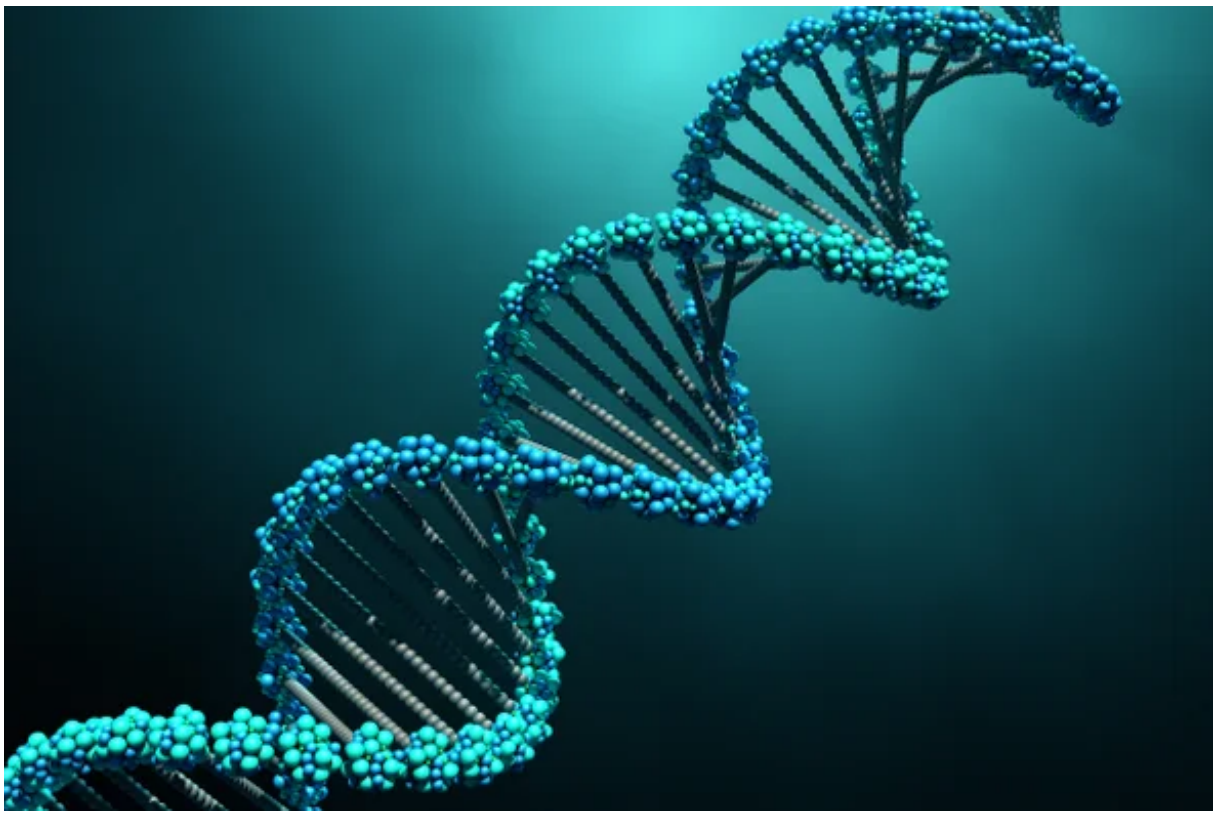
Innovations

MEDICINE

Four Success Stories in Gene Therapy

The field is beginning to fulfill its potential. These therapies offer a glimpse of what's to come

By Jim Daley on November 1, 2021



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After numerous setbacks at the turn of the century, gene therapy is treating diseases ranging from neuromuscular disorders to cancer to blindness. The success is often qualified, however. Some of these therapies have proved effective at alleviating

disease but come with a high price tag and other accessibility issues: Even when people know that a protocol exists for their disease and even if they can afford it or have an insurance company that will cover the cost—which can range from $400,000 to $2 million—they may not be able to travel to the few academic centers that offer it. Other therapies alleviate symptoms but don't eliminate the underlying cause.

"Completely curing patients is obviously going to be a huge success, but it's not [yet] an achievable aim in a lot of situations," says Julie Crudele, a neurologist and gene therapy researcher at the University of Washington. Still, even limited advances pave the way for ongoing progress, she adds, pointing to research in her patients who have Duchenne muscular dystrophy: "In most of these clinical trials, we learn important things."

Thanks to that new knowledge and steadfast investigations, gene therapy researchers can now point to a growing list of successful gene therapies. Here are four of the most promising.

GENE SWAPS TO PREVENT VISION LOSS

Some babies are born with severe vision loss caused by retinal diseases that once led inevitably to total blindness. Today some of them can benefit from a gene therapy created by wife-and-husband team Jean Bennett and Albert Maguire, who are now ophthalmologists at the University of Pennsylvania.

When the pair first began researching retinal disease in 1991, none of the genes now known to cause vision loss and blindness had been identified. In 1993 researchers identified one potential target gene, *RPE65*. Seven years later Bennett and Maguire tested a therapy targeting that gene in three dogs with severe vision loss—it restored vision for all three.

In humans, the inherited condition that best corresponds with the dogs' vision loss is Leber congenital amaurosis (LCA). LCA prevents the retina, a layer of light-sensitive cells at the back of the eye, from properly reacting or sending signals to the brain when a photon strikes it. The condition can cause uncontrolled shaking of the eye (nystagmus), prevents pupils from responding to light and typically results in total blindness by age 40. Researchers have linked the disease to mutations or deletions in

any one of 27 genes associated with retinal development and function. Until gene therapy, there was no cure.

Mutations in *RPE65* are just one cause of inherited retinal dystrophy, but it was a cause that Bennett and Maguire could act on. The researchers used a harmless adeno-associated virus (AAV), which they programmed to find retinal cells and insert a healthy version of the gene, and injected it into a patient's eye directly underneath the retina. In 2017, after a series of clinical trials, the Food and Drug Administration approved voretigene neparvovecrzyl (marketed as Luxturna) for the treatment of any heritable retinal dystrophy caused by the mutated *RPE65* gene, including LCA type 2 and retinitis pigmentosa, another congenital eye disease that affects photoreceptors in the retina. Luxturna was the first FDA-approved in vivo gene therapy, which is delivered to target cells inside the body (previously approved ex vivo therapies deliver the genetic material to target cells in samples collected from the body, which are then reinjected).

Spark Therapeutics, the company that makes Luxturna, estimates that about 6,000 people worldwide and between 1,000 and 2,000 in the U.S. may be eligible for its treatment—few enough that Luxturna was granted "orphan drug" status, a designation that the FDA uses to incentivize development of treatments for rare diseases. That wasn't enough to bring the cost down. The therapy is priced at about $425,000 per injection, or nearly $1 million for both eyes. Despite the cost, Maguire says, "I have not yet seen anybody in the U.S. who hasn't gotten access based on inability to pay."

Those treated show significant improvement: Patients who were once unable to see clearly had their vision restored, often very quickly. Some reported that, after the injections, they could see stars for the first time.

While it is unclear how long the effects will last, follow-up data published in 2017 showed that all 20 patients treated with Luxturna in a phase 3 trial had retained their improved vision three years later. Bennett says five-year follow-up with 29 patients, which is currently undergoing peer review, showed similarly successful results. "These people can now do things they never could have dreamed of doing, and they're more independent and enjoying life."

TRAINING THE IMMUNE SYSTEM TO FIGHT CANCER

Gene therapy has made inroads against cancer, too. An approach known as chimeric antigen receptor (CAR) T cell therapy works by programming a patient's immune cells to recognize and target cells with cancerous mutations. Steven Rosenberg, chief of surgery at the National Cancer Institute, helped to develop the therapy and published the first successful results in a 2010 study for the treatment of lymphoma.

"That patient had massive amounts of disease in his chest and his belly, and he underwent a complete regression," Rosenberg says—a regression that has now lasted 11 years and counting.

CAR T cell therapy takes advantage of white blood cells, called T cells, that serve as the first line of defense against pathogens. The approach uses a patient's own T cells, which are removed and genetically altered so they can build receptors specific to cancer cells. Once infused back into the patient, the modified T cells, which now have the ability to recognize and attack cancerous cells, reproduce and remain on alert for future encounters.

In 2016 researchers at the University of Pennsylvania reported results from a CAR T cell treatment, called tisagenlecleucel, for acute lymphoblastic leukemia (ALL), one of the most common childhood cancers. In patients with ALL, mutations in the DNA of bone marrow cells cause them to produce massive quantities of lymphoblasts, or undeveloped white blood cells, which accumulate in the bloodstream. The disease progresses rapidly: adults face a low likelihood of cure, and fewer than half survive more than five years after diagnosis.

When directed against ALL, CAR T cells are ruthlessly efficient—a single modified T cell can kill as many as 100,000 lymphoblasts. In the University of Pennsylvania study, 29 out of 52 ALL patients treated with tisagenlecleucel went into sustained remission. Based on that study's results, the FDA approved the therapy (produced by Novartis as Kymriah) for treating ALL, and the following year the agency approved it

for use against diffuse large B cell lymphoma. The one-time procedure costs upward of $475,000.

CAR T cell therapy is not without risk. It can cause severe side effects, including cytokine release syndrome (CRS), a dangerous inflammatory response that ranges from mild flulike symptoms in less severe cases to multiorgan failure and even death. CRS isn't specific to CAR T therapy: Researchers first observed it in the 1990s as a side effect of antibody therapies used in organ transplants. Today, with a combination of newer drugs and vigilance, doctors better understand how far they can push treatment without triggering CRS. Rosenberg says that "we know how to deal with side effects as soon as they occur, and serious illness and death from cytokine release syndrome have dropped drastically from the earliest days."

Through 2020, the remission rate among ALL patients treated with Kymriah was about 85 percent. More than half had no relapses after a year. Novartis plans to track outcomes of all patients who received the therapy for 15 years to better understand how long it remains effective.

PRECISION EDITING FOR BLOOD DISORDERS

One new arrival to the gene therapy scene is being watched particularly closely: in vivo gene editing using a system called CRISPR, which has become one of the most promising gene therapies since Jennifer Doudna and Emmanuelle Charpentier discovered it in 2012—a feat for which they shared the 2020 Nobel Prize in Chemistry. The first results from a small clinical trial aimed at treating sickle cell disease and a closely related disorder, called beta thalassemia, were published this past June.

Sickle cell disease affects millions of people worldwide and causes the production of crescent-shaped red blood cells that are stickier and more rigid than healthy cells, which can lead to anemia and life-threatening health crises. Beta thalassemia, which affects millions more, occurs when a different mutation causes someone's body to produce less hemoglobin, the iron-rich protein that allows red blood cells to carry oxygen. Bone marrow transplants may offer a cure for those who can find matching donors, but otherwise treatments for both consist primarily of blood transfusions and medications to treat associated complications.

Both sickle cell disease and beta thalassemia are caused by heritable, single-gene mutations, making them good candidates for gene-editing therapy. The method, CRISPR-Cas9, uses DNA sequences from bacteria (clustered regularly interspaced short palindromic repeats, or CRISPR) and a CRISPR-associated enzyme (Cas for short) to edit the patient's genome. The CRISPR sequences are transcribed onto RNA that locates and identifies DNA sequences to blame for a particular condition. When packaged together with Cas9, transcribed RNA locates the target sequence, and Cas9 snips it out of the DNA, thereby repairing or deactivating the problematic gene.

At a conference this past June, Vertex Pharmaceuticals and CRISPR Therapeutics announced unpublished results from a clinical trial of beta thalassemia and sickle cell patients treated with CTX001, a CRISPR-Cas9-based therapy. In both cases, the therapy does not shut off a target gene but instead delivers a gene that boosts production of healthy fetal hemoglobin—a gene normally turned off shortly after birth. Fifteen people with beta thalassemia were treated with CTX001; after three months or more, all 15 showed rapidly improved hemoglobin levels and no longer required blood transfusions. Seven people with severe sickle cell disease received the same treatment, all of whom showed increased levels of hemoglobin and reported at least three months without severe pain. More than a year later those improvements persisted in five subjects with beta thalassemia and two with sickle cell. The trial is ongoing, and patients are still being enrolled. A Vertex spokesperson says it hopes to enroll 45 patients in all and file for U.S. approval as early as 2022.

DERAILING A POTENTIALLY LETHAL ILLNESS

Spinal muscular atrophy (SMA) is a neurodegenerative disease in which motor neurons—the nerves that control muscle movement and that connect the spinal cord to muscles and organs—degrade, malfunction and die. It is typically diagnosed in infants and toddlers. The underlying cause is a genetic mutation that inhibits production of a protein involved in building and maintaining those motor neurons.

The four types of SMA are ranked by severity and related to how much motor neuron protein a person's cells can still produce. In the most severe or type I cases, even the most basic functions, such as breathing, sitting and swallowing, prove extremely challenging. Infants diagnosed with type I SMA have historically had a 90 percent mortality rate by one year.

Adrian Krainer, a biochemist at Cold Spring Harbor Laboratory, first grew interested in SMA when he attended a National Institutes of Health workshop in 1999. At the time, Krainer was investigating how RNA mutations cause cancer and genetic diseases when they disrupt a process called splicing, and researchers suspected that a defect in the process might be at the root of SMA. When RNA is transcribed from the DNA template, it needs to be edited or "spliced" into messenger RNA (mRNA) before it can guide protein production. During that editing process, some sequences are cut out (introns), and those that remain (exons) are strung together.

Krainer realized that there were similarities between the defects associated with SMA and one of the mechanisms he had been studying—namely, a mistake that occurs when an important exon is inadvertently lost during RNA splicing. People with SMA were missing one of these crucial gene sequences, called *SMN1*.

"If we could figure out why this exon was being skipped and if we could find a solution for that, then presumably this could help all the [SMA] patients," Krainer says. The solution he and his colleagues hit on, antisense therapy, employs single strands of synthetic nucleotides to deliver genetic instructions directly to cells in the body [see "The Gene Fix"]. In SMA's case, the instructions induce a different motor neuron gene, *SMN2*, which normally produces small amounts of the missing motor neuron protein, to produce much more of it and effectively fill in for *SMN1*. The first clinical trial to test the approach began in 2010, and by 2016 the FDA approved nusinersen (marketed as Spinraza). Because the therapy does not incorporate itself into the genome, it must be administered every four months to maintain protein production. And it is staggeringly expensive: a single Spinraza treatment costs as much as $750,000 in the first year and $375,000 annually thereafter.

Since 2016, more than 10,000 people have been treated with it worldwide. Although Spinraza can't restore completely normal motor function (a single motor neuron gene just can't produce enough protein for that), it can help children with any of the four types of SMA live longer and more active lives. In many cases, Spinraza has improved patients' motor function, allowing even those with more severe cases to breathe, swallow and sit upright on their own. "The most striking results are in patients who are being treated very shortly after birth, when they have a genetic diagnosis through newborn screening," Krainer says. "Then, you can actually prevent the onset of the disease—for several years and hopefully forever."

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