

The Scientist: NewsBlog:

Silencing HIV

Posted by [Megan Scudellari](#)

[Entry posted at 7th August 2008 05:11 PM GMT]

With the help of a new mouse model for HIV infection, scientists have shown that gene silencing with RNA interference (RNAi) may be effective in preventing viral entry and replication in T-cells, according to a study published online today (August 7th) in [Cell](#).

Past studies have used RNAi to suppress HIV infection in cultured cells, but researchers did not have a good animal model simulating chronic HIV-infection in which to test the approach. Another challenge has been targeting the therapy specifically to T-cells within a living organism.

"What makes this paper special," says [Ramesh Akkina](#), a microbiologist at Colorado State University who was not involved in the study, "is using an actual animal model." The treatment suppressed viral load and maintained high T-cell levels in mice with humanized immune systems infected with HIV.

The team used two different "humanized" HIV mouse models, both immunodeficient so that injected human cells are not rejected. The "old-fashioned" model, Hu-PBL (human peripheral blood lymphocyte) mice, according to Akkina, are injected with human white blood cells for short term experiments. The second model, Hu-HSC (human hematopoietic stem cell) mice, was first developed in 2004 and later shown by researchers in [Japan](#), the [U.S.](#), and [Switzerland](#) to be a good model for HIV infection. Researchers can transplant hematopoietic stem cells into these mice, which then give rise to a variety of human immune cells, effectively reconstituting a human immune system in a mouse. The stem cells also provide a constant source of replenishment of T-cells so viremia can be tracked in the mouse for as long as a year.

The researchers targeted the siRNA to T-cells with an antibody that binds to a receptor on the T-cell surface. That receptor is often used as an antigen for T-cell therapies because it readily internalizes antibodies that bind to it. They attached a peptide to the antibody to bind the siRNA molecules, like a tow rope to haul the RNA molecules to the T-cells.

The siRNA molecules target three key genes: two highly-conserved HIV viral genes and one T-cell receptor gene, CCR5. "It's important to target different stages of the viral life cycle, such as viral entry and viral replication" said senior author Premalata Shankar, previously at the [Immune Disease Institute](#) at Harvard Medical School and now at Texas Tech University Health Sciences Center.

The researchers first tested the siRNA cocktail as a prophylactic regimen, injecting it in Hu-PBL mice with healthy human lymphocytes and then challenging the animal with HIV. Three out of four siRNA-treated mice retained essentially normal T-cells levels four weeks after infection. Next, they tested the therapy in T-cells already infected with clinical HIV by transplanting HIV-infected human T-cells into Hu-PBL mice and then treating with the siRNA. Again, they saw a drop in virus load and an increase in CD4 T-cell count.

Finally, the team used Hu-HSC mice, with a reconstituted human immune system from hematopoietic stem cells, to test the siRNA treatment. While control mice displayed viremia by the first week after infection, siRNA in naive T-cells protected the mice from infection. "The ones with antiviral siRNA had no sign of infection for about 2 months," said [Priti Kumar](#), an instructor at Harvard Medical School and first author on the paper, after which time the experiment was stopped.

The approach has some drawbacks, said Akkina. For example, the siRNA must be injected repeatedly to maintain the treatment, and it's possible that an individual could develop an immune reaction to the delivering antibody. In 2003, Akkina's lab developed a gene therapy strategy using a [lentivirus vector](#) to deliver the siRNA into the genome of T-cells, therefore not requiring repeat administration of the therapy.

Kumar believes that the need for repeat injections is actually a benefit. siRNA can target to the cytoplasm of T-cells without being incorporated into the genome, where it could have unintended consequence, she explained. Also, she added, the siRNA cocktail could be changed as needed to keep up with mutations of the HIV virus during treatment.

"There is a lot of promise that RNAi can be another feasible therapy for HIV," said Kumar. The team's future goals include finding a method to increase the amount of siRNA that can be delivered and humanizing the delivery antibody (currently a mouse antibody) so that it could someday be used in clinical trials.