



# Gene therapy makes vital leap

The long-anticipated benefits of gene therapy are finally starting to take shape, reports **Clara Pirani**



**Innovation:** Cardiologist David Kaye with V Focus, a device that allows gene therapy to be used to treat heart failure

**Picture:** Michael Potter

It could be mistaken as fodder for a science fiction novel: researchers inject viruses and genes into human organs in an attempt to cure blindness, heart disease, AIDS or cancer.

However, that's the scenario being played out in more than 600 research facilities around the world, as scientists — including many Australians — believe they are on the verge of discovering how to use gene therapy as a cure for many diseases.

In the six years since researchers mapped the human genetic code, gene therapy remains an experimental field of medicine. In recent months, however, a string of trials around the world has yielded promising results.

Gene therapy involves the transfer of a gene into specific cells within the body to replace faulty genes. Last month researchers at the University of Rochester School of Medicine and Dentistry in the US used gene therapy to eliminate arthritis pain and reduce long-term joint damage in mice. Their study, published in the journal *Arthritis and Rheumatism* (2007;56:2038-2048), claimed one injection of the gene therapy relieved 100 per cent of osteoarthritic pain. The therapy also reduced joint damage by nearly 35 per cent.

## GENIE

Gene therapy involves the transfer of a gene into specific cells to replace a faulty gene, or to introduce a new gene whose function is to cure or to favorably modify the clinical course of a disease.

The process involves:

Identification of the faulty gene that causes a specific disease.

The location of the affected cells must be pinpointed.

The healthy gene has to be delivered to the cell.

### Gene transfer

Healthy genes are placed inside a harmless virus and injected into the cell.

Another technique involves manipulating stem cells in the laboratory to accept new genes that can then change their behaviour.

For example, a gene might be inserted into a stem cell that could make it better able to survive chemotherapy.



At the same time, a team at the University of Florida and The Jackson Laboratory in Maine used gene therapy to restore sight in mice with achromatopsia, a form of hereditary blindness that also strikes humans.

They said the discovery shows that it's possible to target and repair retinal cone cells — the most important cells for visual sharpness and colour vision in people.

British scientists from University College, London (UCL) took the research one step further, by attempting to restore a patient's sight using gene therapy.

Robert Johnson, 23, had copies of genes inserted into one of his eyes at Moorfields Eye Hospital in London last month.

Johnson was born with a degenerative disorder — he can only see outlines during the day and nothing at night. It will be several months before it is known if the operation is a success.

Elizabeth Rakoczy, an Australian researcher at the Lions Eye Institute in Perth, who collaborated with the UCL team, believes gene therapy could soon be used to cure some forms of blindness.

“Actually we are very close,” she told ABC Local Radio. “We have been using the same type of system in our dogs and we found that we have been able to restore vision in the dogs. We hope to start human trials this year.”

Last week researchers at The Children's Hospital at Westmead secured \$2.5 million to conduct a cancer gene therapy clinical trial for children with brain tumours.

“The aim of this research initiative is to improve the treatment that can be offered to children who have cancer,” said Peter Gunning, head of the Oncology Research Unit.

“We will be focusing on the bone marrow stem cells of children who are receiving chemotherapy for brain tumours which have

been difficult to cure using current treatment protocols.”

Despite years of investigation into gene therapy researchers are still struggling to find the best way to actually deliver the gene into the body. One of the most promising techniques involves putting the healthy gene inside a harmless virus, which has had most of its own genes removed. The virus is then transferred into the body, usually via a catheter.

Researchers at the Baker Heart Research Institute in Melbourne believe they have developed a device that allows gene therapy to be used to treat heart failure.

The device, created by David Kaye, a cardiologist and head of the institute's experimental cardiology and heart failure division, last month won the Victorian Government's 'Next Big Thing' innovation award.

The ‘closed loop’ catheter system, called V-Focus, allows the circulation of the heart to be isolated from general circulation, limiting the damage that heart failure medication can inflict on other organs.

“It also has the potential to be used in the emerging areas of gene and stem cell therapy where the development of new therapeutic agents has lacked a safe and efficient delivery

system,” the award's judges said.

Kaye says the device could provide an alternative to critically ill patients who would normally require a heart transplant. “It's a new way of delivering genes to the heart.

The procedure, which is similar to the delivery of coronary angioplasty, takes about 20 minutes.

“The genes are packaged into a virus and then that enters the cells. The benefits can last many months.”

Kaye is currently applying for regulatory approval to test the device on humans.

However, researchers at Sydney's Royal Prince Alfred Hospital last year believed it had successfully used gene transfer to cure patients with the bleeding disorder hemophilia.

People with hemophilia lack one of the essential blood clotting factors. The team treated seven hemophilic men with a healthy clotting factor gene. The gene was inserted into a virus that was introduced into the patients' livers through a catheter.

“We showed it to be safe, and we also showed, to our amazement, that we were able to increase the production of this deficient factor by at least tenfold, which would convert someone from severe hemophilia to a much milder form of the disease,” says lead researcher Professor John Rasko.

The trial results, published in the prestigious journal *Nature Medicine* (12, 592 (2006) doi:10.1038/nm0506-592b) was applauded worldwide as one of the first successful applications of gene therapy.

However, the victory was short-lived.

“A couple of months later, just as we were popping the champagne corks, one the patients who was doing extraordinarily well began to experience a decline of the factor production from his own liver, and that was associated with some minor damage to his liver,” says Rasko, who also heads the gene and stem cell therapy program at The Centenary Institute of Cancer Medicine and Cell Biology.

The patient's own immune cells were attacking the therapeutic virus which was coating the gene.

“The individual was fine, in fact he swam a triathlon leg that weekend, when his liver inflammation peaked. But at the same time, the success of the treatment waned, and his clotting factor level returned to the baseline level.”

However, Rasko says the outcome provided researchers with vital information about the way the human body copes with gene transfer.

“This effect was not observed in any of the animal models that we'd used previously.

“There are dogs that have been treated with the same form of gene therapy, and they are perfectly well seven years later and still producing the same level of factor that is able to protect them from bleeding.”

The animals' lack of prior exposure to the virus could explain the different response, Rasko says. “Between 60 to 80 per cent of humans are pre-exposed to this virus. So the human immune system is primed to attack, because it has seen the virus before.”



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Rasko's team is currently developing a trial he believes will overcome the problem.

"We will try to use some form of immune suppression so we can trick the body into ignoring the virus coat for long enough to allow the gene to become permanently established within the liver.

"If we can do that, the relevance will not just apply to hemophilia, but to a range of illnesses including cancer, heart disease and diabetes. Once we learn how to develop gene transfer efficiently, we will really overcome the biggest hurdle presented to gene therapy since the very first clinical trial that was conducted in 1990."

However, researchers and health regulators must also overcome concern from opponents of gene therapy who are worried the technology could be used for non-medical purposes.

Rasko says scientists are already grappling with the ethics of gene therapy.

"As people like myself develop these sorts of cutting-edge technologies, we must be

absolutely vigilant and aware of where this could ultimately go. What happens when we develop the capacity to give a child a gene to make them taller or smarter or faster? It's already a major question being addressing by the sporting world's anti-doping authorities."

Rasko, co-author of *Ethics of Inheritable Genetic Modification: A Dividing Line*, published last year, believes it's up to regulators and researchers to draw a clear line between the use of gene therapy for medical or cosmetic purposes.

"Unlike any previous form of therapy, it alters the genetic make-up of the cells permanently. This technology could be used to change what you are born with. So there are really important ethical questions that are raised by this. The answer is about regulation, and being very aware of the slippery slope. It's another thing altogether to consider using gene therapy for cosmetic outcomes, not medical problems."