HIV/AIDS

Gene therapy takes a cue from HAART: Combinatorial antiviral therapeutics reach the clinic

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For the first time, scientists have tested a combination of three RNA-based gene therapies, delivered via a lentiviral vector, to target HIV in patients. This study not only demonstrates the safety and long-term viability of this approach, but it also highlights areas in which focused improvements in gene therapy strategies may provide the most impact in increasingly translating promise in the laboratory to efficacy in the clinic.

In the 27 years since HIV was identified as the causative agent of AIDS, there has been considerable progress in treating HIV-positive patients. Highly active antiretroviral therapy (HAART) has improved the lives of many, and a 100-fold decrease in treatment costs coupled with heroic levels of international aid have made this drug combination therapy available to millions in the developing world. Unfortunately, HAART does not appear to be a sustainable solution, because it must be continued as a life-long treatment due to viral latency and reactivation, and funding for its use in developing nations is decreasing for a variety of reasons. Additionally, HIV's brute force ability to evolve and escape immune detection has rendered vaccine development particularly difficult, and many researchers question whether a vaccine that prevents infection is even possible. Moreover, prevention and early diagnosis can reduce the number of newly-infected individuals, but these efforts are effective only if populations are receptive to safe-sex practices and lessen the stigma associated with positive diagnoses (*1*). Given these challenges, scientists have been searching for longer-term solutions. Gene therapy has been proposed as a treatment that can, in principle, provide life-long effects with limited medical intervention; however, earlier trials have shown that much progress is still needed.

Is this some fact-checking by STM?

Toward this end, in this issue of *Science Translational Medicine*, DiGiusto and colleagues present results from the first clinical trial of a combination gene therapy, which uses antiviral RNA molecules to target HIV via three distinct mechanisms (*2*). Several HIV-positive patients undergoing treatment for lymphoma—a common disease among such patients—participated in this trial. The gene therapy involved ablating their diseased bone marrow cells, then administering their own previously stored hematopoietic progenitor cells (HPCs). Before transplantation, however, DiGiusto *et al*. transduced a small portion of the HPCs from the four patients with a lentiviral vector that expresses three antiviral RNAs: a ribozyme that cleaves *CCR5* mRNA (a human transcript that encodes a coreceptor used by HIV to enter target cells) to inhibit viral entry, a short hairpin RNA (shRNA) that is cleaved intracellularly to produce a small interfering RNA that targets the degradation of both Tat- and Rev-encoding transcripts (HIV transcripts that play key roles in infection), and a decoy RNA that inhibits the initiation of viral transcription by competing for Tat. Moreover, the gene delivery vehicle, a lentiviral vector, is advantageous for gene therapy as it integrates into the genome of nondividing cells and can thereby provide stable transgene expression; importantly, this trial represents one of the first times that such vectors have been used in human subjects. Although the transduced cells were not sufficiently abundant to suppress or cure HIV infection in this patient cohort, this study represents an important milestone that merits recognition and warrants close examination to educate and inform future efforts.

This is a really long sentence. Is it too late to break it up?

Most importantly, the study demonstrated the long-term survival of transduced cells, suggesting that these results may one day translate into a sustainable therapeutic solution. The isolation of triple therapy-expressing cells up to two years post-transplantation is particularly encouraging, given that a mixture of transduced and untransduced cells was administered. In addition, the work addressed safety concerns with lentiviral vectors. Their stable integration into the host genome offers the potential for sustained transgene expression, yet raises the possibility of adverse events such as the leukemia-like disorders observed in a retroviral vector trial (*3*). After two years, no patients enrolled in this study show signs of vector-associated cancer, perhaps in part because lentiviral vectors do not tend to integrate near the promoter regions of host genes. There were also no apparent safety concerns with therapeutic shRNAs competing with the endogenous microRNA pathway, which plays an important role in regulating endogenous gene expression.

This study also highlights the intrinsic difficulties in designing HIV gene therapy clinical trials, which bench scientists may consider in efforts to engineer improved therapies. The inherent immunological and viral variation among a relatively limited number of patients serve to convolute results of such trials in general, and the lack of unequivocally positive results is thus not in itself a negative result.

Moreover, numerous insights from this study can guide future enhancements. The high copy numbers of the lentiviral-based construct detected in some cells suggests that transduction may not be the bottleneck for therapeutic efficacy, and promoting engraftment and in vivo expansion of transduced cells warrants additional focus. Furthermore, given that patients underwent bone marrow ablation for lymphoma treatment, yet transduced cells continuously decreased in frequency, therapy-expressing cells may have faced a selective *dis*advantage. Because it is unlikely that all future trials will involve a risky complete ablation, it may be necessary to continue developing approaches to confer therapeutic cell population with a selective advantage to compete with existing, untransduced cells while avoiding the risk of unchecked cell proliferation. Finally, this trial, along with others, suggests that HAART interruption and subsequent HIV replication could serve to provide such a selective advantage. HAART interruptions, however, should be balanced with the risk of viral mutational escape re-

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sulting from viral rebound and replication in untransduced cells, and these trade-offs can be studied both in vitro and in silico.

Biomedical research has yet to provide a sustainable solution to the globally entrenched HIV epidemic, and gene therapy offers a highly promising long-term treatment option, if several challenges can be overcome. In this vein, this clinical trial offers much insight into the safety and potential downstream efficacy of lentiviral vectors and RNA-based therapies. Thus, these results not only represent advances for the treatment of HIV, but for the gene therapy field in general.

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