Gene therapy can protect against HIV

An introduced gene conveys long-lived resistance to HIV infection in mice.

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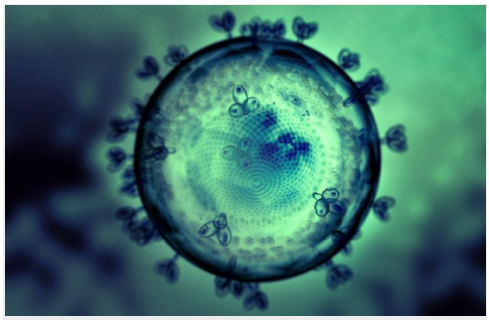
Gene therapy, an approach most commonly explored for curing chronic genetic diseases such as cystic fibrosis, may also prove practical for disease prevention. In research published today in *Nature*[1], scientists in California show that a single injection — which inserted the DNA for an HIV-neutralizing antibody into the muscle cells of live mice — completely protected the animals against HIV transmission.

The road to a vaccine against HIV has proved to be far longer than originally anticipated. More than 2 million adults are newly infected with HIV every year and, nearly three decades after the virus was first identified, researchers haven't found a reliable way to prevent infection. The classic vaccine approach, which uses all or part of an inactivated virus to induce immunity, has yielded little success because HIV has managed to disguise most of the easily-recognised external structures that antibodies would target. Researchers have thus had a tough time finding a molecule that can induce even moderately broad responses against the virus in all its different mutations. So although it might sound extreme to use gene therapy as a preventative treatment for HIV/AIDS, the method could provide a much-needed alternative.

David Baltimore, a virologist and HIV researcher at the California Institute of Technology in Pasadena, and his colleagues used a genetically altered adenovirus to infect muscle cells and deliver DNA that codes for antibodies isolated from the blood of people infected with HIV. The DNA is incorporated into the muscle cells' genome and programs the cells to manufacture the antibody, which is then secreted into the bloodstream. The tactic builds on earlier work by scientists at the Children's Hospital of Philadelphia in Pennsylvania, who in 2009 first described the effectiveness of this technique in preventing transmission of simian immunodeficiency virus, which is similar to HIV but infects monkeys[2].



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Researchers hope to prevent the spread of HIV (virus particle pictured) by using gene therapy to get cells to produce antibodies.

As for the rationale for using gene therapy for HIV: "This is something way out of the ordinary, and it's perfectly reasonable to say that there's no reason to do it if there's an alternative," says Baltimore. "But if there's no alternative — and that's where we're at today — then we should be thinking of new ways to protect people."

Dennis Burton, an immunologist at the Scripps Research Institute in La Jolla, California, who has developed a number of antibodies against HIV, agrees. "Obviously, the best thing of all is a vaccine. That's a tried-and-tested method that carries very few risks. But if that doesn't work, what's our fall-back position?" he asks. "We have these antibodies, and we have them available now. If this works in humans, and that's a reasonable supposition, you'd have something you can do now."

Prolonged protection

Baltimore and his colleagues tested five different broadly neutralizing antibodies, one at a time, in mice with humanized immune systems. Two of the antibodies, called b12 and VRC01, proved completely protective — even when the mice received doses of HIV that were 100 times higher than a natural infection. After 52 weeks, the levels of antibody expression remained high, suggesting that a single dose would result in long-lasting protection. "We showed that you can express protective levels of antibodies in a mammal and have that expression last for a long period of time," Baltimore says. "It sets the stage for human trials."

Providing patients with periodic doses of these antibodies throughout their lifetime would be safer than coaxing antibody production from muscle cells, but it would be far from cost-effective. The gene-therapy approach, by contrast, recruits muscle cells to act as antibody factories and could be administered using a single intramuscular shot.

Experts in the field are cautiously optimistic. "Mice and monkeys don't always tell the truth. It's a really interesting idea, and it should be assessed in clinical trials," says Wayne Koff, senior vice-president for research and development at the International AIDS Vaccine

Initiative in New York. “Until someone shows that we can make these broadly neutralizing antibodies with a [classic] vaccine, I think this is an important concept that should be supported.”

But both Burton and Koff caution that gene therapy comes with its own set of problems. Because the antibody DNA is permanently inserted into the genome, there’s no way to turn it off if someone has an immune reaction against the antibodies. But it won't be known whether such side effects exist until the method is tested in people, something that Baltimore aims to do in the next few years. The researchers at the Children’s Hospital of Philadelphia, meanwhile, hope to get the first round of human trials of their technique started before the end of 2012.

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References

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2. Johnson, P. R. *et al*. *Nature Med.* **15**, 901–906 (2009).