Researchers Test Two Gene Therapy Approaches for Curing HIV

One new approach protects CD4 cells against HIV entry, while another snips out viral genes in infected cells.

November 11, 2021 By Liz Highleyman

Clinical trials exploring novel gene therapy approaches could pave the way for a functional cure, or long-term HIV remission. American Gene Technologies (AGT) is testing genetically modified HIV-specific CD4 T cells that are resistant to viral entry, while Excision BioTherapeutics is developing a method to remove HIV DNA from the chromosomes of infected cells.

Antiretroviral therapy can keep HIV suppressed indefinitely as long as treatment continues. But a reservoir of latent viral blueprints remain hidden in the chromosomes of resting CD4 cells (the main targets of HIV) and can begin churning out new virus when the meds are stopped. HIV cure studies have led to many disappointments over the years, but researchers continue to explore new ways to achieve sustained viral remission without antiretrovirals.

American Gene Technologies: AGT103-T

AGT's Phase I RePAIR trial (NCT04561258) is studying what the company calls a "one-and-done gene and cell therapy treatment" that could enable HIV-positive people to stay off antiretroviral treatment with no fear of developing AIDS or passing the virus on to others.

The experimental therapy, dubbed AGT103-T, involves HIV-specific CD4 T cells that are genetically modified to resist HIV. First, a sample of peripheral blood cells is collected from a patient and CD4 cells that recognize HIV's Gag protein are selected. A harmless lentivirus vector is then used to insert genes that disable CCR5 receptors, which HIV uses to enter cells. Finally, the modified CD4 cells are multiplied and returned to the body.

Researchers learned years ago that people whose CD4 cells lack these receptors, due to an uncommon mutation known as CCR5-delta32, are not susceptible to infection with most strains of HIV. The only two people known to have been cured of HIV—"Berlin Patient" Timothy Ray Brown and Adam Castillejo—received stem cell transplants from donors with this mutation to treat cancer.

Stem cell transplants are too dangerous for people who don't need them to treat life-threatening cancer but scientists have tried to replicate these cures using genetic engineering. Sangamo

Therapeutics uses zinc finger nuclease enzymes to edit out CCR5 receptors from CD4 cells. While this did not cure HIV, some study participants saw a reduction in their viral reservoir and long-term increases in their CD4 count. What's more, three participants had a prolonged delay in viral rebound, researchers reported earlier this year. In 2018, Chinese researcher He Jiankui announced that he had used another technology, CRISPR-Cas9, to disable the CCR5 gene in human embryos in an effort to protect them against HIV.

Last year, preclinical research by scientists at AGT and the National Institute of Allergy and Infectious Diseases provided proof of concept that the new approach can work. But before AGT103-T had been tested in a single patient, the company launched a PR campaign, some media outlets reported that a cure was imminent and advocates were left to counter the hype.

Now, the first clinical trial of AGT103-T is underway—and so far, so good. The study aims to enroll up to 18 participants who have been diagnosed with HIV for at least three years and have been on antiretrovirals for more than two years.

After assessing interim results from the first three participants, the study's independent Data and Safety Monitoring Board saw no serious adverse events and allowed the research to continue at a faster pace, the company recently announced. Two more patients are expected to receive the treatment this month.

"One patient can be lucky. Two can be very lucky. Three is a trend, and so actually the Data Safety and Monitoring Board has decided that they will meet quarterly from now on," AGT CEO Jeff Galvin told ABC 7 News. "We don't need to check in with them between each patient, so that means we can greatly accelerate the clinical trial."

The real test of a functional cure is stopping antiretrovirals to see whether viral load rebounds. The first participants will begin a closely monitored treatment interruption in early 2022.

"Once three more participants are treated in November and December, we can start studying efficacy data," Galvin said. "We expect to see objective markers from studies of treated participants' blood tests by the end of the year and hopefully will have a functionally cured patient by next summer."

Excision BioTherapeutics: EBT-101

Excision BioTherapeutics is taking a different approach, using gene therapy to deactivate HIV's genetic blueprints in cells that have already been infected, thereby halting the production of new virus.

EBT-101, originally developed at Temple University in Philadelphia, uses CRISPR-based gene-editing technology to cut out viral genes integrated into infected cells. The system uses RNA templates to locate HIV proviral DNA in a CD4 cell's chromosomes and cuts this DNA with a nuclease enzyme; the cell's repair mechanism then rejoins the broken ends.

"If you just make a single cut, the virus can mutate around it," Excision CEO Daniel Dornbusch told

Fierce Biotech. “We make multiple cuts to deactivate the viral genome.”

In preclinical studies, the technology was used to excise portions of HIV DNA in human cells in the laboratory and in mice as well as SIV (HIV’s simian cousin) in monkeys. Here, too, press releases were issued about the successful lab cell research in 2016, and media reports claimed that a cure could be just three years away. In reality, the Temple researchers had suggested that their approach might be ready to enter human clinical trials in three years.

That time has now arrived, a couple of years later than estimated. In September, the Food and Drug Administration gave the company the go-ahead to start the first Phase I/II trial of EBT-101. The Temple-Excision team recently received funding to pursue this work from the National Institutes of Health as part of the Martin Delaney Collaboratories for HIV Cure Research program.

EBT-101 is administered as a single IV infusion. Three months after administration, study participants will begin a monitored antiretroviral treatment interruption to see whether the gene therapy delays or prevents viral rebound.

“The goal, of course, is to find the first therapeutic to create functional cures for HIV,” Dornbusch told Philadelphia magazine. “The term ’functional cure’ is an important distinction, as there will be no way to determine if EBT-101 will remove every viral genome from an individual, which is called a ’sterilizing cure.’ However, sterilizing cures are not necessary, as the goal of the therapy will be for individuals to remain HIV negative by RNA testing, maintain normal levels of immune cells and cease taking antiretroviral treatment—achieving a functional cure.”

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