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Cooling down an inflamed immune system

When a good thing goes bad.

Inflammation is the body's way of healing and protecting itself. The characteristic signs of inflammation - redness, heat, swelling and pain – are all attempts by the body to remove the cause of the injury and begin the healing process.

In most circumstances inflammation is beneficial. For example, if you fall over and skin your knee, the injured tissue cells release chemicals that stimulate blood flow and initiate the inflammatory immune response. Neutrophils are the first inflammatory immune cells to arrive at the injured site and function by neutralising any harmful bacteria. A second type of immune cell called macrophages, then aid the healing process by engulfing bacteria and dead cells so that the area is clear for new cells to grow. This form of short-term inflammation (acute) is switched off once the threat has been removed and the healing process is well underway.

Chronic inflammation arises when the inflammatory immune response is not extinguished completely. Like a slow-burning fire, the inflammation becomes self-perpetuating – calling in more inflammatory immune cells when they are not needed. The end result is an excess of activated immune cells that cause damage to healthy tissues.

In Scope 50 we highlighted how uncontrolled inflammatory reactions in the gut can lead to inflammatory bowel disease and other gut health issues. In this issue of Scope we take a look at other diseases with excessive inflammation such as gout, metabolic syndrome and multiple sclerosis, and highlight the strategies our scientists are using to cool down these unwanted immune responses.

OUR RESEARCH
A focus on inflammation

OUR RESEARCH
Gout, obesity, multiple sclerosis

OUR PEOPLE
Volunteering for the Malaghan Institute

From the Director

If you have ever been stung by a bee, burnt your finger or had an ingrown toenail – you know what acute inflammation looks and feels like.

Chronic inflammation is a different story. Falling just below the radar of pain and visible swelling, chronic inflammation can go undetected for years. It is the widespread tissue damage caused by uncontrolled inflammatory immune responses that leads to diseases such as multiple sclerosis, diabetes and arthritis.

For nearly two decades now, scientists at the Malaghan Institute have been focused on understanding our immune system, and how it can be harnessed for the treatment of disease.

With multiple sclerosis and gout, our goal is to develop improved, non-steroidal therapies that turn off unwanted inflammatory immune responses, as described in this newsletter. With other diseases such as cancer however, we are using vaccines to turn the immune system on, which you can read about in the next issue of Scope.

Our immune system is one of nature's most exquisite inventions. All we are doing is finding ways to fine-tune it for optimal health and prevention of illness.

Prof Graham Le Gros

Five plus a day keeps inflammation at bay

The foods we eat play an important role in shaping our overall health. Growing evidence suggests they could also help alleviate disease.

Inflammation is a key feature of many diseases, including asthma. Often described as inflammation of the airways, asthma affects over 20% of New Zealanders. The ability to control lung inflammation through diet, thus reducing the reliance on the corticosteroid inhalers currently used to treat asthma, would be a significant step forward for sufferers.

Working together with Plant & Food Research, Dr Jacquie Harper and colleagues are profiling the anti-inflammatory properties of New Zealand fruit crops to identify candidate fruits that could be utilised to alleviate lung inflammation in individuals with asthma.

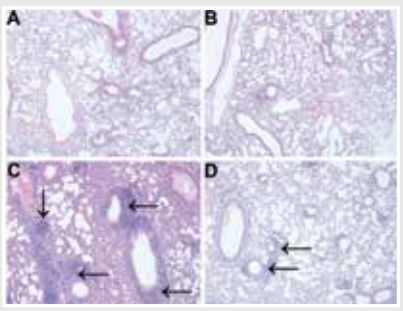
Using mouse models of allergic airway inflammation, Dr Harper and Senior Research Officer Dr Odette Shaw (pictured), have evaluated a range of fruit extracts for their ability to modulate inflammation. In doing so, they have identified a fruit species that is capable of suppressing inflammatory cell infiltration and chronic lung damage.

The effects of these fruit extracts are profound, as can be seen in these images of treated and untreated asthmatic mouse lungs. Uncontrolled airway inflammation can lead to permanent structural changes in the lung, such as increased mucous production and thickening of the walls lining the airways (indicated by arrows in below image).

Dr Odette Shaw.

Dr Shaw was able to show that the fruit species helped repair the inflammation-induced lung remodeling of asthmatic mice, effectively restoring lung function.

These basic research results have shown such great promise that the fruit extracts are now being trialled in asthma patients, in collaboration with Prof Richard Beasley from the Medical Research Institute of New Zealand.



A: Healthy lung. B: Healthy lung treated with fruit extract. C: Asthmatic inflamed lung, with arrows indicating extensive cell infiltration. D: Asthmatic lung treated with fruit extract. Note how this image looks very similar to those of the healthy lungs.

Uric acid – a new look at an old marker of inflammation

Changes in serum uric acid levels are a common feature of many human inflammatory diseases.

Recently there has been a significant escalation in inflammation-related conditions associated with the rise in obesity in developed countries. These conditions include type II diabetes, cardiovascular disease and gouty arthritis – commonly grouped under the term 'metabolic syndrome'.

A common feature of metabolic syndrome is high levels of uric acid in the blood (hyperuricaemia), however, whether hyperuricaemia is the cause or effect of these inflammatory conditions remains to be determined.

Dr Jacquie Harper's Arthritis & Inflammation team (pictured) is looking at how both the crystalline and soluble forms of uric acid influence inflammation and immune cell function in both clinical and basic research settings. Collectively these studies are providing important insights into new potential therapeutic options for the improved management of inflammatory diseases.

Rene McLaughlin, Stefanie Steiger, Dr Odette Shaw, Dr Jacquie Harper, Lisa Shaw.

Gouty arthritis – a clinical perspective

Gout is an intensely painful form of arthritis affecting many New Zealanders. A gout attack is triggered when uric acid crystallises in the joints, causing rapid and painful joint inflammation. Previous research from Dr Harper's team, collaborating with Wellington Rheumatologists Prof Andrew Harrison and Dr Rebecca Grainger, showed that high serum uric acid levels may moderate the inflammatory response to the crystals. To determine how this happens, PhD student Rene McLaughlin is working on a clinical study involving gout patients, collaborating with Christchurch Rheumatologist Assoc Prof Lisa Stamp and Professor Tony Kettle.

Neutrophil cannibalism and gout

Neutrophils are one of the first inflammatory cells to respond to the uric acid crystals that trigger inflammation in gout. Previously thought to be primarily responsible for driving gout attacks, PhD student Stefanie Steiger has now shown that neutrophils could also be part of a cure – once they start 'eating' each other that is! On contact with gout crystals, neutrophils release reactive oxygen species, and then die off. The dead neutrophils are then cleared by other neutrophils. This triggers the cells to produce a protein called TGF-β1, which shuts down inflammation. Dr Harper's team is now exploring different ways to target neutrophil 'cannibalism' in the joints, so they can switch off inflammation at the very early stages of a gout attack.

Obesity

While high serum uric acid levels are a primary risk factor for developing gout, they are also observed in diseases of the metabolic syndrome such as obesity. Research to date has focused on the inflammatory environment in adipose (fat) tissue and there is little information available on how diet-driven obesity affects other immune cell populations. To address this question, Dr Odette Shaw, in collaboration with Auckland Rheumatologist Assoc Prof Nicola Dalbeth, has been investigating how hyperuricaemia alters the inflammatory immune responses of obese and non-obese mice. Her research confirms that obesity does indeed raise the background level of inflammation in non-adipose tissues, but that it does not appear to exacerbate gouty arthritis.

Multiple sclerosis – the silent saboteur

Multiple sclerosis affects 1 in 1,400 New Zealanders.

Multiple sclerosis (MS) is characterised by immune-mediated nerve degeneration, leading to impaired vision, coordination and paralysis. There is no cure. While disease-modifying drugs are available, they are often effective in only a subset of MS patients.

Malaghan Institute Research Associate Dr Anne La Flamme leads a research programme investigating the basic immune cell biology of MS, to understand how to optimise currently available therapies and to develop novel agents that are more effective at treating patients who do not respond to current MS therapies.

One commonly prescribed agent is glatiramer acetate (GA, also known as Copaxone), which is used to treat relapsing-remitting MS. Recent work by Malaghan researchers and other MS research groups using mouse models of MS, has shown that GA alters the activation state of monocytes – a type of white blood cell.

In collaboration with Dr Scott Harding and Dr David Abernathy from Wellington Hospital, PhD student Dr Delgersetseg Chuluundorj undertook a detailed analysis of the physiological effects of GA on the activation of monocytes from patients with MS, and from healthy volunteers. This information will help form the basis of a model that could be used to predict if a patient will respond to GA treatment.

Intravenous gammaglobulin is another immune-modifying therapy used to treat MS, albeit with limited success. Interestingly, Dr Chulunndorj's studies showed that while the effects of intravenous gammaglobulin on monocyte activation were similar, but also distinct, to those induced by GA, the two compounds worked well together. This has positive implications for patients who do not respond to either agent alone.

Sarrabeth Stone.

Complementing this work is that of PhD student Sarrabeth Stone (pictured), who has been investigating how the above agents affect the activation of microglia – a type of immune cell related to monocytes that is found specifically in the brain. It is these cells that are thought to mediate the nerve damage associated with the progressive form of MS, for which there is currently no treatment.

We would like to acknowledge all of the MS patients who graciously donated their blood for this research. This work would not have been possible without their support.

Trekking for MS

It's not often a holiday combines walking, horse riding or mountain biking through some of New Zealand's most beautiful countryside with raising funds for important medical research, but that's exactly what the week long Great New Zealand Trek offers to walkers, mountain bikers and horse riders. The Trek began in 2006 at Cape Reinga and is working its way down the country each year, with the goal of finishing in Bluff in 2020.

Since 2010, funds from The Great New Zealand Trek Charitable Trust have supported our MS research. This year's Trek, held in March, from Alfredton to Lake Ferry in the Wairarapa, raised an incredible $35,000, bringing the total support from the Trek to over $140,000!

"Funds from The Great New Zealand Trek have been vital in allowing us to investigate and test new ideas, while also supporting the development of emerging MS researchers," says Dr La Flamme. "We are incredibly grateful for their support."

For more information on The Great New Zealand Trek and to find out how you can get involved in the first South Island stage, in March 2014, please visit their website: www.greatnewzealandtrek.com.

Theunis Wedzinga (Chairman of The Great NZ Trek Charitable Trust), Dr Anne La Flamme, Leanne Laurence (Trustee), Prof Graham Le Gros during a recent visit to the Malaghan Institute.

Volunteering for Malaghan!

Volunteers play a critical role for many charities and the Malaghan Institute is no exception.

From the Malaghan Friends Committees in various cities, to our AMI Round the Bays helpers, our volunteers are valued members of our team and we couldn't do it without them. We spoke with Denise Udy and Katherine Lowe about volunteering for the Malaghan Institute. Here's what they had to say:

Keen to help?

Contact Jenny Sim on (04) 499 6914 ext 811 or jsim@malaghan.org.nz to find out more.

Denise Udy

Denise has held varied roles over the years from hospital laboratory work, to social work and management. She is currently a member of the Wellington Friends Committee and a weekly volunteer in the Malaghan Institute Development Team.

What made you want to volunteer?

I believe that small things can make a difference and that volunteering is about helping in any way that assists to achieve the goals of the organisation. It's great to be retired and have the time to help.

Was there a personal connection?

No - But I want to acknowledge that since I have been helping with the Wellington Friends of the Malaghan Institute and in the Development Team, I have met some wonderful inspiring people, both volunteers and scientists, who are passionate and committed to the goals of the Institute.

Katherine Lowe

With a background in government policy and currently doing an online creative writing course, Katherine brings some unique skills to her role in assisting with communications at the Malaghan Institute.

What made you want to volunteer?

I had read about Malaghan's work in the newspaper a few years back and was interested and impressed. I really like the Institute's focus on harnessing the body's own immune system to fight scary diseases.

I have the time available at the moment as I'm taking a break from paid work and doing some fun study. Serendipitously, about the time I'd decided to do this, we were looking up the Malaghan website (the chosen charity for my partner's family's Christmas present donation!) and I read about volunteering.

Was there a personal connection?

Like pretty much everyone in New Zealand, I have experienced loved family members and friends having scares with cancer and in some cases dying. I also know plenty of people with asthma and allergies, which can make life miserable.

Why do you think others should volunteer?

There are loads of reasons for volunteering, probably as many as volunteers.

I've really appreciated working on tasks that use my writing skills. As a volunteer, there are opportunities to try new things, learn some new skills, and fit tasks to your particular skills. And of course, the thought of contributing, even in the smallest way to raising more attention and publicity that is always so desperately needed in order to attract funding.

News under the microscope

From Oxford to Kelburn; all for the sake of gut health

Dr Hazel Poyntz is a recent arrival at the Malaghan Institute; she was given the opportunity to come to New Zealand in early 2013 to work as a Postdoctoral Research Fellow with Dr Elizabeth Forbes-Blom in the Gut Inflammation Group. Their research aims to understand the earliest events in food allergy, in the quest to develop new strategies for treatment and prevention.
Dr Poyntz grew up in Hampshire, United Kingdom and studied for her undergraduate degree in Cellular and Molecular Medicine at the University of Bristol. She graduated in 2008 and went on to study for her DPhil at the University of Oxford and qualified in 2012.
During her two years here, Dr Poyntz and husband Dave are looking forward to checking out our ski fields and running tracks. Welcome Hazel, there will be no ribbing from the Kiwi contingent at the Institute about the state of English Rugby or Cricket.

Funding for this research project is provided as a Smart Ideas grant from the Ministry of Business, Innovation and Employment.

Malaghan Institute Charity Golf Tournaments

With the golf season well and truly under way so too are arrangements for the Friends of the Malaghan Institute Annual Charity Golf Tournaments. These events are entering their 16th year and well over $1 million dollars has been raised by our very passionate Friends. We again welcome our loyal supporters and invite new ones to join us.

2013 Events are:

- Hawkes Bay – Friday 1st November at Hastings Golf Club.
- Wellington – Friday 15th November at Manor Park Golf Club, supported by Lexus of Wellington.
- Auckland – Friday 6th December at the Grange Golf Club, supported by the David Levene Foundation.

Inspired to run for a reason

Kirsten Mathews and Rachel Maries (pictured) are two Wellingtonians on a mission. Coming back from a tough year and a past spinal injury, they have set a goal to complete the Adidas Auckland Marathon in November and raise money for cancer research at the Malaghan Institute. "We wanted to run for a cause," says Rachel. "We all know somebody who has fought their battle with cancer, and we have both lost someone close to us." Kirsten says "we would like to support medical research in finding a cure". Having just completed the 13km In the Footsteps of the Marines event and 21km in the Aurora Handicap Marathon they are gearing up for their next 'training' half marathon next month. You can find out more and sponsor them by visiting **www.running4research.com.**

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)
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MALAGHAN INSTITUTE OF MEDICAL RESEARCH

Research is our journey. Cure is our destination.

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