QUEST TO USE CRISPR GENE EDITING TO FIGHT DISEASE GAINS GROUND

As clinical-trial results trickle in, scientists look ahead to more-sophisticated medical applications.

By Heidi Ledford

The prospect of using the popular genome-editing tool CRISPR to treat a host of diseases in people is moving closer to reality.

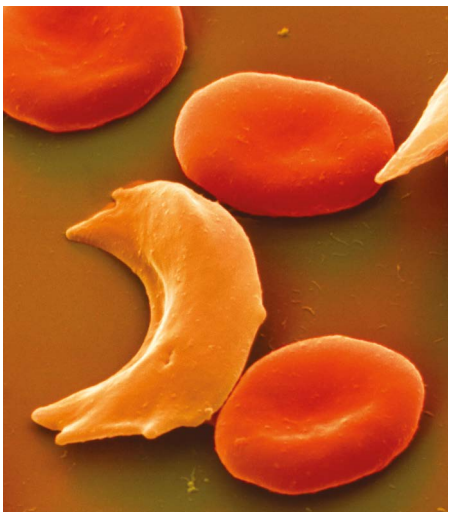
Medical applications of the CRISPR–Cas9 system had a banner year in 2019. The first results trickled in from trials testing the tool in people, and new trials were launched. In the coming years, researchers are looking forward to more-sophisticated applications of CRISPR genome editing that could lay the foundation for treating an array of diseases, from blood disorders to hereditary blindness.

But although the results of clinical trials of CRISPR genome editing so far have been promising, researchers say that it is still too soon to know whether the technique will be safe or effective in the clinic. "There's been a lot of appropriate caution in applying this to treating people," says Edward Stadtmauer, an oncologist at the University of Pennsylvania in Philadelphia. "But I think we're starting to see some of the results of that work."

It has been only seven years since researchers discovered that CRISPR–Cas9, a molecular defence system that microorganisms use to fend off viruses and other invaders, could be used to rewrite human genes. Since then, gene editing has attracted attention for its potential to modify embryos — an application that is ethically and legally fraught if those embryos are destined to become humans (see page 154). But, in parallel, scientists have been testing CRISPR's much less controversial ability to disable or correct problematic genes in other cells to treat a host of diseases.

In 2016, Chinese researchers announced that they had treated the first person with a CRISPR–Cas9 therapy designed to fight cancer. In cells extracted from the participant's blood, the researchers disabled the gene that codes for a protein called PD-1, which holds the immune system in check but can shield cancer cells in the process. The scientists then reinjected the cells.

By late 2019, the US government's clinicaltrials.gov database listed more than a dozen active studies that are testing CRISPR–Cas9 as a treatment for a range of conditions, including cancer, HIV and blood disorders.



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Sickle-cell anaemia is marked by misshapen red blood cells.

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So far, too few people have been treated in these trials for any firm conclusions to be drawn about the safety of CRISPR–Cas9 therapies or how well they work. Preliminary results from two trials — one in which gene-edited blood cells were transplanted into a man to treat HIV infection, and the other in which they were transplanted into three people to treat cancer — showed no signs of clinical improvement.

In both cases, the transplanted cells flourished in the recipients' bone marrow, without any serious safety concerns, but did not produce a clear medical benefit. In the HIV trial, the researchers attempted to use CRISPR to disable a protein that many strains of the virus use to enter cells. But only 5% of the transplanted cells were edited — not enough to cure disease, the researchers said last September (L. Xu *et al. N. Engl. J. Med.* **381**, 1240–1247; 2019). The study is on hold while researchers explore ways to boost that percentage, says Hongkui Deng, a stem-cell researcher at Peking University in Beijing and a lead author of the work.

There are early hints that another trial might meet with more success. CRISPR Therapeutics in Cambridge, Massachusetts, and Vertex Pharmaceuticals in Boston, Massachusetts, treated two people who have the genetic disorders sickle-cell anaemia and β-thalassaemia, in which oxygen-carrying haemoglobin molecules in the blood are depleted. The idea is to use CRISPR to disable a gene that otherwise shuts down production of another form of haemoglobin. Early results suggest that the treatment might have eased some symptoms of the disorders.

Other researchers are itching to move beyond editing cells in a dish. The challenge is in finding ways to transport the gene-editing machinery to where it is needed in the body, says John Leonard, chief executive of Intellia Therapeutics, a biotechnology company in Cambridge, Massachusetts, that is focused on CRISPR–Cas9 genome editing.

Last July, the pharmaceutical companies Editas Medicine in Cambridge, Massachusetts, and Allergan in Dublin launched a trial to treat Leber congenital amaurosis 10, a genetic disorder that can cause blindness, by editing eye cells. Researchers will inject the eye with a virus containing DNA that encodes the CRISPR genome-editing machinery, bypassing the need to guide those tools through the bloodstream to the specific tissues. The virus will be responsible for carrying the genome-editing tools into cells. It is the first trial to attempt CRISPR–Cas9 gene editing inside the body, and early results could be reported this year.

That would be a landmark moment for the field, says Charles Gersbach, a bioengineer at Duke University in Durham, North Carolina. But he and others say that they hope researchers will eventually move away from using viruses to shuttle genome-editing machinery into cells. Deactivated viruses can provoke immune responses, and carry only a limited amount of DNA.

What's more, some gene-editing tools are too large to fit inside commonly used gene-therapy viruses, says Andrew Anzalone, a chemical biologist at the Broad Institute of MIT and Harvard in Cambridge, Massachusetts. These include the souped-up CRISPR systems called prime editors that were first reported last year (A. V. Anzalone *et al. Nature* **576**, 149–157; 2019).

Intellia is looking for a way around using the viruses. The company has partnered with Swiss pharmaceutical giant Novartis to develop fatty nanoparticles that can protect genome-editing molecules as they travel through the bloodstream, but can also pass through the membranes of target cells.

None of the technologies currently being tested is what researchers foresee for the long-term applications of genome editing, says Gersbach. "The approaches that people are taking are the things that we can do today," he says, "but not what we would do if we could design the ideal drug."