from breakthrough medical treatment, he says he is excited about the opportunity to help the world-leading institute on their mission.

"New Zealand needs to be a leader in medical research, and to accelerate that research into changing and saving lives."

IN FOCUS

Fever: Too hot to handle or the body's first line of defence?

Malaghan PhD student Rosemary Jackson is investigating the effect of fever on our immune system. By taking a deep-dive into T-cell activity, her work is challenging whether our current approach to managing fever is the best way to overcome infectious disease.

Rosemary remembers one of the worst experiences of her life. Every inch of her body was aching, she was both delirious and nauseous. The arid, sub-Saharan air stoked the scorching heat of her body. She was lying face down on a mercifully cool slab of concrete, pleading for the heat and pain to leave her body. Rosemary had contracted malaria.

She has come a long way from her time in South Sudan in her early twenties. Rosemary is now back in New Zealand where she is undertaking her PhD in the Gasser Laboratory at the Malaghan Institute, supervised by Dr David O'Sullivan.

"Fever happens when our immune system detects a threat and communicates the presence of an infection to our brains. Our body's thermostat, located in the brain, then turns up the heat," says Rosemary.

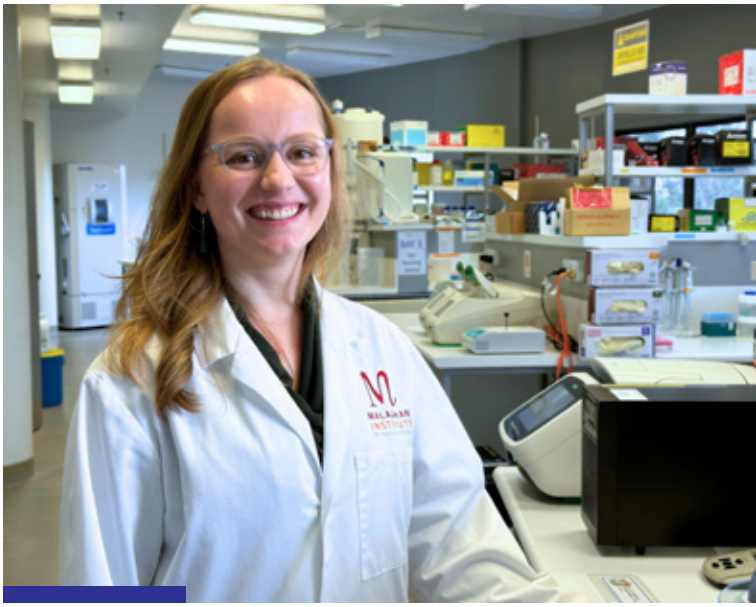
"Fevers serve to aid our body's offensive strategy against the infectious agent. Some evidence suggests the increased temperature results in enhanced immune function, helping white blood cells, including T-cells, kick into gear to overcome the infection.

Rosemary's research is investigating if a mild to moderate fever helps T-cells mount a stronger attack against infections. Specifically, she is looking into how T-cells change on a molecular level during increased temperatures and how long the fever needs to be sustained to bring about any beneficial changes in the T-cells.

"So far, we've found some very interesting results. T-cells that were exposed to fever-like temperatures overnight, showed increased immune activity even several days after being returned to normal body temperature. In contrast, T-cells kept at normal body temperature from the start did not show this same heightened activity."

She will soon begin studying these effects in infectious disease models including influenza, to see how these molecular changes in T-cells may alter the immune response during infection.

"We're hoping that this research will help us to find a more nuanced approach to managing fevers. Rather than having a blanket approach where fever-supressing medicines are used in all cases, perhaps it would be more beneficial to carefully monitor the fever, and let the fever run its course within a reasonable time and temperature window."



▲ Rosemary Jackson

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**

IN THE COMMUNITY

25 years of Wellington charity golf

Swinging to support life-saving medical research, this year marks the Wellington Friends of the Malaghan's 25th annual charity golf day – a fantastic achievement!

"It's been an incredible honour to have such staunch supporters of the Malaghan," says Director Professor Graham Le Gros. "The Friends group right from day one has been instrumental as our voice in the community, rallying people to our cause as well as providing vital charitable funds that increase the pace of our research. I want to thank each and every one, past and present, who has been part of this amazing, hard-working group – your impact on medical research in New Zealand has been profound."

Snotty science at the A&P Show

In October, Māori engagement advisor Georgia Carson and bioimaging scientist Alisha Dabb travelled to Tairāwhiti to attend the Gisborne A&P show as guests of Mātai Medical Research Institute.

It was a fun couple of days speaking to dozens of locals about the Malaghan's research, the role different immune cells have in the body – even the importance of snot in keeping us safe from infection with a hands-on demonstration (using fake snot of course)!

Join #TeamMalaghan for Round the Bays 2025!

#TeamMalaghan is back for Round the Bays 2025! Will you join us in raising vital funds for life-saving medical research? To get involved, simply scan the QR code or visit www.roundthebays.co.nz and register for your event in Wellington, Christchurch or Auckland.

As our way of saying thank you, anyone who raises over $300 will receive their own 'Run for Research' Malaghan T-Shirt to wear on race day!

Malaghan annual report 2024 – **celebrating a year of generosity and impact**

Our annual report for the 2023/24 financial year has just been published and reflects the strides we're making towards finding better ways to prevent and treat disease. The impacts highlighted – across cancer, allergic and inflammatory conditions and infectious disease – are underpinned by support from our community. Thank you, we are so grateful to have you on this journey with us.

To read our 2024 annual report, scan the QR code, or visit **malaghan.org.nz/about-us/annual-reports/**

132 STAFF

10 PHD + MASTER'S STUDENTS

9 POSTDOCTORAL RESEARCHERS

DR KERRY HILLIGAN

CIG WILLIAM E PAUL AWARD FOR BEST PAPER IN CYTOKINE RESEARCH 2023

KYLIE PRICE

AUSTRALASIAN CYTOMETRY SOCIETY CAREER RECOGNITION AWARD 2023

DR PATRICIA RUBIO-REYES

KIWINET EMERGING INNOVATOR AWARD 2023

DR THERESA PANKHURST

TE NIWHA KIA NIWHA LEADER FELLOWSHIP 2024

50 research papers published

12 ongoing clinical studies and trials

1,540 new donors

76 national and international collaborations

8 visiting speakers

18,052 new subscribers to our news and updates

Research is our greatest hope in the fight disease.

At the Malaghan Institute, we're striving to create a world where diseases can be prevented, treated and cured by harnessing the power of the immune system. But we can't achieve this alone – we need the support of our incredible community.

When you support the Malaghan Institute, you are empowering our scientists to develop better, kinder treatments. Together, we can build a future where fewer of our loved ones suffer from or are lost to disease.

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 say thank you and provide you with a donation tax receipt.

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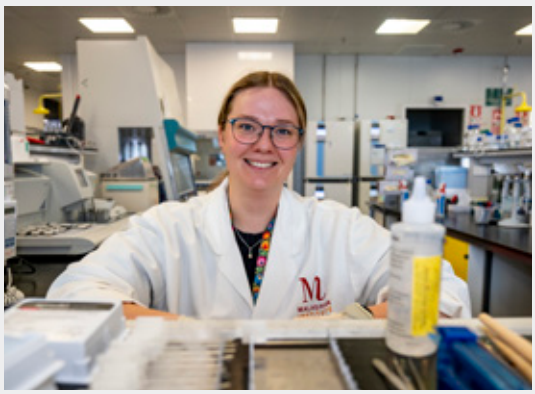

"Without the support from Kiwis like you, we simply wouldn't be able to do the research needed to deepen our understanding of the immune system and discover new opportunities to fight disease."

– Alisha, Staff Scientist

THANK YOU TO OUR PARTNERS

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