The newsletter of the Children's Medical Research Institute November 2004

# under the microscope



*Dr Patrick Tam, Head of Embryology, CMRI*
*Photo courtesy Parramatta Advertiser*

## Cleft gene **singled** out

The cause of cleft lip and palate has always been a complex and unresolved issue. Now, in an international collaboration, CMRI scientists have made a major contribution to understanding the mystery of this condition.

Their breakthrough paper was published in the top journal Nature Genetics in October.

Previous studies on cleft lip and palate suggest it is a so-called 'multifactorial birth defect' implying that several genes work together with environmental factors to cause the condition in babies during development. Approximately one child in every 700 will be born with a cleft lip and palate.

Working with scientists from Canada and six other international laboratories, the CMRI team discovered that a defect of a single gene, called *Pdgfc*, can cause the condition in mice.

"This is the first demonstration that losing the function of this one gene can cause cleft palate," said Dr Patrick Tam, Head of the Embryology Unit at CMRI.

CleftPALS – the Cleft Palate and Lip Society of Australia - provides support and resources to Australian families with children who have the condition, and has welcomed this latest research breakthrough.

*Continued Page 3*

CMRI Jeans for Genes®

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# Director's desk

For many people, it can sometimes be difficult to appreciate just how the basic or fundamental type of research undertaken at the CMRI has immediate relevance to disease prevention or treatment. However, looking back over our history one is struck by the numerous examples of how our work has lead to advances in medical treatments – from microsurgery and better treatments for premature babies in our earlier years to new forms of gene therapy and the potential for more effective and less toxic treatments for cancers in more recent times. It is often only with the benefit of hindsight that the relevance of long term research projects is realised.

In this edition of Under the Microscope, some exciting developments in three of our research units are highlighted. The observation by Patrick Tam's team that in mice losing the function of just one particular gene may lead to cleft palate is a particularly exciting finding in our understanding of this disorder, whilst our Muscle Development Unit's ongoing study on mice has demonstrated that exercise, contrary to popular belief, may be the key to helping children with the muscle weakness disorder nemaline myopathy. And Phil Robinson's Cell Signalling Unit, with the benefit of modern, sophisticated and cutting edge microscopic technology, funded through the generosity of a wide range of supporters, is working towards a new range of experiments which may lead to a new class of epilepsy drugs.

The actual benefits of these long term, focussed research projects will only be fully realised, however, when in years to come, we look back - just as we have experienced in the past.

***Dr Peter Jeffrey***

Professor Rowe is on conference leave.

# Brain spy

Most people would baulk at the prospect of being shut in a tiny, darkened room for months on end, but Dr Andrew McGeachie of the Cell Signalling Unit is positively impatient to disappear into a lonely room at the back of the Institute.

The room contains one of the most cutting edge microscopes available that will allow him to watch the intimate detail of neurons talking to each other as it happens.

Living neurons release tiny packages of chemicals, called neurotransmitters, into the gap between their neighbours to communicate with one another. The new microscope will film this cross-talk through time-lapse photography. CMRI scientists will be able to test the effects of drugs and genetic changes on nerve communication allowing them to work towards new treatments for brain disorders such as epilepsy and schizophrenia.

The 'live imaging' microscope was recently purchased by CMRI at a cost of $200,000. It has a heated platform and other specialised equipment to keep cells alive while they are viewed. A digital camera takes rapid snaps of the cells second by second, or even faster; sophisticated software and a powerful computer then analyse the images obtained.

"We can put fluorescent dyes into the parcels of neurotransmitters in the nerve endings and watch the colour disappear as the neurons release their packages into the synapses (tiny gaps) between neurons," says Dr McGeachie. "We can add drugs or damaged genes to the neurons and see if this changes their ability to release or retrieve the neurotransmitters." The first drugs that will be tested have potential as an entirely new class of epilepsy drugs.

Last year, Dr McGeachie and PhD student, Victor Anggono, visited collaborators in Scotland to learn how to use the microscope (Under the Microscope, February 2004). The microscope set-up is so specialised there are only a handful within Australia.

Previously the best they could achieve in the Institute were nerve endings that had been cut off from the rest of the neuron and collected together in a test tube. "This was useful but not close enough to the real thing, "said Dr Phil Robinson, Head of the Cell Signalling Unit. "Now, viewing these individual, intact nerve endings under the microscope is as close as we can get to what's happening in a living brain. It opens up a whole new vista of experiments that we can do to really understand the detail of nerve cell communication."

The microscope will also have a myriad of uses in other areas of CMRI research including cancer, brain development and embryology.

*Dr Andrew McGeachie prepares to watch the sparks fly as the neurons talk under the new live imaging microscope*

*Muscle researcher Josephine Joya with one of her charges on the exercise wheel*

# Running at full strength

It could sound obvious, but exercise may help increase the strength of children with the muscle weakness disorder, nemaline myopathy. This is the finding from a CMRI study on mice who suffer the same disease.

"It was previously thought that exercise was inadvisable for patients with nemaline myopathy," says Dr Kee of the Muscle Development Unit. The study was published in the high profile journal Human Molecular Genetics in November.

Over the last few years, scientists in the laboratory have been developing the mice, who carry the same genetic change that causes nemaline myopathy in children.

The mice have all the same muscular changes as seen in patients, making them a good model to study the disease and test possible treatments.

The only difference found in the nemaline mice was that they did not develop weakness until the equivalent of middle-age, unlike the childhood onset seen in humans. This was because the mice had a natural ability to grow their muscles bigger – compensating for the weakness in the muscle cells. This gave the researchers a big clue – perhaps exercise, which makes muscle cells grow bigger, would be helpful for patients after all.

If the young nemaline myopathy mice are subjected to periods of inactivity they become weak, much as a patient would suffer if they are bedridden or wheelchair-bound. Their weakness is more severe than a normal mouse that suffers the same degree of inactivity.

> ***"As a direct result of our work the International Nemaline Myopathy Consortium are now considering trialling exercise as a treatment for some patients," says Dr Hardeman, Head of the Muscle Development Unit.***

But Josephine Joya and Dr Anthony Kee, have been putting the weakened mice through a mild endurance exercise programme in the laboratory. They run on exercise wheels, or purpose built miniature treadmills just like the ones you would find at the gym! The weak mice gradually build up their level of activity and ultimately return to full strength.

"We thought exercise would help," said Dr Kee "but we were not expecting such a full recovery."

Another unexpected finding was what was happening inside the muscles as the mice became weak and then recovered. The word nemaline means 'rod' and describes the dense rod-like structures that can be seen under the microscope, clogging up the muscle fibres in nemaline myopathy mice and patients.

"We see even more rods inside the muscle fibres of weakened nemaline mice than usual," says Dr Kee. "But after exercise the extra rods disappear again. This suggests that the exercise is doing more than just strengthening the muscle fibres, it is actually encouraging repair of the damaged fibres," added Dr Kee. The repair seems to include both internal repair of the muscle machinery and formation of new muscle fibres from stem cells within the muscle tissue.

"This is an unusual form of regeneration not seen before in other muscle disorders," said Dr Hardeman, "It needs closer examination, but it is very exciting to discover something so novel. It may reveal new ways that we can aid repair in many muscle disorders."

# Cleft gene
## continued . . .

The *Pdgfc* gene was discovered five years ago by Dr Nagy's team at the Mount Sinai Hospital and University of Toronto in Canada, however nothing was known about where and when it had its effects in development.

This was when the Canadians teamed up with Dr Tam's laboratory to start finding answers. "CMRI has the expertise in studying gene expression patterns, that is where and when genes are active, and working out what happens to the developing mouse if there are mutations in genes," said Dr Tam.

Removing the gene caused a cluster of abnormalities in the mouse embryos including spina bifida and blisters of the skin. But the most significant finding was that in nearly 100% of the embryos there was a distinct cleft palate.

"Four other genes previously known to have an association with cleft palate are unaffected by the loss of *Pdgfc*, indicating that it is acting alone, in a new pathway," said Dr Tam.

Scientists in the collaborating laboratory at the University of Pittsburgh, USA, have now also made some preliminary progress in pinpointing a possible mutation in the PDGFC gene in some cleft palate patients.

"This is an exciting development and shows how valuable animal model studies can be in identifying disease genes," said Dr Tam.

CleftPALS NSW President Roslyn Currey said "While it is early days and the first step in an ongoing research program by CMRI, the implications of the findings for future generations will give tremendous hope, reassurance and encouragement for Cleft parents." Roslyn added "CleftPALS will follow with keen interest any future research activities by the CMRI."

If you would like to know more about CleftPALs, phone: 02 9294 8944 or visit www.cleftpals.org.au


*At the HR Awards Night...*

*Left: Winner of the gala raffle John Davis (left) is congratulated by Sara and Sandy Grant from Silversea Cruises*

*Right: Special guest Kieren Perkins and MC Vince Sorrenti can't say enough about the great work of the CMRI*

# Resources for **Genetic Causes**

CMRI – Jeans for Genes was the charity of choice this year for the Human Resources Magazine, organisers of the Australian Human Resources Awards 2004. The black tie event, which was telecast live on SBS, was held at the Westin Hotel, Sydney and raised over $18,000 for research into genetic diseases. Over 540 people from the Australian corporate sector attended the event with special guest speakers including Australian Olympian Kieren Perkins, and Steve Vamos Managing Director of Microsoft Australia.

A gala raffle held on the night raised over $13,000. Silversea Cruises kindly donated a seven day ultra-luxury cruise for two valued at over $14,000 as first prize and HR Partners donated a $1500 travel voucher. John Davis, National Managing Partner of Sparke and Helmore Solicitors, could not believe his luck when he won the cruise. Congratulations also to Julie Mills who won second prize. The Westin Hotel also generously donated a night for two as a lucky door prize.

SILVERSEA
*Above and Beyond All Expectations*

Michael Jordan, basketball player extraordinaire, again donated a personally signed pair of jeans which were auctioned by the Master of Ceremonies, comedian Vince Sorrenti. The jeans were painted on by talented Sydney artist, Steve Lopes and went to successful bidder Luke Buttah from Refshure for $5100.

# Jeans for Genes 2004 **- Update**

To date, Jeans for Genes Day has raised over $3.6 million this year, with money still coming in. So it looks like we are on target to match last year's fantastic result of $4.1million, a great achievement in what has been a difficult year for charities. Well done Genies you've done it again! Thank you for your support.

*NB. For those who still haven't sent in their money, we would be grateful if you could get it in the post to us as soon as possible.*

Plans have already begun for next year's Jeans for Genes with some huge names getting involved and we mean HUGE!

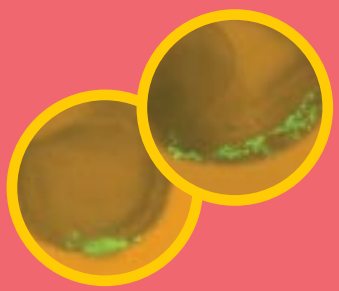
**Stay tuned and don't forget to put it in your diary - Jeans for Genes Day 2005 – Friday August 5.**

# **Mapping** the mouse

In keeping with his reputation as a world leader in mammalian development, Dr Patrick Tam and his team in the Embryology Unit have accomplished a cutting edge technical advance that has brought them a step closer to a complete developmental map of the early mouse embryo.

The research, published in the high profile journal Developmental Biology in October, will lead to better understanding of why certain birth defects occur.

The cells of the very early mammalian embryo are divided into three main tissue layers which go on to form all the organs and tissues of the body.



*Green marks the spot: green cells can be seen in an early mouse embryo just a few hours after the 'shock' (left). 24 hours later the green cells have multiplied and begun to form the gut (right). (Photographs by Poh-Lynn Khoo)*

Dr Tam's team has painstakingly mapped two of these layers, the ectoderm and mesoderm, which develop into organs such as the brain and nervous system, and muscles and bones, respectively. Over the last 14 years Dr Tam and his team have perfected microsurgical grafting techniques in mouse embryos that they used to draw up a "fate map" for the two layers showing which cells become which organs.

The third layer, the endoderm, which generates the gut and organs such as the pancreas, liver, thyroid and lungs, had remained difficult to map. It is a single layer of cells which is too small for applying the microsurgical techniques.

A new technique called whole-embryo electroporation was developed which uses a mild electric shock to open up tiny holes in the cells, allowing miniscule pieces of DNA to enter the cells in a mouse embryo growing in a dish. The DNA contains a gene that produces a fluorescent green colour, making them brightly visible under the microscope.

The fluorescent endoderm cells then multiply and change to start forming organs and their progress can be tracked in living mouse embryos under the microscope.

"Knowing the earliest origins of the liver, thyroid and pancreas will allow us to study the genes involved in their formation and potentially overcome the birth defects associated with these endodermal organs," said Dr Tam.

# See the world with Science

*Enjoying Australian scientific hospitality, German students (from left to right) Nadine Wolf, Cornelia Kroger and Carolin Willmer*

See the world, meet great people and develop your career. Sound like the dream job? Three scientists recently arrived at CMRI certainly think so! German students Carolin Willmer, Nadine Wolf and Cornelia Kroger are savouring the international flavour a science career can dish up.

Carolin and Nadine are both studying for a degree in Molecular Medicine at the Erlangen-Nürnberg University and Cornelia is completing her research project for Honours in Biology at the University of Heidelberg.

CMRI's reputation obviously reaches far and wide, as the student's supervisors at two different universities recommended CMRI as the place to gain first-rate experience.

Carolin says, "In our fourth year of study, we have to do practical training. Nadine and I decided it would be great to do this overseas and our mentor at university immediately recommended Patrick Tam's Embryology lab at CMRI."

Similarly, after being impressed by a seminar on telomerase and cancer, Cornelia's Professor suggested contacting leaders in the field - Roger Reddel and Tracy Bryan at CMRI.

Overseas experience is highly regarded in scientific research. The skills learned and the contacts made from an international experience are invaluable.

Dr Patrick Tam, head of the Embryology Unit says "Many of our best researchers leave Australia to broaden their research expertise in laboratories overseas; it is good to know that Australia and CMRI is a preferred destination for scientists from other countries who wish to study abroad. In the past few years, my laboratory has hosted visiting scientists from USA, France, Japan, Hong Kong and now, for the first time, Germany."

Cornelia said, "I really enjoy the environment here at CMRI, the facilities are excellent, the atmosphere is great and the scientists are world-class. All three of us are really lucky to have had the chance to come and work here."

# Prevention is better than cure...

## And the key to prevention lies in research. It's as simple as that!

There are over 10,000 known genetic disorders. To correct these and many other disorders research is needed to find the causes.

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## Thanks for your help.

# Committee Power

## COMMITTEES

### Welcome - New Committee

CMRI came into being nearly 50 years ago through the hard work of young mothers in the suburbs and regional areas who joined forces to raise money and build awareness of the need for research into childhood disorders. Continuing on in that tradition Narelle Williams from Sydney's north-western suburbs decided to gather a group of friends together to form **The Burbs Committee** and organise a charity Ball in the Burbs for next year. "We are a group of fun-loving suburban mums utilising our spare time to work towards helping CMRI with their vital research," says Narelle.

### Northern Beaches

A sell out crowd were captivated by the fascinating and amusing address by psychological thriller writer Gabrielle Lord at the Luncheon held at the Royal Prince Alfred Yacht Club in Newport.

### Quirindi

The Windy Woolshed Ball, held in the largest woolshed in the Southern Hemisphere, really was a night to remember. The committee transformed the venue into a gaily coloured village green with maypoles and lanterns and guests were amply provided with delicious homemade fare.

### Ku-ring-gai

Media personality Lisa Wilkinson entertained 200 guests at the Jeans for Genes lunch in August at Roseville Golf Club. Lisa talked about her time as the youngest Editor of Dolly, something she couldn't have dreamed of when she was a schoolgirl, sneaking looks at Dolly under her desk!

### Tamworth

Community spirit has rallied to save the annual Carols in the Park after rising costs and lack of sponsors had threatened the 20 year tradition. Joblink Plus has offered to sponsor the event and provide volunteers, and the continuing support of the Northern Daily Leader will ensure this year will be the best ever. Join the fun on 12 December.

### Racquet

Delighted guests enjoyed a gourmet Melbourne Cup lunch, with so much fun and conversation that the actual Big Race came second. Thank you to the Committee for a splendid venue and fabulous food and to Dr Lorel Colgin from CMRI for her perspective on her cancer research.

### Lakkariba

The Blue Mountains community have rallied to the cause by purchasing our cards and merchandise from the Committee. Thanks also go to the Hazelbrook Ladies Bowling Club for choosing the CMRI for their charity bowling day.

### Port Hacking

The Port Hacking River was awash with gaily decorated crafts at the annual Putt Putt Regatta. Community spirit was alive and well as an empty, yes empty, carton of beer was auctioned for $501.Who says fund-raising is difficult!

## SUPPORTERS

### Earle Page College – Coast Run Silver Jubilee!

The huge success of the 25th Earle Page College Charity Coast Run has brought the total raised for CMRI to $180,000 over the last 25 years. Many thanks to Run founder Brent Gregory, a student at the University of New England college in 1980, and to all those who have come after him for their continued commitment.

### Treasury of Crafts – 10th Anniversary

The team have raised over $46,000 for CMRI in the last 10 years by donating a percentage of the proceeds from their craft fairs. This year's Christmas Craft Fair is on 3 and 4 December at the Don Moore Community Centre, North Rocks and 18 December at Dural Memorial Hall.

*Top to bottom:*

*Gabrielle Lord signing her latest novel 'Spiking the Girl' with delighted guests at the Northern Beaches Luncheon;*

*Narelle Williams, new president of The Burbs Committee, with her family;*

*Left to right, Bronwyn Wannan, Til Symonds (President of the Quirindi Committee), Libby Gardiner and Barry Philps at The Windy Woolshed Ball;*

*Cathie Piper, guest speaker Lisa Wilkinson and Fancy Jeans competition winner Linda Lorimer at the Ku-ring-gai Jeans for Genes luncheon.*