ANZAC Research Institute
discovery
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Scientists and patients join to celebrate advances in CMT research

More than 30 men, women and children were guests for a unique lunch at the ANZAC Research Institute on 13 January. All are related either genetically or through marriage and are members of a wider group known as the Sanderson family which is at the centre of advanced research into Charcot-Marie-Tooth disease.

This family has an inherited neurological disease in which females may be carriers of a mutant gene, while males display incurable symptoms in which hands and feet muscles in particular are weakened. Although not fatal, CMT disease can cripple for life.

Scientists at the ANZAC Research Institute have led the world in discovering the genetic mutation that causes CMT and are now working to identify a drug which will slow or stop the destruction of the motor neurons that are affected in the hands and feet.

"It's exciting for the family because it's transparent - they can come and see what we're doing," said Associate Professor Marina Kennerson of the Northcott Neuroscience Laboratory, as the families gathered for lunch before touring the Institute's laboratories.

"For us, as a scientist you don't necessarily get to see the patients, so it's exciting for me to see the family and know that your work has been helpful to such a lot of people."

Many of the luncheon guests were meeting for the first time. Some had sought medical assistance without knowing until recently they had distant relatives similarly affected.

Professor Garth Nicholson, who has spent three decades investigating CMT, told them DNA and genealogical research suggested all those present for the lunch who carry the affected gene or show symptoms of the particular sub-type known as CMTX3 are descended from a Mr Sanderson who migrated from Scotland to New Zealand more than a hundred years ago. Having identified so many patients in the same wider family group had assisted the research team.

CMT patients and their families j oin staff from the Northcott Neuroscience Laboratory for a very special lunch


Professor Garth Nicholson obtains a skin biopsy from patient Jacob Adams whose feet have been affected by CMT but at this stage is still able to work as a panel beater

"In this family we have shown a DNA rearrangement causes their CMT. This is the only place in the world where this new mechanism can be investigated because nobody else has a family like this big Sanderson family, with this form of DNA rearrangement," said Professor Nicholson, who took advantage of the gathering to obtain tiny skin biopsies from a number of young men who are affected by CMT. Each sample of skin tissue is just 3 millimetres long.

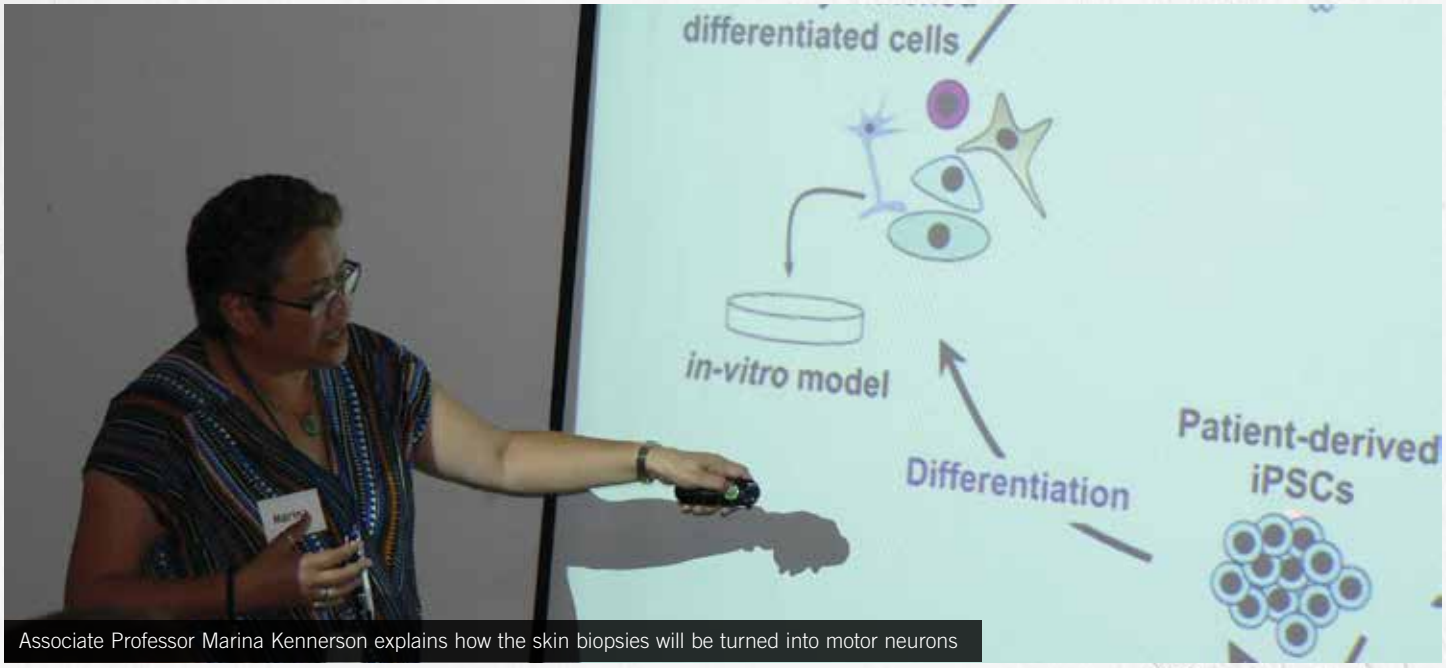
"When we get the skin biopsies we send them to a company which is going to re-program them for us," explained Marina Kennerson.

"Then we have a PhD student, Anthony Cutrupi, now at the University of Miami, who is learning how to grow those re-programmed cells and make them into motor neurons."

Garth Nicholson takes up the story:

"We try to turn them into nerves. Then we have to grow them and look after them. Then we stain them in different ways so we can see the inner workings of the nerve cell and look for something that's not quite right, and then we've got something to screen with drugs. So it's all extremely logical."

Opening a Pandora's box



Associate Professor Marina Kennerson explains how the skin biopsies will be turned into motor neurons

Associate Professor Marina Kennerson has been researching CMT for 25 years, with a focus for the past 13 on the wider family group known as the Sanderson family.

A significant breakthrough came last year when her colleague Dr Megan Brewer and a team from the ANZAC Research Institute published a paper identifying a chromosome insertion as the cause of CMTX3.

Associate Professor Kennerson says the discovery was made possible by advances in scientific techniques including whole genome sequencing.

"We had to look at all of the genome, not just the genes, but all of the genome, because their DNA mutation is what we call a structural variation mutation, and it involves not just a single base pair change but theirs involves hundreds of thousands of base pairs.

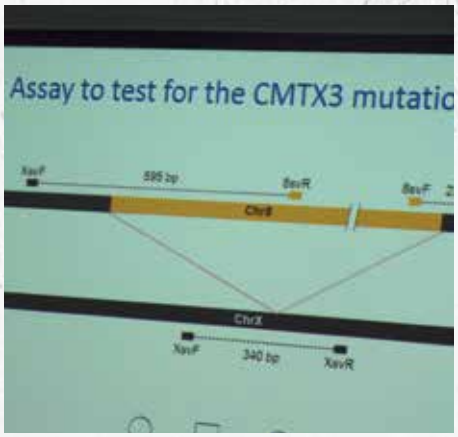

Dr Megan Brewer's research led to the identification of the mutation that causes CMT

"Now that we know what the DNA mutation is we have to actually find how the DNA rearrangement causes the disease which is probably to dysregulate a particular gene, and then we want to work towards therapy for the families.

"You find one thing and then you've opened up a Pandora's box of other things, so we need to know which potential gene has been dysregulated as a result of this DNA mutation occurring. We're very excited because now we can take skin cells from a patient and make motor neurons from them."

Professor Garth Nicholson told the families over lunch that it's unlikely we will be able to re-grow nerves which have died, but the aim is to find a drug which will limit the effects of CMT.

"What we think is happening is that the regulation of some important gene is defective. We need to find the mechanism of what is going wrong and whether we can we fix it," he said.



"If the gene is turned off you can turn it back on. We think we should be able to do that, hopefully with a drug already approved. First we have to find out what it is we're looking at and then work out which drug will work. We may find that drugs which are already available will help to some extent. If we could make these boys with CMT even 50% better that would be really worthwhile.

“We didn’t know what was going on”

Andrew Last, whose two sons are both affected by Charcot-Marie-Tooth disease, expresses the frustration experienced by so many families – the frustration of knowing their boys will never recover and the frustration of running up against community ignorance.

“My older boy was diagnosed when he was 12,” Andrew explains.

“We didn’t know what was going on, there was no understanding of it. Everyone thought at the start that he was just clumsy, and then when we started seeing doctors, it took about a year and a half before we found out what the story really was. At that point it had degenerated to where he couldn’t walk properly and his hands were affected.

“With our younger son we thought he’d dodged a bullet. It didn’t manifest in him until he was 16. He was playing soccer and football in high school and didn’t have a problem. Then he went on school holidays and in six weeks went from doing that to where he couldn’t walk properly. We couldn’t believe it happened, it came on so suddenly.

“You look around the families here and it can be so different. Someone will have very minor disabilities and perhaps not even realise they have it, all the way through to where there’s someone in a wheelchair, and then there’s everything in between. There are so many variations.”

Steven Last was one of the patients who provided a skin biopsy. He and Jacob Adams had never met before but discovered their great grandmothers were sisters.

Andrew also sounds a warning that families affected by CMT must not bury their heads in the sand.

“I go to great lengths to tell everyone in my family about it, but families are an interesting dynamic because half the time they don’t want to know anything about it. You get shunned. You tell them over and over what the boys have and you get met with this blank stare. It doesn’t sink in. And then they’ll come up to you and say “the boys look bored. Why don’t they go out and kick a ball.” Or “why don’t they get guitar lessons” and you say “they can hardly write with a pen.”

The biopsy involves just a tiny amount of skin tissue being taken, to be sent to the USA so nerves can be grown from it.

“We have a daughter too, and more than likely she’ll be a carrier. We’re hoping that down the track they’ll come up with something because we don’t want to see this again. We can’t do anything about it but Professor Nicholson and the others can, maybe finding a way to isolate it and a way to deal with it.”

Andrew Last, his wife and son Steven talk to Prof Garth Nicholson during the lunch

Donations welcomed by researchers

During the lunch in January the ANZAC Research Institute was pleased to announce it had received a donation of $10,000 from Amy Somes and Rob Welborn, earmarked specifically for further CMT research. Their donation was a response to a fundraising site set up by Carlie and Luke Boyle, who have two young boys affected by CMTX3: www.gofundme.com/CMTwontbeatme

The problem of attracting funds for research into CMT was something addressed by Professor Nicholson.

"Because this is not a killer and is not a cancer gene or a MS gene, we can't raise money for this sort of non-fatal stuff. It is basically a life-long problem," he said.

"The rough figure is that 50 percent of patients with all forms of CMT can't work and therefore need a lifetime of support from the government. So the cost, when you multiply it out, can be more than cancer. But because it's not as emotional as people dying, it's harder to raise money."

The Northcott Neuroscience Laboratory team was introduced to the families

CMT affects both sensory and motor nerves, weakening the muscles in the arms and feet, leading to foot deformities and impaired sensation in feet and hands. One in every 2500 Australians – so about 9000 people – may show signs of axonal degeneration, the dying back of the ends of these nerves. Patients can find it difficult to perform even the simplest of tasks, such as opening a can or bottle top, fastening shirt buttons or opening a door handle.

For more information on research visit the ANZAC Research Institute website www.anzac.edu.au For further information on CMT see the Charcot-Marie-Tooth Association website www.cmt.org.au

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