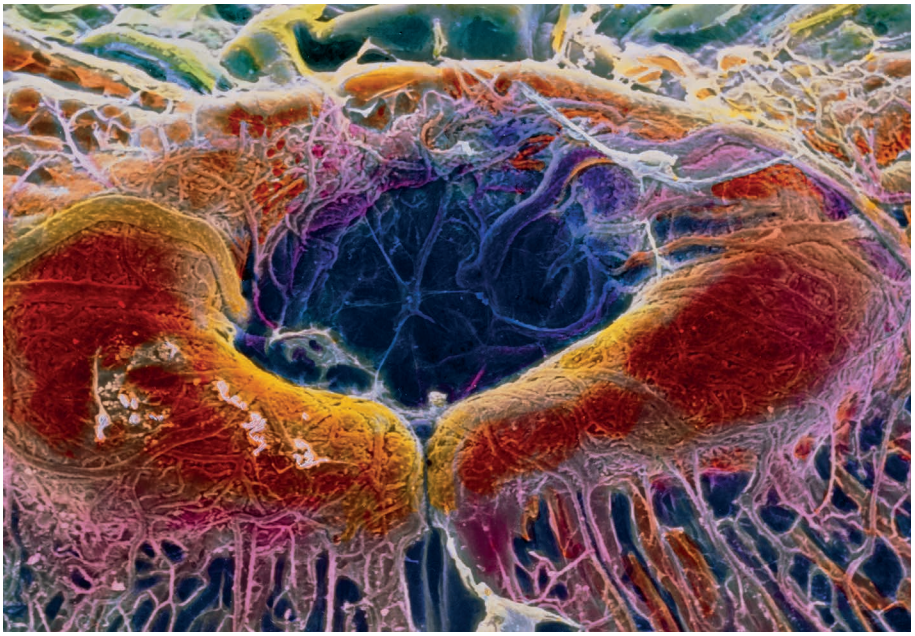

P. MOTTA/DEPT. OF ANATOMY/UNIV. ROMA LA SAPIENZA/SPL

The US government might approve a gene therapy to prevent retinal cells (pictured) from degrading.

GENETICS

FDA advisers back gene therapy

Treatment for blindness could become the first approved in the United States to target disease-causing mutations.

BY HEIDI LEDFORD

Advisers to the US Food and Drug Administration (FDA) have given gene-therapy researchers a taste of victory after decades of struggling to develop treatments that correct for disease-causing mutations.

In a unanimous vote on 12 October, a panel of external experts declared that the benefits of a gene therapy to treat a form of hereditary blindness outweigh its risks. The FDA is not required to follow the guidance of its advisers, but it often does. The agency's final decision on the treatment, called voretigene neparvovec (Luxturna), is expected by 12 January.

An approval in the lucrative US drug market would validate gene therapy's recent renaissance. "Things are beginning to look more promising for gene therapy," says geneticist Mark Kay of Stanford University in California.

Made by Spark Therapeutics of Philadelphia, Pennsylvania, Luxturna is designed to treat individuals who have two mutated copies of a gene called *RPE65*. The mutations impair the eye's ability to respond to light and, ultimately, lead to the destruction of photoreceptors in the retina. The treatment consists of a virus loaded with a normal copy of the *RPE65* gene. The virus is injected into the eye, where the gene is expressed.

In a randomized controlled trial that enrolled 31 people, Spark showed that, on average, participants who received the treatment improved their ability to navigate a special obstacle course (S. Russell *et al. Lancet* **390,** 849–860; 2017). This effect persisted for at least a year. The control group showed no improvement overall. This was enough to convince the FDA advisory committee that the benefits of the treatment outweigh the risks.

"Things are beginning to look more promising for gene therapy."

Over the past three decades, gene therapy has weathered extreme highs and lows. In the early 1990s, gene therapy was red hot, says David Williams, chief scientific officer at Boston Children's Hospital in Massachusetts. "You couldn't keep young people out of the field," he says. "Everyone wanted in."

Then came the death in 1999 of a young patient enrolled in a gene-therapy clinical trial, and the discovery that a gene therapy used to treat children with an immune disorder could cause leukaemia.

Investors backed away from the field, and some academics grew scornful of it. Although European regulators approved one gene therapy in 2012, for a condition that causes severe pancreatitis, many doubted that it worked. (The company that makes it has announced that it will not renew its licence to market the drug when it expires on 25 October.) "You're too smart to work in this field," a colleague told Kay. "It's a pseudoscience."

MEASURED EXPECTATIONS

But some researchers kept plugging away at the problem, improving the viral vectors that shuttle genes into human cells. Over time, new clinical trials began to show promise, and pharmaceutical companies became more interested in developing treatments for rare genetic diseases.

Now, demand for gene-therapy vectors is so high that suppliers are oversubscribed, and researchers have to wait between 18 months and 2 years to get some of the reagents that they need for clinical studies, says Williams.

In the past few years, gene therapies have shown promise in clinical trials for a range of diseases — including haemophilia, sickle-cell disease and an immune disorder called Wiskott–Aldrich syndrome. On 4 October, Williams and his colleagues reported a successful trial of gene therapy to treat cerebral adrenoleukodystrophy, a devastating and sometimes fatal disorder of the nervous system and adrenal glands (F. Eichler *et al. N. Engl. J. Med.* http://doi.org/cd77; 2017).

The FDA approved its first gene therapy, a treatment in which immune cells are engineered to combat cancer, on 30 August. Unlike Spark's therapy, the cancer treatment does not target a specific disease-causing mutation, and it is administered to immune cells that are removed from the body, engineered and then re-infused.

That is why researchers say that an FDA approval for voretigene neparvovec would be a landmark. "The general concept of gene therapy is replacing or compensating for a missing gene, and that's what this does," says Matthew Porteus, a paediatric haematologist at Stanford. "People are so excited."

But Spark's treatment also highlights the limitations of this generation of gene therapies. Although the treatment seems to improve vision, it is still unclear how long the virus will continue to express the normal *RPE65* gene — and thus how long its effects will last.

"I think we still need to have major improvements in the technology before we're going to be able to cure these diseases," says Kay. "But along the way there may be treatments that help make improvements." ■