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MALAGHAN INSTITUTE OF MEDICAL RESEARCH

Trial results offer hope to Kiwis with incurable blood cancer

WHAT'S INSIDE

From the Director

In this issue of Scope I am excited to share the success of our CAR T-cell phase 1 trial, and our wider ambition to bring it to New Zealand as a mainstream therapy.

I applaud our team of world-leading scientists for their resolve to make this treatment available here in New Zealand and with their innovations, a step up from what is currently available elsewhere in the world.

Ultimately the power to change health outcomes for the better lies in our own bodies. That is, by using the powerful tools already provided to us by our incredible, sophisticated immune system, we can provide gentler, more effective ways to prevent, treat and cure disease through highly personalised medicine. Not just in cancer, but a whole host of other debilitating and life-threatening conditions can be improved by better understanding how to work with the immune system – whether that be by strengthening and fortifying it, or by subtly nudging it in a positive direction.

Thank you for your support.

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

Trial results offer hope to Kiwis with incurable blood cancer

The Malaghan Institute's unique CAR T-cell therapy has shown the promise of being safer than leading commercial CAR T-cell products in treating certain types of blood cancer, while remaining effective.

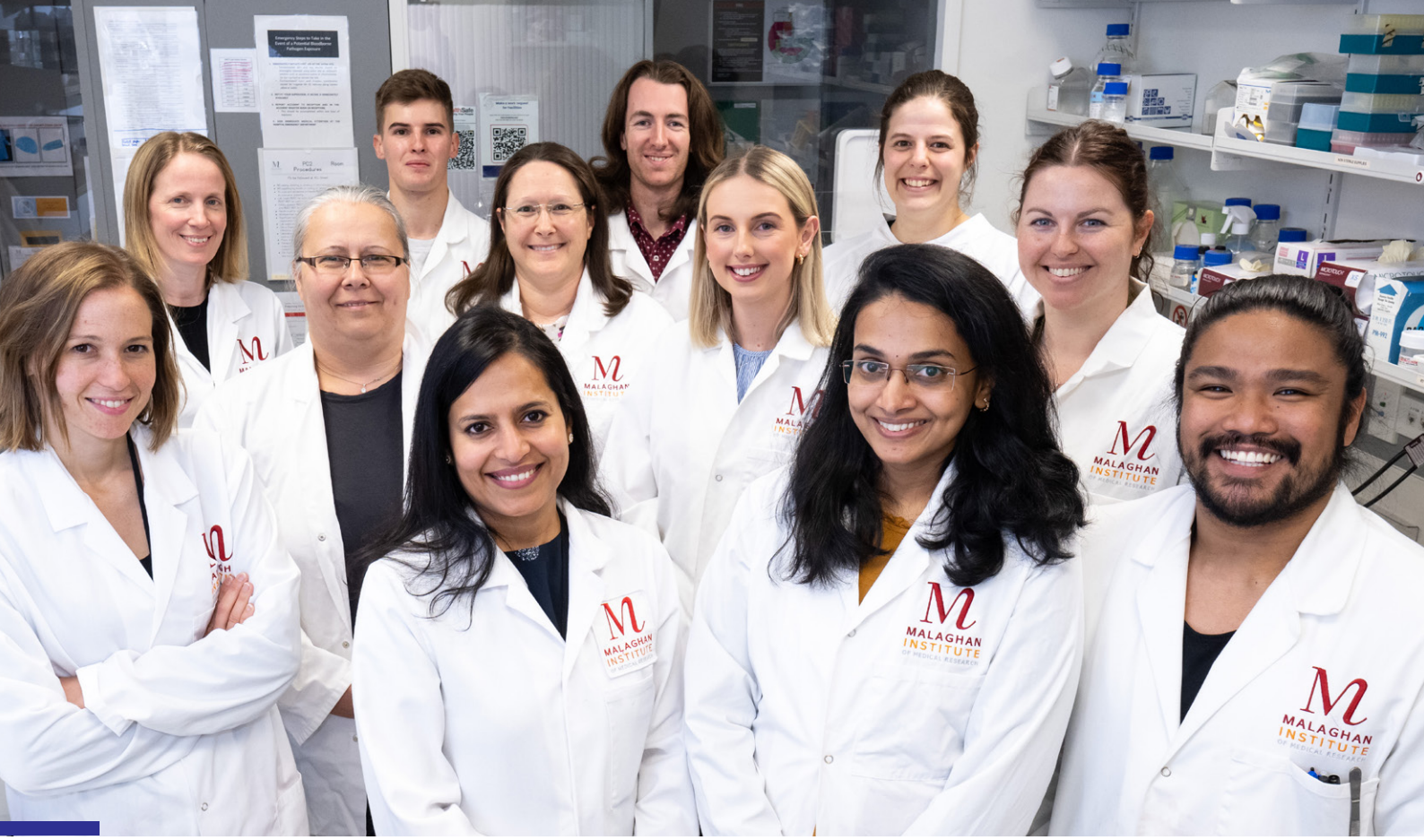
The ENABLE phase 1 safety trial found no limiting toxicities at any of the doses tested. Importantly, none of the participants developed neurotoxicity or severe cytokine release syndrome – common side effects of some commercial CAR T-cell therapies. The trial also showed promising effectiveness, with around half of the participants' lymphomas in complete response three months after receiving the treatment – that is, there was no sign of cancer.

"These results suggest our new CAR T-cell therapy may reduce risk of severe side effects, while remaining effective," says Malaghan Institute Clinical Director Dr Rob Weinkove. "We are preparing for a larger trial to confirm this."

The trial began in late 2019, in partnership with Wellington Zhaotai Therapies Ltd, treating 21 New Zealanders with relapsed or refractory B-cell non-Hodgkin lymphoma who had exhausted all conventional treatment options. Participants received an experimental form of a novel 'third generation' CAR T-cell therapy at increasing doses, primarily to test the safety of the therapy.

The CAR T-cells were manufactured from participants' own immune cells at the Malaghan Institute, with the treatment administered at Te Whatu Ora Capital, Coast and Hutt Valley.

"It's fantastic to show that we can do this in New Zealand," says Dr Weinkove. "This is a hugely ambitious clinical trial proving we can conduct cutting-edge trials that draw international attention.



▲ ENABLE CAR T-cell team. Cover: GMP technicians Charlotte Irvine and Reigh Aguinaldo

"Even more importantly, it demonstrates that we can develop high-tech manufacturing here in New Zealand, and that there are no insurmountable obstacles to delivering new cancer treatments like CAR T-cell therapy in our hospitals."

CAR T-cell therapy works by separating a patient's own immune cells (T-cells) from their blood, and modifying them by introducing a new genetic sequence. The T-cells then make surface receptors called CARs which enable the T-cells, now CAR T-cells, to identify and attack the patient's cancer.

Like building blocks, CARs are made of distinct subunits or domains made out of proteins. Each domain plays a different role that works together to help the T-cell find and kill a cancerous cell. The Malaghan Institute's CAR T-cells include an additional 'TLR2' domain which Dr Weinkove and his team believe has helped make them safer.

"Our CAR T-cell product shares one of its domains with commercial CAR T-cell therapies called axi-cel (Yescarta) and brexu-cel (Tecartus). Axi-cel and brexu-cel are very effective treatments, but neurotoxicity affects up to half of recipients. We think that adding the new TLR2 domain in our construct has lowered the neurotoxicity rate, hopefully while maintaining effectiveness," he says.

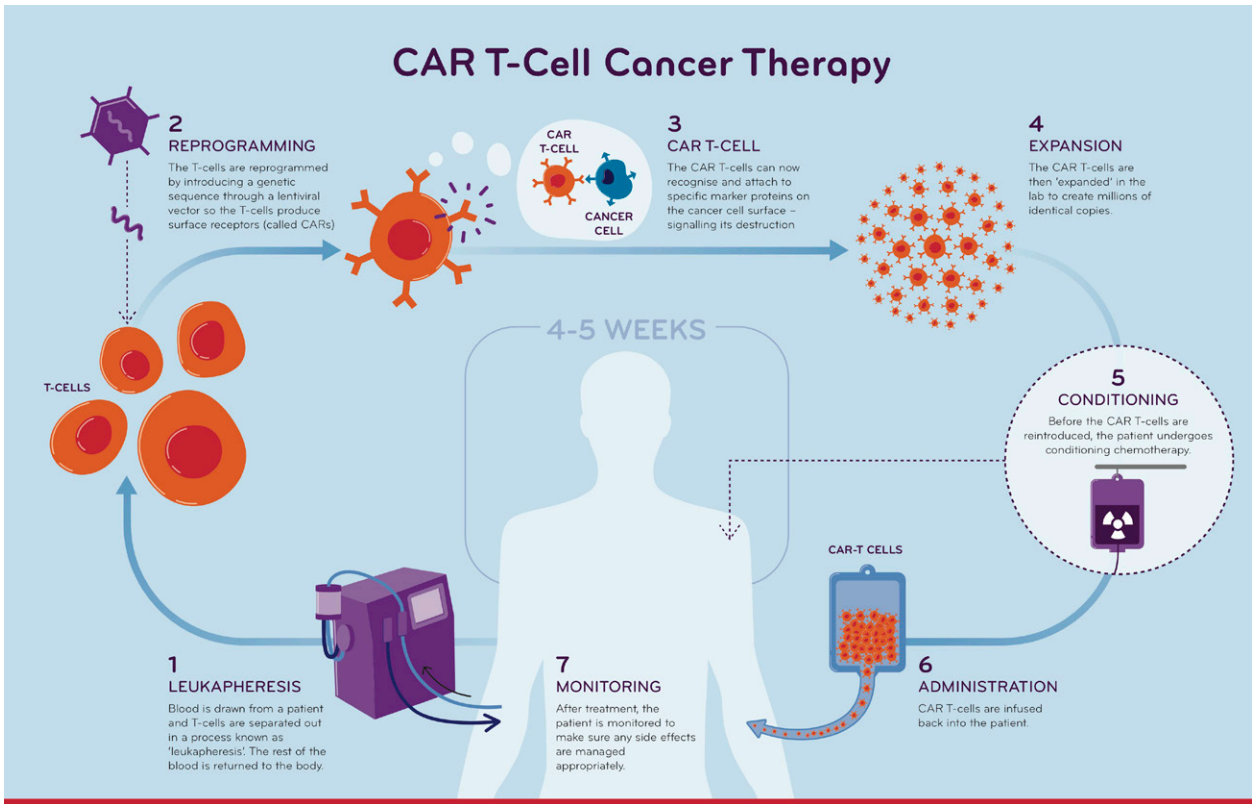
"Our laboratory research programme, supported by Freemasons New Zealand, suggests that our CAR T-cell product has a low risk of neurotoxicity because the new TLR2 domain has changed levels of the chemicals or 'cytokines' that can drive inflammation in the brain. Apart from the direct benefit to patients, a low neurotoxicity rate means that we can treat patients without routinely admitting them to hospital for monitoring, lowering costs for the health system."

> "It's fantastic to show that we can do this in New Zealand. This is a hugely ambitious clinical trial proving we can conduct cutting-edge trials that draw international attention."

The next phase of this programme is to improve the manufacture and delivery of CAR T-cells using cutting-edge automation technology. "We are already treating patients in an 'expansion cohort', for which we have automated the CAR T-cell manufacturing process with our partners at BioOra, and we are giving the CAR T-cells as an outpatient therapy," says Dr Weinkove.

"This cohort is helping us prepare for a phase 2 trial, in which we would like to treat a larger number of people across New Zealand, to learn exactly how effective our treatment is, and to get more information about side effect rates."

As a phase 1 safety trial, patients could only enrol to the ENABLE trial after they had exhausted all other treatment options, says Dr Weinkove.



"This is difficult, because people often have side effects from their prior chemotherapies, such as low blood counts or kidney damage, and because if their lymphoma progresses while we are making their CAR T-cells, we have limited options to control the disease. Because the toxicity rates are low in the phase 1 trial, we aim to treat patients earlier in their treatment pathway in a phase 2 trial.

Dr Carl June, Richard W Vague Professor in Immunotherapy at the University of Pennsylvania and BioOra board member, recognised as a pioneer of CAR T-cell therapy, says the ENABLE trial's phase 1 CAR T data to be presented at the American Society of Hematology annual meeting are a step forward for the treatment of CD19-expressing lymphomas.

"Dr Weinkove and his team at the Malaghan Institute and BioOra have shown efficacy that is on par with commercial CAR T, but the safety signal appears superior. This lays the foundation for outpatient delivery and management and expanding indications of their CAR T programme."

Dr Weinkove says the team here in New Zealand has taken this process all the way from developing a new CAR T-cell manufacturing process, establishing clinical and safety procedures, and treating and following-up patients. Their ultimate goal is to make CAR T-cell therapy a standard of care in New Zealand hospitals.

"We are hugely grateful to the patients who have taken part and to their whānau, and for the Malaghan Institute's many supporters."

The ENABLE trial was funded by the Ministry of Business, Innovation and Employment, Thompson Family Foundation, and by private donors, with additional support from Leukaemia & Blood Cancer New Zealand and Life Blood. The Malaghan Institute's CAR T-cell research programme has been supported by Freemasons NZ and the Health Research Council of New Zealand. Dr Weinkove received a Clinical Practitioners Research Fellowship from the Health Research Council.

RESEARCH SUGGESTS **HOOKWORMS COULD OFFER PROTECTION FROM SEVERE COVID SYMPTOMS**

▲ Dr Kerry Hilligan

Prior infection by a parasitic hookworm has been shown to protect mice from severe SARS-CoV-2 disease, offering a potential explanation as to why certain human populations seemed to fare better during the height of the Covid-19 pandemic.

"This work stemmed from an observation that certain regions in the world didn't fare as badly from the early days of the pandemic as you would expect," says Malaghan Postdoctoral Research Fellow Dr Kerry Hilligan who collaborated with colleagues at the National Institutes of Health, USA, on the study, published in *Science Immunology*.

"Countries throughout Africa and Asia were reporting fewer cases of severe infections, such as hospitalisations or death, much less than the rest of the world. This was the case even when accounting for some confounding factors in the data and lower reporting rates."

"What's interesting is that these regions strongly correlate or overlap with areas where hookworm infections are endemic – consistently present within the population. We think that perhaps this endemic infection by hookworms is causing a population-wide 'interference' in the establishment of more severe SARS-CoV-2 viral infections."

'Infection interference' is a term used to describe the observation that in some cases people don't get sick from more than one infectious organism at a time. Most recently we've seen this effect in the Covid pandemic, where it is thought that people recovering from a SARS-CoV-2 infection have a few weeks of relative immunity from the other respiratory viruses before they become susceptible again. The reasons for this phenomenon aren't yet fully understood, but are of particular interest to Dr Hilligan.

"It's generally accepted that as an infection activates and stimulates the immune system, there's the additional benefit of this stimulation excluding or preventing other organisms from gaining a toe hold," says Dr Hilligan.

"What is really interesting to explore is that this effect seems to hold true regardless if it's a virus, bacteria or a parasite in the case of Covid-19.

"What my collaborators Dr Oyebola Oyesola, Dr P'ng Loke and Dr Alan Sher at the National Institutes of Health and I wanted to know is whether we could test this effect in relation to the current pandemic and whether we'd see similar protective effects."

The collaboration found that the mice infected with hookworm were less likely to develop severe Covid symptoms and recovered from the infection much more quickly than their counterparts, even after the worms were cleared from the body.

Looking more closely at what was going on at a cellular level, the study observed that the hookworms were affecting a transformational change to specific type of lung-resident immune cells called macrophages.

"Post-helminth infection we could see a stark difference at the transcriptomic level – the level at which different genes are switched on or off – between macrophages that have been exposed to helminth infection and those that haven't," says Dr Hilligan.

While the research is preclinical and yet to be translated to humans, the researchers are currently focused on better understanding these macrophages and what the hookworms are doing to them to drive such a change in behaviour.

"Looking forward we want to understand the signals that bring in these T-cells to the lung. Leading on from that, we want to understand more about what the worm is doing to create these specialised macrophages, and whether we can replicate this effect, without the need for the worm as an intermediary."

The research was funded by the Intramural program of the National Institute of Allergy and Infectious Diseases, National Institutes of Health, United States.

Study sheds light on why fruit and vegetables are so good for gut health

Recent research is offering new insight into how fruit and vegetables might protect against inflammatory bowel diseases.

“These findings offer a deeper understanding of the intricate relationship between our diet and immune health,” says Malaghan Institute Senior Research Fellow, Dr Jeffry Tang, from the Gasser Laboratory. The study is funded by the High Value Nutrition National Science Challenge, Ko Ngā Kai Whai Painga.

“It’s a significant step towards understanding and potentially developing dietary strategies to manage inflammatory bowel diseases.”

Over 20,000 people are afflicted with inflammatory bowel diseases in New Zealand alone. It refers to diseases characterised by chronic inflammation of the gastrointestinal tract, often caused by the over activation of immune cells in the gut.

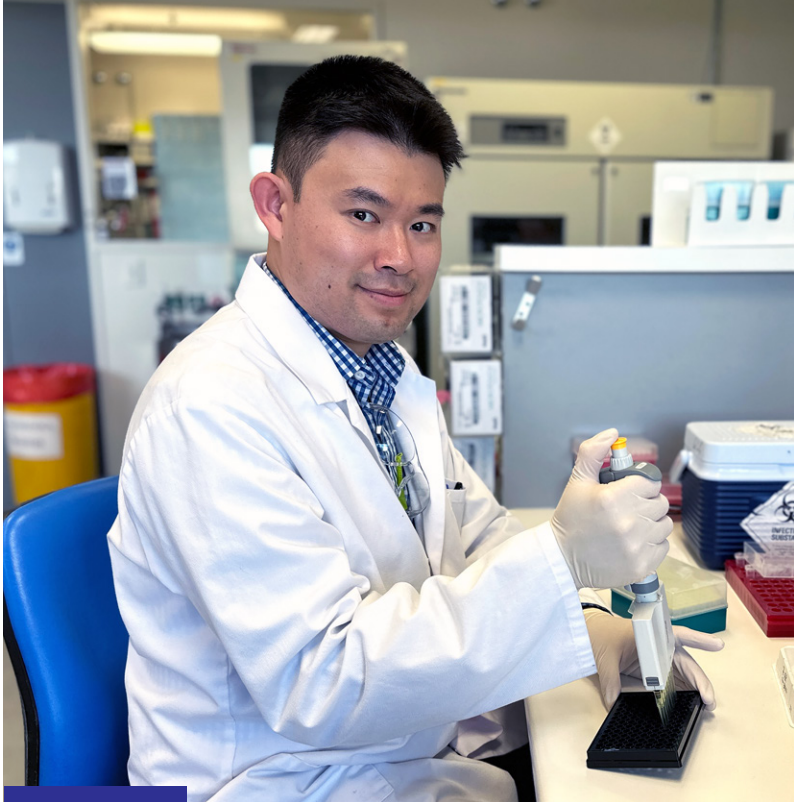
For the immune system to maintain equilibrium in the gut, it must strike a delicate balance. It needs to be sufficiently active to effectively combat infectious diseases, yet not so aggressive that it induces inflammation in intestinal cells. This equilibrium is achieved by various immune cells: some amplify immune responses, while others foster tolerance to the diverse stimuli within the gut. With inflammatory bowel diseases, this balance is tipped so the immune system overreacts.

“Diets rich in fruit and vegetable are believed to help maintain a healthy intestine and be especially beneficial for people with inflammatory bowel disease,” says Dr Tang.

“What we don’t exactly know is why. Why are fruits and vegetables good for immune balance? This is a black box we have to unpackage.”

With this novel study, Dr Tang and his team have started to answer these questions, building the bridge between nutritional immunology and chemistry.

Previous studies looking at individuals with ulcerative colitis, a type of inflammatory bowel disease, have found that their CD4+ T-cells, a distinct population of immune cells, have an altered expression of a molecule called G Protein-Coupled Receptor 15 (GPR15). The role of



▲ Dr Jeffry Tang

GPR15 is to help CD4+ T-cells migrate from the blood to the gastrointestinal tract, suggesting that modulating its expression could have some therapeutic benefit for inflammatory bowel diseases.

“We found this really interesting because we have been examining another molecule called the aryl hydrocarbon receptor (AhR) which seems to control GPR15 expression,” says Dr Tang.

“While it was known that active compounds from fruits and vegetables can interact with AhR, it was unclear whether this can translate to the regulation of GPR15 expression, particularly in CD4+ T-cells.”

This led Dr Tang and his colleagues to explore whether the well-documented health benefits of eating fruits and vegetables might be linked to their role in directing beneficial immune cells to the gut through GPR15, while redirecting inflammatory cells away from it.

“We studied specific compounds derived from eating fruits and vegetables, namely polyphenol and glucosinolate metabolites. We showed they can indeed modulate AhR activity and GPR15 expression in CD4+ T cells,” says Dr Tang.

The findings suggest that the interaction of dietary compounds with AhR might control the migration of immune cells towards the gut and thereby dampen local inflammation.

“Our study points to specific compounds derived from fruit and vegetables that may positively affect immune balance. This is only the tip of the iceberg but it’s a step forward in uncovering the intricate ways in which dietary compounds might influence our gut health.”

Malaghan researcher named as KiwiNet Emerging Innovator

Dr Patricia Rubio-Reyes has been selected as a KiwiNet Emerging Innovator for her invention which advances cutting-edge CAR T-cell therapies.

Working in the Hermans Laboratory, Dr Rubio-Reyes has invented a mechanism to deactivate CAR T-cells after administration, effectively providing a safety switch to 'turn off' CAR T-cells if they have severe side effects.

Her invention also has wide-spread applications across other cell therapies, doubling up as a method that can be used to detect cells that have been genetically modified. She is currently in the process of finalising the patent.

▲ Dr Patricia Rubio-Reyes

As part of the year-long KiwiNet Emerging Innovator Programme, Dr Rubio-Reyes will be provided with financial support and mentorship to build industry connections and the knowledge needed to understand the commercial potential of her invention.

"After working in the lab for the last 14 years, I have found a new passion for commercialisation and this programme provides the tools for me to learn what happens between the lab and industry," says Dr Rubio-Reyes.

FREEMASONS NEW ZEALAND RENEWS SUPPORT FOR CAR T-CELL THERAPY

Freemasons New Zealand has continued its support of research into cutting-edge cancer therapy at the Malaghan Institute, pledging a further $200,000 a year for the next three years towards our CAR T-cell programme.

The funding, which has surpassed $1.2 million since the Freemasons first started supporting the research in 2018, has played an important role in bringing CAR T-cell therapy to New Zealand.

"The initial support was for two years and in 2020, this was extended for a further three years to 2023," says Freemasons New Zealand Grand Master Pat Cooney.

"Based on the research and clinical results over the past five years, Freemasons New Zealand is excited to be able to continue a further three years of support for the CAR T-cell programme as it enters the next phase in a multi-centre trial, which will hopefully ultimately lead to the development of a commercially viable option in the fight against cancer which affects so many New Zealanders whether directly or indirectly.

"Freemasons are keen to make a difference in New Zealand, and the continuing involvement with the Malaghan Institute in its CAR T-cell programme fits seamlessly within our desire to bring improvements to the communities in which we live, work, and serve as Freemasons."

Malaghan Institute Director Professor Graham Le Gros says the renewed support from the Freemasons is hugely beneficial, not just for the clinical programme, but for wider CAR T research and development as a whole.

"I would like to acknowledge and thank Freemasons New Zealand for enabling this life-giving CAR T-cell therapy to become a reality here in New Zealand. In addition to the funding, the confidence and fearless can-do mentality their support has given our research teams have been an important part of getting this essential cancer therapy established here in New Zealand for all New Zealanders who need it."

FREEMASONS New Zealand

IN FOCUS

Allergy development and the importance of fundamental research in scientific advancement

Marie-Sophie Fabre is a Senior Research Officer in Dr Olivier Lamiable's team in the Ronchese Laboratory. Her research aims to understand the changes that occur when immune cells encounter allergens.

She runs experiments to understand the role specialised immune cells called dendritic cells play in early allergy development. Equipped with tentacle-like arms, dendritic cells act as sentinels, roaming the body and sampling anything they come across – from potential threats like infectious viruses and bacteria, to harmless substances such as dust mites, pollen, or nuts – presenting their findings back to the rest of the immune system.

"If deemed harmful, the immune system prepares the body to mount a rapid and powerful immune response against the threat," says Marie-Sophie.

"After this initial confrontation, the antigen isn't forgotten – it's stored in the immune system's memory. This means that if the same antigen makes another appearance, the response will be even swifter and more potent."

This mechanism proves highly effective against actual threats like viruses or bacteria. However, it becomes problematic when the initial substance marked as a threat is, in fact, harmless. In such cases, the immune system's powerful response is triggered against something benign.

"We're aiming to decipher the extent to which dendritic cells influence the decision-making process, especially when determining if a benign substance should be treated as a threat, leading to allergies," says Marie-Sophie.

Marie-Sophie is trying to identify what changes occur in the dendritic cell during this process of early allergy development by deciphering the function of genes that are activated in dendritic cells.

"We're hoping this will give us some insight into exactly which cellular signals are given by the dendritic cells that cause the allergies to develop," she says.

"It's painstaking work because we are switching off one gene at a time to see the effect it has on the process of allergy development."

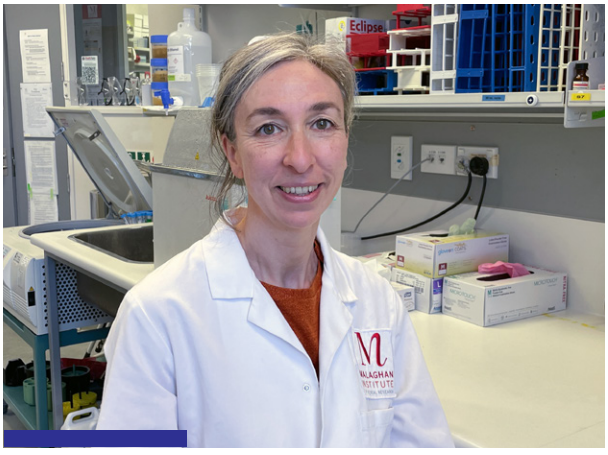
One of the problems in current-day research is that funding is often dependent on justifying the research with potential applications. Though this seems logical, it doesn't account for the fact that scientific advancement does not follow a straight line.

"The importance of fundamental research is often overlooked but what many people don't realise is that to cure disease, first you must understand disease."

Basic research, like that conducted in the Ronchese Lab, contributes to our understanding of processes such as genetics and cell signalling that can be applied to a wide range of research fields.

Marie-Sophie's motivation for pursuing her research comes from the opportunity to learn and build knowledge.

"As long as I know more today than I did yesterday, I know I'm in the right career," she says.



▲ Marie-Sophie Fabre

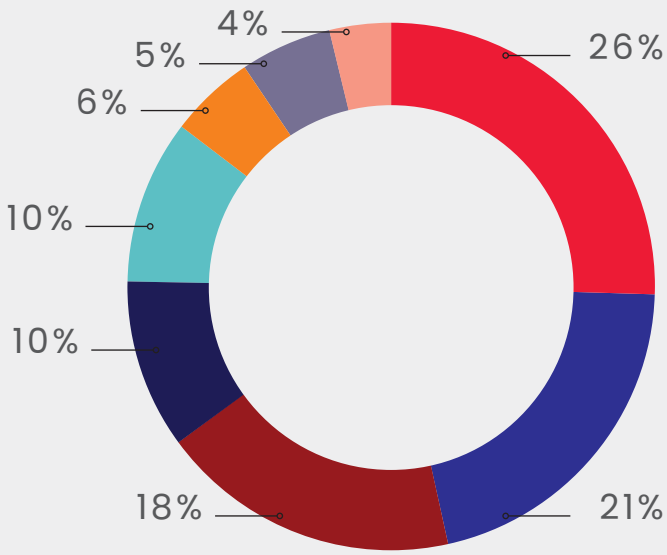
In Focus is a monthly e-update taking a close up look at our research and the scientists behind it. If you're not already subscribed, you can sign up on our website **malaghan.org.nz**

SURVEY RESULTS

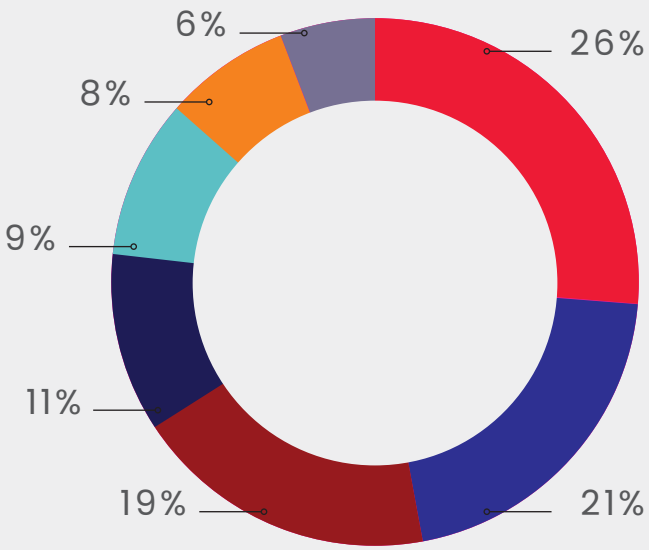
A huge thank you to everyone who completed our supporter survey. As a charity, it's important to us that we understand what interests you about the Malaghan Institute and motivates everyday Kiwis to support biomedical research discoveries in New Zealand. We will be working hard to apply the results of our survey to continue to achieve great outcomes for the health and wellbeing of New Zealanders and to consistently improve the way we communicate our research with you.

WHY DO YOU CHOOSE TO SUPPORT MEDICAL RESEARCH?

- To advance science and medical research in New Zealand
- We need better ways to prevent and treat disease
- I want things to be better for our future generations
- I have been personally affected by a disease you are researching
- It is important to me to donate to a New Zealand charity
- To honour a loved one
- Medical research has helped save my life or the life of a loved one
- To support a specific researcher or area of research



WHICH OF MALAGHAN'S CURRENT RESEARCH PROGRAMMES ARE MOST IMPORTANT TO YOU?



- Cancer research
- CAR T-cell therapy
- Immune health research
- Allergic disease research
- Infectious disease research
- Inflammatory disease research
- Hookworm therapy

CELEBRATING YOU,
our wonderful community

Thank you! With our last Scope for 2023 we extend a heartfelt thank you for supporting the Malaghan this year. Our research simply would not be possible without the wonderful support from our community.

We would like to acknowledge all our supporters, our partners, our Friends groups across the country and individuals in the community who have supported us through sharing their stories, helping raise awareness of the Malaghan Institute and highlighting the importance of life-saving medical research in New Zealand. Together, we can change health outcomes for all New Zealanders.

COMMUNITY EVENTS IN THE SPOTLIGHT

Our partners are a vital part of the Malaghan, providing incredible support with community events and fundraising, all towards our goal of making disease a smaller part of our lives through research into the immune system.

The past few months have been busy with events across the regions. In September, our friends at Spy Valley Wines in Blenheim generously hosted 'In Conversation' with Professors Graham Le Gros and Franca Ronchese, and in late October, the Hawke's Bay Friends of the Malaghan hosted their 22nd golf day at Hastings Golf Club, kindly supported by Lexus of Hawke's Bay. For the month of November, Just Paterson have been raising awareness and funds through Malaghan Month. For every house they sell in November, they donate $1000 to our life-saving research.

Thank you! All of this is instrumental in helping us achieve our goal of providing better, gentler treatment options for New Zealanders living with disease.

▲ Thank you to Spy Valley Wines for hosting our 'In Conversation' science evening in Blenheim. The conversation covered everything from CAR T-cell therapy, allergy research and Covid vaccines to hookworm therapy, where New Zealand research stands globally and the future of human health!

▲ Thank you to all our partners and supporters involved with the recent Hawke's Bay Friends of Malaghan golf day, an enjoyable day for more than 100 golfers all teeing off to support the institute and raising more than $25,000 in the process.

▲ Thank you to BM Accounting and Jarden for serving delicious beef sliders and refreshments at the recent Hawke's Bay golf day at Hastings Golf Club.

Ain't no mountain high enough

A huge thank you to Robyn Miller, who took on the incredible challenge of trekking to Mount Everest Base Camp, 5,364m above sea level, raising money for cancer research in memory of her beloved husband Stuart, who was tragically another life lost to this awful disease.

Here at the Malaghan Institute, we rely on the support of our incredible community to fund our life-saving research. Every contribution brings us one step closer to a future without diseases like cancer. Thank you Robyn, and to everyone who has fundraised for us. If you would like to fundraise for the Malaghan, please visit donate.malaghan.org.nz/raise-for-research

MALAGHAN LEGACIES

Ian and Rita Campbell recently left a generous legacy to the Malaghan.

"I'm really very proud of what Mum and Dad have contributed with their bequests.

"I think Mum was the main driver behind the gift to the Malaghan. Mum was a nurse and then there was also my little sister's illness, it was very hard time for our family," says son Mark.

Mark's younger sister Sandra was diagnosed with leukaemia at six years old. The diagnosis was in the 1970s, and while treatment options were available, sadly Sandra passed away when she was just 18 after battling the illness for 12 years.

"Mum and Dad decided to bequest much of their estate. They lived good lives and really didn't want for anything. They were thrifty, much of what was in home would have been from when they were first married, including the pots and pans set. If it wasn't broken, it didn't need replacing".

Ian and Rita spent most of their married lives in the Wellington suburb of Newlands.

Mark believes his parents thought it was important to give back and he honoured their decision.

Mark is also considering a gift in his will, following his parents' values and because he believes it's the right thing to do.

"Cancer research is a very important cause for our family."

The Malaghan Institute is very honoured to have received the legacy gift from Ian and Rita to support cancer research. Mark hopes to visit the institute next time he's in Wellington.

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

donate.malaghan.org.nz/giftinyourwill

Diseases don't take a break over the festive season, so neither do we!

Please, support life-saving research these holidays and continue to give hope to those living with disease, this season and many more to come.

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

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

THANK YOU TO OUR PARTNERS

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