SCOPE 65
A MALAGHAN INSTITUTE PUBLICATION

MALAGHAN INSTITUTE OF MEDICAL RESEARCH

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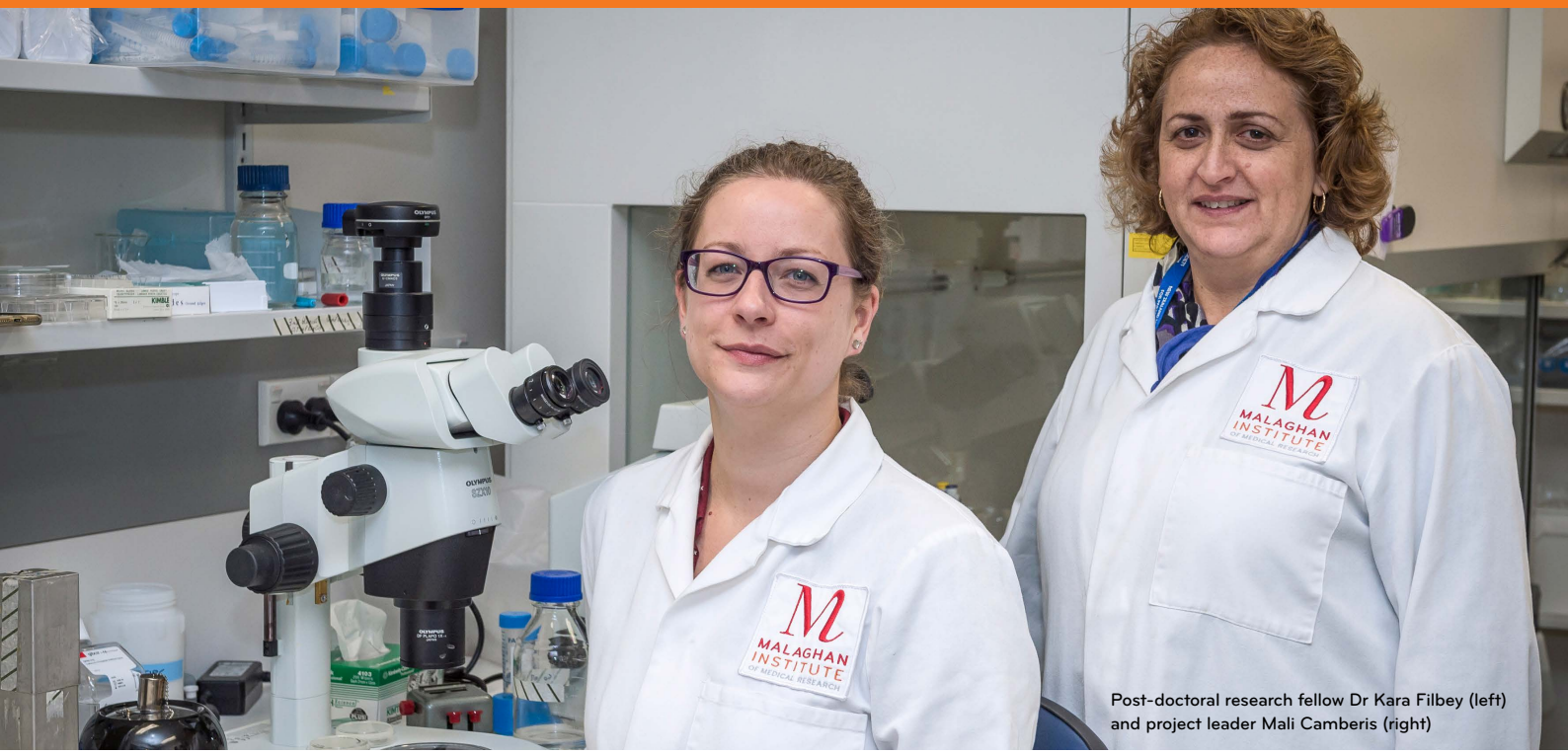


Post-doctoral research fellow Dr Kara Filbey (left) and project leader Mali Camberis (right)

An unexpected find: new pathways to target hookworm infection

In the course of researching asthma, Malaghan scientists have identified a new target for hookworm therapy, based on the worm's blood-feeding habits.

Published in PLOS Pathogens, the asthma, allergy and parasitic disease programme has identified the novel feeding pathway, which unlocks an exciting new area of research. With further experimentation, the discovery may one day help combat human hookworm infections, which affect over a billion people worldwide.

Traditionally, hookworms such as helminths have been considered to only start feeding on blood once they enter their hosts' gut. However, postdoctoral researcher Tiffany Bouchery has demonstrated using a preclinical model of human hookworm infection that blood feeding occurs as soon as the worm enters the host's body.

"What we've found, quite unexpectedly, is that the worm starts blood feeding as soon as it enters the body, in the first three days of infection," says Professor Graham Le Gros.

"This insight could lead to new ways of targeting the species of hookworm that commonly infect humans, because once it is in the gut it's very hard to deal with and causes a whole host of health issues."

Prof Le Gros' team were able to interrupt this blood feeding via anti-malarial drugs – preventing the worms from safely digesting the iron found in red blood cells. They have yet to begin work to explore how this insight applies to human infection.

"While not what we set out to find, this piece of research is very exciting. In terms of its potential and where it could lead, improved therapies for people suffering from hookworm will be a major milestone in the fight against tropical diseases.

"It also gives us a deeper mechanistic insight into how other worms may be similarly affected when they first start migrating into the body and how we might use this knowledge to work with worms to our advantage."

From our Director

With International Day of Immunology falling on April 29, I've been reflecting on the current state of immunology in New Zealand and what major developments are on the horizon.

CAR-T cell therapy is leading the revolution. It's about more than just treating cancer – this technology, which involves re-programming immune cells to fight cancer in more precise and targeted ways, is proving time and again to be the leader in a new dawn of immunotherapy.

I am hugely excited that here at the Malaghan Institute we're developing the scientific disciplines that can really test the limits of CAR-T cells. With our expertise in innate T cells, inflammatory cells and the ligands that can stimulate them, we're bringing together the necessary elements to really explore how we can use CAR-T cell technology in positive ways for New Zealand.

In combination with other emergent therapies, I can foresee a time where we hold the power to design our own immune system to deal with all health issues, not just cancer.

Thank you for your support.

Prof Graham Le Gros
CNZM FRSNZ FRCPA (Hon)
Director

RESEARCHERS IDENTIFY

New role for key molecule in early-stage development of allergic response

Researchers at the Malaghan Institute have identified the role a key molecule plays in the initial development of an allergic response, opening doors for research into future treatment options for asthma and allergy sufferers.

Published in *Proceedings of the National Academy of Sciences of the United States of America*, the immune cell biology team pinpointed a new role of Thymic stromal lymphopoietin (TSLP), a molecule involved in the development of T helper 2 (Th2) immune cells during an allergy.

This research helps explain the rapid development of Th2 cells during an immune response. Programme head Professor Franca Ronchese says the discovery means that potential therapies blocking the interaction between TSLP and Th2 cells may help in the suppression of damaging inflammation and allergic disease.

"TSLP accelerates the development of inflammatory cells in tissues that can cause disease, something that was not known previously," says Prof Ronchese.

"People thought that TSLP acts mainly at different stages of the immune response, and maybe only in the lung and the skin. We're saying no, it has a broader role than that and really drives these cells to become inflammatory."

While the research team has not yet explored potential treatment opportunities of preventing TSLP in developing Th2 cells, the work conducted by Prof Ronchese and her team does give supporting evidence of TSLP blockers in existing clinical trials.

The Immune Cell Biology team (2017)

Global effort in the fight against cancer

Breakthroughs don't happen in isolation. Typically, they are the steady accumulation of advancements made through scientific collaboration and networking, often spanning the globe.

Both national and international collaborations are vital to finding cures for disease. Collaboration gives researchers greater access to knowledge, insight and tools, broadening their perspectives and fast tracking discovery.

The Malaghan Institute's cancer gene transfer project, under the umbrella of Professor Mike Berridge's Cancer Cell Biology programme, is one such example. From a Federation of European Biochemical Societies-sponsored mitochondrial meeting in Prague in 2009, the seed was planted in the mind of meeting convenor Professor Jiri Neuzil, that germinated into a collaborative agreement following an Australasian meeting in Akaroa a year later.

It took another four years for the Malaghan Institute to gather bulletproof evidence for how healthy mitochondria are transferred to cancer cells with damaged mitochondrial DNA, which contributes to their survival, publishing the results in the leading scientific journal, *Cell Metabolism*. Prof Neuzil's laboratories at Australia's Griffith University and at the Czech Institute of Biotechnology were key to the initial publication success that has now amassed almost 200 citations.

Since 2015, this collaboration has only grown, with seven publications and two manuscripts under revision. The work has involved contributions from researchers in other laboratories in Australia, Czech Republic, Korea, Portugal, USA, Germany, Sweden, India, France, the Netherlands, and of course, New Zealand. A truly global effort in the fight against cancer.

Cancer Cell Biology programme leads Professor Mike Berridge (left) and Dr Melanie McConnell (right)

Skin microbes: The key to halting the allergic march?

Atopic dermatitis (eczema or AD) is one of the first allergic conditions infants and young children develop, and is one of the first steps taken on the 'allergic march': a trend of escalating allergy symptoms that worsen as we age. By preventing the initial development of eczema through the monitoring and control of skin microbes during childhood, can we potentially halt the allergic march before it begins?

"Absolutely," says Professor Graham Le Gros. "Our immune system doesn't exist by itself, it exists in close connection with the microbiota around our body. The skin microbiota plays a clear role in the initiation of allergic responses.

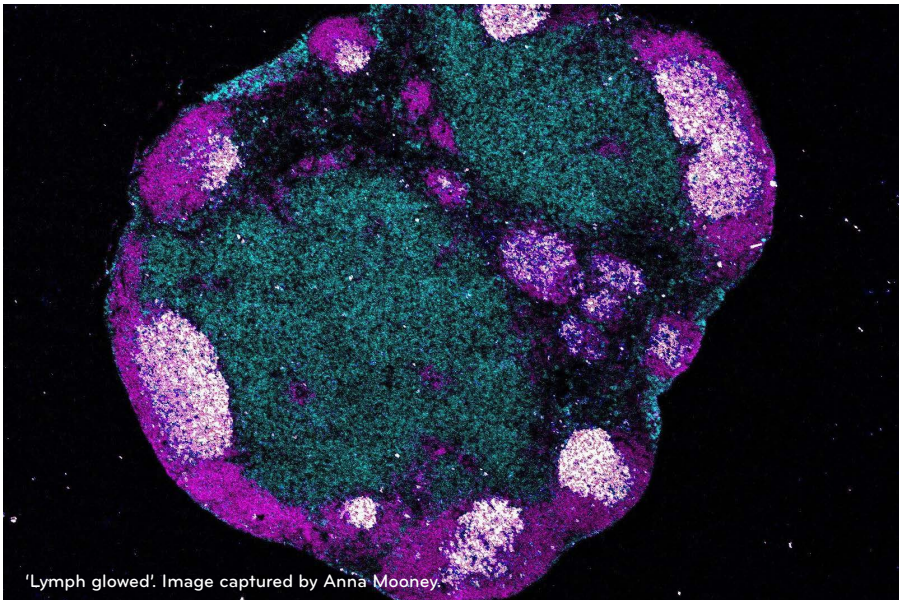
"Understanding this relationship in more detail could lead to better ways of stopping the development of allergic diseases like eczema and food allergy, preventing the allergic march in individuals."

Dr Karmella Naidoo has been working at the Malaghan Institute answering this very question. The subject of her recently completed PhD, during which Dr Naidoo established models of AD in mice to study the allergic march in depth.

"Atopic dermatitis patients have a completely different microbiota on the skin compared to healthy individuals," says Dr Naidoo. "We know that certain species of bacteria, in particular Staphylococcal strains, colonise most of the skin of an individual with atopic dermatitis.

"By putting a stop to allergic sensitisation early on, there's a good chance we'll be able to halt the allergic march before it begins. In that, we are hypothesising that skin microbes will have a large role to play and are researching them intensively."

Dr Karmella Naidoo



'Lymph glowed'. Image captured by Anna Mooney.

Malaghan Institute microscopy photo competition Winner 2017

Each year, the Malaghan Institute runs an in-house competition celebrating the amazing things captured down the end of a microscope. Master's student Anna Mooney faced stiff competition in taking first place for her image of a mouse lymph node.

Anna says her image, Lymph Glowed, shows a glowing lymph node in the process of antibody production following vaccination.

"The B cell follicle (purple) is interspersed with germinal centres (pink). In the germinal centres, B cells are in a rigorous competition, undergoing intense rounds of mutation to try and improve the quality of their antibody. Their judges, the T cells (green), can be seen speckled throughout germinal centres. Only B cells with the best antibodies will be favoured by T cells to win the prize, differentiating to an antibody-secreting plasma cell to fight infection."

The Malaghan Institute would like to thank the sponsors of this competition, Interlab, Invitro and Vic Books.

OUR PEOPLE:

Dr Katherine Woods

The Malaghan Institute welcomed the talented Dr Katherine Woods to our Translational Immunology programme at the beginning of 2018. Hailing from Ireland, Dr Woods received her PhD from Trinity College Dublin and most recently worked as a postdoctoral fellow at the Olivia Newton-John Cancer Research Institute in Melbourne. Dr Woods brings a wealth of expertise in immunology and cancer research to the Institute.

"My work at the Malaghan Institute will be looking at the relationship between the gut and other body sites in the development of allergic disease. In particular, we're interested in how the gut microbiome affects the development of the immune system. The majority of our immune cells reside in the gut and the dynamic interactions between the diet, gut microbiota and our immune cells are fascinating, and only beginning to be understood. Through experimental models we can address these questions to find out more about how these interactions are occurring, and ultimately how we may manipulate them therapeutically."

'Seahorse' fuelling next stage of cancer cell metabolism research

The Malaghan Institute has recently acquired a new piece of technology that allows scientists to accurately measure the fuel consumption of cells in real time. This technology – the Seahorse XF Analyser – will deliver benefits across the Institute, including helping us better understand the energy demands of immune and cancer cells during development, and find ways to inhibit their metabolism.

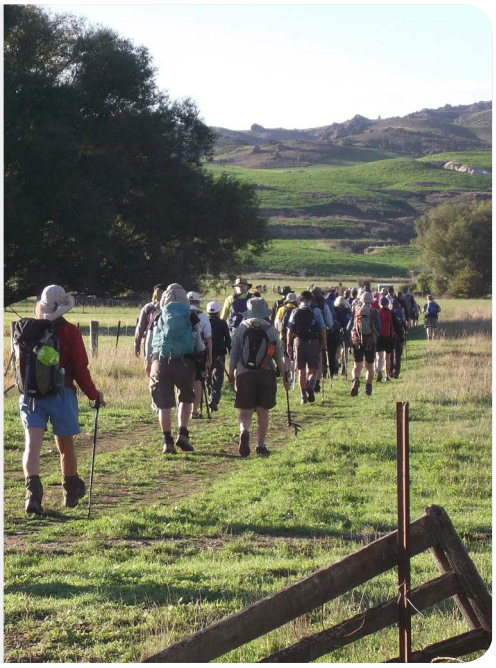
How cancer cells use energy says a lot about how they work and what they need to stay alive. At different stages of growth – from primary tumour to metastatic growth – the energy demands and types of fuels cells use can vary greatly.

"Glycolysis and oxidative phosphorylation are the major energy-producing pathways in the cell," says senior research manager Carole Grasso. "Most cells have the ability to switch between these two pathways, thereby adapting to changes in their environment."

With the ability to directly measure the oxygen consumption rate and the extracellular acidification rate in real time, the Seahorse enables researchers like Carole to get a closer look at the metabolic activity of cancer cells.

One of the long-term goals for the Seahorse is to understand what happens to the metabolic needs of cancer cells when they're damaged by therapeutic drugs and irradiation. How do their energy demands change? What happens to their mitochondrial DNA? Does damaging the mitochondria cause cancer cells to take up healthy mitochondria from the environment? Gaining a better picture of this process may one day help to make cancer treatments more effective, or find ways of blocking mitochondrial uptake in cancer cells.

Great New Zealand Trek 2018: Stage 13 completed



More than 400 participants and support crew descended on the picturesque Central Otago settlement of Ophir to take part in the Great New Zealand Trek in early March. The trek wound through beautiful Otago countryside on foot, horseback and bicycle, ending up in the town of Lawrence.

Professor Anne La Flamme, whose multiple sclerosis research is supported directly by funds raised by the trek, took part again this year. "As always, the trek was fantastically organised thanks to the dedicated efforts of the Trustees and volunteers."

The 2018 Great New Zealand Trek was bittersweet with the passing of Hepa Paewai in late February. Hepa was an integral part of the trek for over ten years, scouting out and planning the route months in advance and helping guide trekkers during the event. The Malaghan Institute would like to thank Hepa and his partner Kitty, for all their hard work and dedication to supporting MS research in New Zealand.

Maurice Capstick Scholar Award recipient: Joshua Lange

Congratulations to Malaghan Institute PhD student Joshua Lange for receiving the Maurice Capstick Scholar Award. The award, which provides up to $10,000 towards international collaborations or training, will be a valuable contribution towards Josh's time at the University of Oxford.

Josh is currently finishing his stay at the Weatherall Institute at Oxford, collaborating with world-expert Professor Vincenzo Cerundolo to further develop the novel immune cell vaccines created at the Malaghan Institute for use in cancer immunotherapy.

In focus: GBL Personnel

A long-standing supporter of the Malaghan Institute, lab partners GBL Personnel have helped to secure funding for the cell biology laboratory at the Institute.

"The GBL Personnel team collectively chose to support the Malaghan Institute, from a number of charitable options, on an ongoing basis as many of us have had cancer touch the lives of our families and loved ones, and we have great respect and gratitude for the ground-breaking research conducted by the Institute."

The GBL Personnel team have visited the Malaghan Institute facilities on multiple occasions and attended the most recent Wellington Community Research Update. We would like to thank GBL Personnel for their continued support.

The Malaghan Institute wishes to acknowledge the support of the Health Research Council of New Zealand

Health Research Council of New Zealand

Upcoming community events

Rotary Club of Port Nicholson Charity Dinner | Friday 4 May, 6.30pm
Please contact our Community Fundraising Manager for more information
cholland@malaghan.org.nz or 04 499 6914 ext.821

Wellington Research Update | Thursday 10 May, 5.30pm
Please contact our Community Fundraising Manager for more information
cholland@malaghan.org.nz or 04 499 6914 ext.821

Malaghan Institute Hawke's Bay Golf Tournament, Hastings | Friday 26 October
Please contact our Head of Development for more information
jsim@malaghan.org.nz or 04 499 6914 ext.811

Malaghan Institute Auckland Golf Tournament, Remuera | Monday 19 November
Please contact our Head of Development for more information
jsim@malaghan.org.nz or 04 499 6914 ext.811

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Research is our journey. Cure is our destination.

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