SCOPE 63
A MALAGHAN INSTITUTE PUBLICATION

MALAGHAN INSTITUTE OF MEDICAL RESEARCH

MALAGHAN INSTITUTE OF MEDICAL RESEARCH | NEW ZEALAND | WWW.MALAGHAN.ORG.NZ | JULY 2017

Dr Oliver Gasser and Research Officer Yanyan Li

How our immune system and gut microbiome influence each other

Earlier this year, The Malaghan Institute was excited to appoint Dr Olivier Gasser as our new Translational Immunology Group Leader. His group strives to uncover the complex ways in which our immune system and gut microbiome influence each other.

Microbes in our gut play a key role in keeping our body healthy. Many of the mechanisms are unclear, but it is often metabolites produced by the microbes that provide us with benefits. Dr Gasser focuses on the translocation of compounds from the gut to the bloodstream that act as natural adjuvants for immune responses to vaccines. If these responses are good, the immune system becomes better equipped to fight infections.

Other recent studies investigated the negative implications of the microbiome on health. One publication in Cell Host & Microbe linked age-related changes to the microbiome to increased gut permeability. This 'leaky gut syndrome' can result in systemic inflammation, a leading cause of premature death in the elderly. Dr Gasser has also seen this mechanism in his own research, but with varying outcomes. For instance, in patients with HIV, the virus also causes the gut lining to deteriorate, quickly exhausting the immune system from overstimulation. In a disease like cancer, however, chemotherapy increases gut permeability in order to induce a strong immune response.

These findings suggest that our gut microbiome can be both beneficial and detrimental to us under different circumstances. Dr Gasser highlights the importance of nutrition & microbiome research: "It is crucial that we understand the fine balance between a healthy microbiome and one that causes health problems if we want to find and improve therapies for many diseases."

Differing findings like these show the importance of scientists across the world sharing and discussing new ideas. The body works as a whole, vastly complicated system. It is through collaboration that we will move towards a true understanding of its challenges.

From our Director

From womb to teenage years, our immune system is transforming. It learns how to recognise friend from foe, toxin from nutrient and invader from helper. It studies the challenges of our environment and readies itself for the unknown.

As we age, our immune system seems to run out of steam. Infections successfully fought in our youth have greater consequences if encountered again. The rate of disease drastically increases amongst the elderly, at enormous costs to public health systems and more importantly, on an individual level to quality of life.

This is a large area of unmet health concern. We are yet to discover the origins of many geriatric diseases. We want to uncover if and how they are linked to our ageing immune system and whether we could use this knowledge to extend its vitality. The first progressions in this field have investigated how our gut microbiome impacts the immune system. I am thrilled to have Dr Olivier Gasser here as our Translational Immunology Group Leader, studying these interactions.

Thank you

Graham Le Gros

Prof Graham Le Gros
CNZM FRSNZ FRCPA (Hon)
Director

Powering the Brain with Mitochondria

Professor Mike Berridge

Five years ago, Professor Mike Berridge and his colleagues pointed their research focus to mitochondrial transfer between cells to explain unexpected results. Mitochondria are the powerhouses of cells, producing much of the energy required for maintenance and function. These organelles possess their own DNA and in their absence, many types of cells perish.

Previously in cell biology, it had been widely accepted that genes do not transfer between cells. This was overturned by Prof Berridge and his group, who showed mitochondria moving to tumour cells that did not possess mitochondrial DNA. This breakthrough sparked an array of questions about mitochondrial transfer in health and disease and continues to be a major focus of Prof Berridge's work today.

The current challenge is deconstructing mitochondrial transfer in the brain. Nearly all neurological diseases present altered bioenergetics involving mitochondria. To understand these diseases, we must understand how mitochondria and cells behave in the brain. Prof Berridge's group use a glioblastoma brain tumour model without mitochondrial DNA to observe mitochondrial transfer from surrounding cells. They aim to identify the donor cells and the signals involved. With this knowledge, Prof Berridge theorizes that techniques could be developed to prevent transfer, halt tumour growth and address many neurological diseases.

Exploring mitochondrial transfer will not only help us understand cancer cell biology, but also, normal cell biology. "If this function has been retained throughout evolution, there must be a significant reason," contemplates Prof Berridge. We are only scratching the surface of where this promising area of research could lead. Scientists across the globe have expressed interest in collaboration, opening up opportunities to combine knowledge and resources. Unpacking the intricacies of brain bioenergetics could ultimately help us combat neurological dysfunction.

Small device, big opportunities – sequencing genomes with a MinION

These days, bench-side laboratory work is intertwined with complex computational work, called bioinformatics. Analysis technologies transform data into meaningful results and open new avenues of research. For the past six months, Dr David Eccles and Dr Jonathan Ewbank have been sequencing the genome of Nippostronglyus brasiliensis. "Nippo" is a parasite with a life-cycle similar to human hookworm, which infects millions of people worldwide. As people with hookworm infection seem to be protected from allergic diseases like asthma, researchers at The Malaghan Institute are interested in understanding more about Nippo.

Sequencing an organism's genome allows us to understand its unique biology and abilities; for instance, how it infects a host. Dr Eccles and Dr Ewbank use a sequencing device the size of a muesli bar, called MinION, from Oxford Nanopore Technologies. DNA from Nippo is fed into the device and within minutes, it starts reading the DNA sequence.

Previous attempts to sequence Nippo, even a year ago, failed because the established technology could not overcome the complex nature of its genome. "It was like trying to piece together a 10,000-page book using extracts of 100 letters," describes Dr Ewbank. "Now, we get stretches of 100,000 letters in one go; whole chapters at a time. We can then integrate them back into the whole book, or in this case, the genome."

With parasitic worms emerging as a potential therapy for diseases like coeliac and asthma, it is crucial to enhance our understanding of their genome and biology. The research findings of this project and others at The Malaghan Institute are contributing in a major way to this goal.

Informing Immunotherapy – profiling Innate T cells in cancer

In the quest for treating a disease as diverse as cancer, multiple approaches are explored in our cancer research programmes. Ellie-May Jarvis is one of the few people in New Zealand undertaking a combined medical degree and PhD and she was drawn to The Malaghan Institute's reputation for high-class research.

PhD Student Ellie-May Jarvis

Along with other members of the Cancer Immunotherapy Programme, she studies a group of cells crucial to our immune response but largely overlooked by cancer research –innate-like T cells.

Most T cells in our body respond only to a specific antigen or signal. Innate-like T cells make up a large proportion of our immune cells, sometimes up to 10%, and can be stimulated by several signals. This means we have a huge cell population able to be activated simultaneously and produce a strong immune response. Ellie-May works with both clinicians and scientists to profile the function of these cells in cancer patients and develop treatments that trigger an immune response against the disease. "The smartest way to progress something into a real treatment is to know as much as we can," she explained.

To examine cell function, Ellie-May applies a variety of technologies available at The Institute, from flow cytometry to cytokine bead arrays. "If cells from a cancer patient show decreased innate-like T cell function, we could potentially tailor our immunotherapy to correct that," she summarized. "If we saw no function or cells remaining, that could be an indication to take another approach."

Research projects like Ellie-May's build on the potential for precision medicines. By identifying how specific cancers affect innate-like T cell populations, treatments could be devised to work in conjunction with other immunotherapies currently in clinical trials.

Optimizing the use of antipsychotic medicines for Multiple Sclerosis

Professor Anne La Flamme

Professor Anne La Flamme and her Multiple Sclerosis (MS) research group recently published encouraging results of preclinical work involving atypical antipsychotic agents (AAP) such as risperidone and clozapine modifying the inflammatory environment within the central nervous system in the international journal Multiple Sclerosis Journal – Experimental, Translational, and Clinical.

Building on research which demonstrated the ability of the AAP risperidone and clozapine to modify the disease course in an animal model of MS, the research group aimed to further investigate how best to administer clozapine as a possible treatment for MS.

Results of this study show that orally administered clozapine significantly reduced disease severity, and the level of reduction was dependent on the dose. It was also effective when administered before and after the onset of symptoms. In comparison to other AAP, clozapine was the best at reducing disease severity. While clozapine had only modest effect on the body's immune cells, it had significant effect on immune cells in the central nervous system – our brain's immune cells.

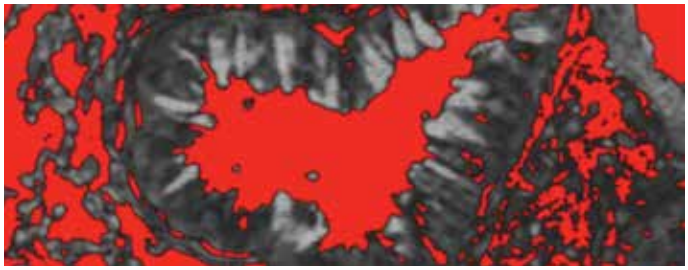
These studies indicate that clozapine is an effective immunomodulatory agent with the potential to treat immune-mediated diseases such as MS.

Out of the box approaches to treating Asthma

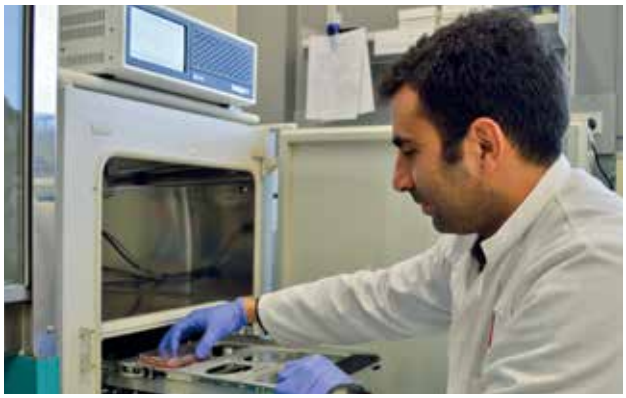
Asthma is caused by an overreaction of the immune system to harmless environmental triggers that we breathe in, touch or eat. In every case, the same part of the immune system is activated, the Th2 immune response, which normally functions to protect us from parasitic worm infections. Understanding the signals that trigger the initiation of asthma is critical for the development of treatments that selectively suppress only the asthmatic immune response.

"It is very difficult for us to advise patients on how to avoid asthma attacks " Professor Graham Le Gros explains. "There are different types of asthma and different patients can react differently to the same trigger. How they respond depends on their immune system and their genetic make-up. It will be vital to develop research to a more individualised level – similar to our immunotherapy approach in cancer research."

While individualised treatments for asthma and allergy are desirable, parasitic worm infections have been linked to a dampening of allergic and asthmatic symptoms in many patients. We are trying to understand how this phenomenon could be applied in a therapeutic setting for inflammatory diseases of the lung, skin and gut.



A bronchiole in lung of allergic specimen



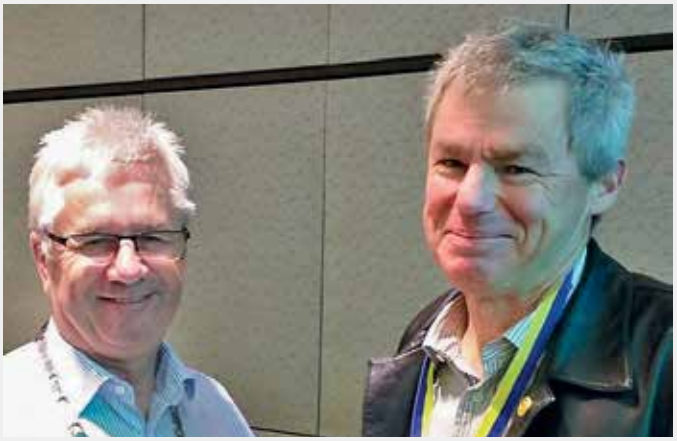
Staff scientist Alfonso Schmidt operating IncuCyte

Live-cell analysis -See what the cells are doing as they do it!

The IncuCyte S3, the latest edition to our Hugh Green Cytometry Core facility, is a flexible assay platform that sits inside a standard tissue culture incubator and automatically acquires and analyses fluorescent images of living cells.

This exciting technology enables our scientists to set up experiments not possible before, such as continuous monitoring of cellular kinetics over weeks or months. Cells remain in an incubator while the images are being acquired, giving minimal cellular disturbance, thus protecting cell health and morphology.

Our scientists will be able to gain a better understanding of cell health, function, migration, invasion and other workflows such as transfection efficiency or dilution cloning.



Prof Graham Le Gros awarded Rotary's highest honour.

Our Director Prof Graham Le Gros was recently honoured by the Rotary Club of Port Nicholson.

He was made a Paul Harris Fellow in recognition of his contribution to medical research which is focused on the health and well-being of all New Zealanders.

In accepting the award Prof Le Gros mentioned how extremely heartened he is to see the recognition for the positive difference the Institute makes to our nation.

Port Nicholson Rotary President Mark Cassidy pictured above with Prof Le Gros said "Rotary believes that Graham exemplifies the humanitarian and educational objectives of Rotary."

Auckland Funding Manager appointed

Raewyn Roberts

Institute Director Professor Graham Le Gros recently announced the establishment of a new position in the Auckland region with the appointment of Raewyn Roberts as Auckland Funding Manager.

Raewyn has been involved with the Malaghan Institute for several years in an advocacy role and is very excited to be taking up this new role. "I have long been a supporter of the Institute and the research that is being carried out and feel privileged to be able to work with supporters and potential supporters within Auckland" Raewyn mentioned.

Raewyn would be delighted to speak to anyone wishing to find out more about the Institute and can be contacted by **Email:** rroberts@malaghan.org.nz or **Ph:** 021 170 5197

Research From Bench to Bedside

Professor Ian Hermans

Every scientific researcher's ultimate aim is to discover and develop new treatments to cure diseases and improve human health.

The Malaghan Institute is a very unique place to translate bench side research into real treatments.

"We decided early that we wanted to move novel ideas into the clinic as soon as possible," explains Professor Ian Hermans, Leader of our Cancer Immunotherapy Programme. "Thanks to governmental funding and the noteworthy support of our donors, the Institute is in a distinctive position to invest in specialized laboratories and staff." With the cutting edge research technology and the treatment-based approach that the Institute provides, Prof Hermans' research has advanced a cell-based cancer vaccine into clinical trials.

Thank you to our partners

Performance Partner

LEXUS

JUST PATERSON REAL ESTATE LTD MREINZ

Hotels Wellington

gbl PERSONNEL

nichecom

ThermoFisher SCIENTIFIC

KINETICS GROUP

Community Events

20th September | Wairarapa Community Research Update at Masterton Toyota

19th October | Wellington Friends Cocktail Function at Botanical Gardens

26th October | Hawke's Bay Research Update at Lexus of Hawke's Bay

27th October | Hawke's Bay Charity Golf Tournament at Hastings Golf Club

20th November | Auckland Charity Golf Tournament at Remuera Golf Club

For further information please contact:
fundraise@malaghan.org.nz or phone 04 4996914

Malaghan Month – October

This year we will celebrate Malaghan Month in October with the generous support from our partners Just Paterson Real Estate Ltd and LEXUS New Zealand. Malaghan Month's aim is to raise national awareness about the Institute's advancing medical research programmes. Keep an eye out for further information on www.malaghan.org.nz.

Recent grants

April – June 2017

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

Arthur N Button Charitable Trust
Edith Rose Isaacs Estate
EM Pharazyn Charitable Trust
Hugh Green Foundation
FH Muter Charitable Trust
Infinity Foundation Limited
Jennifer Smith Family Trust
John Holt Memorial Trust
Thanksgiving Foundation Limited
The Dr Marjorie Barclay Charitable Trust
The Great New Zealand Trek Charitable Trust Inc.
The Southern Trust

YES! I'D LIKE TO ACCELERATE THE PACE OF RESEARCH.

NAME ..... ADDRESS .....

EMAIL .....

I'd like to donate $ ..... to help accelerate the pace of research.

☐ **I would like information about leaving a gift in my will to the Malaghan Institute.**

DONATION METHOD

☐ **Credit Card** – Visa / MasterCard / AMEX / Diners

Card number ☐☐☐☐ ☐☐☐☐ ☐☐☐☐ ☐☐☐☐ Expiry ☐☐/☐☐

Name on card ..... Signature .....

☐ **Cheque** – Payable to the Malaghan Institute of Medical Research

Please return to PO Box 7060, Wellington, 6242

Online – www.malaghan.org.nz/support-our-research/donate

Electronic Transfer – Bank Account 06 0507 0052635 30

Please call to inform us of your donation so we can send your tax receipt. Donations over $5 are eligible for a tax refund of up to 33%.

Or call **0800 MALAGHAN** (0800 625 244) to make a donation over the phone

MALAGHAN INSTITUTE OF MEDICAL RESEARCH

Research is our journey. Cure is our destination.

T: +64 4 499 6914 | PO Box 7060 | Wellington 6242 | New Zealand | www.malaghan.org.nz | info@malaghan.org.nz