

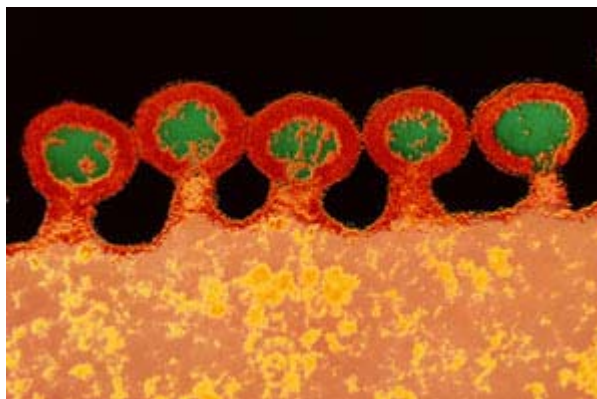
Shutting the Door on HIV Scientists engineer human cells to keep the virus out

By [Kate Dalke](#)

February 7, 2003

featured article

President Bush's State of the Union address last week put AIDS and HIV in the news again with promises of more money for drugs, care and prevention. Despite phenomenal knowledge about the virus that causes AIDS, the disease still eludes easy treatment and scientists continue to pursue new strategies.



HIV viruses budding from surface of human T-cell.
© NIBSC / Photo Researchers, Inc.

One strategy is an effort to prevent HIV from getting inside human cells by removing the "doorknob" the virus uses to get in. The effort combines three of the hottest tools in science: stem cells, gene therapy and RNA interference. The goal is to someday modify a person's stem cells to make them resistant to HIV and then return these cells to the body where they can fight disease.

The premise is simple: engineer human cells that keep HIV out. Normally HIV enters a cell and then directs the cell to make thousands of viruses that will eventually kill the cell and move on to other cells in the body.

The scientists are trying to prevent this disaster by blocking HIV from getting into cells at all. To get inside, the virus grabs onto a receptor on the human cell—a kind of doorknob. HIV opens the door and enters the cell.

So the scientists made human cells without the "doorknob," called the CCR5 receptor. Some of these cells were not infected when they exposed the cells to the HIV virus. To engineer the cells, the researchers inserted short pieces of RNA that disrupted cells from making the receptor. The technique is known as RNA interference.

"The technique is highly specific and extremely potent," says David Baltimore of the California Institute of Technology in Pasadena, who led the research. "We're changing the cell so it's resistant to viral infection."

The technique is being used in cultured cells and clinical trials are still a long way off. As a next step, Baltimore is working with Irving L. Weissman of Stanford University in California, who has pioneered new ways to isolate stem cells.

Together with Weissman, Baltimore hopes to marry RNA interference with stem-cell transplants to create a new therapy for patients already infected with HIV.

A therapy might work like this: A doctor extracts stem cells from a patient and treats these cells with RNA to remove the CCR5 receptor. These "protected" stem cells are reintroduced into the patient's bloodstream.

The "protected" cells would be healthy enough to fight infections and would survive to create daughter cells that are also resistant to HIV. There would be less chance the body would reject the transplant because the stem cells are the patient's own cells.

"Potentially, we could reengineer the body's immune system so it's protected for life," says Irvin S. Y. Chen of the University of California in Los Angeles, who collaborated with Baltimore on the project.

Weissman cautions that it is still "way too soon" to know which patients are right for the therapy. The technique must still be tested in mice and then monkeys.

The inspiration for the research comes from people who never catch HIV, despite having unprotected sex or sharing needles with infected individuals. These people have mutations in both genes that make the CCR5 receptor, and the virus cannot get in. Scientists have known about this phenomenon for decades, but developing drugs that could eliminate the protein has been slow going.

RNA interference offers a new and accurate technique to remove the receptor. The research hinged on finding a good delivery vehicle to get the short RNA strands into human cells—and keep them turned on.

‘Potentially, we could reengineer the body's immune system so it's protected for life.’

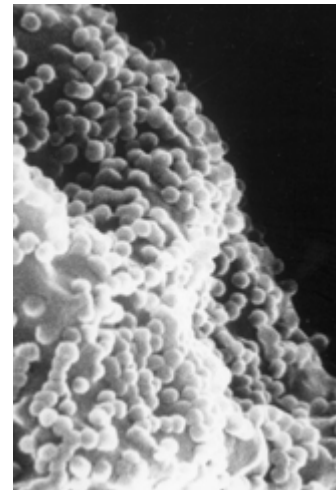
As it turns out, the HIV virus itself was the best delivery vehicle. The scientists used a disabled HIV virus, stripped of all its disease-causing genes. Its only instructions are to insert the RNA package into the human cell, a form of gene therapy.

Gene therapy is a field that has struggled to find success in a clinical setting. The US Food and Drug Administration recently suspended a number of gene therapy trials after children in France developed cancer during gene therapy.

The researchers will have to confront similar issues if the research eventually moves into a clinical setting, says Chen. For now, their work is moving ahead.

Other researchers in the field are also using this type of gene therapy together with RNA interference. Inder M. Verma of the Salk Institute in La Jolla, California has used this technique to 'silence' specific genes in mice, which then passed the silenced genes on to their offspring.

The great thing about gene therapy is that the RNA gets into a cell and keeps on working, says Verma, who has been studying these types of disabled viruses since the mid 1990s. He was not involved in the HIV study.



Thousands of HIV molecules sit on the host cell surface.
Courtesy Heinrich Gottlinger

The most effective strategy against HIV would combine blocking HIV's entry into the cell and disrupting the virus if it gets inside. The strategy could be used in all sorts of infectious diseases, says Chen, including Hepatitis C and Hepatitis B.

Chen and Baltimore are testing the technique in mice, before moving onto the Rhesus monkey, which has the same CCR5 receptor as humans.

See related GNN articles

»[Gene-silencing study seeks cancer genes](#)

»[Silencing Genes in HIV](#)

...

[Qin, X. *et al.* Inhibiting HIV-1 infection in human T cells by lentiviral-mediated delivery of small interfering RNA against CCR5. *Proc Natl Acad Sci USA* **100**, 183-188 \(January 7, 2003\).](#)

[Tiscornia, G. *et al.* A general method for gene knockdown in mice using lentiviral vectors expressing small interfering RNA. *Proc Natl Acad Sci USA*. Published online January 27, 2003.](#)

[Back to GNN Home Page](#)