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The Quest to Overcome Gene Therapy's Failures

Tragic side effects plagued the field's early years, but researchers are finding ways to minimize the risks

By Tanya Lewis on November 1, 2021



Credit: Luisa Jung

Audrey was six months old when her parents first noticed something wasn't right. Without warning, her body stiffened, and her eyes rolled into the corners of their

sockets for hours at a time. Despite visits to multiple specialists, no one knew what was wrong. Her doctors prescribed seizure medication—lots of it—which sedated her but did not stop the eye-rolling. Finally, they confessed that they did not know how to help and sent Audrey and her parents home with a handful of pamphlets about living with a disability.

Genetic tests later diagnosed Audrey with a condition known as aromatic l-amino acid decarboxylase (AADC) deficiency, caused by mutations in a single gene. The extremely rare disorder manifests in infancy and lowers the activity of AADC, an enzyme that is critical for making the brain-signaling chemicals dopamine and serotonin. It causes severe developmental and motor disabilities, as well as sleep and mood problems. Most children with the condition are unable to talk, sit up or support their own weight.

After years of frustration, Audrey's parents enrolled her in a clinical trial led by Krystof Bankiewicz, a professor of neurosurgery at the University of California, San Francisco, and the Ohio State University College of Medicine. The gene therapy Bankiewicz and his colleagues were testing uses a harmless virus as a vector to introduce an intact version of the gene responsible for making the AADC enzyme. Seven children participated in the trial. The researchers injected the virus directly into each child's brain near neurons they hoped would start making AADC and, subsequently, dopamine.

The children ranged in age from four through nine years old at the beginning of the trial (Audrey was six at the time). The results were dramatic: by three months after surgery, six of the seven children stopped having oculogyric crises—the distinctive eye-rolling that is a hallmark of the disease. The seventh child also improved initially but died seven months later from complications of the disease itself, Bankiewicz says. A year postsurgery all six surviving children could control their heads normally, and four could sit independently. After a year and a half, Audrey and one other child were walking with hand support and learning to use muscles they had previously been unable to command. So far none of the children has shown any serious side effects.

Outcomes like Audrey's would not have been possible without decades of research and patients who volunteered for experimental treatments, knowing they could be risking their lives, to help move gene therapy forward. Serious side effects, some deadly, threatened to derail the field in its early years, prompting researchers to step

back and reconsider their approach. Convinced of the promise of genetic cures and of the potential to find safer, more precise gene delivery methods, they persisted.

Since then, gene therapy has yielded some notable successes [see "[Success Stories](#)"]. Yet the quest to control side effects is far from over. As in any pioneering field of medical science, researchers must strike a balance between advancing knowledge that could help cure devastating diseases and proceeding with caution to protect patients.

FIRST DO NO HARM

Jesse Gelsinger was 18 years old in 1999, when he joined one of the first clinical trials of gene therapy [see "[The Gene Fix](#)"]. Gelsinger suffered from an inherited genetic disorder called ornithine transcarbamylase (OTC) deficiency, which causes toxic levels of ammonia to build up in the blood. Untreated, that buildup can lead to vomiting, lethargy and, in severe cases, death. The condition affects up to one in 50,000 infants and is caused by mutations in the *OTC* gene. Standard treatment for the condition involves a restricted diet and supplementation known as alternative pathway therapy. Gelsinger was being treated for the condition and had a mild case, but he occasionally experienced episodes of high ammonia levels, known as hyperammonemia, once even slipping into a coma.

The gene therapy trial he enrolled in used a type of cold virus known as an adenovirus that had been engineered to deliver a working version of the *OTC* gene to his liver cells. Gelsinger was one of two participants receiving the highest dose. Within days of the treatment, however, his condition declined rapidly. His body launched a severe inflammatory response that led to organ failure and, ultimately, brain death.

A few years later several children who had been treated with gene therapy for a severe immune disease developed cancer.

Research funding dried up, and many investigators abandoned the field. But those who remained began to make improvements in both the safety and the efficacy of viral vectors. They also began exploring a gene-editing method called CRISPR, which could enable more targeted therapies but came with a new set of risks.

Gene therapy has come a long way since Gelsinger died—Audrey is living proof of that. Yet researchers remain vigilant about the specter of side effects. “We’re in a

very different place now,” says Mark Batshaw, the physician who helped to lead the trial involving Gelsinger more than 20 years ago and is now a developmental pediatrician at Children’s National Hospital.* “We know a lot more about vectors. We know a lot more about the immunity that is associated with that. And I think there’s a lot more care.”



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After Gelsinger’s death, the U.S. Food and Drug Administration banned James Wilson, the scientist whose laboratory developed the therapy Gelsinger received, and his institution, the University of Pennsylvania’s Institute for Human Gene Therapy, from conducting human trials for at least five years. An FDA notice cited repeated and deliberate violations of the trial protocol for an investigational drug. The agency suspended all research at Wilson’s institute, too.

But it was not the end for gene therapy or for Wilson’s career. “There was a precipitous decline in enthusiasm in supporting the field,” Wilson says. Nevertheless, “there were a few of us who continued to work on gene therapy,” he says. “We pivoted from clinical applications to basic science around the delivery of genes.” Wilson and his colleagues turned back to the lab bench to understand what went wrong in Gelsinger’s death. Their best hypothesis is that he had antibodies to adenovirus from a previous exposure to the virus and that these relics of a former infection supercharged his immune system’s response to the adenovirus vector.

Wilson and other researchers took a hard look at the issue of side effects and how to minimize them. Because the viral vector seemed to be the biggest risk, they switched to adeno-associated viruses (AAVs), which proved far safer. Today AAVs are used in numerous therapies, including an approved drug for spinal muscular atrophy. “I’m glad we stayed with it,” Wilson says.

LEARNING FROM FAILURE

Around the same time as the Gelsinger trial, scientists in France and England were working on a therapy for severe combined immunodeficiency syndrome (SCID), a

genetic condition that affects at least one in 50,000 babies. It is sometimes referred to as “bubble boy disease” because those afflicted with it, primarily boys, are born without an immune system and must live in isolated, sterile environments to keep from getting sick. It can be cured with a bone marrow transplant from a matched donor, but only about a quarter of affected children find such a match. Without treatment, children with SCID usually die within the first year of life.

For their vector, the researchers turned to a group of viruses called gammaretroviruses because they believed them to be efficient at delivering genetic material to cells. In a pair of clinical trials, they targeted a form of SCID that is passed down from a mother to her baby on an X chromosome, known as SCID-X1. It is caused by errors in a gene that encodes a protein called IL2RG. In both trials, the patients’ own bone marrow stem cells were collected and isolated. The researchers used a gammaretroviral vector to insert a working copy of the *IL2RG* gene into them, then reinfused the modified cells. Initially the therapy appeared somewhat successful: most of the 10 children who were treated started producing functional T cells—an important component of a working immune system. But within three to six years half the subjects developed leukemia, and one died. The viral vectors are believed to have activated a known cancer-causing gene. The FDA halted all U.S. trials involving a retroviral vector aimed at modifying bone marrow stem cells.

“Our knowledge came from animal models,” says Marina Cavazzana, a pediatrician and hematologist at Paris Descartes University’s Necker Hospital, who wrote the clinical protocol and handled patient follow-up for the clinical trial in France. The problem, she says, is that the animal models were unable to predict human toxicity. “I stopped the clinical trial, we came back to the bench, and we tried to explain the reason for these side effects. And we came back again to the clinic,” she says.

David Williams, chief of hematology and oncology at Boston Children’s Hospital, was involved in those early SCID trials. “In the end,” he says of both the SCID trials and Gelsinger’s trial, “you have to try these things in human beings to completely understand the benefits versus the risks.”

When Williams and his colleagues resumed their work on SCID a decade later, they created a modified version of their gammaretrovirus to avoid activating cancer-causing oncogenes. It still prompted the development of just one type of immune cell, however, and recipients required continued intravenous injections to maintain

production. But nearly a decade later none of the subjects has shown signs of leukemia or other side effects.

It was yet another viral vector that helped to push the SCID effort across the finish line. In 2016 a team led by Ewelina Mamcarz, a bone marrow transplant specialist at St. Jude Children's Research Hospital in Memphis, launched a trial for SCID-X1 using a lentivirus (a virus related to HIV) as a vector. Researchers built a "firewall" into it that would prevent the activation of any parts of the genome that might cause leukemia. Mamcarz and her colleagues also pretreated patients with chemotherapy to make room for the modified bone marrow stem cells.

Mamcarz's team has treated a total of 18 infants with this gene therapy. To date, about five years post-treatment, none has developed leukemia. "We are hopeful we're kind of out of the woods now, but we will continue to monitor patients closely," Mamcarz says. "My anxiety level was much higher when we started [the trial] because there was so much unknown," she says. "I think I can sleep at peace now, years into this gene therapy in infants, but we never rest."

Concerns about gene therapy's side effects have also been front of mind for researchers working on other conditions. Sickle cell disease, which affects about 300,000 infants born every year and occurs more commonly among people of African descent, has long been a prime target for gene therapy because it, too, is caused by a single-gene defect. This condition causes red blood cells to take on a sickle shape and clump together, making them unable to transport oxygen efficiently. People with the disease experience debilitating pain crises, strokes and other problems, and it can be fatal. Although treatments exist, the only cure is a risky bone marrow or stem cell transplant.

Bluebird Bio, a biotech company in Cambridge, Mass., reported promising results from a clinical trial of its sickle cell gene therapy in late 2020. Nineteen patients were treated with a lentiviral vector containing a working version of the gene that encodes a component of adult hemoglobin—all 19 stopped having severe pain crises within six months. But more than five years later two patients in a different cohort developed a rare blood cancer called acute myeloid leukemia.

The FDA placed a clinical hold on the Bluebird Bio study, as well as several similar trials, while the company investigated these cases. Bluebird Bio's own investigation

found that the leukemia was unlikely to be related to gene therapy. According to Rich Colvin, Bluebird Bio's chief medical officer, in one of the cases the viral vector was not found in the cancer cells, and in the other, viral DNA was present but had not integrated into any gene known to be involved in leukemia development. In June 2021 the FDA lifted its hold on the trials, which have since resumed.

Bluebird Bio is also testing a gene therapy for patients with X-linked adrenoleukodystrophy (ALD), a devastating disease that primarily affects boys and gives them only a five- to 10-year life expectancy. In that trial, one of the 67 patients developed myelodysplastic syndrome, a condition that can lead to leukemia, and this time it was found to be related to the viral vector. The FDA has now placed the trial on hold. Colvin says the benefits of the therapy still outweigh the risk of ALD, which would have proved fatal. But he knows it is a delicate balance: "I think you have to have humility when you're manipulating the human genome."

RISK VS. BENEFIT

Viral vectors, by their very nature, can insert themselves into an undesired part of the target cell's genome. But newer technology is enabling much more precise edits to a gene. The CRISPR technique is already being used in some gene therapies. Although there is a potential risk of so-called off-target effects on other parts of the genome, these have not been observed in the early clinical trials.

In a trial sponsored by Cambridge, Mass.-based CRISPR Therapeutics and Boston-based Vertex Pharmaceuticals involving CRISPR gene therapy, two patients with sickle cell disease and 20 patients with a related condition called beta thalassemia saw near-complete improvement of their symptoms, according to unpublished data. Although longer-term follow-up is needed, David Altshuler, chief scientific officer at Vertex Pharmaceuticals, calls the results a "medical and scientific milestone."

With all new therapies, the risk of side effects must be considered in the context of the diseases being treated. A condition such as AADC deficiency can be fatal, and Audrey's mother, Carrie, knew that when she enrolled her daughter in the U.C.S.F. clinical trial. She was desperate and figured any improvement would be better than the status quo.

Three years after enrolling Audrey in the trial, Carrie says that her daughter is a “totally different kid.” She doesn’t have the eye-rolling anymore. She is learning to eat food by mouth and to speak some words. Thanks to her talking device—a touch-pad machine that allows her to activate spoken, computer-generated phrases—she can communicate. Carrie says that before the treatment, her daughter could understand what people were saying, but she could not express herself. “Now she can just really speak her mind,” Carrie says.

Audrey continues to struggle with some things, including balance and speech. But her life today is far from what it might otherwise have looked like. And in that one gene therapy’s success, Carrie says, other families can find hope. “If we don’t do it, we know the end result,” she says. But “if it can do anything, even a little bit, it’s already a win.”

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**Editor’s Note (10/20/21): This sentence was edited after posting to include Mark Batshaw’s current affiliation.*

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