SCOPE 79
A MALAGHAN INSTITUTE PUBLICATION

MALAGHAN INSTITUTE OF MEDICAL RESEARCH

Dietary fibre and its impact on type-2 diabetes

How immune cells respond to diet

WHAT'S INSIDE

From the Director

You may notice that this issue of *Scope* is a bit different to previous issues. *Scope* has always been a unique insight for our many supporters into the research and developments at the Malaghan Institute, a curated collection of recent science stories, as well as new content written for *Scope*.

From cancer and allergies to inflammatory and infectious diseases – everybody has their own personal interests in our research, so we aim to cover a wide range of what's happening at the Malaghan Institute in each issue.

So, we are pleased to present you with a slightly bigger *Scope* with longer-form stories about the research that matters to you. The focus of our content will remain the same, but you can expect to see more of it. We hope you enjoy, and we always love to get your feedback.

As always, it is the support of our community that sets the tone and direction for our research and drives our ambition to harness the immense power of the immune system to save lives.

Thank you,

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

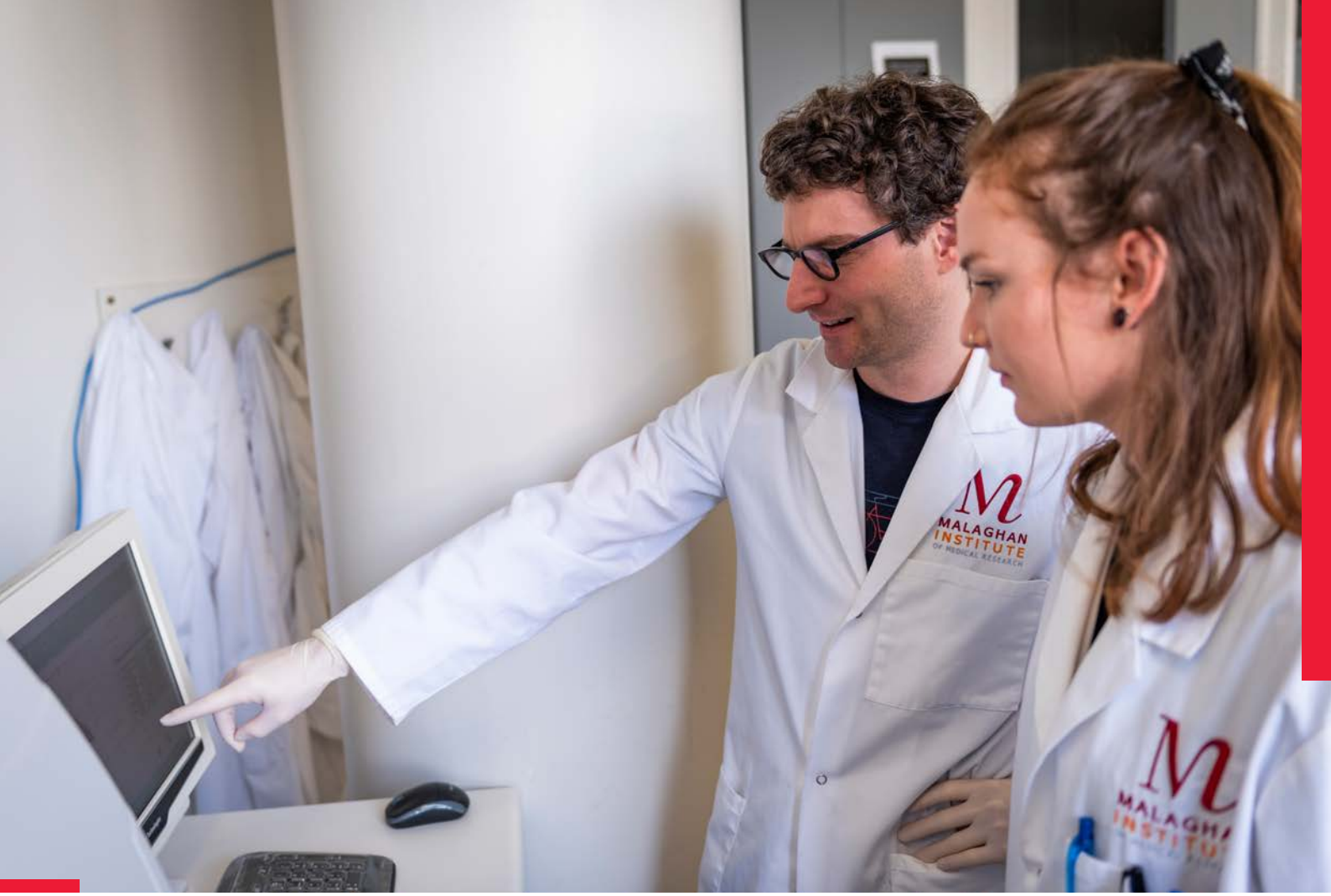
Investigating the impact of dietary fibre on type-2 diabetes

A clinical study is investigating the effects of increased dietary fibre on immune cell function and blood sugar levels for people living with type-2 diabetes, with the aim of offering insight into better ways of managing the disease.

"We're looking to identify possible links between the clinical benefits of increased dietary fibre intake to changes in immune cell activity and metabolism," says Malaghan Institute Senior Research Fellow Dr David O'Sullivan, who is running the study with Dr Olivier Gasser in collaboration with Professor Jeremy Krebs at the Centre for Endocrine, Diabetes and Obesity Research in Wellington. The study is funded by the High Value Nutrition National Science Challenge, Ko Ngā Kai Whai Painga.

"By increasing our understanding of how specific immune cells respond to diet and how this impacts a disease like diabetes, in the future we may be able to tailor therapies to achieve better outcomes," says Dr O'Sullivan.

Around a quarter of a million Kiwis are affected by diabetes, with type-2 diabetes the most common, and rates for Māori and Pasifika people 2-3 times higher than people of European ethnicity according to the Manatū Hauora Ministry of Health. The disease is characterised by a combination of impaired insulin secretion and insulin insensitivity leading to an inability to properly regulate blood glucose levels. Elevated glucose levels substantially increases the risk of secondary diseases such as heart attacks and stroke.



▲ Dr David O'Sullivan (left) and Hannah van der Woude

Around a quarter of a million Kiwis are affected by diabetes, with type-2 diabetes the most common, and rates for Māori and Pasifika people 2-3 times higher than people of European ethnicity.

At the immune system level, people living with type-2 diabetes typically display chronic low-grade inflammation and an increased inflammatory response, markers that are thought to contribute to the progression of this disease.

Unlike type-1 diabetes, environmental factors such as obesity, unhealthy diet and inactivity can play a role in the development of type-2 diabetes, and contribute to the worsening of symptoms. However, healthy dietary changes can both reduce the risk of disease onset and help regulate blood glucose level fluctuation to a safer range. Diets high in fibre are thought to have a greater effect.

The study will compare participants with type-2 diabetes while on their regular diet over the course of 14 weeks, before and after natural fibre supplementation, to explore how increased fibre intake impacts their immune cells and gut microbiota. The study will also assess blood glucose levels and whether the increase in fibre consistently lowers these levels.

"Dietary fibre has a multitude of effects from improving gut health to supporting a beneficial microbiome and influencing immune responses," says Dr O'Sullivan.

Fibre is digested by the bacteria that live in our gut into smaller components known as short-chain fatty acids. These molecules then pass through the lining of the gut to be taken up by waiting immune cells and used for various functions – including metabolism.

"High fibre diets correlate with a decrease in inflammatory markers and we've seen in preclinical models that dietary fibre can modulate immune cell metabolism, leading to a rebalancing away from pro-inflammatory responses, which we hope translates to better outcomes for people with type-2 diabetes."

NURTURING A GROWING IMMUNE SYSTEM

A new study has its sights set on better understanding the far-reaching consequences for a person's health and wellbeing of nurturing a growing immune system.

Funded by the High-Value Nutrition Ko Ngā Kai Whai Painga National Science Challenge, the SUN (Seeding throUgh FeediNg) study is investigating whether introducing dietary fibre to babies as they first start to eat solids can promote good gut and immune health.

The study involves researchers from the University of Auckland, AgResearch, Plant & Food, Massey University's Riddet Institute, the University of Otago and the Malaghan Institute.

In the first months and years of an infant's life, their immune system is learning to recognise what is good, what is harmful, and what's needed to keep them healthy.

"We're interested in this really transformative phase of an infant's immune system development."

"We know that the human gut microbiome – the bacteria and other microorganisms living in our gut plays a major role in our health", says Professor Clare Wall at the University of Auckland's Faculty of Medical and Health Sciences, who is leading the study. "Babies are born with hardly any gut bacteria. Their gut microbiome develops during their first months of life, influenced by their mode of birth delivery, milk feeding and environment."

Professor Wall says few studies have looked at how the introduction of solids along with continued milk feeding impacts this development, and the complementary feeding period is a great opportunity to introduce foods that optimise a baby's health.

"Our motivation is to have a deeper understanding of how the introduction of complementary foods effects the development of the infant microbiome and how this interacts with and influences the immune system."

The study kicked off in January this year and is expected to continue into late 2023, with mothers introducing a fibre-rich supplement – a kūmara powder paste – as their baby starts solid foods but is still breastfeeding or receiving infant formula. Lasting around four months per participant, a number of samples will be collected to gather insight into how the infant's microbiome and immune profiles change in comparison to a control group, and whether this might correlate to any known health benefits.

Malaghan Institute Postdoctoral Research Fellow Dr Alissa Cait will be analysing changes to the infants' immune systems.

"I'm investigating how a fibre intervention might change the trajectory of immune cell maturation – between six to ten months. We're interested in this really transformative phase of an infant's immune system development – an early life critical window where all signs point to having the greatest impact and where you're most likely to have successful interventions."

Conditions such as allergies, chronic inflammation and autoimmunity are often life-long diseases. What causes a person to develop these diseases, and their specific genetic and environmental triggers, is still largely unknown and varies dramatically from person to person. However, many allergy researchers agree that it's what happens early in life that often determines how severe the disease symptoms and progression might be.

"Understanding more about the development of cell types in early life is really interesting. Very few studies have been done at this age so it's all very exploratory, which makes it exciting." says Dr Cait.

Discovery offers clues on what causes immune cells to drive allergic disease

A study by the Le Gros Laboratory has uncovered genetic clues that help explain how certain immune cells can cause allergic disease. The paper, published in *Immunology and Cell Biology*, brings us one step closer to preventing the cellular mechanisms that drive the development of allergic and inflammatory diseases by targeting the specific immune cells that trigger them.

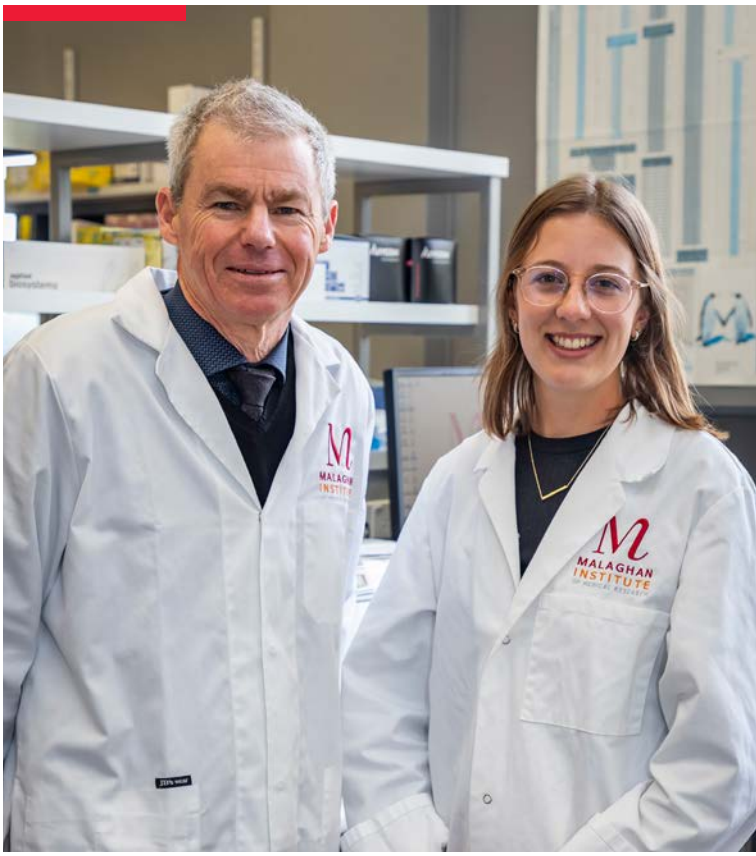
Allergies and autoimmune conditions are caused by immune cells mistakenly labelling harmless materials, such as food, pet dander or even healthy tissue, as dangerous or life-threatening. Responding to the perceived attack as real, the resulting immune response can range from a light rash to anaphylactic shock. What causes specific immune cells to trigger allergic and inflammatory responses and whether we can design therapies to prevent this from happening is a key area of research for scientists like Dr Jodie Chandler who completed her PhD in the Le Gros lab.

"We know Tfh already play an important role in allergic responses, but we wanted to better understand how Tfh cells develop in the body."

"Our research focussed on a specific type of T-cell called a T-follicular helper cell (Tfh)," says Dr Chandler. "Tfh cells play a critical role in the body where they help B-cells to activate and start producing antibodies. Without Tfhs we wouldn't get effective antibody production, which is critical to help combat diseases!"

In an allergic setting, Tfh cells help generate a specific antibody that binds to immune cells that trigger the release of histamines, causing classic allergic symptoms that are typically combatted with anti-histamines.

"We know Tfh already play an important role in allergic responses, but we wanted to better understand how Tfh cells develop in the body."



▲ Dr Jodie Chandler (right) with Professor Graham Le Gros

"Specifically, we wanted to know if Tfh cells can develop into type 2 helper T-cells (Th2) that play a pivotal role in allergic diseases. Understanding what makes a Th2 cell a Th2 cell is an important part of developing strategies to prevent them promoting allergic disease."

Th2 cells are strongly linked to the development of allergic diseases such as asthma or eczema. They are triggered when exposed to specific allergens and initiate dangerous inflammation in the body.

"We found that when we delete Tfh cells in animal models we still see Th2 cells present in the skin, driving allergic disease. This indicated that no, Tfh cells do not further develop into Th2 cells – at least in the skin. – implying they're originating from somewhere else in the body," says Dr Chandler.

"Our findings are important as the more we know about Th2 development, and what drives their development, the more potential pathways we have to disrupt the mechanisms that promote allergic disease."

Dr Chandler completed her PhD at the Malaghan Institute in 2021. She has since taken up a position as a Postdoctoral Research Fellow at University College London.

Thank you for another amazing year in research!

OUR PEOPLE

127 STAFF

12% GROWTH FROM 2020-21

64% RESEARCH STAFF

11 PHD + MASTER'S STUDENTS

18 POSTDOCTORAL RESEARCH FELLOWS

PROFESSOR MIKE BERRIDGE

SHORLAND MEDAL

Awarded by the New Zealand Association of Scientists

OUR COMMUNITY

$8.6 MILLION

RAISED IN PHILANTHROPIC SUPPORT

37% OF TOTAL FUNDING

300+ MEDIA ARTICLES

Jodi Butler's March for the Malaghan

RAISED OVER **$19K**

Colin MacDonald's March for Myeloma

RAISED OVER **$35K**

OUR RESEARCH

KEY AREAS OF RESEARCH AND DISCOVERY

CANCER

INFECTIOUS DISEASE

ALLERGIC + INFLAMMATORY DISEASE

IMMUNE HEALTH

40
PAPERS PUBLISHED

7
CLINICAL TRIALS + STUDIES

KEY COLLABORATORS

VACCINE RESEARCH + DEVELOPMENT

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

CAR T-CELL THERAPY

Guangzhou Institutes of Biomedicine & Health
Wellington Zhaotai Therapies
BioOra

HOOKWORM THERAPY

James Cook University

ALLERGIC + INFLAMMATORY DISEASE

National Institutes of Health
Weizmann Institute of Science

Extracted from the Malaghan Institute's Annual Report for the year ending 31 July 2022

LE GROS LABORATORY

Allergy and parasitic disease. Hookworm therapy.

BERRIDGE LABORATORY

Brain health. Neurodegenerative disease.

HERMANS LABORATORY

Cancer immunotherapy. Infectious disease. Vaccines.

GASSER LABORATORY

Immune health. Gut microbiome.

RONCHESE LABORATORY

Allergic and inflammatory disease.

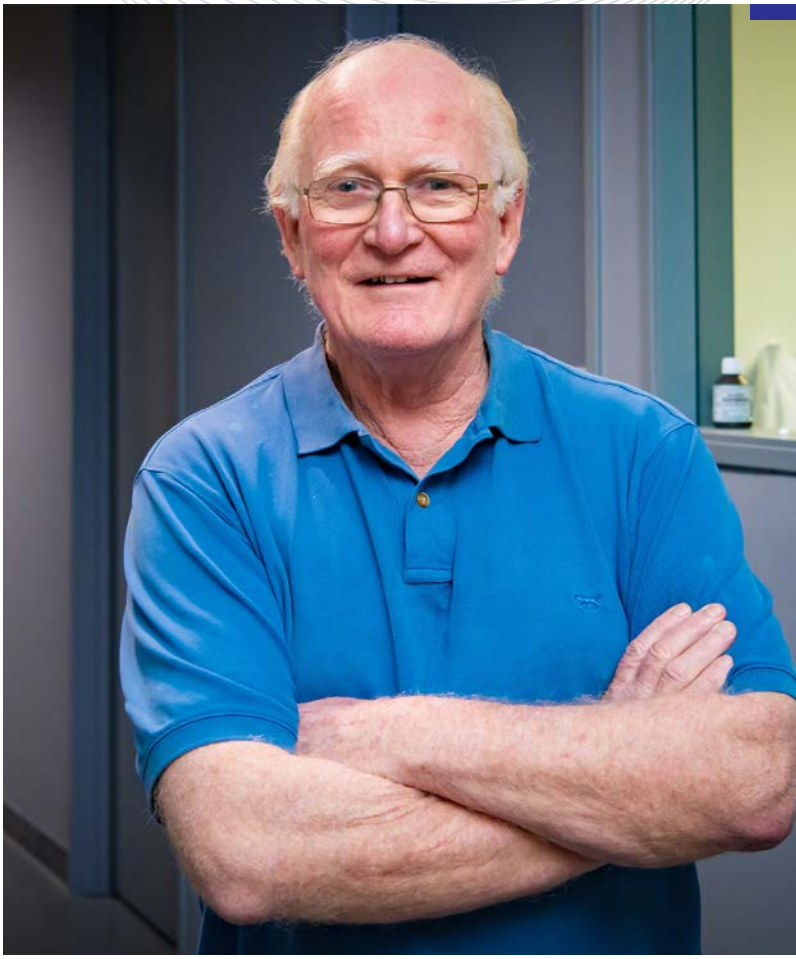
WEINKOVE LABORATORY

Cancer immunotherapy. CAR T-cell therapy.

PROFESSOR MIKE BERRIDGE: A JOURNEY THROUGH THE FRONTIERS OF THE BIOLOGICAL SCIENCES

What do decades of cutting-edge research look like? Arguably, Professor Mike Berridge is a prime example, having spent his career spanning some of the most important scientific advancements of our time.

Acknowledging this lifetime of excellence in research, Prof Berridge has received several notable accolades, including the prestigious Shorland Medal in late 2021, awarded by the New Zealand Association of Scientists in recognition of major and continued contribution to basic or applied research that has added significantly to



▲ Professor Mike Berridge

1968
Began his research career on hormones and plant growth with an MSc at the University of Auckland.

1969
Started his PhD in the mechanisms of plant cell growth at the University of Auckland.

1972
Worked as a postdoctoral researcher at Purdue University (USA), helping lay the foundations of molecular biology.

1974
Appointed staff scientist at the Medical Research Council's National Institure of Medical Research in London in the field of developmental biology.

2015
Landmark discovery of mitochondrial transfer between cells providing vital clues in understanding how some cancers are able to 'bounce back' from certain treatments like chemotherapy.

2016
Awarded the Health Research Council's Liley medal recognising outstanding contributions to health and medical sciences in the field of cellular metabolism.

2021
Awarded the New Zealand Association of Scientists' Shorland Medal.

2022
Recieves a higher doctorate recognising over 45 years of cutting-edge research (conferred from 2021).

scientific understanding or resulted in significant benefits to society. In December he will receive a Doctor of Science from Te Herenga Waka—Victoria University of Wellington.

Prof Berridge's decades-long scientific career spans the globe and several fields from plant biology to cancer metabolism where his discoveries have challenged paradigms of molecular biology that he grew up with. As one of the founding scientists at the Malaghan Institute, Prof Berridge has helped propel scientific research in New Zealand to the world stage.

More than 50 years into his career, he is still brimming with questions and eager to know how far he can push the frontiers of biological research.

In more recent years, his work in cancer made a fundamental discovery – demonstrating for the first time that mitochondrial DNA can move from surrounding normal cells to tumour cells with defective mitochondrial DNA, overturning a central dogma of the time.

"At the time, it was widely accepted that the genes in our DNA that encode proteins are constrained within cells and partition between cells when they divide," says Prof Berridge.

However, Prof Berridge's findings shook that accepted belief – showing that in times of cellular stress, mitochondria, along with the DNA inside them, can move from one cell to another, with healthy cells 'donating' mitochondria to their struggling neighbours to help them recover.

"Since cancer cells are in a continuous state of stress from things like chemotherapy and radiation, this may be a mechanism used by tumours to overcome this stress and continue to grow and wreak havoc on the body."

This discovery has opened a whole new avenue of cancer research around the world, research that Prof Berridge and his team continue to investigate at the Malaghan Institute in collaboration with research teams at Griffith University and in Prague.

More than 50 years into his career, he is still brimming with questions and eager to know how far he can push the frontiers of biological research.

"It's in my nature to ask questions," says Prof Berridge. "One thing I've learned as a scientist is that you have to be comfortable with the unknown and asking questions is the way to focus your research and find some answers."

1976

Returned to Wellington as a Malaghan Research Fellow to establish his own lab at Wellington Hospital and Victoria University that became part of the Wellington Cancer and Medical Research Institute (later renamed the Malaghan Institute of Medical Research).

1980s

Collaboration with Dr Fu-Kuen at Amgen characterising the red blood cell hormone, erythroprotien, and its receptor – a key step in developing the first medications fot treating anaemia.

1990s

Research into how glucose is transported and absorbed by cells of the body leads to some of the first cellular models of how cancer cells manage energy production to rapidly gorw and proliferate.

2003

Awarded a James Cook Fellowship in health sciences by the Royal Society of New Zealand Te Apārangi

PRESENT

Professor Mike Berridge leads the Berridge Laboratory at the Malaghan Institute. He has a number of ongoing national and international collaborations across a range of research areas.

RE-TELL: telling the patient side of CAR T-cell cancer therapy

Giving a voice to New Zealand patients undergoing CAR T-cell therapy is an important part of the Malaghan Institute's CAR T-cell programme, to identify ways to improve patient care and CAR T-cell delivery, and ensure it is accessible to all New Zealanders.

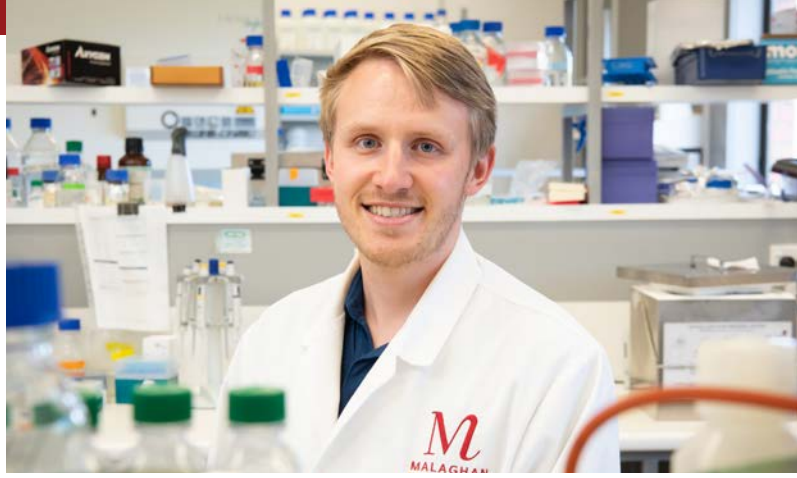
With a distinct population, geography, culture and infrastructure, introducing and integrating a new clinical therapy into the New Zealand healthcare system comes with its own set of opportunities and challenges.

CAR T-cell therapy is no different. Since treating the first participant in late 2019, the Malaghan Institute's ENABLE trial – a first for New Zealand – has required careful planning and a nuanced approach to CAR T-cell delivery and patient care every step of the way. The RE-TELL study is an important part of this process. Run by Malaghan Institute clinician Dr Robbie Fyfe, in collaboration with Francis Health and Janssen, the study is helping paint a picture of the patient side of CAR T-cell therapy so the clinical team can optimise quality of care, and address any real or perceived barriers to accessing this ground-breaking treatment.

"We've conducted interviews with 19 people to date," says Dr Fyfe. "They represented a wide range of different groups including CAR T-cell patients, both treated in the ENABLE trial and those who received CAR T-cell therapy abroad, hospital staff who helped patients through treatment, and administrative staff who were involved in the organisation and logistics of bringing patients to Wellington for treatment.

"We got feedback on their experience and how it could be improved in the future. This included questions about how we can ensure a national CAR T-cell service in New Zealand is available to all, equally."

Currently, the ENABLE trial operates out of Wellington Hospital, requiring most participants to travel between regions to receive treatment. The process of making and manufacturing CAR T-cells takes several weeks from the initial visit, during which time participants return home before coming back to Wellington for treatment.



▲ Dr Robbie Fyfe

Afterwards, there are check-ups with clinical staff to monitor for side effects and treatment response. Dr Fyfe says that each step along the treatment process affects people differently. Patient needs, and those of their support person, must be considered and accounted for if CAR T-cell therapy is to become an equitable standard of care.

"We want to ensure New Zealanders can access this treatment in a fair and equitable way."

"We have had referrals from Waitemata to Dunedin. For many participants, travelling to Wellington, first to extract their T-cells and then four weeks later to receive CAR T-cell treatment in hospital, can be difficult both practically and financially," says Dr Fyfe.

"This is something that we see globally. The people who receive new, life-changing therapies often live in close proximity to research hospitals, which are usually in cities. We want CAR T-cell therapy to be accessible to all New Zealanders, so we hope to establish more treatment centres across the country once we reach our phase II clinical trial. This means more people can be treated too."

The full findings from the RE-TELL study will be published soon, but the team are already looking at applying some of the findings to the clinical programme – such as exploring ways to reduce the time spent in hospital.

"Being far from home and away from loved ones for a significant period of time during an already difficult time can be really challenging for patients," says Dr Fyfe.

"If we can identify CAR T-cell therapies that are effective without a high rate of severe side effects, patients could receive their treatment as an outpatient, attending the hospital for check-ups."

Dr Fyfe says New Zealand is in a unique position. "Against the backdrop of our very own CAR T-cell clinical trial, we can observe how revolutionary CAR T-cell therapies are being implemented aboard in places such as the UK, US and Australia, and we can plan how to tailor this treatment for our own population."

Back in the community!

A big thank you to all our Friends groups, supporters, collaborators and communities for making us welcome as we have been getting back into the community. It has been a tough couple of years with the impact of Covid restrictions and infections affecting all of us.

Thanks to your unwavering support we have managed to weather the storm and emerge on the other side. We held a well-received research update at Lexus of Hawke's Bay in October, and the Hawke's Bay Friends of the Malaghan hosted a fantastic charity golf event the next day, arranging some of that special Hawke's Bay hospitality and weather!

The Hugh Green Foundation also organised an outstanding golf day for the benefit of the Malaghan last month and we recently held a special supporter screening of A Mild Touch of Cancer at the Penthouse Cinema in Wellington.

November has been completed with another great charity golf day on the calendar, thanks to the hard work of the Wellington Friends at the Royal Wellington Golf Course. Although not quite as warm as Hawke's Bay, we enjoyed a fantastic day. Thank you again to our generous communities for welcoming us back and sticking with us through the last couple of years. It is great to see you again in person!

As December rapidly approaches, I hope you all enjoy a well-deserved relaxing holiday period filled with family and loved ones.

Thank you

LAURA GOLLAND
Head of Fundraising

1 Kirsty Horgan and her son Sam, David Downs and film director Annie Goldson at A Mild Touch of Cancer screening.

2 Professor Graham Le Gros, Graham Malaghan and Peter Gregory at the Lexus of Hawke's Bay Golf Tournament.

3 The happy winners of the Friends of the Malaghan Wellington Golf Tournament.

4 Professor Graham Le Gros at our Hawke's Bay research update at Lexus of Hawke's Bay.

Give the gift of research this festive season.

By supporting the Malaghan Institute you are providing hope to those living with disease now and in the future.

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

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.

THANK YOU TO OUR PARTNERS

LEXUS · hrc Health Research Council of New Zealand · KINETICS GROUP making IT work for you. · HUGH GREEN FOUNDATION · BOLTON HOTEL The independent · SPY VALLEY WINES · JUST PATERSON · FREEMASONS New Zealand

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