



Teaching our immune system the necessities of life

Why a good 'immune' education is so important.

It is now widely accepted that allergic diseases such as eczema, asthma, food allergy and hayfever, are mediated by the immune system. The role of the immune system is to defend us from external infections ranging from the tiniest viruses to large parasitic worms. Before it can do so however, like a young child, it needs to be taught right from wrong.

From birth, our body is in constant interaction with its environment, which either supports or attacks it. Newborn infants are protected during this vulnerable period by their mother's antibodies through breast milk, but as they grow and develop, so too does their own immune system. The thymus is where the immune system receives its initial training before we are born. It is now hypothesised that the gut is where the immune system continues this education, and learns about normal safe environmental bugs and commensal microbes, and what are dangerous pathogens and toxins.

In allergic individuals however, the immune system seems to get this wrong. One theory is that the development of their immune system is suppressed from a lack of childhood exposure to infectious agents, symbiotic microorganisms and parasites, resulting in the increased incidence of allergy. Whether this is the consequence of the immune system not learning the necessities at the right time of life is unknown. Though it would make sense that by removing the good bugs that help train our immune cells, along with the bad pathogens that cause disease, we are inadvertently interfering with our immune system's natural education.

Here at the Malaghan Institute, our scientists believe that the key to tackling the growing global epidemic of allergic disease is to re-educate the allergic immune response through the use of vaccines. In this issue of Scope, we update you on our progress.

OUR RESEARCH

The allergic
immune response

OUR RESEARCH

Eczema, Food
Allergy and Asthma

AMI ROUND THE BAYS

Run for Research

From the Director



New Zealand has a problem and it's not mollycoddled kids, or over-zealous parents - generation A, the allergy generation has been born.

The evidence lies all around us. Local supermarkets now regularly stock a wide variety of dairy-free or gluten-free foods, something that would have been a rare find a generation ago. Most early childhood centres are peanut-free and dinner invitations routinely request notification of any special dietary requirements. So what has happened - why now in the 21st century, is allergic disease such a global health issue? The sad truth is that we just don't know.

Compared to our grandparents, our lifestyles are different. Our children spend more time indoors and there is a growing obsession with antibacterial products; but whether these alone account for the explosion of allergic disease in recent years remains unknown.

Before we can start developing therapies that more effectively treat asthma and allergy, we first need to understand the allergic disease process. In recent years we have made significant progress into unravelling the very early stages of the allergic immune response, which we believe holds the key to treating allergic disease. In this issue of Scope, we highlight this important work.

Prof Graham Le Gros

Halting the 'allergic march'

Numerous studies have shown that childhood allergic diseases can progress from one form to another throughout a child's life – a phenomenon termed the 'allergic march.'

Eczema is usually the first sign of allergic disease in young infants and is often associated with an underlying food allergy. As children outgrow their food allergies they are likely to go on to develop asthma. Then as their asthma improves, they can be affected by hay fever in their teenage years.

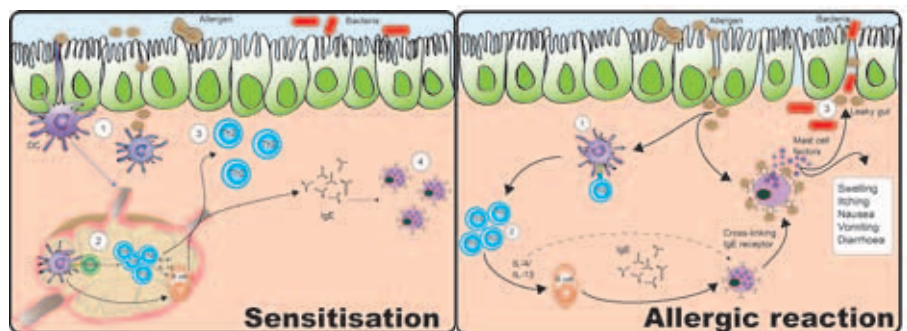
Scientists now believe that prevention of allergic disease early in life is critical, to halt progression along the allergic march. Since allergic disease is immune-mediated, the most obvious target for new therapies is the earliest stages of the allergic Th2 immune response.

The Th2 immune response normally functions to protect us from parasitic worm infections. Why it reacts to house dust mites or food proteins (referred to as allergens) in some children is unclear. What we do know however, is that a child doesn't just suddenly become allergic – their immune system has to have seen the

allergens beforehand and become sensitised to them.

Specialised immune cells called dendritic cells (DC) play a central role in this early sensitisation process (see diagram). They are present in tissues such as the skin, nose, lungs and gut, so are one of the first cell types to encounter potential allergens. The dendritic cells respond to the allergens by activating naïve T cells to Th2 cells, though surprisingly little is known about the mechanisms involved. This triggers a cascade of events - including IgE antibody production and release of histamine from mast cells – that cause the itching, swelling and wheezing we associate with allergy.

By unlocking the secrets of the allergic switch that signals the early development of allergy, our scientists are revealing key targets for therapies aimed at halting its progression.



The key cells and molecules involved in the allergic immune response. The numbers indicate steps within the allergic pathway that our scientists are currently investigating. Image courtesy of Dr Lisa Connor and Dr Elizabeth Forbes-Blom.

Scratching the surface of the Th2 immune response

The skin is a unique organ in that it interfaces directly with both the immune system and the external environment.

On a daily basis our skin is exposed to bacteria, fungi and viruses, as well as a multitude of potential allergens – basically anything we touch has the potential to evoke an immune response. Fortunately for most of us, the protective barrier function of the skin stops this from happening.

Allergic reactions in the skin are normally associated with eczema, also known as atopic dermatitis – a dry and scaly rash that can be unbearably itchy. House dust mites, moulds and animal dander can all trigger eczema in sensitised children. Eczema symptoms can also indicate the presence of an underlying food allergy.

Recently, several candidate immune signaling proteins called cytokines have been proposed as the link between

allergens, the skin epithelium and the development of the allergic immune response. One molecule in particular, called thymic stromal lymphopoietin (TSLP), has been identified as playing a significant role in driving the development of allergic disease in humans.

Allergic & Parasitic Diseases PhD student Sotaro Ochiai is using novel disease models and flow cytometry techniques to investigate how TSLP instructs dendritic cells to activate naïve T cells and initiate the Th2 immune response.

This knowledge will help us determine if TSLP is a potential target for therapies aimed at treating and preventing eczema, and other allergic diseases.

Getting to the guts of food allergy

Through the development of novel experimental models our scientists have been able to reveal for the first time, the earliest cellular and molecular events involved in allergic sensitisation in the gut.

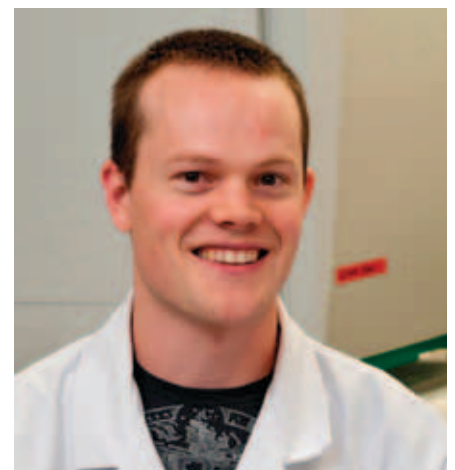
In Scope 46 we reported how Dr Elizabeth Forbes-Blom and Prof Graham Le Gros had used these models to make the startling discovery that under some circumstances, exposure of the skin to peanuts can lead to the development of peanut specific allergic immune responses. Their work also highlighted the importance of concomitant Staph infections in amplifying this process in individuals with eczema.

In related research, Prof Le Gros' PhD student Marcus Robinson has been working with Dr Ali Hodgkinson from AgResearch to understand why milk is an allergen. Cow's milk is one of the most common causes of food

allergy in infants, affecting one in 50 children. The ultimate goal of Marcus' work is to define the factors that contribute to milk allergy and apply this knowledge to the development of an allergy friendly infant formula.

When Marcus first started this project, very little was known about the complex interactions between the gut and the host immune system. By dissecting apart the various cytokines and cell types involved, Marcus has built up an extensive picture of the many factors that contribute to the allergic disease process in the gut. He has also made significant progress into understanding how the immune system in the gut responds to milk and what

components of milk contribute to the development of allergy. This work is currently being prepared for publication.



Food allergy PhD student Marcus Robinson.

‘Punching’ holes and fruit punch - our next asthma therapies?

As often happens in science, a stumbling block in one area of research can present a solution for another.

While working on the development of a dendritic cell cancer vaccine, Prof Franca Ronchese's research team discovered that specialised cells called cytotoxic T lymphocytes (CTL) were killing off the dendritic cells before they could do their job. Although this presented somewhat of a problem to the long-term effectiveness of the cancer vaccine, it raised the possibility that CTL killing of dendritic cells could be used to turn off unwanted immune responses – such as those that cause asthma.

Asthma remains one of the most prevalent allergic diseases in the world. It is a chronic inflammatory disease of the airways, characterised by wheezing, coughing, chest tightness and shortness of breath.

It is the influx of immune cells into the airways that causes the symptoms of asthma. If we can stop this from happening, then in theory, we can prevent the development of an asthma attack. Previous research had shown that activated CTLs can prevent airway inflammation, but we didn't know how.

Prof Ronchese's research has now revealed that activated CTLs can kill allergen-presenting dendritic cells in the airways by effectively 'punching' holes in them, through release of a pore-forming protein called perforin. With fewer dendritic cells around to activate the disease-mediating Th2 cells in the airways, there is



Asthma PhD student Naomi Baker.

consequently less allergic airway inflammation. Identifying how best to target the activity of these cells with immunotherapy is the subject of ongoing investigation.

We all know fruit is good for us; it is loaded with fibre and vitamins and tastes great too. But did you know that some fruits might actually help reduce the lung inflammation associated with asthma? In collaboration with Plant & Food Research, Dr Jacquie Harper and her Arthritis and Inflammation team have shown that certain fruits can reduce the influx of damage-causing inflammatory cells into the lung in experimental models of asthma. This is an exciting area of research that could lead to the development of fruit-based foods for improving the management of inflammatory conditions such as asthma.

Why New Zealand needs this research

New Zealand's asthma and allergy rates are amongst the highest in the world, affecting up to 20% of our population.

"We thought we could stop the onslaught of allergic disease by removing the cause – if there was a family history of food allergy, parents were encouraged to delay the introduction of high risk foods," says Prof Graham Le Gros. "However, since implementing these avoidance strategies, asthma and allergy rates have actually gone up."

"What we need is a more rational approach, which can only be achieved through evidence-based knowledge about the allergic disease process."

The collective goal of the Malaghan Institute's asthma and allergy research is to develop an immunotherapy or vaccine that specifically shuts down the allergic Th2 immune response before it has the chance to cause any damage. The steroid inhalers currently used to treat allergic disease work in the same way, only they suppress all immune responses – both good and bad. This can leave users more susceptible to common infections.

Immunotherapy is a far better approach for treating allergic disease, because it targets the underlying cause of the allergic disorder, not just the symptoms.



Dr Elizabeth Forbes-Blom.

Join us in the Run for Research!

With summer fast approaching, so too is another exciting event – the 2013 AMI Round the Bays on Sunday 17 February! Once again we're the Official Charity Partner of this iconic event.



Our Run for Research fundraiser provides a fantastic opportunity to take part in AMI Round the Bays and show your support of our scientists.

Earlier this year individuals and teams helped raise an incredible \$35,000 in the Run for Research – and with your help we are confident this record can be broken!

You don't have to be the super fit, athletic kind to take part – the main event is an enjoyable and achievable 7km fun run/walk around the beautiful bays of Wellington.

How can you help? Join the Run for Research fundraiser and represent us at the start line! Participate with your family, friends, school, colleagues or any group you wish. If you are unable to take part but you still want to show your support – let us know. You will be able to make a donation in support of someone taking part, and there will be volunteer opportunities during the lead up to the event.

Why is it important to us? We love Wellington and this is a great way to get involved with our local community. It's also an active way to raise awareness of the Malaghan Institute, the important research we do and help raise funds to keep it going.

For more information:

- please visit www.malaghan.org.nz/runforresearch
- contact Victoria Hale on 04 4996914 ext. 821
- email runforresearch@malaghan.org.nz



Melissa Moon wants you to join her

World renowned Wellington runner and Malaghan Run for Research Ambassador, Melissa Moon, is a firm believer in supporting charities that help our communities in a positive way, and she wants you to join her in supporting the 2013 Run for Research.

"Every one of the 12,000 participants will know of someone who is affected by one of the conditions the Institute researches from cancer to arthritic conditions. For me personally I suffer from allergies, both food and pollen based, which can be very debilitating as an athlete and in general daily life," says Melissa.

"The Run for Research combines a passion of mine – running and exercise – with an important cause in our society. With over 12,000 people expected to participate in this wonderful Wellington event it is a fantastic opportunity to create valuable awareness of what the Malaghan Institute is all

about – improving the health of people in our community."

"Education and research not only provides me with hope and answers, but does the same for our wider community."

"Please join me in supporting the Run for Research – together we can make a real difference."



Melissa Moon (Photo courtesy of the Dominion Post).

News under the microscope

Malaghan Month at Just Paterson

October was Malaghan Month at Just Paterson Real Estate. They celebrated three years of partnership with the Malaghan Institute and since 2009 - when they lost their much loved company co-founder, wife and mother Sally Paterson to brain cancer - they've been raising funds to help the Malaghan Institute find a vaccine for the disease.

In the three years to date, they have raised over \$190,000 and for Malaghan Month they upped the ante. During October, they donated \$1,000 to the Malaghan Institute for every house sold and also celebrated the partnership with some fun activities, which saw the company holding many special events to raise funds for, and awareness of, the cancer vaccine work of the Malaghan Institute.

This is going to be an annual undertaking, so be sure to 'like' the Just Paterson Facebook page (www.facebook.com/JustPaterson) and you can keep up-to-date with all the fun for next year!

Recent Grants (June - Oct 2012)

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

- James Russell Lewis Charitable Trust
- Cuesports Foundation Ltd
- Southern Trust

Franca NEXT woman of the Year Finalist



We would like to congratulate our very own Prof Franca Ronchese on being named as a finalist for the 2012 NEXT Woman of the Year awards. Although she didn't win, this recognition of Franca's tireless dedication to the development of a more effective immune-based therapy for cancer is an inspiration to us all.

Rotary Club of Port Nicholson donate \$17,000

Earlier this year the Rotary Club of Port Nicholson held their Annual Quiz and Charity Auction event to raise funds for several deserving charities. The Malaghan Institute would like to thank the Club for their amazing support and donation of \$17,000 to be put towards our research. Overall the event raised a fantastic \$34,500 with the remainder of the money to be donated to Outward Bound, YouthQuest and the Rotary Foundation.

Every little bit counts



Recently we had a visit from two very special young ladies who generously donated their pocket money to the Just Paterson Malaghan account. Their mum Anna said it was the girls, Ruba (8yrs) and Rose (6yrs), idea to give their pocket money with a vision to "help buy some new lab equipment to help the scientists." They also thought "it would be pretty cool, in about twenty years, to tell their grandchildren that they had helped find a cure for cancer." Thank you Ruba and Rose for such a wonderful gesture.

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Congratulations and thank you to Vicki Watson of Auckland (pictured left) who recently completed the nine day, 551km, Cycle Queensland

event and fundraised over \$1,200 for the Malaghan Institute. Well done Vicki!

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
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