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Finetuning gene therapy

Researchers are edging closer to reliable gene therapy, providing a revolution in healthcare.

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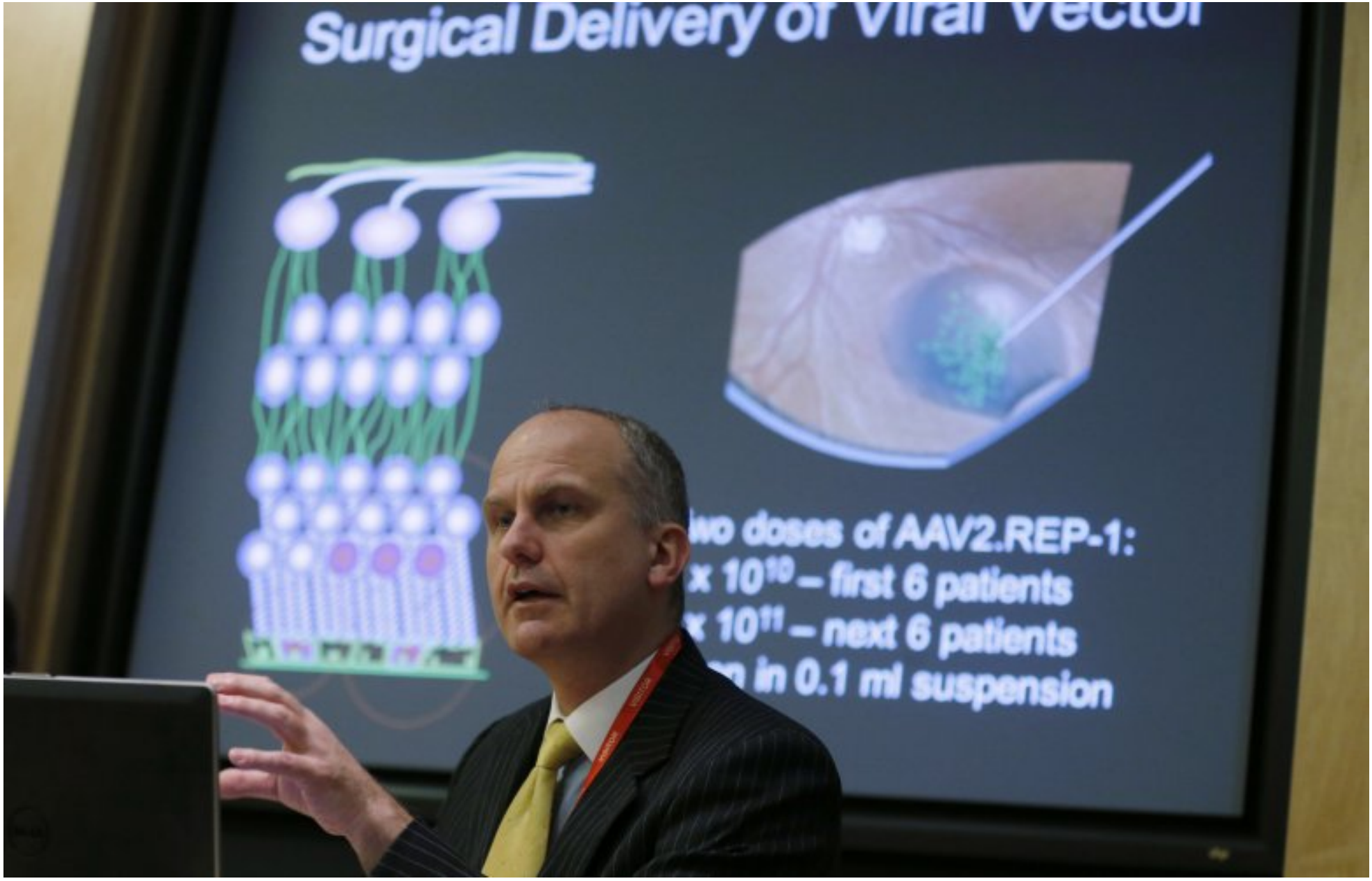

Oxford University's Robert MacLaren reports on the first clinical trial of gene therapy for choroideremia blindness. AP

The timing seemed perfect. Soon after the announcement that an experimental procedure in France treated two babies with a rare and fatal disease, a little boy with the same illness arrived at a Sydney hospital.

The babies suffered from X-linked severe combined immunodeficiency, or SCID-X1, a genetic disorder that left them with a severely weakened immune system and the inability to fight common infections. Standard treatment for SCID-X1 is a bone marrow transplant, which effectively gives the children a new and functioning immune system. But this treatment only has a high success rate if there is an appropriate donor, and this boy, like many, didn't have one.

It was hopeful news then, that in 2000 two SCID-X1 babies were successfully treated using gene therapy, a radical approach that uses genes to treat diseases. Here, stem cells were taken from the infants' bone marrow, engineered to hold a working version of the gene they lacked and reinserted into the babies. Similar trials had been conducted since 1975 but had failed. This was a major medical milestone.

With few options for the Sydney patient, Ian Alexander, now a professor at the University of Sydney, contacted the French team for more details about their breakthrough experiment. Soon his team was ready to conduct Australia's first gene therapy trial. "It was daunting and exciting at the same time," he says. "We were very anxious that things would go well for the patient, and the family." At first, the treatment seemed to be working, but after several months the boy was admitted to hospital with another infection. Ultimately, for this patient, the

procedure didn't have long-term benefits.

This experience epitomises the field of gene therapy research: "Cycles of rising hope and sinking despair," as one researcher put it. But now, the treatment finally appears to be hitting a critical point. Last year, gene therapy was successfully used to treat patients with haemophilia B and a rare form of blindness.

In 2012, the European Union approved its first gene therapy product – Glybera – which treats a genetic disorder where patients cannot break down fat molecules. "That was a huge step forward," says Casey Maguire, an assistant professor at Harvard Medical School. The approval sparked increased investment into gene therapy, with Pfizer announcing in December a multimillion-dollar injection into the field.

"We're on the cusp of seeing genetic therapy working for a lot of conditions," says Dr Samantha Ginn, Alexander's colleague at the Children's Medical Research Institute in Sydney. "After so long, the promise is really starting to pay off."

There are many approaches to correct defective genes using gene therapy, which largely depend on the disease being targeted. For example, if a gene has mutated to create a toxic product, such as cancer, scientists may snip out the dangerous DNA using a technology dubbed gene editing. While small trials have shown promising work in this area, a more tested approach is called gene addition. This works in cases where the defunct gene has stopped working, or gone silent, such as SCID-X1. Here, scientists can implant a working copy of a gene into a patient using vectors, which are often viruses. Viruses make very promising carry bags because they evolved to penetrate the walls of cells and some can slip into human DNA.

However, there are risks with using viruses, which were fully realised in 1999 when Jesse Gelsinger – an 18-year-old boy with a rare, genetic, metabolic disorder – signed up for a gene therapy trial in Pennsylvania. A working gene wrapped in a refashioned, and weakened, virus was infused into the teenager's artery. Dr Steven Raper, at the University of Pennsylvania, had given this treatment to 17 other patients, with few side effects. But 98 hours after the infusion, Gelsinger died. The virus triggered an immense immune response leading to multiple organ failure. *The New York Times* reported that Raper attended the teenager's funeral, reciting a passage by Thomas Gray: ''Here rests his head upon the lap of Earth, a youth to Fortune and Fame unknown. Fair Science frowned not on his humble birth.''

In the wake of this tragedy came the announcement of a triumph in France. "I don't think any of us were expecting an imminent success," says Alexander. Using a different virus, a team at Hôpital Necker – Enfants Malades in Paris treated two SCID-X1 babies with gene therapy. Ten

months on, the infants had a functioning immune system and were free of infections. “Many of us were delighted but surprised,” he says.

But soon after the publication, one baby in the French trial developed leukaemia as a result of the treatment. Frustratingly, the virus had stitched itself into a dangerous portion of the DNA, ultimately producing cancerous cells. By 2008, four more patients who had since undergone the therapy had leukaemia.

The reports sparked an international effort to develop safer virus-based vectors. Last October, a study published in *The New England Journal of Medicine* reported that several SCID-X1 patients were given gene therapy using a virus specifically engineered not to integrate into precarious parts of the DNA. While it’s too early to call the protocol a success, genetic analysis revealed that the virus had shoehorned itself into parts of the DNA unlikely to lead to tumours.

Meanwhile, four of the five SCID-X1 patients treated who originally developed cancer successfully underwent chemotherapy and are in remission. In 2010, it was announced that seven SCID-X1 patients who had early treatment, including those who survived the leukaemia, were doing well, nine years after treatment.

Promising results have also emerged using another virus, called the “adeno-associated virus” (AAV), which isn’t known to cause human disease. The newly approved Glybera, for example, uses a vector made from AAV.

Dr Amit Nathwani at the Royal Free Hospital in Britain employs a modified AAV to deliver genetic material into patients with haemophilia B. Last November, Nathwani reported that 10 patients who received the treatment four years ago had significantly improved symptoms, with few side effects. Feeling optimistic, Nathwani believes his therapy will hit the market within 10 years.

While safety has improved, one “big problem” remains, says Maguire. In many cases, our immune system has already been exposed to the natural viruses that are modified for gene therapies. This means that our immune cells may remember and attack the gene-carrying viral packages, rendering them inactive.

Researchers are working around this by choosing rare AAV strains, or even forgoing viruses and building vectors from scratch using synthetic nanoparticles enmeshed with DNA. Another strategy is to tackle diseases where the viral packages can be directly injected into parts of the body with few immune cells, such as the brain or eye.

Recently, six patients with a rare, genetic form of blindness called choroideremia were treated using gene therapy. An Oxford University team led by Professor Robert MacLaren injected a corrective gene yoked with AAV directly into the retina of the patients. Reporting in *The Lancet* last March, he said the virus managed to ferry the gene into the cells of the retina, improving the sight of all the patients. One patient said he could see stars again, which he hadn't for a "long, long time". According to MacLaren, the technique could soon help patients with more common causes of blindness, such as age-related macular degeneration.

While the results are hopeful, "the optimist has to be steeled," says Matthew Simunovic, an ophthalmologist currently working with MacLaren's team. In 2011, gene therapy was used to treat another genetic form of blindness called Leber's congenital amaurosis. Initially hailed as a success, by 2013 it emerged that certain cells in the patient's eye were still deteriorating. This suggests, says MacLaren, "that more work was needed to work out the correct dose of gene therapy".

Meanwhile, hundreds of clinical trials continue today. Scientists in the field are confident, with Maguire recently writing in a paper about the current state of gene therapy of "dreams coming true". Indeed, "exciting" is a word many researchers are using, but with past false dawns in mind, they use it cautiously.

TAGS: gene therapy SCID-X1 Ian Alexander Steven Raper Amit Nathwani Robert MacLaren

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