GENETIC MEDICINE

Gene therapy sees early success against progressive blindness

Treatments for inherited eye diseases show promise in clinical trials, but worries linger over how long the beneficial effects will last.

BY HEIDI LEDFORD

Ophthalmologist Eric Pierce is no stranger to difficult conversations. During his years at the Boston hospital Massachusetts Eye and Ear, he has counselled both adults and the parents of young children who have been newly diagnosed with genetic retinal diseases that will ultimately leave them blind.

But progress against one such disease has led Pierce to change how he presents his diagnosis. "We're on the threshold of a new era," he now tells anxious parents. "I do believe there will be a therapy for your child so that they won't experience the full course of this disease."

Pierce's optimism is grounded in early data from tests of gene therapy in animals and humans. On 12 October, researchers reported success with using gene therapy in dogs against a form of retinitis pigmentosa[1], a genetic disease that causes light-sensitive photoreceptor cells to degenerate over the course of years. The results unexpectedly showed that the approach worked well even in mature dogs that had already lost some photoreceptor cells, a sign that the strategy might also work in humans, who have often reached that stage well before diagnosis.

And on 10 October at the Retina Society annual scientific meeting in Paris, a biotechnology company presented encouraging data from a trial in humans. The company found that its gene therapy for a degenerative eye disease caused by a mutation in the *RPE65* gene improved sensitivity to light in all 21 treated patients. Although other research groups using the same approach have seen some reversal of similar gains, the company, Spark Therapeutics of Philadelphia, Pennsylvania, plans to apply to the US Food and Drug Administration for regulatory approval of its therapy in 2016. If the treatment is approved, the company could be the first to bring a gene therapy to market in the United States.

"This is definitely a time of great promise," says Stephen Rose, chief research officer at the Foundation Fighting Blindness in Columbia, Maryland. "It moves the whole field of gene therapy forward."

Gene therapy has endured a bumpy road. After years of promising advances, the field almost came to a screeching halt in 1999. A death in a trial of gene therapy to treat an inherited metabolic disorder caused a scandal and sowed fears about the technology's safety. But an ardent few continued in the face of widespread scepticism and limited funding. The most notable success was a treatment for the genetic immune deficiency disease X-SCID, although it caused leukaemia in some patients.

It was during this time that some gene-therapy researchers began to see a glimmer of promise in treating eye disorders. The eye is partially shielded from the immune system, reducing the likelihood of an immune attack on the virus used to introduce the genes. (Such an immune response was blamed for the 1999 death.) The eye is also relatively easy to access, allowing surgeons to inject the virus near to the cells in which the gene is needed. Because more than 200 genes are associated with retinal disorders, the opportunity for genetic correction was clear.

Researchers began with mutations in *RPE65* that are associated with one type of vision loss. The enzyme encoded by *RPE65* is crucial for converting light into electrical signals that travel to the brain, and for sustaining the eye's photoreceptors. Without a functioning enzyme, the photoreceptors gradually degrade, progressively crippling vision. The researchers hoped to halt this process by using a virus to shuttle a functional *RPE65* gene into the eye.

In 2007, three teams launched the first clinical trials aiming to do just that, and included a team that would go on to found Spark in 2013. Positive results[2–4] published in 2008 rejuvenated interest in gene therapy, says Luk Vandenberghe, a virologist who studies gene therapy at Harvard Medical School in Boston. "They truly validated the concept of gene therapy that people had been pursuing for decades," he says. "The field has really turned around."

But earlier this year, two of those three teams announced setbacks. They reported[5,6] that the effects were waning in some patients as early as one year after treatment. ▶

VISION FOR THE FUTURE

Broader reach for gene therapy

Although gene therapy is showing promise against vision loss caused by mutations in the gene *RPE65*, such mutations account for less than 2% of the total burden of inherited diseases that cause retinal degeneration. Hundreds of genes have been implicated in such disorders; tackling them individually would require laborious research, clinical testing and regulatory approval for each one. Instead, researchers are seeking ways of using gene therapy to treat a larger set of patients.

Some are looking for ways to protect neurons in the eye from degeneration, regardless of which gene is involved in the process. Such 'neuroprotective' approaches under consideration include inducing cells to express a protein called RdCVF, which protects the cone cells in the eye that enable colour vision.

At Harvard Medical School in Boston, Massachusetts, Connie Cepko's laboratory is testing the effects of inducing the expression of a gene called *NRF2*, which activates antioxidant responses, to see whether those defences could protect photoreceptors from damage.

Others are taking a second look at GDNF, a neuroprotective protein that has been explored for its possible use as a treatment for Parkinson's disease and that may also protect photoreceptors in the eye.

Researchers at GenSight Biologics in Paris and at RetroSense Therapeutics in Ann Arbor, Michigan, are taking a different tack. They hope to replace damaged photoreceptors by inducing the eye's retinal cells to express light-sensitive proteins called channelrhodopsins. But channelrhodopsins are less sensitive to light than the eye's natural photoreceptors, so GenSight is also developing special goggles that patients would wear to amplify the light signals reaching the eye. **H.L.**

At Spark, chief scientific officer Kathy High says that her team has yet to see any decline in its patients even eight years after treatment. She notes that subtle differences in the protocol might have given Spark's treatment an edge. The virus that Spark engineered may have expressed *RPE65* at particularly high levels, she notes, and the company also adds a surfactant molecule when injecting the virus to prevent it from sticking to the needle during injection.

But vision scientist Artur Cideciyan of the University of Pennsylvania in Philadelphia, who works with one of the teams that reported a decline in gains after gene therapy, is still not convinced that Spark's results will endure. He says that Spark has not yet announced data as detailed as those that the other teams used to measure the growth — and then decline — in their patients' visual fields.

Even so, the diminishing effect in human trials need not indicate a fundamental flaw in the approach — or in gene therapy as a whole, says Vandenberghe (see 'Broader reach for gene therapy'). "All the tweaks haven't been fully worked out," he says.

Pierce, as a clinician, considers even tentative progress a huge achievement. He recalls the time when the only support that he could offer some of his patients was to recommend dietary supplements that might slow the disease. "Years of efficacy in a chronic degenerative disease is a huge success," he says. "And to have some optimism in the conversation is fantastic." ■

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FISHERIES

Cuba forges links with United States to save sharks

Improved diplomatic relations feed a budding environmental partnership.

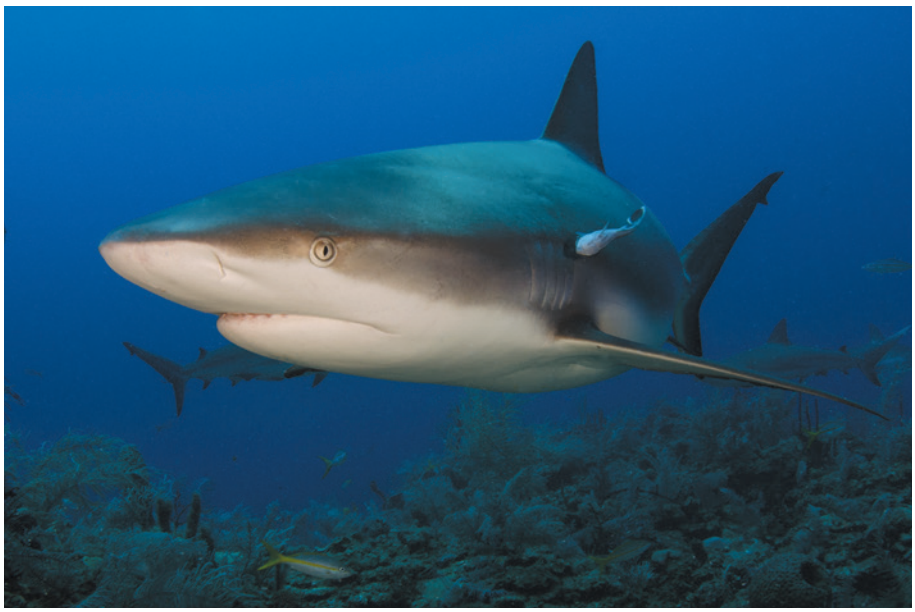
BY JEFF TOLLEFSON

Cuba is surrounded by sharks. Fishermen catch them, residents eat them and, increasingly, tourists are coming to see them. Now the island nation is gearing up to manage them, and its efforts are bolstering a nascent environmental partnership with the United States.

"It's a big step forward for Cuba and the region," says Jorge Angulo-Valdés, head of the Marine Conservation Group at the University of Havana's Center for Marine Research and a visiting professor at the University of Florida in Gainesville. "It's time for us to get together, identify common goals in resource management and make them work."

On 21 October, Cuba plans to release a management plan that will lay the groundwork for research and, eventually, regulations to protect extensive but largely undocumented shark and ray populations. Roughly half of the 100 species of shark resident in the Caribbean Sea and Gulf of Mexico have been seen in Cuban waters, including some — such as the whitetip (*Carcharhinus longimanus*) and longfin mako (*Isurus paucus*) — that have experienced sharp declines elsewhere. The Cuban government has consulted with environmentalists and academics from the United States and other countries in developing the plan.

"Cuba is a kind of biodiversity epicentre for sharks," says Robert Hueter, director of the Center for Shark Research at the Mote Marine Laboratory and Aquarium in Sarasota, Florida, who is one of those working with the Cuban scientists. "The science is not at a level yet to do rigorous stock estimates, but we are moving in that direction with this plan."



PETE OXFORD/MINDEN PICTURES/GETTY

The Caribbean reef shark (*Carcharhinus perezii*) is one of many species that can be seen in Cuban waters.

Most of what is known about Cuba's shark populations has come from the fishing industry, which often captures sharks as by-products of its regular operations. The Cuban government has already established marine protected areas along 20% of its coastline and is planning to expand that network within the 70,000 square kilometres of its coastal fishery. It has also begun to regulate the equipment used in fishing, and is looking to establish catch limits for various fish species, including sharks.

Both US and Cuban scientists say that the collaboration is helping to pave the way for more formal cooperation now that the two cold-war foes have re-established political relations. In April, the US National Oceanic and Atmospheric Administration (NOAA) sent a research vessel on a cruise around the island with Cuban scientists. And on 5 October, US secretary of state John Kerry and Cuban officials announced at an oceans conference in Chile that the two