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## How to mend a broken heart

Heart disease and electronic pacemakers may be a thing of the past sooner than expected. In a novel use of gene therapy, preliminary research from CMRI suggests damaged heart tissue can be brought back to life with a dose of DNA.

Heart disease is a major cause of death across the country, killing 20 percent of all Australians. When heart muscle is damaged, during a heart attack for example, scar tissue forms, disrupting the heart's electrical system, weakening the heart. If these scar cells can be reprogrammed to behave like heart muscle cells, it may mean a totally new treatment for this costly and debilitating condition.

This exciting research, conducted by PhD graduate and cardiologist Dr Eddy Kizana at the CMRI in collaboration with Westmead Hospital, The Children's Hospital, Westmead and the University of Sydney, was published in the leading journal 'Circulation' in February. Dr Kizana was supported by a Fellowship from the National Heart Foundation of Australia. He has since moved to Johns Hopkins Medical Institute, Baltimore, USA, to take up a post-doctoral research position.

These early experiments involved adding two extra genes to the cells. Dr Ian Alexander, Head of the joint CMRI-Children's Hospital at Westmead Gene Therapy Research Unit, explains, "Adding the genes is like reprogramming the cells; the first gene programs the cell to be electrically excitable and contract like a muscle cell, the second gene allows the cells to communicate with each other – essential for the electrical pulse of the heart to be passed on. The scar cells take on totally new characteristics."

Although an electronic pacemaker can be a good remedy for this type of heart disease, the device does eventually wear out. Dr Alexander adds, "With extensive research it may be that gene therapy can give a patient's own cells the capacity to be repaired for life. More work must be done, but our studies on cells grown in the laboratory show that this may be an exciting new application for gene therapy."

Adult heart disease patients may not be the only ones to benefit in years to come. "This technique could prove to be beneficial not only for heart disease patients but in many conditions where the heart fails to beat correctly, including congenital diseases like heart block in children," says Dr Alexander.



*Dr Eddy Kizana and daughter Teresa*



# Director's desk



Even now, four weeks after the event, the patterns and rhythms of Australian life remain overshadowed by the devastation and loss of life following the Indian Ocean earthquake and the subsequent tsunamis. The frailty of human existence as revealed by a single natural

catastrophe rather than from equivalent man-made events such as the bombing of Dresden, Hiroshima or Nagasaki, half a century ago when the details were, under the circumstances, suppressed, seems to be perceived differently.

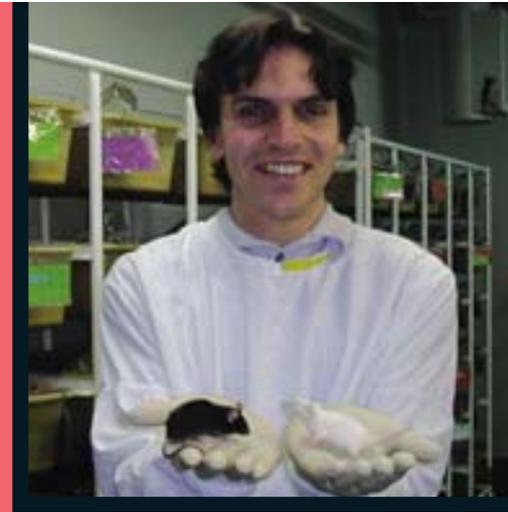
While the international aid response has been impressive what is now becoming evident is the extraordinary bravery and resilience of those directly affected as they seek to rebuild their lives. We can only hope that the resources to which Australians have made a magnificent contribution will be effectively and appropriately utilised. While many have expressed some surprise at the extent of the response from the Australian public, those of us at the CMRI who have benefited from its generosity over the years are not.

At this time it would appear that the application of techniques learned from past bitter experiences, such as in Rwanda and Sudan, have controlled major outbreaks of disease and, already, experts from the various aid agencies are involved in seeking to create a semblance of normality in various communities.

While it is a sobering thought that world events have, over the past fifty years, resulted in the creation of several major groups capable of responding to major disasters, the skill, bravery and commitment of the staff involved must be deeply admired and supported. These people are true professionals and have studied and analysed the critical issues essential for the successful conduct of relief efforts in many parts of the world. While the availability of modern medical treatment and surgical techniques has improved over the years, the broader public health concerns of adequate food, clean water, proper sanitation and psychological interventions remain critical for both the immediate and long-term. Unfortunately, it is only at times such as these that the talents and skills of these specialists are appreciated to be quickly forgotten when the events fade from the news.

Professor Peter Rowe

Mark Corbett with the nemaline myopathy mice who helped him make his discovery



## Weak solution

It's a common problem in medical research, that all too often we can identify a genetic change that causes a disease in a patient, but we are still left wondering as to how that change causes a problem in a particular organ. It is frustrating as it blocks the way to identifying potential treatments for the disease.

PhD graduate Mark Corbett of the Muscle Development Unit may have solved that problem when it comes to the childhood muscle weakness disease, nemaline myopathy. The work, published in the excellent journal *Annals of Neurology* in January, is the first to address the mechanism causing the weakness and paves the way for a new diagnostic test for patients.

Mark has now moved on to take up a post-doctoral research position at the Women's and Children's Hospital in Adelaide, but the work on nemaline myopathy is continuing at CMRI.

"Mark came up with the hypothesis, designed the experiments to test his ideas and brought the techniques into the lab – everything you'd want a PhD student to achieve," says Dr Edna Hardeman, Head of the Muscle Development Unit.

One of the genetic mutations that can cause nemaline myopathy lies in a gene called tropomyosin. There are usually two versions of the tropomyosin protein in skeletal muscle, alpha and beta, and they prefer to work together in pairs with their opposite number. But when there is a mutation in the alpha-tropomyosin gene, as in some patients with nemaline myopathy, the mutant protein pairs with itself and the beta version almost disappears. "A change in the composition of the muscle fibre like this would really affect the regulation of muscle contraction," said Dr Hardeman

Under the microscope, the first sign of damage in the muscle fibres is the appearance of rod-like structures, but these may just be a hallmark of the disease rather than the cause. "Mark has shown in both mice and patients that the disappearance of the beta-tropomyosin precedes the appearance of the rods, confirming it as the most likely cause of the weakness," said Dr Hardeman.

The disappearance of the beta-tropomyosin is also the key to a new diagnostic test for the disease. "We can detect this by separating the muscle proteins on an electrophoresis gel and looking for the disappearance of the tell-tale band that represents beta-tropomyosin," said Dr Hardeman. "It will make it much quicker to narrow down which of the seven possible genetic mutations is causing nemaline myopathy in a patient."

# Your Wish is Granted

CMRI scientists have once again proved they are the cream of the crop, winning a cluster of grants in the latest round of research funding announced by Australia's National Health and Medical Research Council (NHMRC) and other granting bodies in November.

## The guts for genetics

Dr Patrick Tam's Embryology laboratory will be well on the road to producing a complete map of the embryonic origins of all the tissues and organs in the mouse with the help of an NHMRC Project Grant. Dr Lorraine Robb at the Walter and Eliza Hall Institute in Melbourne will collaborate on the project with them to investigate the development of the gut and associated organs. They will identify the genes that control the development of these tissues using cutting edge DNA microarray technology – a tool that can screen the activity of thousands of genes in one quick experiment. "It's expensive technology," says Dr David Loebel, Kimberly-Clark Research Fellow, "but this grant and the ongoing support we get from CMRI donors and sponsors will allow us to make the most of the technology."

## Cancer combatants

Dr Roger Reddel and Axel Neumann in the Cancer Research Group, together with Dr Patrick Tam in the Embryology Unit also gained an NHMRC Project Grant. This will aid their search for the normal counterpart of a cellular process that has gone horribly wrong in cancer cells. ALT is one of the mechanisms that cancer cells use to avoid the normal limits placed on cell division. "If we can discover the normal mechanism that has been hijacked by cancer cells to make ALT happen it will help us to predict and avoid possible side-effects of any new anti-cancer drugs designed to block ALT," said Dr Reddel.

Dr Alessandra Muntoni of the Cancer Research Group is the recipient of the highly competitive NHMRC Peter Doherty Fellowship for outstanding young researchers. Alessandra, who is also a clinical doctor, joined CMRI two years ago after completing her PhD at the Beatson Institute of Cancer Research in Glasgow, UK. The grant will support Alessandra over the next four years as she aims to uncover the secrets of a structure called an APB that is found in cancer cells that use the ALT mechanism. "We think APBs may be hiding information that may lead to new cancer treatments," said Alessandra.

## Masters of muscle

Dr Edna Hardeman and her team in the Muscle Development Unit have won two NHMRC Project Grants that will enable them to pursue some exciting discoveries made last year. They will investigate the unexpected finding that there is regeneration occurring in the muscles of patients and mice with the muscle weakness disorder, nemaline myopathy. It should lead to better understanding of how to encourage regeneration in all muscle disease. "We will also use mice to look at the other genetic mutations that cause nemaline myopathy in children," said Dr Hardeman, "this will help us to identify differences in the muscle pathology seen under the microscope and so improve diagnosis for patients."

In collaboration with Professor Peter Gunning at the Children's Hospital at Westmead, the team will also delve deeper into the nature of a new structure discovered in muscle and its possible role in muscular dystrophy. They will screen patients with muscular dystrophy to see if the gene they discovered in mice is also a cause of the disease in humans.

## An eye for genes

The Eye Genetics Group in the Embryology Unit, led by Dr Robyn Jamieson, has received a grant from the Ophthalmic Research Institute of Australia. The project to investigate eye development and glaucoma genes will involve an interesting collaboration with Dr John Grigg, Ophthalmologist at the Children's Hospital at Westmead and Sydney Eye Hospital. Glaucoma can affect children and adults and may result from abnormalities in the development of the front part of the eye. It leads to raised pressure in the eye, damage to the optic nerve, visual disability and blindness. Understanding the genetic basis of these conditions will open the way for development of new treatments.

Left to right:

New NHMRC Peter Doherty Fellow, Dr Alessandra Muntoni;

Looking for eye development genes with a grant from the Ophthalmic Research Institute of Australia; Dr Robyn Jamieson (centre) with team members Marja Mihelec (left) and Chris Willcock (right).



# Jeans for Genes Be a Star in 2005

## 2004 Result Update

The latest total for Jeans for Genes Day 2004 is \$3.96 million and money is still coming in. This is the second best result ever! Thank you to everyone who supported us this year. If you haven't already, please send in your badges and monies as soon as possible – it would be great to hit the \$4 million mark!

## Razzle n' Dazzle

2005 is going to be an exciting year. This year Jeans for Genes Day will be held on Friday 5 August. The theme for the year is 'Star Studded Genies' with stars from all over the world donating their dazzle to help Jeans for Genes. To date we have received star quality jeans from Kate Hudson, Darryl Hannah, Jane Fonda, Shirley McLaine, Anjelica Huston and Geoffrey Rush to name just a few.

Australia's swimming hero Ian Thorpe, has also agreed to support the cause by allowing us to use a replica of his jeans, donated and painted in 2003 by artist Paul Newton, for our \$10 pin. Ian's jeans were sold at auction for a record breaking \$26,000. Now everyone can support Jeans for Genes with a mini replica Ian Thorpe pin.

## An early start to a great campaign

Support has already begun with Jeans for Genes ambassador Hayden Tee donating proceeds from the musical Godspell which was held on Friday 28 January, to the new CMRI committee "The Burbs." Hayden, who directed the show, said he felt compelled to do more for the organisation after attending a CMRI Discovery Day late last year. "Both the performers and myself were extremely excited to help the cause," said Hayden Tee during rehearsals.

If you are doing something special for Jeans for Genes day this year please let us know. If your company is interested in being a sponsor we have a number of events which may be of interest to you. For further information please contact Julijana Trifunovic – National Campaign Manager – Jeans for Genes on 02 9687 2800 or via email [jtrifunovic@cmri.com.au](mailto:jtrifunovic@cmri.com.au)



Busy volunteers (left to right) Lesley Brooks, Denva Barber and Janet Cooper

## Three cheers for volunteers

Retirement may bring leisure time, opportunities to make choices, travel, new hobbies and new friends, but there is a wonderful band of retirees who also include volunteerism as part of their activities.

CMRI is extremely lucky to have a very happy band of 'vollies', young and old, who come through our doors every day of the week. Our Tuesday crowd are Denva Barber, Lesley Brooks and Janet Cooper. Denva and Lesley have been coming to CMRI for an amazing eight years, while Janet is a relatively recent recruit. Their commitment and dedication is a wonder to behold and all can put their hands to any task asked of them – picking, packing, counting, sorting, making phone calls, using computers. The list is endless but all so valuable, saving the CMRI thousands of dollars which can be directed to our research programs.

So why do they volunteer? Denva and Lesley agree, "It provides a sense of satisfaction and worth."

"It gives me a chance to do something completely different," says Denva.

"When we are here we really are looked after and made to feel part of the CMRI team," added Lesley. "It's nice to feel needed."

CMRI is always looking for volunteers around Jeans for Genes time. If you would like to help out, call Jennifer or Kelly on 02 9687 2800.

## How to mend a broken heart - add two genes

Depicted in the 'O' on the front cover and seen here in more detail are fibroblast cells (scar cells) that have been gene-modified to behave like heart muscle cells. The first gene, MyoD, makes the cells produce muscle proteins (red) and the second gene, Connexin 43, produces proteins (green) that open up communication channels between the cells so the electrical activity of the heart can flow through the scar cells. The cells nuclei can be seen in blue (Photograph by Dr Eddy Kizana).



Hayden Tee (bottom right) with his talented cast and crew







# Committee Power

## Sad loss for Griffith

Griffith lost a much loved friend and very active community member, when Yvonne Hamilton, founding member of the Griffith Committee of the CMRI, passed away in October 2004. 'Von' was President of the Committee for many years and was involved in many other organisations. CMRI sends its condolences to all her family and friends.

## Thumbelina

Congratulations to Julie Newlands of Epping, the delighted winner of the Committee's Christmas Hamper Raffle, and second prize winner Robbie Nicholson.

## Gosford

Bobbie Shailer entertained the Gosford Committee and friends with her amazing floral Christmas creations at a Christmas Afternoon Tea fundraiser.

## Tamworth

After risk of cancellation the Carols in the Park were the biggest and best ever thanks to enormous community support and sponsorship from Joblink Plus, The Northern Daily Leader, Kevin Anderson and local Rotary Clubs. Fabulous entertainment was provided by Country music stars and supergroup the Wolverines.

## Canberra

Over 700 guests enjoyed the company of Their Excellencies Major General Michael Jeffery and wife Marlena in the magnificent grounds at Government House in Canberra. An astounding \$70,000 was raised from Christmas sales and the wonderful luncheon.

## Wagga Wagga

In the midst of harvest and after four years of drought Wagga Wagga was recently struck with eight frustrating stormy days. But nothing dampened the spirits of Committee members and hordes of visitors as they enjoyed the quality crafts and produce that the annual fair had to offer.

## Strathfield

The Thanksgiving Lunch at the American Club in Sydney was a great success with Lori Callahan from Allianz giving a passionate and amusing insight into the meaning of Thanksgiving.

## Hunter Hall

CMRI were the delighted recipients of a cheque for over \$11,000 from the Hunter Hall International Ltd Shareholder Nominated Charitable Donations Scheme. Many thanks to everyone at Hunter Hall for their generosity.

## Dates for your Diary

### Strathfield Committee

Buffet Luncheon with an entertaining floral demonstration and jewellery and gifts to buy. Pennant Hills Bowling Club, Yarrara Rd, Pennant Hills. 16 March, 12pm

### Vaucluse/Double Bay Committee

Annual Tennis Day Classic. Mixed doubles, all players invited, non-players welcome for lunch at 'Fairwater', Double Bay. Sunday 22 March. Enquiries Jan Madigan 02 9645 4331

### Hills Committee

Mother's Day Luncheon hosted by John Mangos and celebrity guest at the lavishly refurbished Doltone House, Jones Bay Wharf, Sydney. Tuesday 3 May

### Racquet Committee

Annual Card Day, St Ives Bowling Club, 18 April. Contact Prue Kellaway on 02 9974 4197 to book a table

### Thumbelina Committee

Enjoy a fun night of Bowlers, Bobbies and Beefeaters at 'The Pavilion on the Park', Sydney, and find out the winner of the Grand Raffle for 2005 - a trip for two to the UK. Creative Gourmet, have kindly sponsored one of the airline tickets as part of their "Have a Creative Gourmet Berry Break" campaign. Saturday 4 June. For dinner and/or raffle tickets and more information please call Ossie or Lesley Pitts on 02 9417 1160

For information on all events contact Jennifer Philps on 02 9687 2800

*Clockwise from far left:*

*At the Canberra Committee luncheon, left to right: Carolyn Forster, Meredith Nichol, Dr Phil Robinson of CMRI, Their Excellencies Mrs Marlena and Major General Michael Jeffery and Patti Payne;*

*Selling cold drinks at the Wagga Wagga Fair, left to right: Louise Golden, Isobelle Golden, Alexandra Stone and Claudia Kurrle;*

*At the American Club in Sydney for a Thanksgiving Luncheon, left to right, Stephen Ryall (CMRI), Strathfield President Nita Trollope, Lori Callahan of Allianz and Jennifer Philps (CMRI);*

*Gosford Committee president Alison Elms (right) with floral artist Bobbie Shailer;*

*The Racquet Committee celebrate a successful year of fundraising. Left to right: Nan Douglas, Joan Moore, Deidre Woosnan and Alyson Wormald;*

*Stephen Ryall of CMRI accepts a generous cheque from Peter Hall and Suzanne Daniel of Hunter Hall International Ltd.*