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# discovery

## SCIENCE AND SURGERY COMBINE TO TREAT VOLCANO VICTIMS

The eruption of the White Island volcano in New Zealand on 9 December resulted in huge challenges for rescuers and medical teams – among them the surgeons, anaesthetists and nurses in the specialist burns unit at Concord Hospital.

Five Australian tourists were brought home in medically equipped military aircraft to be admitted to Concord. One man succumbed to severe injuries, but remarkably, within a fortnight the other four patients were showing positive signs of recovering well.

Professor Peter Maitz, Medical Director of the burns unit and leader of the ANZAC Research Institute's Burns and Reconstructive Surgery Group, says the survival and rehabilitation of these patients will be in no small part due to the knowledge and confidence gained from 15 years of significant research at the ARI.

"These burns are called pyroclastic burns," said Professor Maitz, explaining that the medical team found itself working in uncharted territory.

"There's very little in the literature and certainly for us, it was the first time we have had burn injuries with that background. These people had isolated wounds, like three large wounds on one leg and then the upper back. Some people were hit by rocks, some had embedded pieces of volcanic eruption in their backs that had to be dug out, quite deep, similar in fact to what we saw after the Bali bombing where we had to remove pieces of shrapnel.

"All of them had very bad inhalation injuries. They inhaled toxic gases which get absorbed into the bloodstream and it has a systemic effect, usually a central nervous effect."

But how to treat the burns, which in the worst case were to 65% of the body?

"We received the patients and within 24 hours we very aggressively removed what we microscopically judged to be damaged tissue – everything!" said Professor Maitz.

"It was a very large operation. We had a surgical team of five, an anaesthetic team of six people, and a nursing team of 12 people, all at the same time, for any one patient. So we created a very large open wound, and instead of saying we will immediately replace the lost skin

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Director of Burns Unit Professor Peter Maitz (right) with Senior Burns & Plastics Surgeon Assoc. Professor Peter Haertsch

## MESSAGE FROM THE CHAIR: A TIME OF CHANGE AND OPPORTUNITY

Professor Andrew McLachlan AM

As 2020 commences it is important reflect on what has been achieved at the ANZAC Research Institute in 2019. The ARI is nothing without its fantastic medical researchers who are the engine room of innovation. I continue to be impressed by the calibre and impact of the research across a range of scientific and therapeutic areas.

As we see in this newsletter, Associate Professor Georgina Clark has linked with Kira Biotech to translate fundamental research from bench to bedside, putting the ARI at the frontline in treating immune disorders. NHMRC research grant funding continues to be intensely competitive, so it was heartening to see that teams led by Prof Marina Kennerson and Prof Hong Zhou have been awarded Ideas Grants, reflecting both the calibre of the research and innovative ideas generated in the ARI. These achievements come from our ability to create

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## MESSAGE FROM THE CHAIR: A TIME OF CHANGE AND OPPORTUNITY

the right environment for researchers to be successful. I extend the sincere thanks of the board to our Director, Professor David Handelsman, who continues to lead with energy and drive, as he has done for the past 20 years.

This year we celebrate 20 years of the ANZAC Research Institute and planning is underway for suitable events to recognise this great achievement and plan for the next 20 years. The board recently finalised the terms of reference for a strategic review with a view to ensuring the ARI remains at the forefront of high quality medical research. The board continues to work on the strategic plan with a focus on the priority issues of fundraising, strengthening partnerships and sustainability including succession plans for the ARI leadership.

My special thanks to Professor Bob Lusby, former chair, for his leadership and stewardship over many years. Bob has made a lasting impact. I thank all board members for their passion and commitment to the ARI, with special thanks to Kerry Hogan-Ross and Paul Levins who step down after years of faithful service. We welcome to the board Professor Mark Rees, Deputy Dean at the University of Sydney, and Gillian Davidson, a partner at Sparke Helmore Lawyers.

Lastly, I would like to thank our key partners, the Sydney Local Health District and the University of Sydney, for their support and effective collaboration.

Professor Andrew McLachlan AM
Chair, ANZAC Health & Medical Research Foundation

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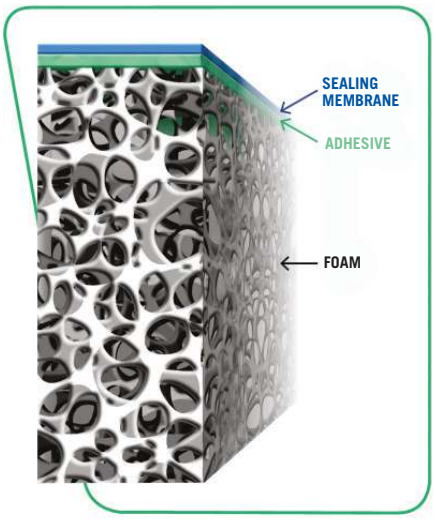
## SCIENCE AND SURGERY COMBINE TO TREAT VOLCANO VICTIMS

with skin grafts, which is the traditional way, we took a material which is available that replaces the function of the skin, not permanently, but for some time.

"We decided to use a bioengineered product, developed in Adelaide, commercially available, but it had never been used on pyroclastic burns anywhere in the world."




That material, NovoSorb BTM (Biodegradable Temporising Matrix), had undergone clinical trials only two years ago at hospitals including Concord. It acts as a prosthesis for the skin. A base level is like a sponge and on top is a transparent sealing membrane. It allows the body to grow within this for about three weeks while a patient recovers, and while the patient's own skin is being grown in a laboratory from biopsies. The material then can be removed and skin grafts applied, one small operation after another, bit by bit.

Professor Maitz says the surgical team felt comfortable exploring this pioneering technique because the ANZAC Institute researchers are an integral part of the treatment team.

"We have clinical teaching meetings and clinical rounds where all patients are discussed, and the research team, the basic scientists as well as the senior scientists, all come to these meetings together with the surgeons, the intensivists, the microbiologists, all in one group. So our research team, the Burns and Reconstructive Surgery group, has been translational from the beginning. Sometimes, literally, what happens in the lab physically gets taken from the lab to the operating room. The scientists are integrated in the clinical world."

Another important factor in the patients' recovery has been to modify their intake of food to account for changes in the way their bodies respond to the burn disease. Again, this is based on the findings of scientists at the ANZAC Research Institute.

Professor Maitz explains that the research was aimed at finding out what energy, in responding to burn injuries, does the body burn, and what should be given in the right proportion of carbohydrates, protein and fat.

"We all know that once people have used up all their energy sources which store fat, they lose a lot of weight and they then start using up their muscles to produce energy. It's called negative metabolism, or catabolism. The long term effect of this is that people have a very long recovery because now they have to rebuild their muscles because they have no strength left.

"This study was very interesting in showing there is a very delicate balance between carbohydrates, protein and fat, and it changes all the time. So in the earlier phase this proportion is different from, say, after three months. The recovery from a severe burn takes roughly two years."

It will be three months before anyone knows with certainty how well the patients will have recovered, but Professor Maitz is optimistic.

"As we stand now we expect that these patients will do well. The treating team has been successful and comfortable because of the research background of the ANZAC Institute and the scientists there who make everyone understand that, yes, we can actually do this – we can use this artificial skin concept, plus this prosthesis for our largest organ and it's safe to do so, even in a mass casualty environment."

Associate Professor Georgina Clark (centre) with members of the Dendritic Cell Research group

# DENDRITIC CELL DISCOVERIES COULD CHANGE TRANSPLANT SURGERY

## INSPIRED AND DEDICATED RESEARCH OVER 20 YEARS

The achievements of the Dendritic Cell Research group at the ANZAC Research Institute have led to a commercial venture which, if successful, has the potential to revolutionise transplant surgery and autoimmune disease, and save thousands of lives world-wide.

Professor Derek Hart

In 1981 Professor Derek Hart, then a Rhodes Scholar at Oxford University, first floated the idea that the problems of immuno-suppression, which can result in a patient's body rejecting transplanted organs or tissue, could be overcome by the injection of antibodies.

Almost four decades later, the late Derek Hart's vision is set to become a reality with the formation of Kira Biotech, an emerging Australian biotechnology company in which DendroCyte Biotech Pty Ltd, a company set up to manage the Dendritic Cell Group's intellectual property, has a significant shareholding. Kira has secured $20 million funding to develop as a commercial product an antibody known as KB312 which has been developed by the team at Concord.

As group leader Associate Professor Georgina Clark explains, this unique set of white cells is a key factor in causing, for example, a bone marrow transplant to fight the body, or the patient to fight a transplanted kidney.

"The fighting is being done by dendritic cells that are becoming activated. Our antibody stops the cells being activated, so it removes them before you can get the rejection happening.

"This antibody, KB312, is a really specific immune-suppressant and we have shown in animal models that it is safe to use."

With the financial backing of Kira Biotech, the antibody can now be taken to the next stage of development, with clinical trials and then to commercial production.

"The actual large scale production of the antibody has to be worked out," says Georgina Clark.

"We generally grow it in small containers. For testing in the clinic, this will need to be in at least a 500-litre container so there's a huge scaling up process that is beyond our capabilities. Kira will contract people in Queensland who are able to do that.

"Once we have the large amount it can go through all the processes to make it safe to put into humans – finding out how stable it is in the fridge, how you administer it, probably

intravenously, how often, how concentrated it needs to be – all those things have to be decided.

"It's a fantastic breakthrough and one of the biggest recent investments in Australian biotech. It will change the face of immune suppression globally."

The $20 million investment for Kira to develop KB312 commercially has been led by One Ventures ($10m) which has its Healthcare Fund III backed by the Australian Government's Biomedical Translation Fund, IP Group ($7.5m) and the Advance Queensland Business Development Fund ($2.5m).

The project will be led by Kira's founding CEO, Dr Dan Baker, a rheumatologist and immunologist with vast experience in the USA of developing commercial drugs for immunology.

"Kira's research program focuses on immune tolerance and targets cells and pathways that are key activators of the immune response in patients with diseases such as rheumatoid arthritis, systemic lupus erythematosus and type 1 diabetes," says Dr Baker.

The development of KB312 could not have happened without the passionate belief in finding this antibody that Derek Hart continued to express, right up until his death from cancer in December 2017. Together with his wife and research partner, Georgina Clark, his dedication brought him to the ANZAC Research Institute after earlier appointments in Brisbane and Sydney.

Professor Clark says the breakthrough could not have happened without the support of the management of the ANZAC Research Institute and the wonderful team who continue to work on dendritic cells.

"This antibody has come through five institutions and everyone here has put in a huge amount. The guys here have improved the chances of it being successful and could be used in other areas.

"It's a gamble – but that's why we're here, to make life better for people."

Professor David Handelsman, the Institute's Director, commented, "This wonderful step forward is the culmination of more than 20 years' work by Georgina and Derek to create what may easily look like an overnight sensation.

"We at the ANZAC Research Institute are immensely proud of Georgina, who has carried this work through to bring their joint discoveries and innovations to an important stage of practical clinical application.

"It is only with such persistent, inspired and dedicated work that real progress is made in medicine from discoveries, for which the immediate purpose is not always known at the time, to applications that brighten, enhance and prolong the lives of patients."

As an indication of just how significant the discovery of KB312 could be world-wide, it's been estimated that 12 per cent of the population will be affected by an autoimmune disease in their lifetime. The economic impact of autoimmune diseases in Australia is $30 billion each year – twice that of cancer. In the US more than 50 million people are affected by autoimmune disease.

# GIVING OPPORTUNITIES

**All gifts over $2.00 are tax deductible**

Please use this form if you wish to make a donation to help the ANZAC Institute in its exciting medical research, or if you would like to receive further information. We would love to hear from you, our supporters.

☐ Yes – I would like to help the ANZAC Health & Medical Research Foundation

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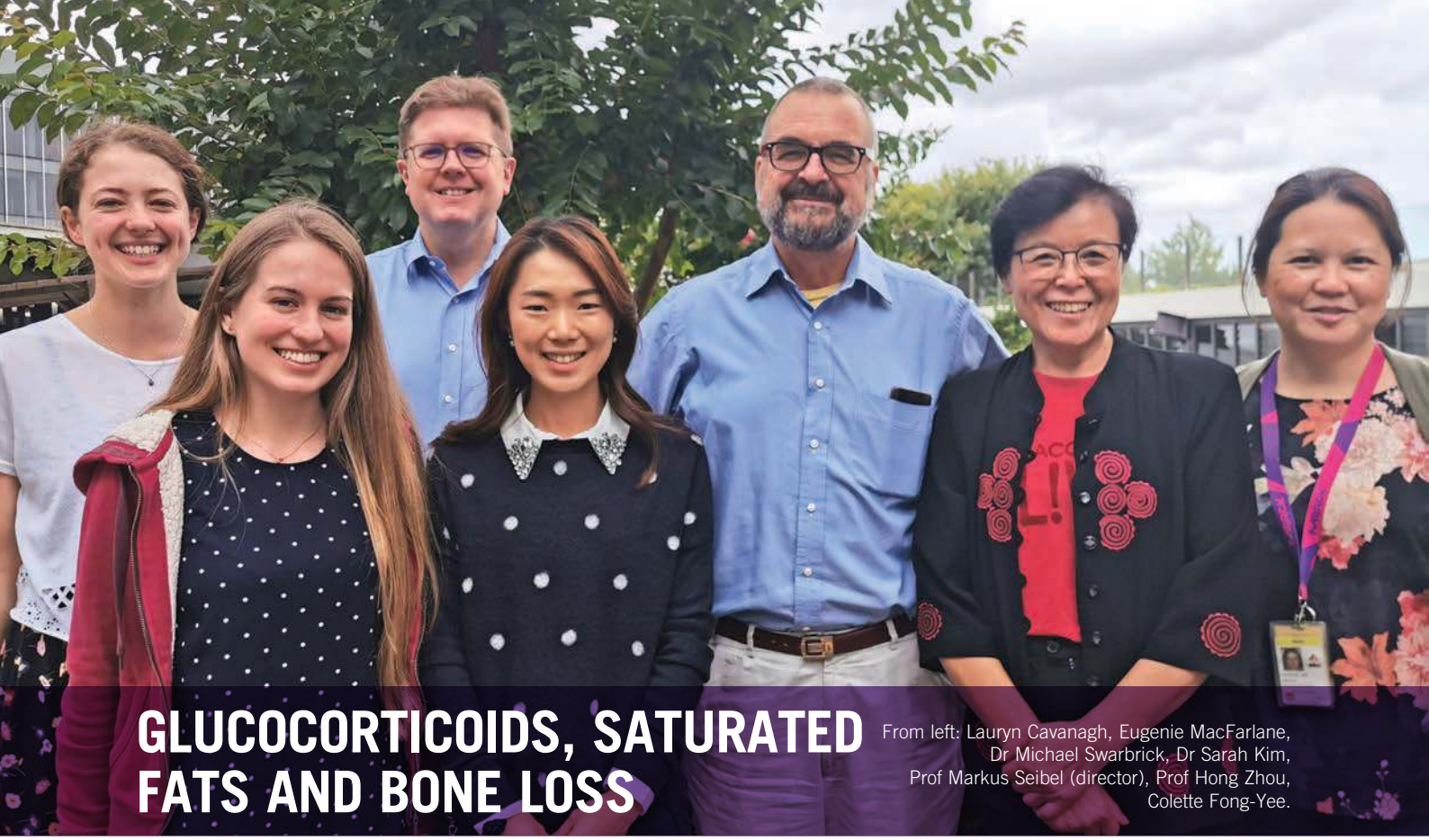

# GLUCOCORTICOIDS, SATURATED FATS AND BONE LOSS

From left: Lauryn Cavanagh, Eugenie MacFarlane, Dr Michael Swarbrick, Dr Sarah Kim, Prof Markus Seibel (director), Prof Hong Zhou, Colette Fong-Yee.

The Bone Biology group, headed by Professor Markus Seibel, has received a three-year Ideas grant from the NHMRC to continue investigations into the role that saturated fats play in causing loss of bone density and contribution of bone to diet-induced obesity.

Studies in mice, led by Professor Hong Zhou, Dr Michael Swarbrick and Dr Sarah Kim, have shown already that a diet high in saturated fats promotes bone loss, in addition to the well-known effects on obesity, insulin resistance (pre-diabetes), and cardiovascular risk factors.

"Traditionally people think that if you have obesity, your bones will be stronger because of the greater load," says Professor Zhou.

"But that's not always the case. Over the last ten years, research has shown that obese people, particularly those who eat a lot of saturated fat and carry lot of their weight around their middle, actually have a higher risk of bone fracture and osteoporosis. Foods high in saturated fat include fatty meats, full-fat dairy and tropical oils like palm and coconut oil. When we feed mice this high-fat diet, we have found it substantially reduces bone quality, and that these changes are due to increased levels of certain steroids, called glucocorticoids, in the bone-forming cells (osteoblasts)."

To study this in more detail, the team then blocked glucocorticoids specifically in the bone-forming cells, using genetically-modified mice. When they fed the genetically-modified mice the high-fat diet, they found that their bone density was not affected at all. To their surprise, the mice did not get fat either, and there were no signs of insulin resistance.

"This was an exciting discovery for us, for two main reasons. First, we showed that high-fat diets cause bone loss by activating glucocorticoids within the bone-forming cells. This gives us a target for future drugs to treat or prevent osteoporosis," says Professor Zhou.

"Secondly, and potentially more importantly, we found that blocking glucocorticoids within the bone–forming cells also stopped the mice from getting obese and pre-diabetic. These mice could eat whatever they wanted, and didn't get fat or diabetic."

"So a small change in the bone-forming cells produced whole-body changes that could prevent obesity. We have some early results showing that when the genetically-modified mice were challenged with the high-fat diet, their bone-forming cells were able to increase their metabolism to deal with the extra energy. This finding raises the possibility that obesity and osteoporosis may have a common underlying cause, and that in the future we may be able to treat both diseases with one drug."

The research team then treated bone chips with various fatty acids, and found that only palmitic acid activated glucocorticoid **activity**. Palmitic acid is the most common saturated fatty acid found in animals, plants and microorganisms. It is found naturally in palm oil and palm kernel oil, as well as in butter, cheese, milk and meat.

Professor Zhou says the next step will be to feed mice a diet enriched just in palmitic acid, to confirm that this particular saturated fat is bad for bones.

"We would also like to prove that the skeleton is a significant energy user in the body. We know that the brain and skeletal muscle use most of the body's energy, up to 75%, with much of the rest stored in tissues like fat. Previously, no-one would have thought that bone burns any of the remaining energy. The studies haven't been done yet, but it would be really interesting to find out whether we can activate cells in bone to burn energy, as we think this would have great effects for preventing obesity and diabetes."

# ANOTHER STEP CLOSER TO UNDERSTANDING DISEASES OF MOTOR NEURONS


Marina Kennerson

"I'm really excited for the whole team because it's been a long journey," says Marina Kennerson, recipient of an NHMRC Ideas grant of $782,000 over the next three years, and recently promoted by the University of Sydney to the academic rank of Professor.

As Principal Scientist in the Northcott Neuroscience group at the ANZAC Research Institute, Professor Kennerson has spent almost 30 years studying hereditary neuropathies and motor neurone disorders, with particular emphasis on Charcot-Marie-Tooth neuropathy.

Although not fatal, CMT causes patients to lose the use of muscles in the feet and hands, leaving them with chronic disability, unable to work and dependent on carers. During the past few years the ANZAC Institute team has led the way in identifying several of the gene mutations which cause the disease.

"But of the cases we work with, 40 per cent are still genetically unsolved," says Professor Kennerson.

"We need to end this diagnostic odyssey for these people. We need to go into the more difficult area of where the DNA doesn't code the genes but where DNA elements that control the genes may be causing disease. It's what we used to call junk DNA. Now we know it's not junk DNA but is very important.

"With this project we've been able to find some families where we've found large structural variations and DNA rearrangements. If you find a gene that doesn't have a mutation you have to start thinking about what pieces of DNA might be switching it on, switching it off, controlling it. It's like looking at the switches and circuits that control a light bulb, not the light bulb itself."

The NHMRC grant will allow Professor Kennerson and her senior researchers, Dr Gonzalo Perez-Siles and Dr Ramesh Narayanan, to investigate ways of identifying dysregulated genes among these structural variations.

"For CMT we have to look at the right tissue that is affected, and that is in the nerves, the neurons," Professor Kennerson explains.

"If you have a muscle disease taking a biopsy of the muscle is possible. If you have nerve or brain diseases, taking a nerve biopsy is very invasive and we avoid doing that sort of thing. So I've set up this pluripotent stem cell program which allows us to reprogram skin cells from the patient and then turn them into motor neurons with their own genetic structure including the key mutation causing their disease. Then if we have the motor neurons we have the correct tissue to look for gene expression that has gone wrong."

As well as studying the motor neurons in cell culture dishes, the team will be able to investigate abnormal gene expression in a tiny worm, known as *C.elegans*, to research the consequences of genetic variations in a living creature.

The NHMRC grant will allow Professor Kennerson and her senior researchers, Dr Gonzalo Perez-Siles and Dr Ramesh Narayanan, to investigate ways of identifying dysregulated genes among these structural variations.

Professor Kennerson says the NHMRC grant recognises the urgent need to define a high quality structural variation map and highlights the importance of this group of genome variants.

"Our project will influence future genetic testing for inherited peripheral neuropathies, not just for CMT but also for other neurological diseases," she says.

"It will also provide a target for the development of drug or gene therapy treatments."