CRISPR and LASER ART Eliminate HIV in Mice

A third of mice treated with gene editing technique plus long-acting antiretrovirals showed no remaining traces of HIV.

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Researchers have devised a new approach that uses CRISPR gene editing and slow-release antiretroviral therapy to target the reservoir of latent HIV in resting immune cells—a key barrier to a cure. Two out of seven mice treated with the combination remained virus-free after the antiretrovirals were stopped.

"Our study shows that treatment to suppress HIV replication and gene editing therapy, when given sequentially, can eliminate HIV from cells and organs of infected animals," researcher Kamel Khalili, PhD, of the Comprehensive NeuroAIDS Center at Temple University said in a press release.

However, while this research offers proof of concept that a combination of gene therapy and intensive antiretroviral treatment might be able to eliminate latent HIV, much work remains to be done before it can be tested in clinical trials, and it may not be practical for widespread use.

Although standard combination antiretroviral therapy is highly effective at stopping HIV replication, leading to undetectable viral load in the blood, HIV's genetic blueprint remains hidden in resting T cells and can reactivate if the cell is awakened. Full eradication of HIV therefore requires the removal of this proviral HIV DNA from host cells.

As described in recent report in Nature Communications and in a poster at this year's Conference on Retroviruses and Opportunistic Infections, Khalili, Howard Gendelman, MD, of the University of Nebraska Medical Center, and colleagues used CRISPR-Cas9—a gene therapy technique that can remove selected segments of DNA—to snip out proviral HIV DNA from T cells in mice with a human-like immune system.

For two months prior to gene editing, the mice were treated with long-acting slow-effective release antiviral therapy—dubbed LASER ART—to maintain an ultra-low level of HIV in the body. Chemically modified versions of the antiretrovirals rilpivirine (marketed as Edurant), dolutegravir (Tivicay), lamivudine (Epivir or 3TC) and abacavir (Ziagen) were packaged into nanocrystals, which deliver the drugs to tissues harboring dormant HIV, such as the

lymph nodes and the gut, and release them slowly over weeks.

Five weeks after a single IV injection of the CRISPR-Cas9 treatment and eight weeks after the last LASER ART administration, HIV could not be detected in two of the seven mice. Replication competent HIV was not found in their blood, lymphoid tissue, bone marrow, spleen or brain using multiple sensitive tests. The remaining five mice experienced viral rebound. The researchers did not see any off-target effects, meaning the CRISPR tool did not make any unintended gene edits.

The study authors also showed that when immune cells from the dually treated and now virus-free mice were transplanted into HIV uninfected humanized mice, no infectious progeny virus could be detected, indicating that the transferred cells did not harbor usable viral genetic material.

However, HIV was readily detected in all 16 mice that were treated with either CRISPR or LASER ART alone. According to the researchers, this suggests that LASER ART improves the ability of CRISPR to edit out proviral DNA by minimizing the amount of integrated virus.

“These data provide proof-of-concept that permanent viral elimination is possible,” the study authors concluded.

"The big message of this work is that it takes both CRISPR-Cas9 and virus suppression through a method such as LASER ART, administered together, to produce a cure for HIV infection," Khalili said. “We now have a clear path to move ahead to trials in non-human primates and possibly clinical trials in human patients within the year.”

It is unclear why the dual treatment did not work in a majority of the mice. It is also not yet known whether it will work in people with HIV or whether it can remove all viral DNA from all cells—even a few remaining cells containing usable genetic material can trigger viral rebound. Finally, it remains to be seen whether this approach could be scaled up for widespread use and whether the risks are worth the benefits given the availability of effective and well-tolerated antiretroviral treatment.

Click here to read the study abstract.
