

# under the microscope

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## Today's scientists for tomorrow's children

The Children's Medical Research Institute (CMRI) is an independent organisation committed to unlocking the mysteries of disease. Our scientists investigate conditions such as birth defects, cancer, and epilepsy. Our philosophy is that major advances in prevention and treatment come from research into the fundamental processes of life. Our work is made possible by our community of supporters and Jeans for Genes®.



**CHILDREN'S  
MEDICAL  
RESEARCH  
INSTITUTE**

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## GENIE ME, GENIE YOU, GENE-IUS!



Baby Gene-ius Louis Cromer

The Children's Medical Research Institute's million dollar spectrometer, purchased with funds generated through our successful 'Jeans for Genes' campaign, was instrumental in a momentous new scientific discovery: **composition of the core enzyme, telomerase, which is present in 85% of human cancers** (see Page 3.)

This achievement, and many others, is due to the ever increasing support of the Australian public on 'Jeans for Genes Day' and throughout the year. In 2007 we hope to raise the most funds ever for our dedicated researchers, and make another big contribution to the health of future generations of Australians.

To make this possible the 'Jeans for Genes' team has grown and they have some exciting new ideas for the future.

**'Jeans for Genes Day' – Friday August 3 2007**

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# Director's desk



The Children's Medical Research Institute strongly believes that the biggest medical advances will come from fundamentally new insights into how the human body works and what goes wrong in disease. Obtaining these insights takes years of persistent work and creative thinking to transcend the limitations of our current knowledge. CMRI recruits top scientists to work on problems that are of critical importance, and with your help provides the resources that enable them to do this. Then we expect to get completely **unexpected** results. One of the scientists who works in Dr Phil Robinson's research unit, which is known for its groundbreaking research on transmission of signals among nerve cells, was recently named Young Researcher of the Year by Cure Cancer Australia Foundation! (See news item about Dr Megan Fabbro). Dr Fabbro has found that one of the proteins this research unit has been studying for many years also has a key role in the way cells multiply. Therefore, medicines targeted against this protein could possibly be used to block the multiplication of cancer cells. So CMRI's neurochemistry team may have found a new way of treating cancer! Nothing could illustrate better the excitement of basic research, the impossibility of predicting exactly where it will lead, and the promise it holds for transforming the treatment of diseases.

A handwritten signature in black ink, appearing to read 'Roger Reddel'.

Roger Reddel  
Acting Director

# Cancer Research gets Transformation in NSW

A major development in cancer research is the opening of a new unit at CMRI. The Cell Transformation Unit will study the function of a tumour suppressor protein, p53, which is one of the body's natural protectors against cancer.

The launch was attended by the Assistant Health Minister (Cancer), the Hon. Frank Sartor, as the new unit will receive generous funding through the Cancer Institute NSW Research Leaders Program Grant, an initiative of the NSW state government.

To head up the team is Professor Antony Braithwaite, a well-known scientist in the field of cancer research, who was recruited from overseas. He will not only create a new research group but also, perhaps more importantly, lend support to other research groups around New South Wales.

His team will study how p53\* functions to prevent cancers. This will be done using animal models and using studies with cells in the laboratory. The team will also look for natural variants in p53 and in other components of its regulatory pathway, which may make some people more susceptible than others to developing conditions that speed up ageing and cancer onset. They will study a large number of volunteers for this purpose about whom much medical information is known.

Minister Sartor is keen to have this new team, particularly Professor Braithwaite, play a key role in furthering the work of other cancer research groups in New South Wales, through a Research Leaders Program. This aims to strengthen current cancer research activities, perhaps link research teams across the state and offer advice to other cancer research groups. It would position New South Wales as a key player in cancer research. The CMRI is able to fund this unit thanks to the support of the Cancer Institute NSW, which has pledged \$3.25 million over five years.

*\* The P53 gene is recognised by cancer researchers as having a major role in signalling cell death.*



Prof Jim Bishop, Lord Mayor Cr David Borger, Nathan Rees, Minister Sartor, Prof Braithwaite and Ms Tanya Gadiel declare the Cell Transformation Unit officially open

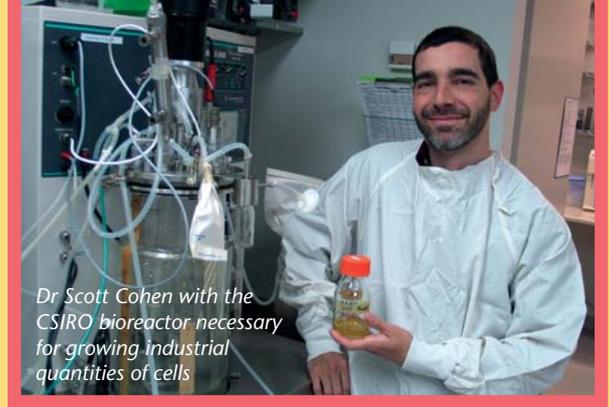
# CMRI scientists identify core enzyme in 85% of cancers

Research into cancer, anticancer treatments, and ageing has been advanced through the identification of the composition of human telomerase - an enzyme integral to 85% of all cancers.

Cancer researchers around the world have studied telomerase since its discovery 18 years ago but they were working somewhat in the dark. The actual protein composition was unknown, scientists believing it contains any mixture of 32 proteins. A study, headed by Dr Scott Cohen of the Children's Medical Research Institute reveals that telomerase contains just 2 proteins.

"Until now, researchers studying telomerase have not been sure what they're working with," said Dr Cohen, whose study was supported by The Cancer Council NSW and the National Health and Medical Research Council Australia, and published by leading journal *Science*.

Dr Roger Reddel, acting director of CMRI and an international cancer research expert, believes the identification 'switches on a light' for basic cell biology and cancer research.



*Dr Scott Cohen with the CSIRO bioreactor necessary for growing industrial quantities of cells*

"Telomerase is the target of an extensive global effort to develop anti-cancer treatments. This discovery sharpens the focus of these efforts and no doubt will speed up the process of delivering successful treatment," said Dr Reddel.

Dr Cohen developed a brilliant new purification technique that made the telomerase identification possible and will be useful for scientists requiring purified telomerase, a step towards development of anti-telomerase drugs.

"No-one has previously been able to purify telomerase because, within each cell, it's a very rare enzyme. Each cell has about 20 molecules of telomerase – compared to about 20 million molecules each of some abundant enzymes," said Dr Cohen. "I had to pull out one part in 100 million, which is roughly a teacup of water from an Olympic swimming pool."

These findings will significantly enhance the ability of cancer researchers to further study telomerase.

Dr Cohen's identification of the composition also makes research methods such as x-ray crystallography possible for telomerase, which would be another major step towards identifying new anti-cancer drugs.

## Bubble Boy Disease

Boy in the bubble disease - so called because boys with the condition were kept alive in sterile plastic bubbles – occurs in approximately 1 in 60,000 baby boys. Unfortunately boys inheriting the disease, called SCID-X1, have a gene mistake on the X chromosome, leading to a loss of white blood cells - making them highly susceptible to infection.

Researchers in our Gene Therapy Research Unit (GTRU)\* took part in the first gene therapy trial for this disease and treated one young boy. Although most of the children treated in the trial developed a healthy immune system, this little boy's immune system only partially recovered, and the scientists have been interested in what was happening in his cells and whether this might explain his incomplete recovery.

Our scientists have recently pieced together the inner workings of blood cells, particularly cells called natural killer (NK) cells. They have pinpointed how a signalling problem (which usually prevents the generation of mature white blood cells called T cells) still allows generation of faulty NK cells that are present in some of these infants, like the boy treated in Sydney and not in others.

Scientists already knew that immature white blood cells receive signals to mature, through receptors located on their cell surface.

And the gene error in bubble boy disease disrupts one part, or subunit, of these receptors. Our scientists wondered if patients with NK cells can make a small amount of the normal receptor subunit; just enough to signal to the cell to become an NK cell but not enough to generate a T cell.

Using a combination of normal and patient's cells, and cells genetically altered to produce various amounts of receptor subunit; the researchers have now demonstrated that when only a small amount of the particular subunit is produced, it is only enough to allow signalling to generate NK cells. This is important information for the development of new gene therapy trials for bubble boy disease, which may be influenced by the presence or absence of NK cells.

\*The GTRU is a joint initiative of CMRI and The Children's Hospital at Westmead.

In the 'O' on the front cover, cells from the bubble boy patient demonstrate signalling sufficient to make NK cells. The signal is visible as a green colour located in the blue nucleus of one of the patient cells, which are labelled with a red fluorescent dye.



*Members of the GTRU*

# Embryo Development:

## A snapshot of the complexity of gene function

A critical time in the development of the mouse is during the two and a half days after a tiny embryo containing about 100 cells embeds into the womb. In a quick succession of events, it grows into an embryo with a thousand cells, which are programmed to form very specific parts of the body.

Dr David Loebel, Kimberly-Clark Research Fellow, and Dr Patrick Tam, Head of the Embryology Unit, have gathered together the most up-to-date information on the genes involved in setting up this early body plan. Information on the functions of genes known to be involved in this process, many of which encode proteins involved in signalling, was collated in an invited review article for the internationally renowned journal, *Nature Reviews Genetics*.

"It is the correct balance between when and where these genes are 'switched on' that is believed to determine the fate of each cell and its descendants," says David. Based on the data from a large volume of work by many scientists, it is now possible to reveal a complex yet elegant network of genetic activities in the early embryo. These can control the communication between cells, their movement and changes in their appearance and function over time.

"This review represents a snapshot of what we know about how an embryo gets ready to embark on its journey of development," says Dr Tam. "Because genes involved in early mouse development could also be instrumental in the development of other embryos, this knowledge will help us to understand how early human embryos develop and what may cause birth defects."

While David and Patrick were labouring over their article, Dr Sabine Pfister and Kirsten Steiner have reviewed the pattern of activity of over fifty genes that are 'switched on' in the mouse embryo at the same early stage of development.

They have also painstakingly examined their own experimental data on other genes in embryos at eleven separate developmental stages, some only a quarter of a day apart.

Although the individual cells in an embryo do not look different under a microscope, the genes 'switched on' in these cells, at specific times and in discrete regions of the developing embryos, demonstrate that there are already many distinct types of cells before we can tell them apart.

Kirsten and Sabine have collated a list of genes that might mark specific populations of cells as they emerge in the embryo. "To this date, no signature genes for any particular type of cells have been found," says Kirsten. "This may reflect the uniquely flexible nature of the embryonic cells, which may be very similar to stem cells."



Dr Patrick Tam with Dr David Loebel and Kirsten Steiner

# 2007 National Young Researcher of the Year

CMRI's Dr Megan Fabbro has been named a Cure Cancer Australia 'National Young Researcher of the Year.' This is a fabulous achievement as the awards are a major event within the Australian medical and scientific communities, and attract nominations from the very best young cancer researchers.

Megan has made important discoveries about the ways in which two key breast cancer proteins are regulated during cell division - especially the final stage of cell division. Her research is enabling us to understand the error(s) that may occur during cell division and contribute to cancer development - information already being used to search for possible new anti-cancer drugs.



Professor Martin Tattersall (Chairman Cure Cancer Australia's Medical Grants Advisory Committee), Dr Megan Fabbro and Mr Max Gosling, Chairman Cure Cancer Australia Foundation (Photo courtesy of Cure Cancer Australia)

# Jeans for Genes®

## Genies Wanted

Already we have secured over 100 sites throughout Australia to sell merchandise on the streets, at stations and in shopping centres. If you or your company (staff volunteering programs) would like to participate in **Teams for Genes**, please contact Lynda Dave 02 9687 2800 or go to our website [www.jeans4genes.com.au](http://www.jeans4genes.com.au) for more information.



Genies Linda Facaris and Helen Pearce

Sophie Lee

## Jamm for Genes®

Musicians from everywhere are coming onboard to support 'Jamm for Genes' this year. From August 3 – 5 music venues and musicians will be raising money for the CMRI. Ambassadors include country music favourites – Adam Harvey, Becca Cole and the McClymont sisters. Other well-known musicians supporting the cause include: Jon Stevens, Glenn Shorrock, Courtney Act, Jade McCrae and Anthony Callea. Find out who is playing where and how to get involved at [www.jamm4genes.com.au](http://www.jamm4genes.com.au)

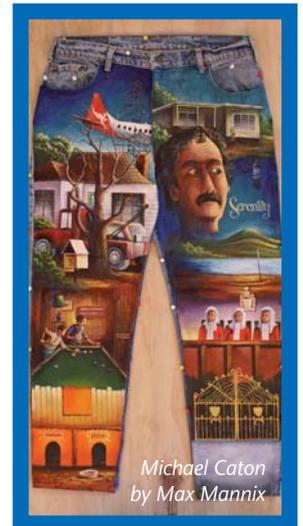


Glenn Shorrock, Jon Stevens, Jade McCrae, Adam Harvey and Mark Gable with scientist Carina Rubio

Jon Stevens

## Jeans for Genes Art Auction – Dare Devil Denims

The 'Jeans for Genes Art Auction' is to be held this year on Thursday 12 July at the Four Seasons Hotel, Sydney. Proudly sponsored by Toyota Financial Services this event is not to be missed. Once again Channel 7's anchor woman Chris Bath will be the master of ceremonies and Ray Hadley will be the celebrity jeans auctioneer. Brigitte Bardot, Jennifer Hawkins, Annie, Sir Richard Branson, Dame Edna Everage, David Copperfield and Eva Longoria are just a few of the celebrities who have donated their jeans to this great event. Tickets are \$240 pp or VIP tables of ten, \$3,300. For bookings and more information please contact Chris McGee 02 9687 2800 or go to the website [www.jeans4genes.com.au](http://www.jeans4genes.com.au)



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## Do it with Denim®

Do you know anyone who is studying fashion design, interior design/ decorating or textiles? They can take part in the hottest initiative for creative design students while supporting 'Jeans for Genes'. Exhibitions of works will be in a number of locations including: QVB in Sydney, Castle Towers Shopping Centre in Sydney, Chadstone Shopping Centre in Melbourne, Malvern Shopping Centre in Melbourne and ECC Lighting in Sydney. For exhibition and fashion parade dates, registration and more information go to [www.doitwithdenim.com.au](http://www.doitwithdenim.com.au)



Ricki Lee is proud to be the Do it with Denim ambassador

## 'Jeans on the Greens – Charity Golf Day' – Friday May 25 2007

That's right the club has allowed players to wear their jeans! Swing on by and have a fabulous and fun day at 'Jeans on the Greens', to be held at Oatlands Golf Club, Sydney. A number of packages and a few sponsorship packages are still available. Call Christine McGee 02 9687 2800.



## Launch of the new Jeans for Genes Website

Check out our website – it is fresh and new [www.jeans4genes.com.au](http://www.jeans4genes.com.au)

Jeans for Genes is a major fundraiser of the Children's Medical Research Institute

# Mapping the embryo: The finishing line in sight



Cover of the journal *Development* showing Heidi's picture of a 7-day mouse embryo, painted to depict two endoderm populations going separately to the head-end (red) and the tail-end (green).

The development from a single cell into a complex embryo is an amazing feat and it happens as if there is a blueprint, on which every part of the body is put together perfectly. Since 1990, CMRI scientists have been studying the mouse as a model to find out if there is a body plan for embryonic development.

The Embryology Unit have been 'mapping' the fate of every group of cells in the mouse embryo during gastrulation. This is a critical phase when all kinds of cells in the body are emerging, even though the embryo is

not much bigger than a grain of rice. They approached the project by studying, in turn, each of the three layers of cells that make up the embryo. Seventeen years on, they are now down to the last layer called the endoderm (which forms the gut) and are close to having a complete map of the embryo.

Poh-Lynn Khoo, Heidi Bildsoe and Samara Lewis, have nearly completed the map showing where different parts of the gut of the mouse embryo come from and how the developing gut cells may move around. The findings are published in the highly respected journal *Development*.

Surprisingly the head-end and the tail-end parts of the gut are formed first, followed by the rest of the middle part. "In two days of development, the mouse embryo generates all the cells that are needed to make a complete gut and also puts them into the right places," says Dr Tam, Head of the Embryology Unit. The team, in collaboration with Dr Lorraine Robb of the Walter and Eliza Hall Institute of Medical Research in Melbourne, also found that cells move to the front of the embryo because they are pushed from behind by other cells that come in later.

**"We are leading the world in the mapping of the mouse embryo.** Only by understanding the full sequence of events and what each of these cells will become, using an experimental model, can we hope to understand how the human body develops," says Dr Tam. "Now we have completed the gastrulation phase of gut formation all that is left is one more set of experiments to add more detail to the endoderm map. We are very excited since the finishing line is finally in sight."

# Dynamin Debate

A controversy over how the nerve cell protein dynamin I interacts with other proteins within a cell has just been resolved by CMRI scientist Dr Mark Graham. Along with co-workers in our Cell Signalling Unit and collaborators at the University of Southern Denmark, Mark has found seven sites on dynamin I that can be altered – ultimately affecting nerve cell signalling.

Nerve cells control our memory, learning, behaviour, speech, emotions and movement and so on. They do this firstly by conveying tiny millivolt electrical impulses within the cell and then they transmit small messengers called neurotransmitters between cells. These neurotransmitters are stored in around 200 small containers called vesicles within each nerve cell ending.

After neurotransmitter release, the vesicles are re-formed and refilled to allow more nerve cell signalling - a process called endocytosis. Our scientists previously demonstrated that dynamin I interacts with protein partner syndapin I, to pinch off new vesicles from the cell membrane at the nerve ending. They know this process is controlled by the removal of phosphate molecules from specific sites on the dynamin protein and previously identified two crucial sites.

A recent paper disputed these findings, claiming that dynamin I could only be altered at an entirely different site. Mark and the team were, therefore, determined to unravel exactly who was right. Using a new method to better purify the protein and our highly sophisticated mass spectrometer they confirmed the two original sites (and a third known site) and also found four new sites on the dynamin I molecule.

"We have now ranked the importance of each site, and the two sites we identified first are the most significant for nerve communication," says Dr Phil Robinson, Head of the Cell Signalling Unit. "This new information is significant as we are looking at blocking endocytosis as a treatment for conditions such as epilepsy."



Dr Mark Graham



# Committee Power

## Committees

**Thumbelina Committee** and friends thoroughly enjoyed a river cruise up the Port Hacking River on a glorious day in February.

**Gosford Committee** young supporter Johanna Elms received an **Order of Australia Award** for academic excellence, volunteerism and personal achievement from the Governor General. This is a fantastic accomplishment and we wish Johanna well.

At the **Strathfield Committee Luncheon**, Peter Cousens captivated the capacity crowd at the RAC Sydney with anecdotes of his life, interspersed with marvellous renditions of our favourite melodies.

## Other Supporters

The **Rotary Club of Parkes** kindly donated a cheque, from their very successful Christmas raffle of a specially built cubby house. Thank you Rotarians for your weeks of dedicated ticket selling.

A big thank you goes to the extraordinary **Calendar Girls** who raised an incredible \$65,500 with their masterpiece the 'Bush and Beach 2007 Calendar'.

Verelle Heinicke has lost two children with Leigh disease and organised an exciting fundraiser to support CMRI. On a perfect tropical evening 175 guests arrived for **'Jazz at the Junction'** a sumptuous meal and dancing. Thank you Theodore community.



# Dates for your Diary

**Sunday 20 May the Judith Hyam Memorial Trust Fund** invite you to the stage show **'Italian Delight'** with Joey Fimmano at Wentworthville Leagues Club. Call Diana Mahony 02 9630 5572.

**Friday 25 May** will be the inaugural 'Jeans on the Greens' charity golf day, a golf lunch and charity dinner at Oatlands Golf Club. Call Christine McGee 02 9687 2800 for more details.

**Wednesday 30 May the Beecroft Committee** are organising a card and games day at Castle Pines, Castle Hill. Contact Mary Howell 02 8850 1271.

**Monday 2 July the 'Jeans for Genes Launch'** will take place at the Art House Hotel Sydney. Details Christine McGee 02 9687 2800.

**Friday 8 June** come along to **CMRI's 'Science in the Suburbs'** evening event with guest speaker Dr Phil Robinson. This initiative is supported by the Australian Government as part of National Science Week. Details Ruth Hardman 02 9687 2800.

**Friday 15 June Tamworth Committee** will hold a Card Day, so come along and play Bridge, Solo and enjoy a delicious lunch – non-players welcome. Call Anne Fenwicke 02 6766 4215.

**Thursday 9 August to Wednesday 29 August** CMRI's science communicators will travel to regional towns in NSW to present an exhibition called: 'It's a Scientist's Life' (see Page 8). Contact Jane Fleming 02 9687 2800.

*Pictured from left to right:*

*Meredith Barrett, Bronwyn Christensen, Verelle Heinicke and Susan Wagner who organised 'Jazz at the Junction';*

*Calendar girls with photographer Gary Barnes, Gerringong Committee President Margaret Weir (third from right) and CMRI's Jennifer Philips;*

*CMRI's Ruth Hardman with Peter Thompson and President Paul Parry;*

*Strathfield President Joyce Thiele with Peter Cousens;*

*Johanna with Adjunct Professor Brian O'Keefe (Foundation Secretary for the Order of Australia Association) in February;*

*Thumbelina Committee Cruise.*



In March Simon Upton launched his **'Women'** exhibition at Blue Sydney, Taj Hotel at Woolloomooloo, in support of CMRI. One hundred percent of the sale of the photographs will go to the Institute, and they can be viewed on our website at [www.cmri.com.au](http://www.cmri.com.au)



*Australia's first super model and entrepreneur June Daly Watkins*

