The New York Times
nytimes.com

December 10, 2002

Gene Therapy for Hemophilia Shows Some Promise

By ANDREW POLLACK

A new approach to gene therapy shows tantalizing evidence of working in a patient with hemophilia, doctors said yesterday. But the patient also developed signs of liver injury, forcing the clinical trial to halt.

The patient, in his 30's, was given the gene for Factor IX, a protein that helps the blood to clot and is lacking in people with hemophilia B, the less common of two forms of the disease.

In the two to four weeks after the treatment, the level of the clotting factor in the patient's blood stayed above 10 percent of the level in a healthy person. That is the highest level ever seen in a gene therapy trial, high enough to virtually eliminate the need for routine infusions of clotting factor, doctors reported yesterday to the American Society of Hematology in Philadelphia.

"It shows the proof of principle," said Dr. Mark A. Kay of Stanford University, who presented the results at the conference.

The patient has not had to have an intravenous infusion of Factor IX in the six weeks since he received the gene therapy, despite suffering some minor injuries that would have normally required such treatment.

By the sixth week, however, the level of Factor IX has fallen, to 3 percent of normal. Although that would still reduce the severity of the disease, a further big drop would make the treatment ineffective, Dr. Kay said. Unless gene therapy can keep the Factor IX levels high for years -- as it has been shown to do in dogs -- the treatment will not be practical, he said.

Moreover, starting in the fourth week, the patient's liver enzymes rose as much as nine times as high as normal, a sign of liver injury. The patient never felt sick, and the liver enzymes now seem to be falling again toward normal, Dr. Kay said.

Still, the investigators agreed with the Food and Drug Administration that no new patients should be treated until doctors determine whether gene therapy causes the liver problem.

The stock of Avigen, the company in Alameda, Calif., that developed the treatment, fell sharply yesterday, to $7.75, down $1.65.

There are already concerns about the risks of gene therapy after the death of a teenager in 1999 who was treated for another disease and a more recent case in which a 3-year-old in France developed a disease that resembled cancer. The hemophilia treatment uses an adeno-associated virus, a different type of virus

to ferry the genes into the body from the technique in those two cases.

This is the second halt for this hemophilia trial. It was briefly delayed last year after the gene-carrying virus was found in patient semen, meaning that the gene could theoretically pass to subsequent generations.

Dr. Kay and his collaborator, Dr. Katherine A. High of Children's Hospital of Philadelphia, had previously reported that genes injected in the muscles caused patients to make some Factor IX. But doctors said yesterday that the levels were never high enough to make a difference.

The new study involved putting the genes into the liver. Four patients given lower doses showed no effects. The patient for whom the treatment showed signs of working received a higher dose. A second patient was treated with the higher dose three weeks ago, but it is too soon to say whether it is working.

Another gene therapy, developed by Transkaryotic Therapies of Cambridge, Mass., and tested by Dr. David A. Roth of Harvard, has also shown signs of reducing the need for clotting factor for up to 12 months. Some of his 12 test patients produced up to 2 percent to 3 percent of normal levels, said Dr. Roth, who also presented data yesterday.