



## **Gene Therapy for a Cure: Progress Still Being Made**

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Because of the early success in curing hemophilia in dogs using gene therapy, many people believed that a cure in humans would quickly follow. It was a tremendous let down when none of the 41 people who have received hemophilia gene therapy saw a sustained increase in the amount of factor in their blood. The good news is that researchers are continuing to learn more about the reasons the previous gene therapy treatments did not work and are developing new approaches.

Information presented this spring at the Eighth Workshop on Novel Technologies and Gene Transfer for Hemophilia and at the World Federation of Hemophilia Congress in Vancouver detailed what scientists have learned. One of the most promising approaches to gene therapy used a common virus, AAV (adeno-associated virus). The genetic material was removed from inside the virus and replaced with the gene for producing factor IX. When injected into the body, the virus inserts the factor IX gene into cells which begin making factor IX proteins. These proteins replace those missing in hemophilia B. This technique was successful in dogs, whose bodies began producing factor IX. When it was tried in humans with hemophilia B, the level of factor IX in the blood rose at first but then quickly dropped to the level it had been before. As was reported last year, the researchers learned that this was due to the ability of the body's immune system to recognize AAV. After inserting the factor IX gene into a cell, AAV stayed on the surface of the cell long enough for the immune system to recognize and destroy it and the cell to which it was attached.

This explained why the factor IX levels quickly dropped in humans who received the gene therapy. The question remained of why the approach worked in dogs. Researchers now know the answer. AAV is a virus that infects almost all humans. It is easily recognized by our immune systems. However, it is a new virus for dogs. Their immune systems cannot react to it as quickly. In dogs, the virus has time to disappear from the surface of the cell producing factor IX before the immune system can destroy it. This knowledge has led scientists to consider two new approaches. The first approach is to change the virus that is used. The AAV has several subtypes. The subtype used in the previous trials was AAV2. The immune systems of the majority of people are familiar with this virus. Researchers are now trying AAV8, a rarer subtype. Only two to five percent of humans have been previously infected with it. This should mean that the immune system will take longer to react to it, hopefully allowing the virus to dissolve and avoiding the destruction of the cell that was given the factor IX gene.

The second approach is to suppress the body's immune system when the gene therapy is given. The temporarily weakened immune system will not be able to destroy the virus or the cell making factor IX. Tests of these two approaches are planned in Philadelphia and London.

Other researchers are working with other methods for gene therapy, including using different types of viruses and getting the gene into the body's cells without using viruses at all. They are also changing the gene for the factor protein so that the new factor produced in the body does not cause inhibitors.

With several different approaches being tried, the chances of success are increased. People with hemophilia still have reasons to be optimistic about a cure from gene therapy. Reports provided by the NHF

from the Workshop on Novel Technologies and Gene Transfer for Hemophilia were used in writing this article. News stories about regular advances in bleeding disorder research are available from the National Hemophilia Foundation's website at [www.hemophilia.org](http://www.hemophilia.org).