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MALAGHAN INSTITUTE OF MEDICAL RESEARCH

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Gut health – new frontiers in immunology

The gut holds a unique position in the body, serving as the interchange between our external environment (via the food we eat), the billions of microbes that call it home, and our immune system. Over 70% of our immune system is located in the gut, but we are only just beginning to understand the depth of its influence. Given its enormous complexity, it's unsurprising that uncovering meaningful information from the gut – especially how it influences human health – is like looking for a needle in a haystack.

"The gut is a complex and multi-faceted organ with many different functions," says Malaghan Institute Director Professor Graham Le Gros. "It's difficult to probe and to analyse, and it can only truly be understood by looking at the wider context of the microbiome, the biochemistry of food and the function of immune cells. And that's exactly what we're doing."

The Malaghan Institute has been steadily pooling expertise from different disciplines – bringing together a world-leading superteam across metabolics, immunology, nutrition and physiology – for a more holistic and comprehensive view of the immune system and the gut.

And thanks to recent advancements in analytical technology, and the ability to process billions of cells in a short space of time, the Institute's scientists can now investigate some of the big questions about the relationship between our gut, our immune system and our health.

Feeding our gut and the microbes that call it home

We are what we eat, but also, we are our microbes. The gut is responsible for taking the food we eat and turning it into fuel to power our cells. But on their own, our bodies can't break down food into useable components – or 'metabolites' – we rely on the billions of bacteria that live in our gut, otherwise called the microbiome. Our immune system regulates the microbiome, and in turn is influenced by the types of metabolites produced by the microbiome – a feedback loop that affects not just the health of our gut, but of the rest of our body too.

To tackle how diet and the microbiome affect our metabolic health, Dr Olivier Gasser and his Translational Immunology team have several ongoing research projects, investigating how metabolites generated by the microbiome spread throughout the body and influence the behaviour of immune cells in the brain, lung and skin. By better understanding what metabolites and microbes contribute to a healthy immune system, we can then determine whether we can improve things like immune responses to vaccines through certain dietary manipulations.

Continues inside ->

From the Director

Across the board, we are moving into a new era of technological sophistication, which is enabling us to uncover and understand critical disease pathways in the areas of infectious disease, gut health, cancer and inflammatory disease like never before.

As sophistication grows, so too does opportunity to find new treatments and cures that are tailored – not just individualised, but appropriate for the stage of a person's life and their health. By better matching a treatment to a patient and their disease, the more effective the resulting treatment will be, with fewer side effects. This ultimately makes it more cost-effective than traditional therapies.

These powerful new tools have been made possible thanks to the generous support of our community. I would like to thank all our supporters for your time and effort in helping us achieve more in improving the lives of New Zealanders.

Thank you for your support.

Prof Graham Le Gros
CNZM FRSNZ FRCPA (Hon)
Director

Continued from front page

Understanding the role of immune system in the gut

A healthy immune system means a healthy gut, which in turn benefits the rest of the body. When things go awry, or the immune system is not doing its job, we want to know what led to this imbalance, and whether we can use diet, microbes – or a combination – to steer the immune system back on course.

To understand how to improve a troubled immune system in the gut, we must understand what a 'healthy' immune system looks like. One of the overarching goals of our therapeutic hookworm programme is to use parasites to teach us how a healthy immune system adapts and responds to a harmless infection. By quantifying how the immune system responds to a parasite, especially at the site of infection in the gut, we can then take this data and apply it in the context of inflammatory diseases.

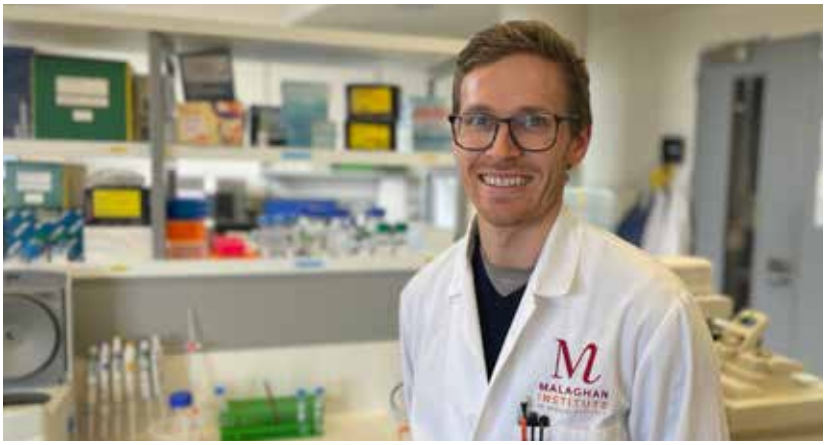
We also know that many immune disorders have their origins in the gut. So we're using cutting-edge bioinformatic and gene sequencing techniques to track various immune cells as they develop, to help identify what the root causes are that nudge these cells towards causing disease.

From the lab to the clinic

When dealing with the complexity of gut-health interactions, fundamental laboratory research can only go so far. The best way to understand the gut in the context of human health is in a clinical setting.

The Malaghan Institute recently recruited gastroenterologist Dr Tom Mules to bridge the gap between laboratory and clinical work.

"Tom plays a key role in our gut health programme – as the clinical link helping us run clinical trials and studies focusing on the gut," says Prof Le Gros. "As a clinician, he is an expert in the physiology of the gut, and is well placed to help us understand how different components of the gut may be influencing different aspects of immune-related disorders such as ulcerative colitis and inflammatory bowel disease."



Dr Tom Mules

Building better CAR T-cell technology

With the astronomical success of CAR T-cell therapy, it's hard to believe that this groundbreaking cancer treatment is still in its infancy. Just as the first automobiles bear little resemblance to today's cars, CAR T-cell technology has much room for improvement, despite already saving many lives around the world.

Here in New Zealand, our ENABLE phase I clinical trial involves 'third generation' CAR T-cells – the third iteration of this novel technology – with second generation CAR T-cells licensed for use in places like Europe, the United States and Australia. The hope is that third and subsequent generations of CARs build and improve upon this treatment with fewer toxicities and side effects. Clinical Director Dr Rob Weinkove explains:

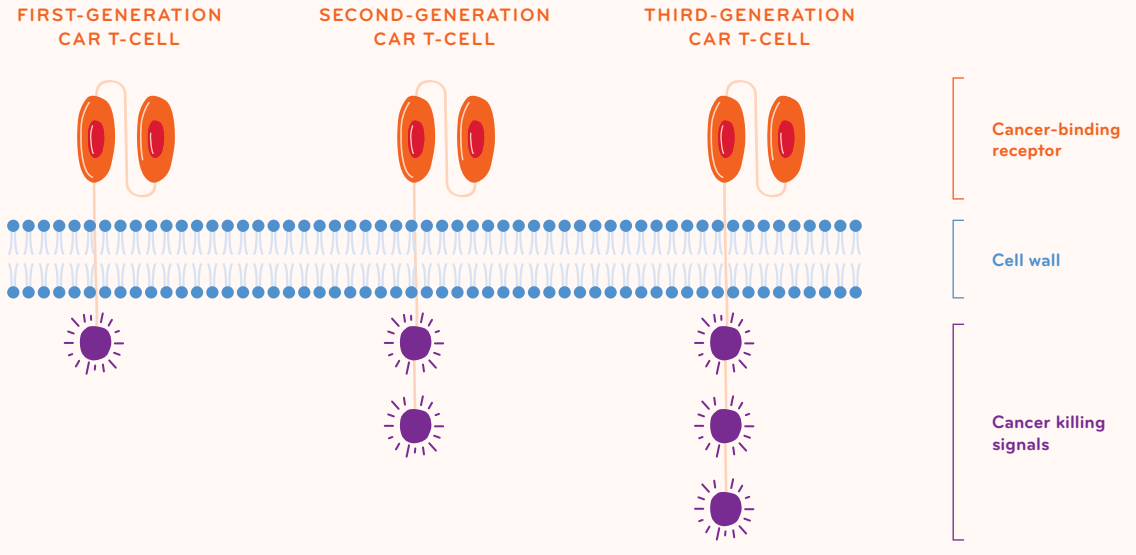
"The term 'third generation' relates to the structure of the 'CAR' – the receptor that makes CAR T-cells work. Developed in the late 1980s, first generation CAR T-cells sent only one type of signal (or alert) when they encountered a tumour cell, and they did not effectively eradicate the tumours. By the 2010s, second generation CAR T-cells provided two types of signal to the T-cells, improving the CAR T-cells ability to kill tumour cells. In 2018, several second generation CAR T-cell products were licensed for use by the US Food and Drug Administration. However, while many recipients fare well, at present, most patients with aggressive B-cell lymphomas, myeloma and B-cell acute leukaemias relapse after receiving second generation CAR T-cell therapies, indicating the need for further improvements.

"Building on the second generation versions, third generation CAR T-cells have three portions within the CAR that signal to the T-cell to kill its target. Several third generation CAR T-cells are in clinical trials, including ours."

The third generation CARs in development around the world all use different types of signals, trying to determine which one(s) have the best results. At the Malaghan Institute, our third generation CARs – developed in partnership with Wellington Zhaotai Therapies – use a unique signal we hope will make the therapy more effective.

"This additional signalling domain emulates a 'danger' signal, effectively making the CAR T-cells act as if they are seeing a bacterial infection," says Dr Weinkove. "This unique domain adds to the effectiveness of CAR T-cells in laboratory models, and our current trial programme is assessing if this addition is both safe and effective in patients."

While the ENABLE trial is still underway, the Freemasons CAR T-cell Research Programme is already finding new ways to improve on both the manufacture and delivery of CAR T-cells, and researching new kinds of CARs with better signalling and in-built 'safety switches' to rapidly deplete CAR T-cells should a patient experience negative side effects.



Repurposed drug shows promise in promoting MS recovery

Multiple sclerosis (MS) is a neurodegenerative disease characterised by chronic inflammation in the brain which causes progressive damage to neural cells - resulting in physical and cognitive disability. While MS symptoms can be managed by controlling this inflammation, to date there are limited options for the repair and recovery of these damaged neurons.

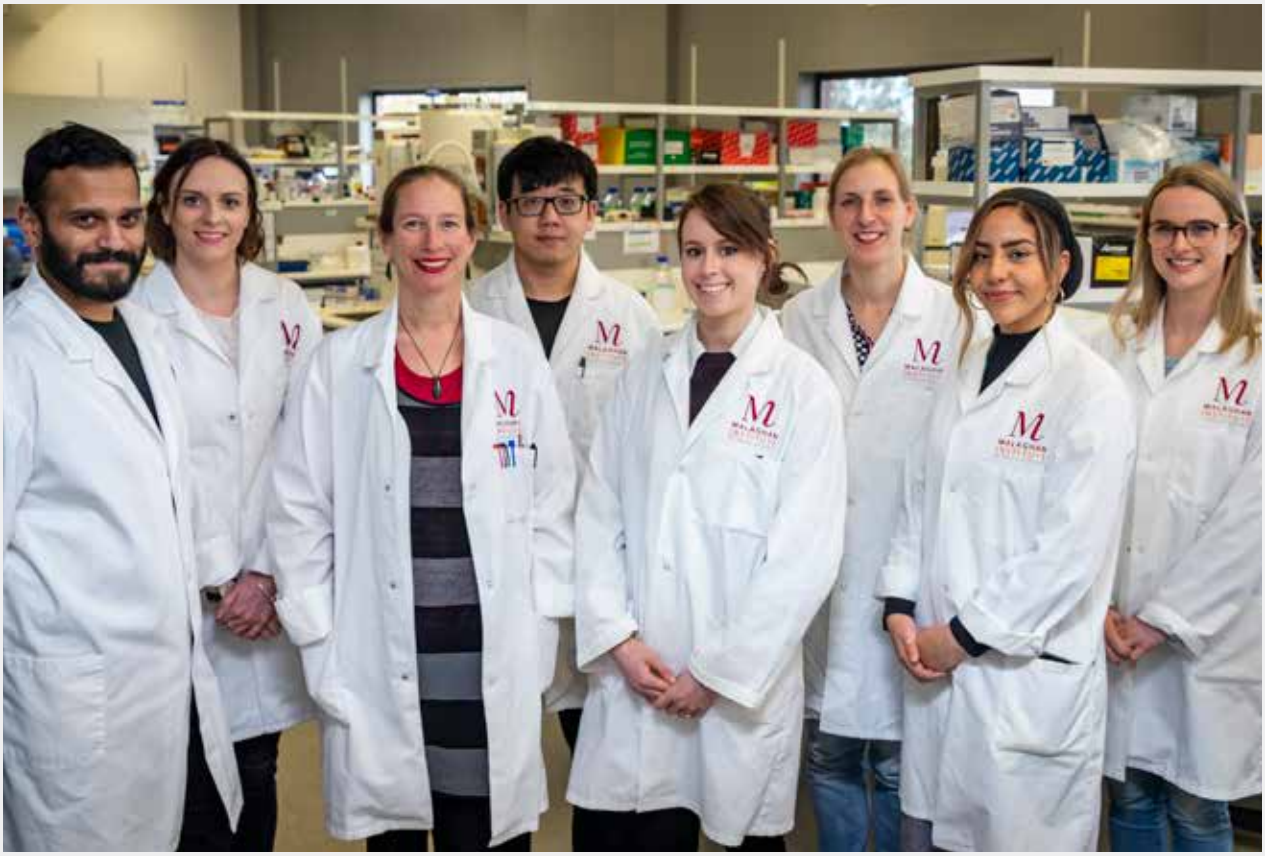
However, a recent publication by Malaghan Institute MS Programme Leader Professor Anne La Flamme, Victoria University of Wellington Associate Professor Bronwyn Kivell, and University of Kentucky Professor Thomas Prisinzano has shown that the drug nalfurafine has the potential to not only slow the accumulation of disability, but also to restore function in experimental models of MS.

Already in use, nalfurafine has been used clinically for years in treating a non-MS condition. Due to it's history, it has proven to be safe and well-tolerated in patients, making it a promising candidate to be repurposed for MS patients.

"We are now raising funds to enable a clinical trial of nalfurafine in people with MS to build on this significant step forward in our understanding of its potential," says Prof La Flamme.

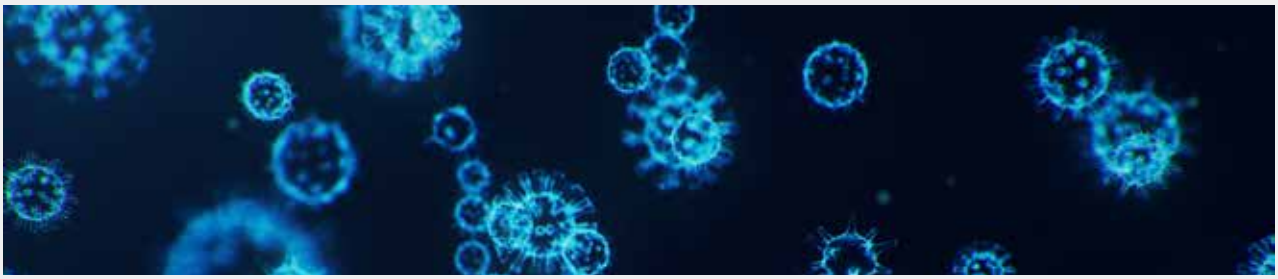
Prof La Flamme, Assoc. Prof Kivell, and Prof Prisinzano last year co-founded a spin-out company, Rekover Therapeutics, with investment from the New Zealand Innovation Booster Fund, a partnership between the University's commercialisation arm, Wellington UniVentures, and Booster Financial Services.

"We are now raising funds to enable a clinical trial of nalfurafine in people with MS to build on this significant step forward in our understanding of its potential"



The Malaghan Institute's multiple sclerosis research team

New technology platform provides close up look at cells



How a cell behaves tells us a lot about its role and its function. When we want to know what a cell is up to, one way we can do this is by looking at its outputs – such as the kinds of proteins it's making or the chemical signals it's producing. But looking at a cell's outputs to determine its function is like looking at a cake and trying to figure out its ingredients. We can get a general idea of what's going on – but if we really want to know what's happening, and more importantly why, we need to get a closer look. In the context of cells, when we want a closer look at what's really going on inside cells, we need to look at their genes.

When a cell wants to make a protein, it 'transcribes' a small portion of its genetic material that contains the instruction on how to make it. These instructions, or 'RNA transcripts' are then carried to the cell's manufacturing components which construct the protein based on the instructions. By knowing which transcripts the cells are making, and how many of them are made, we can build a much more detailed and accurate picture of what's going on inside the cell at a given point in time.

This is the level of detail that our latest piece of technology, the BD Rhapsody operates at. It will provide scientists from around the country the ability to look in-depth at what genes are active in a sample, and better determine what the immune cells were up to at the time of collection.

"Single-cell RNA sequencing is a very powerful technique. It gives us a snapshot of the gene expression of an individual cell," says Sventja von Daake, Cytomic Specialist in the Institute's Hugh Green Cytomety Centre. "One of the exciting things about the BD Rhapsody is that a huge number of cells (around 20,000) can be sequenced at the same time while collecting data on the RNA from each individual cell.

"Previously, if we wanted to do a similar experiment, we would need to send samples overseas. This was problematic because it required us to freeze samples for transportation, which often alters or even damages the sample, affecting the quality of results."

While still in its testing phase, the RNA sequencer is already proving a useful tool for several Malaghan research groups. Having access to such powerful tools helps our scientists create more informed hypotheses, accelerating our discovery potential for understanding and treating disease. The Immune Cell Biology team has already started using this technology to investigate how immune cells in the skin develop and acquire their skin-specific roles, an important step in the development of allergies and atopic disorders.

Thank you to our partners

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The Malaghan Institute wishes to acknowledge the support of the Hugh Green Foundation

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- Make a credit card donation over the phone – please call the fundraising team on 0800 625 244.
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- Donate online via our donation page (www.malaghan.org.nz/donate).
- Make a donation directly into our bank account: 06-0507-0052635-30.
- Set up a regular monthly payment from your credit card using the form below.
- Set up an automatic payment from your bank account using the enclosed form.

And please do remember, we're here to help, so don't hesitate to contact us on 0800 625 244 or email fundraise@malaghan.org.nz.

Grants Nov 2020 – Apr 2021

We would like to acknowledge and thank the following Trusts and Foundations for their support:

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MALAGHAN INSTITUTE OF MEDICAL RESEARCH

Harnessing the power of the immune system.

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