Researchers Study CRISPR Gene Editing to Cure HIV

EBT-101 is novel gene-editing therapy that uses “molecular scissors” to cut HIV out of cells.

December 28, 2022 By Liz Highleyman

Building on decades of basic science research, Excision BioTherapeutics recently announced that the first participant in a Phase I/II clinical trial has received a CRISPR-based therapy designed to cut HIV out of human cells, potentially resulting in a cure.

This study is evaluating the safety and efficacy of the therapy, dubbed EBT-101, in people with HIV who have an undetectable viral load on daily antiretroviral therapy. The initial participant was treated in July, and the therapy has been well tolerated so far, according to the company. The man was expected to start an analytical treatment interruption in the fall, a carefully monitored discontinuation of antiretrovirals to see whether his HIV rebounds.

> This is the single most ambitious clinical foray for CRISPR - in fact for all of genome editing - since its trials began in 2009.
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> Gregorspeed, Excision.
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> Everyone in the field and beyond is rooting for you.
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> https://t.co/DWxkGbOhKG
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> — Fyodor Urnov (@UrnovFyodor) September 16, 2022

“We believe EBT-101 can address the long-standing unmet needs of people living with HIV by removing HIV DNA from their cells, thereby eradicating their infections,” Excision cofounder Kamel Khalili, PhD, chair of the Department of Microbiology, Immunology and Inflammation at the Lewis

Katz School of Medicine at Temple University in Philadelphia, said in a press release. “We believe we are well-positioned to collect key data that will enable our efforts to translate the success this approach has shown in animal models to human clinical trial participants.”

Antiretroviral therapy can keep HIV replication suppressed as long as treatment continues. But the virus inserts its genetic blueprints into the DNA of human cells and establishes a long-lasting reservoir that is unreachable by antiretrovirals and invisible to the immune system. These so-called HIV proviruses can lie dormant in resting T cells indefinitely in the presence of antiretrovirals, but they usually start churning out new virus soon after the drugs are stopped.

The presence of latent virus has made curing HIV nearly impossible, save for a few people who received stem cell transplants for cancer treatment and essentially rebuilt a new immune system from HIV-resistant donor cells—a procedure too risky, cumbersome and expensive for wide use.

Researchers have explored many strategies to achieve a functional cure, or sustained remission without antiretrovirals, including “shock and kill” (waking up dormant proviruses) and “block and lock” (keeping proviruses asleep indefinitely), but progress has been elusive. As its name suggests, Excision’s approach involves excising, or snipping proviral DNA out of human chromosomes, thereby depleting the viral reservoir.

EBT-101 is a CRISPR therapy designed to cure HIV with a single administration. The novel gene-editing approach uses next-generation nucleases, enzymes that act as “molecular scissors” to cut DNA at specific locations. It employs an adeno-associated virus to deliver CRISPR-Cas9 nucleases and dual guide RNAs targeting three sites within the HIV genome that tell the enzymes where to cut.

Excision’s foundational technologies were developed in Khalili’s lab at Temple University and the University of California Berkeley lab of CRISPR pioneer Jennifer Doudna, PhD, who in 2020 shared a Nobel Prize for her gene-editing work.

As Jason Mast described in Endpoints News, Khalili has been working on HIV since the 1980s and on CRISPR-based gene editing for nearly a decade. In 2014, his group published a groundbreaking study showing that CRISPR-Cas9 could excise integrated HIV proviral DNA from the genome of human cells in the laboratory, something many experts thought would be impossible. A study published in 2019 showed that the approach worked in mice. The following year, a study of monkeys showed that the technology could excise SIV (an HIV-like simian virus) from cells and reduce the viral reservoir; monkey studies also demonstrated long-term safety.

This preclinical research paved the way for the EBT-101 Phase I/II trial (NCT05144386)—the first to test CRISPR for an infectious disease in humans—an open-label study evaluating the safety, tolerability and preliminary efficacy of the therapy. Participants will receive a single IV infusion of EBT-101 at one of three dose levels. At week 12, they will be assessed for eligibility for an analytical treatment interruption; the first man should have reached that milestone sometime in October. After the initial 48-week period, all participants will be enrolled in a long-term follow-up study (NCT05143307). The initial study is expected to be completed in 2025, and the follow-up

study will continue for 15 years.

The trial aims to enroll nine HIV-positive men who have been on stable antiretroviral therapy for more than two years with no regimen changes or missed doses in the past three months, an undetectable viral load for the past year and CD4 count above 350. They should be willing to undergo antiretroviral treatment interruption and prepared to take measures to prevent HIV transmission during that time. Exclusion criteria include resistance to two or more antiretroviral drug classes, treatment changes due to virological failure, use of long-acting injectable antiretrovirals, prior use of any gene therapy and various underlying conditions, including hepatitis B or C.

The California Institute for Regenerative Medicine—an agency created by a ballot initiative to fund stem cell research—has awarded Excision a $6.85 million grant to support the clinical development of EBT-101 for HIV. The company is also working on similar therapies to cure herpes, hepatitis B and other persistent viral infectious diseases. Other research teams are developing approaches to help CRISPR access HIV proviruses in hard-to-reach areas of the genome and using CRISPR-Cas9 gene editing to delete the CCR5 receptors HIV uses to enter cells.

While the CRISPR approach may be able to cut HIV out of many, maybe even most, infected cells, leaving even a small residual reservoir could rekindle viral replication. Many experts think a combination strategy—for example, mixing approaches that disable or destroy the virus while boosting immune responses—will be the key to a functional cure.

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