News in focus

ELISABETH SCHNEIDER CHARPENTIER/LOOK AT SCIENCES VIA SPL

A child receives a gene therapy for Duchenne muscular dystrophy.

CAN GENE THERAPY BE SAVED FROM IMMUNE-SYSTEM SABOTAGE?

People treated with gene therapy cannot receive a second dose for fear of a dangerous immune response. Researchers hope to find a way around this.

By Heidi Ledford

When Donavon Decker volunteered for a trial of a gene therapy, it wasn't for his own benefit. Decker has a genetic muscle disorder, but the trial aimed to assess only the therapy's safety, not its effectiveness. And the experimental treatment — a virus that would shuttle a healthy gene into his cells — would be injected into a muscle in his foot and was not expected to travel much farther.

What's more, his immune response to the virus might rule out future treatments: an assault mounted by his immune system on the virus could not only disable the therapy but also harm Decker.

Decker thought of his family — he had four sisters and two nieces with the same condition, limb-girdle muscular dystrophy — and enlisted anyway. And, he thought, scientists would eventually work out a way to quench immune responses to the virus, giving people like him access to future gene therapies.

Nearly a quarter of a century later, that has not happened. "It's a big disappointment to me," he says. "I really didn't think I was going to be here 25 years later and still not be able to be re-dosed."

The field of gene therapy has blossomed over the past decade, generating a stream of official approvals for various treatments and a burgeoning pipeline of clinical trials. But the inability to administer more than one dose of a virus carrying restorative genes limits what gene therapy can do. At the American Society of Gene and Cell Therapy annual meeting in Baltimore, Maryland, on 7–11 May, researchers presented myriad potential ways of overcoming the problem, from suppressing immune responses to cloaking the virus or leaving it out altogether.

"This is a huge issue for the field," says Martin Kang, who develops gene therapies for respiratory conditions at the Medical

University of South Carolina in Charleston.

The need for a solution has become clearer as researchers have learnt more about gene therapy. Long-term data show that the effects of some gene therapies wane over time (M. Muhuri *et al. Mol. Ther.* **30**, 1364–1380; 2022); others might need to be given in multiple doses to provide a significant benefit even in the short term. And many people are ineligible to participate in clinical trials at all because of previous exposure to adeno-associated viruses (AAV), relatively harmless viruses that are used in many gene therapies and that circulate in the environment.

"These are the new heartbreaks in the rare-disease community," says Annie Kennedy, chief of policy, advocacy and patient engagement at the EveryLife Foundation for Rare Diseases in Washington DC. "There's now this new measure that you have no control over: whether or not you have a pre-existing antibody."

Studies in multiple countries have estimated that 30–70% of the population has antibodies that can neutralize AAV. Some families, eager to enrol a loved one in a clinical trial, will choose to self-isolate for years to minimize the risk of exposure to AAV.

Taming side effects

Scientists working on mice have searched for years for drugs that prevent immune responses to gene therapy. Some are testing medications that prevent rejection after organ transplants. Others are trying to dampen the activity of antibody-producing cells called B cells.

But so far, the results have been disappointing. "There's a ton of work in this space," says Lindsey George, a paediatrician at the University of Pennsylvania in Philadelphia. "But I haven't seen anything that's really viable coming out."

One problem might be the intense focus on B-cell responses, says Kang, because other immune cells called T cells can also remember past encounters with viruses. T-cell responses "might play a larger role than people realize", he says.

At the Baltimore meeting, researchers presented the results of animal studies suggesting that more effective methods might be on the horizon. Nicholas Giovannone, an immunologist at Regeneron in Tarrytown, New York, described antibodies that block a key protein called CD40 that is used by both B cells and T cells. Mice given the antibody before AAV had levels of antibodies against the virus that were indistinguishable from those of mice that had not been given AAV. "We think this might be a one–two punch where we can tackle both the B- and T-cell response," Giovannone said.

Kang and his colleagues have also been trying to mute T-cell responses since finding that their experimental gene therapy for a genetic lung disorder called surfactant protein B deficiency might need to be readministered to achieve long-term benefits. At the meeting, Kang reported results from his team's efforts to suppress T-cell and other immune responses to AAV by inserting certain genetic sequences into the virus. The researchers found that one dose of this enhanced gene therapy suppressed some immune responses against AAV in mice — but not all.

To their surprise, a second dose of the gene therapy was effective against the respiratory ailment. It's a mystery why the approach worked despite the residual immune responses, says Kang, but might have something to do with the fact that the therapy was administered directly into the lungs, rather than the bloodstream.

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As is often the case in medicine, it might ultimately take a combination of approaches to achieve re-dosing of gene therapies, says Julie Crudele, a gene-therapy researcher at the University of Washington in Seattle. "The answer is likely to be a cocktail."

Others are focusing on alternatives to AAV. At the meeting, Chris Wright, head of translational research at Ring Therapeutics in Cambridge, Massachusetts, presented data showing that a class of viruses called anelloviruses can evade detection by the mouse immune system, can shuttle DNA into mouse cells and can be administered multiple times safely.And many researchers are working on non-viral alternatives, such as fatty particles that can carry DNA or RNA into cells,.

Long wait

Decker has decided to take matters into his own hands and is raising money to launch a company focused on non-viral methods of gene therapy. Last time he was tested for AAV antibodies, 14 years after his clinical trial, he was still positive.

Despite his frustration, Decker does not regret his decision to participate in the clinical trial 25 years ago. Two weeks after he was treated, the death of a teenager named Jesse Gelsinger in another gene-therapy study sent the field spinning. It would take years to right itself, and Decker is grateful that he was able to contribute to data that might have helped the field to progress even during turbulent times.

"The only reason, in my opinion, that gene therapy is even possible today is because of the trial I was in," he says.

WHO WILL MAKE ALPHAFOLD3 OPEN SOURCE?

Researchers want fully accessible versions of DeepMind's blockbuster protein-structure model.

By Ewen Callaway

When Google DeepMind unveiled AlphaFold3 — the latest edition of its revolutionary protein-structure-prediction AI — in *Nature*[1] in May, it came with a hitch. Unlike a previous version[2], there was no computer code describing the advance to accompany the paper.

The London-based company reversed course days later, promising to release the code by the end of the year. But the omission has set researchers worldwide racing to develop their own open-source versions of AlphaFold3, an artificial-intelligence (AI) model that can predict the structure of a protein, as well as other molecules, including potential new drugs. Other scientists are doing their best to hack the web version of AlphaFold3 that DeepMind released to skirt its limitations.

"It would be bad if capabilities that are just so fundamental to our ability to do drug discovery and other things that are relevant for human health end up getting locked up," says Mohammed AlQuraishi, a computational biologist at Columbia University in New York City. His 'OpenFold' team has already begun[3] coding an open-source version of AlphaFold3 that it hopes to complete this year.

Scientists disappointed

DeepMind's initial withholding of code for AlphaFold3, as well as the 9 May publication in *Nature*, irked many scientists (*Nature*'s news team is independent of its journal team). *Nature*'s policies say that code associated with studies should typically be made