Gene-Modified T Cells Persist for a Decade, Without Major Risks, in HIV Studies

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Genetically modified T cells—notably CD4 and CD8 cells—administered to people living with HIV participating in one of three clinical trials conducted between 1998 and 2002 are detectable more than a decade later, suggesting that single infusions of cells altered to target or block HIV have the potential for long-term efficacy. According to the paper, published in the May 2 issue of Science Translational Medicine and summarized in a University of Pennsylvania news release, the long-term safety of using retroviral vectors to deliver genetic payloads to T cells is also apparent, helping offset earlier concerns about the procedure.

“We have 43 patients, and they are all healthy,” says senior author Carl June, MD, of the University of Pennsylvania in the news announcement. “And out of those, 41 patients show long-term persistence of the modified T cells in their bodies.”

Gene therapies have long been eyed for their potential in the field of HIV, specifically as a way to render CD4 cells immune to infection and as a way to modify CD4 and CD8 cells to target virus that persists in long-lived cellular reservoirs that aren’t affected by antiretroviral therapy. One notable example of a gene therapy approach currently under investigation involves Sangamo Biosciences’ zinc finger nuclease (ZFN)-based therapy to strip CD4 cells of their CCR5 receptor and render the cells impervious to HIV infection.

“If you have a safe way to modify cells in patients with HIV, you can potentially develop curative approaches,” June says. “Patients now have to take medicine for their whole lives to keep their virus under control, but there are a number of gene therapy approaches that might be curative.” A lifetime of anti-HIV drug therapy, by contrast, is expensive and can be accompanied by significant side effects.

Two central questions regarding gene modification of T cells remain, however.

First, is it safe? Viruses are the most efficient way to widely distribute and integrate altered or man-made genetic bundles into cells, either while in the body or more commonly, after being removed from the body, treated, expanded and ultimately reinfused. A lingering concern has been that the use of viral vectors and alterations of human DNA may lead to mutations inside cells that

can potentially increase the risk of cancers, notably leukemia.

Second, do genetically modified cells persist in the body? It is believed that cells endowed with enhanced or novel functions need to be maintained in high enough numbers for several years—if not a lifetime—to achieve maximum efficacy in treatment and curative approaches. This has been an important variable in the ongoing Sangamo ZFN trials—not only do modified cells need to effectively block HIV, they need to survive and thrive in various compartments in the body.

The three clinical trials conducted by June and his colleagues involved a retrovirus vector used to modify T cells so that they carry a highly specific HIV-targeting "chimeric" receptor containing CD4 (needed to target a protein on HIV's surface) and a "zeta" subunit of the CD3 receptor (needed to activate cells against HIV). Papers reporting initial results demonstrated some effects on HIV levels in various reservoirs, at least in the weeks and months following treatment, without any serious safety problems.

Though June and his colleagues were unable to report long-term antiviral activity and efficacy data—the studies were not designed for such—the researchers were required by the U.S. Food and Drug Administration to follow participants for up to 15 years, in light of the earlier concerns regarding cancer and other long-term side effects of therapy. By extension, June's group was also able to conduct annual tests to see if the modified T cells at least persisted in their bodies.

With more than 500 years of combined safety data between the 43 patients followed for roughly 11 years, June's group is "confident" that the retroviral vector system is safe for modifying T cells, they explain in the news announcement. More specifically, they write in their Science Translational Medicine report, "there was no evidence of vector-induced immortalization of cells; integration site distributions showed no evidence of persistent clonal expansion or enrichment for integration sites near genes implicated in growth control or transformation." In other words, there was no evidence that the genetically modified cells were undergoing the mutations associated with cancer development.

June and his colleagues note that the worrying side effects associated with gene therapy in years' past were seen when viral vectors were used to modify stem cells. His group's results confirm those of other studies, indicating that the target cell for gene modification—in this case, mature CD4 and CD8 cells—plays an important role in the long-term safety for patients.

"T cells appear to be a safe haven for gene modification," June says.

The multiyear blood samples also show that the gene-modified T cells have persisted in the patients' blood for more than a decade. "In fact," the researchers point out, "models suggest that more than half of the T cells or their progeny are still alive 16 years after infusion, which means one treatment might be able to kill off HIV-infected cells for decades."

The prolonged safety data, thus far indicating that the potential benefits outweigh potential risks, means that it might be possible to test T cell–based gene therapy to treat diseases that aren't life-

threatening, such as arthritis.

“Until now, we’ve focused on cancer and HIV-infection, but these data provide a rationale for starting to focus on other disease types,” June says. “We view this as a personalized medicine platform to target disease using a patient’s own cells.”

"Engineered T cells are a promising form of synthetic biology for long-term delivery of protein-based therapeutics," the researchers conclude. "These results provide a framework to guide the therapy of a wide spectrum of human diseases."

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