SCOPE 50
A MALAGHAN INSTITUTE PUBLICATION

MALAGHAN INSTITUTE OF MEDICAL RESEARCH | NEW ZEALAND | WWW.MALAGHAN.ORG.NZ | APRIL 2013

Gut health

More than two millennia ago, Hippocrates said, "all disease begins in the gut." Only now are we beginning to realise just how right he was.

An understanding of the importance of a healthy gut to overall health and wellbeing is gaining momentum. In recent years there has been an explosion of scientific research showing an association between poor gut health and diseases such as diabetes, heart disease, obesity and inflammatory bowel disease. No longer is the gut considered simply a digestive tube that connects one end of the body to the other. Yet this is still its primary role.

Everything we eat and drink passes through the gut along the gastrointestinal (GI) tract, which is home to 100 trillion bacteria. To put this number in perspective, this equates to 10 times as many bacteria in the human gut than human cells in the entire body! These bugs – gut microbiota as they are known – play crucial roles in regulating nutrient absorption by our intestinal cells, in metabolism and in immunity.

Recent research has shown that the particular makeup of the different species of bacteria living in the gut is influenced by diet and lifestyle. Frequent use of antibiotics, stress and diets low in fibre can deplete the levels of beneficial gut bacteria, leading to poor gut health.

In addition to the gut microbiota, the second closely related variable that contributes to gut health is the gut barrier. The gut barrier functions to keep all the good gut microbiota in, and all the bad bugs, viruses or toxins in our food out. It is the integrity of this barrier that is thought to determine whether we tolerate or react to the foods we eat.

Gut health is now recognised as a new objective in medicine and our scientists believe that the key to a healthy gut is the gut immune system.

A NEW OBJECTIVE IN MEDICINE
Gut Health

WE CELEBRATE A MILESTONE
Scope turns 50

AMI ROUND THE BAYS
Run for Research

From the Director

"You are what you eat." We have all heard the expression, but what does it really mean?

The importance of eating a diet high in fruit and vegetables for good health is nothing new; we have had it drummed into us since childhood. However, only recently have we come to realise just how much our lifestyles and the food we eat can affect the health of our gut, and as a consequence, our overall health and wellbeing.

The link between gut health and diet has received renewed interest in recent years. Studies by Australian Immunologist Professor Charles Mackay have shown that the level of fibre in a diet can have a considerable effect on the composition of the gut microbiota. This in turn can affect immune responses, and predispose an individual to inflammatory diseases such as food allergy, inflammatory bowel disease and obesity.

Understanding more about the gut immune response and how it can influence gut health is an exciting new area of immunology that we believe presents new opportunities for treating inflammatory diseases.

Prof Graham Le Gros

Immune regulation in the gut

Our gut is our most important immunological organ.

The gut mucosa contains more immune cells than all other organs of the immune system combined. It is capable of driving powerful immune responses against invading viruses and bacteria, while protecting the harmless gut microbiota that we need for good digestion.

When the gut barrier becomes permeable, by way of lifestyle or for genetic reasons, the internal contents of the gut can start to leak into the bloodstream. Since these components do not belong outside of the gut, the immune system views them as a threat and attacks them. It is these misdirected immune responses against gut bacteria and food proteins that are thought to contribute to the development of several inflammatory diseases including inflammatory bowel disease and food allergy.

Malaghan Institute gastrointestinal allergy and inflammation specialist

Dr Elizabeth Forbes-Blom.

Dr Elizabeth Forbes-Blom believes that management of the gut immune response is key to a healthy gut. She is using experimental models of gut inflammation to address the emerging hypothesis that immune dysfunction in the gut leads to altered microbiota, inflammatory bowel disease, food allergy and metabolic syndrome.

Taken together these findings will provide therapeutic targets for the prevention and treatment of gut allergy and inflammation.

What is the link with jawed fish?

Scientists now believe the evolution of our highly specialised 'adaptive' arm of the immune system (this is the form of immunity that develops throughout life) is linked intrinsically with the gut.

Approximately 450 million years ago primitive jawed fish evolved by forming gill supports into the hinged jaw. This enabled the fish to capture and eat larger prey. The 'jaw hypothesis' suggests that the adaptive immune system evolved in the gut regions of these primitive fish to help fight infections resulting from injuries caused by their newfound ability to chew bones and scales.

Described as the biological equivalent of the 'Big Bang', the evolution of adaptive immunity appears to have been made possible by the invasion of a putative immunoglobulin-like gene in the fish, by a gene from bacteria. This conferred on the ancestral gene the ability to rearrange itself and generate different immunoglobulin-like molecules – thus increasing the 'weaponry' available to the fish to fight infection.

Identifying the critical gut immune cells

The gut immune system faces unique challenges, not least of which is the sheer size of the organ it has to protect.

The surface area of the adult digestive tract is estimated to be equivalent to that of a tennis court. With such a large area to cover, the gut immune system must work extra hard to prevent pathogens from entering into circulation. It also has to continuously confront an enormous microbial load.

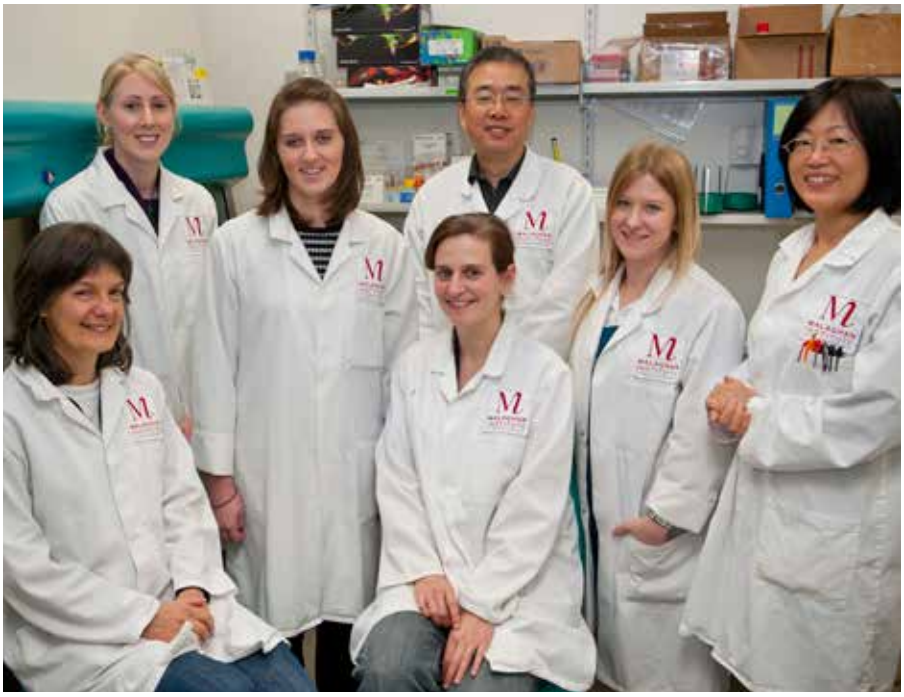
It is no wonder therefore that the gut immune system sometimes gets it wrong, and sets off unwanted immune responses against harmless compounds (allergens), resulting in allergic diseases such as food allergy.

Allergens or bacteria that penetrate the gut barrier are engulfed by a specialised class of immune cells called dendritic cells. Dendritic cells, of which there are several different types, are rare immune cells that are central to the initiation of all immune responses.

Through careful investigation of the gut immune system, Research Fellow Dr Lisa Connor and Masters Student Kerry Hilligan identified a novel population of gut dendritic cells that have the capacity to drive the allergic Th2 immune response.

Understanding more about this particular class of gut dendritic cells will provide important insights into the signals that direct immune responses towards an allergic phenotype.

This knowledge could aid in the development of therapies for allergic diseases such as food allergy.



Immune Cell Biology Group Leader Prof Franca Ronchese, Naomi Baker, Kerry Hilligan, Evelyn Hyde, Dr Jianping Yang, Dr Lisa Connor, Dr Shujie He.

Catherine Plunkett.

A key regulator – IL-25

Does the cytokine IL-25 hold the key to preventing gut dysfunction?

Scientists at the Malaghan Institute have identified the cell signaling protein interleukin-25 (IL-25) as an important regulator of gut immunity. It has profound effects on gut associated disease models, however the immunological mechanisms by which IL-25 regulates gut health remains unclear.

PhD student Catherine Plunkett has been using a combination of experimental mouse models of gut dysfunction and human clinical samples to further investigate the role of IL-25 in the regulation of gut inflammation. Contrary to expectations, Catherine's experiments revealed that IL-25 expression actually inhibits intestinal inflammation. Mice deficient in IL-25 have an earlier onset and exhibit greater severity of experimental colitis compared to normal controls. This finding is supported by clinical studies that demonstrate the production of IL-25 is defective in IBD patients.

Intriguingly, IL-25 deficient mice have a greater propensity to be obese, a phenomenon that is currently being investigated. These approaches offer the potential to significantly advance our understanding of the pathogenesis of multiple chronic inflammatory diseases.

Going down to the lab to eat worms

Parasitic worms have a reputation for causing disease. So the idea of being deliberately infected with them to improve your health might seem, literally, hard to swallow.

Mali Camberis.

A few decades ago the same could probably be said of bacteria. Yet probiotic capsules containing billions of live bacteria are now taken routinely to stimulate digestion and boost immunity, particularly after prolonged antibiotic use. So why not worms?

The idea of taking a dose of worms to improve health is actually not as farfetched as it might sound. In the past decade there have been several clinical trials overseas investigating the potential of using live helminth worms (specifically pig worm and whipworm eggs – not the kind you find in your garden) to calm the gut inflammation associated with ulcerative colitis, IBD and Crohn's disease. In recent years there has also been considerable interest in helminth therapy for autoimmune disorders such as multiple sclerosis. Although the treatment isn't for everyone, patients involved in the studies reported an easing of their symptoms, with minimal adverse effects.

The reason helminth therapy is thought to have such promise is simply because parasitic worms are so successful at controlling the gut environment they live in. They release factors that dampen down the immune system and have been shown to restore the balance of good gut microbiota.

Malaghan researchers Mali Camberis and Dr Tiffany Bouchery-Smith (pictured on front cover) are in no doubt that helminth worms have the ability to influence the development of immune responses. Working alongside Professor Graham Le Gros, they have been studying the rodent nematode *Nippostrongylus brasiliensis*, to gain a better insight into how these worms are able to modulate host gut immune responses. The knowledge from which will feed into the development of therapies for diseases where the immune response is overactive, such as IBD, colitis, asthma and allergy. It also has implications for diseases requiring a boost in immunity such as cancers of the gut.

Our 50th Scope!

For over 20 years now we have shared stories from the Malaghan Institute through our Scope newsletters. With this issue we hit the mid-century mark. While the faces might look different and the technology more advanced, the original goal as stipulated in one of the first issues of Scope has not changed:

"To seek to discover, by scientific research, the nature, origins and causes of disease. To make the best use of knowledge thus gained by improving the prevention and treatment of disease, and by disseminating and teaching that knowledge."

We hope you enjoy reading our Scope newsletters as much as we enjoy bringing them to you. Next stop, Scope 100, imagine where we will be then.


Scope

Scope 1991.

Running for Fun, Running for Good...Running for Research!

Sunday 17 February marked our second year as the Official Charity Partner of the iconic Wellington event AMI Round the Bays, and our third and most successful Run for Research to date.

Run for Research team photo – 7km group.

Despite some drizzle for those who started early for the half marathon, spirits were high at the sell-out event and the atmosphere was one of excitement, anticipation and community spirit. The Malaghan Institute Run for Research brought together people of all ages, from all walks of life and fitness levels, however a uniting feature was their motivation to get behind a great cause and support our research. Thanks to everyone who got behind the Run for Research, over an incredible $40,000 was raised!

More than 250 people took part as Run for Research fundraisers with another 166 people supporting via our Limited Run for Research Entries which enabled those who missed out on registering before the event sold out to take part and support the Malaghan Institute. One such person was the event's Half Marathon winner, Hamish Carson who finished the race in 1:08:51! Having been a short-mid distance competitive runner until AMI Round the Bays 2013, Hamish's debut half marathon ended up being one incredible achievement. Another inspiring person who took part in the Run for Research was Island Bay mother of five, Sarah Christie, who eight weeks after a scary run in with a 1.2 kilogram malignant ovarian tumour, used this as a chance to get back into running and support research into diseases including cancer.

The Run for Research received some great promotion through a fantastic looking Run for Research branded Lexus RX SUV that was out on the streets of Wellington, thanks to Lexus of Wellington and Z Energy. It also received great backing by Malaghan Ambassadors, world-renowned runner Melissa Moon, Newstalk ZB radio DJ Jason Pine and sports reporter and athlete Meghan Mutrie. It is thanks to our ongoing partnership with AMI Insurance and Sport Wellington that we have this valuable opportunity to connect with the community and to raise awareness of the Malaghan Institute, while providing a way for people to make a difference by fundraising in support of our research. We are humbled by the enthusiasm and dedication of the individuals and teams who took part in the Run for Research and the support of those in the community who donated. Thank you to everyone involved in making the 2013 Run for Research such a great success!

Left photo: Half Marathon winner Hamish Carson (R), Right photo: Sarah Christie (L).

Thank you to the following organisations for their amazing support of the 2013 Run for Research:

principal supporter

ami insurance

sport Wellington

CLEMENGER BBDO

LEXUS OF WELLINGTON

ENERGY

News under the microscope

A painting a day for cancer research

Nelson Lakes based cancer survivor Jan Thomson wanted to do something to support cancer research. Being a full-time artist, Jan decided to paint a watercolour a day for a month with the proceeds going to the Malaghan Institute. "Cancer is something that affects all of us, and research into preventing it could save the life of someone close to you," says Jan. "It has already saved mine!" Jan painted a magnificent selection of watercolours and over $2,800 was raised. Thank you Jan for such a wonderful gesture. (Jan pictured with some of her paintings).

Central Districts Field Days

March 7 – 9 saw the Malaghan Institute take part in the 2013 Central District Field Days held at the Manfeild Car Racecourse, Feilding. Several supporters, budding scientists and new friends popped in to say hello. 30,000 plus visitors enjoyed the huge variety of exhibits and we were proud to be involved. Masterton visitor, Mike Coffey, was the lucky recipient of the James Cook Grand Chancellor Wellington and Hurricanes Super 15 gift package. (Kylie Price pictured with a visitor to the Malaghan Institute exhibit).

How cannibalistic immune cells could help treat gout

With the onset of cooler weather, one of arthritis' most painful forms is more likely to rear its ugly head. Latest research from the Malaghan Institute reveals how a form of cellular 'cannibalism' could ease the symptoms of gouty arthritis. PhD student Stefanie Steiger and Head of the Malaghan Institute's Arthritis & Inflammation research programme, Dr Jacquie Harper (pictured) have revealed that white blood cells called neutrophils could be part of a cure – once they start 'eating' each other that is. Read more about this work in our next issue of Scope or visit www.malaghan.org.nz.

Recent Grants (Nov 2012 - Mar 2013)

Our sincere thanks to the following Trusts and Foundations for their recent support:

- Infinity Foundation
- Margaret Neave Charitable Trust
- Cuesports

BeSmart Sahara Charity Challenge Auction

The BeSmart Sahara Charity Challenge has really cranked up. Wellington personal trainers Greig Rightford and Willie Tokona completed 5 marathons in 5 days in preparation for their April assault on the 254 km Marathon des Sables. Whilst challenging themselves with the "ultimate test" Greig and Wille are raising awareness and funds for the Malaghan Institute. Supporters also gathered at the Queens Wharf Ballroom, Foxglove at the Wellington Waterfront for a Sports Auction. Legendary sports broadcaster John McBeth MC'd what was a fun evening that raised $26,000. Bring on the Sahara!! You can follow every kilometre on www.malaghan.org.nz.

Six ways to support our research:

As New Zealand's leading independent medical research institute, the Malaghan Institute is reliant on grants and public support for its valuable work. We are registered with the Charities Commission and all donations over NZ$5 are tax deductible. There are several ways for you to get more involved.

To find out more, contact Victoria Hale on 04 499 6914 x 821 or email vhale@malaghan.org.nz alternatively, visit our website www.malaghan.org.nz

1. MAKE A DONATION
2. SET UP AN AUTOMATIC PAYMENT
3. LEAVE A BEQUEST IN YOUR WILL
4. BE A SPONSOR (corporate or individual)
5. JOIN A VOLUNTEER FRIENDS GROUP
6. LIKE US ON FACEBOOK
   Visit www.facebook.com/MalaghanInstitute

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