'Bubble kid' success puts gene therapy back on track

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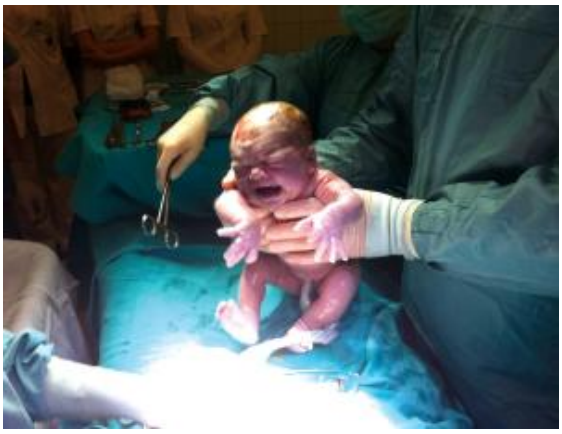
Five children with a genetic disease that wipes out their immune system have successfully been treated with gene therapy

Editorial: "Gene therapy needs a hero to live up to the hype"



Nina: born with a bad gene *(Image: courtesy of the Warnell Family)*

MOST parents dream of a 5-week-old baby who sleeps through the night, but Aga Warnell knew something was wrong. Her baby, Nina, just wasn't hungry in the way her other daughters had been.

Within weeks, Nina became very ill, says her father, Graeme. She was admitted to hospital with a rotavirus infection. Then she picked up pneumonia.

It turned out Nina had a condition called severe combined immunodeficiency (SCID). She had been born without an immune system due to a genetic defect. It is also known as "bubble boy" disease, since people affected have to live in a sterile environment. "The doctors said 'you need to prepare yourself for the fact that Nina probably isn't going to survive'," says Graeme.

A year-and-a-half later, Nina is a happy little girl with a functioning immune system. She has gene therapy – and its latest improvements – to thank for it.

SCID was the first condition to be treated with gene therapy more than 20 years ago. A virus was used to replace a faulty gene with a healthy one. But in subsequent trials, four young patients were diagnosed with leukaemia two years after receiving a similar treatment. An 18-year-old also died following a reaction to a virus used in gene therapy for a liver condition. It was the start of a rocky road (see "Trials and tribulations of gene therapy").

Gene therapy has come a long way since, and Nina's case, along with others, mark a turning point: researchers seem to have found a safer way of manipulating our genes.

Preliminary results for the first two children to receive the improved SCID gene therapy – 18 months ago – were presented at the European Society of Gene and Cell Therapy conference in Madrid, Spain, last week. The children's immune systems have continued to improve since receiving the treatment, says Bobby Gaspar of Great Ormond Street Hospital in London, who led the trial.

Three further children – including Nina – have been treated since then, and they too are showing signs of a full recovery.

All five had a form of the disorder called ADA-SCID, caused by a faulty gene for adenosine deaminase. This enzyme usually dispatches a toxic molecule from white blood cells. In its absence the toxin builds up, killing the cells that fight infections.

Stem cells were harvested from Nina's bone marrow and given a working version of the *ADA* gene, before being injected back in. That was in April, and she wasn't expected to show much of an

improvement before December. But by August her white blood cell count had nearly doubled, and today she has the immune system of a healthy newborn baby.

"At last, the successes are beginning to be more than the failures," says Inder Verma at the Salk Institute in La Jolla, California. "All of the hard work has come to a point where gene therapy could become a more routine modality of medicine."

The concept of gene therapy is simple: insert a working gene into a person with a faulty version, and its product should overcome the defect. But the reality is more complicated, because you need something to integrate the gene into the patient's DNA and persuade the cells to read it. In other words, you need a vector.

Viruses are the obvious choice as they survive and spread by inserting their genes into the host's genome. Retroviruses work like this, so were the first choice for the initial gene therapy trials. The problem is that they insert genes at random locations in the genome, as well as inserting regulatory sequences that can sometimes activate nearby genes and trigger cancer.

To overcome this, researchers have turned to lentiviruses. These still insert genes randomly, but can be modified to disable some regulatory sequences. "The new generation of lentiviral vectors is much safer, although the risk is not zero," says Patrick Aubourg at the French National Institute of Health and Medical Research in Paris. "However, we don't use gene therapy to treat a toothache, we try to treat diseases which result in early death."

Earlier this year, three children with a degenerative enzyme disorder were successfully treated using a modified lentivirus, along with three with an immune disorder called Wiskott-Aldrich syndrome. Promising results have also been seen in degenerative disease adrenoleukodystrophy and the blood-cell disorder beta-thalassaemia. Around 700 gene therapy trials using lentiviruses are ongoing.

Other vectors are showing promise too. For example, adeno-associated virus (AAV) doesn't insert its genes into the genome, but places them alongside it, meaning they get read but are not passed to subsequent generations of cells. That is a problem if you are interested in relatively short-lived cells, like immune cells, but not if you want to modify neurons or liver cells, which last decades.

In Madrid last week, Amit Nathwani of the Royal Free NHS Trust in London announced that six people treated for haemophilia using AAV in early 2011 are still producing the blood clotting factor they previously lacked.

It's a principle that could be applied to other diseases where you want a protein or enzyme to be released into the blood, says Maria Limberis at the University of Pennsylvania in Philadelphia.

As for Nina, her health continues to improve and the family is emerging from the isolation they chose to help protect her. It wasn't an easy decision to enrol in the trial, says Graeme. "But we thought if we can cure Nina by doing something that's going to advance medical practice and maybe help other children, then that's the route we should take."

This article appeared in print under the headline "Nowhere to hide for faulty genes"

Trials and tribulations of gene therapy

1990 First approved gene therapy trial. Immune cells from 4-year-old Ashanti DeSilva are given working versions of the *ADA* gene to treat severe combined immunodeficiency disorder (SCID). It works, but only temporarily.

1992 ADA-SCID is successfully treated through gene therapy on stem cells harvested from bone marrow.

1999 18-year-old Jesse Gelsinger dies following an immune reaction to the virus vector used to insert the corrected gene. US Food and Drug Administration suspends several trials pending re-evaluation of ethical and procedural practices.

2000 Announcement that two boys in France with X-linked SCID or "bubble boy" disease have been cured using gene therapy.

2002 French SCID trial suspended after four children develop leukaemia as a result of the retrovirus vector.

2003 Chinese company Shenzhen SiBiono GeneTech gains approval for treating head and neck cancer with Gendicine, a modified adenovirus carrying a tumour-suppressor gene.

2003 Researchers in the US begin the first human trial using a modified lentivirus (pictured below). It is a disabled HIV virus carrying a gene to inhibit replication. Trial is a success.

2009 Eight-year-old Corey Haas, who has a rare inherited eye disease and is almost blind, gains normal vision following gene therapy to replace a retinal pigment protein.

2009 Progression of the degenerative disease adrenoleukodystrophy is halted in two boys using gene therapy.

2010 An adult with blood disorder beta-thalassaemia no longer needs monthly blood transfusions following gene therapy to insert a corrected beta-globin gene into stem cells that make blood.

2011 Six people with clotting disorder haemophilia B see a reduction in symptoms after gene therapy on liver cells.

2012 Glybera becomes the first gene therapy drug to be approved in the West, with European approval to treat lipoprotein lipase deficiency.

2013 Two papers describe the treatment of children with a degenerative disorder called metachromatic leukodystrophy and immune disorder Wiskott-Aldrich syndrome using gene therapy (*Science*, doi.org/pnv; doi.org/ppk).

This week Announcement that five children with ADA-SCID have been successfully treated and are doing well.

physics rocks her universe

Maybe...

father of inflation?

glow

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