

CLINICAL TRIAL UPDATE

At the last several gene therapy workshops, there was a sense of excitement and anticipation as scientists announced new clinical trials and reported preliminary results of ongoing studies. This year the mood shifted. Rather than looking around the next bend, researchers took time to reflect upon how they got here and what has been learned. Five phase I trials have been initiated, four completed, and no new trials have opened.

Why the lull in new trials? The most straightforward answer is: no new therapies have proven clinic-ready. On a broader level, this plateau may be explained with several responses—the inherent pace of science; the decrease in funding for not only gene transfer, but biotechnology in general; the lack of qualified patients interested in enrolling and the frustration with results of previous trials. All of these were mentioned by participants as possible contributing factors. The five clinical trials have employed the full spectrum of techniques and approaches. (For detailed information on these trials log onto www.hemophilia.org.) One performed the gene transfer in cells grown outside the body; the remaining four delivered genes, packaged in viral vectors, into the body. Scientists have tested three types of viruses to shuttle the genes: retrovirus, adeno-associated virus (AAV) and adenovirus. The liver was the cell target in some trials, and muscle was the endpoint in one. Three trials have been completed as planned, one is ongoing and the fifth closed following treatment of one subject. David Roth of Beth Israel Deaconess Medical Center recapped results of one of the first clinical trials, in which gene transfer was performed in cells removed from the body. All 12 subjects handled the treatment well; some reported a decrease in the frequency of bleeds; though measurable increases in factor VIII (FVIII) could not be detected. A larger



phase II trial is now in the planning stages.

The two most recent studies, conducted by Avigen Corporation of Alameda, California, and GenStar Therapeutics of La Jolla, California, were designed to deposit the gene for factor into the liver. GenStar's trial in patients with hemophilia A closed after treat-

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David Roth, MD



Mark Kay, MD, PhD

ing a single subject. The individual had an immune reaction to treatment and researchers were unsuccessful recruiting more subjects to participate.

In Avigen's study, six individuals have received gene transfer for hemophilia B using an AAV vector. All of the subjects tolerated treatment well. However, while researchers were able to successfully transfer the desired gene into the cells, levels of factor IX (FIX) production never rose beyond 2% of normal in five of six subjects. The sixth subject, who received the highest dose, showed greater promise with factor levels rising to 12% of normal, high enough to noticeably improve the lives of those with severe hemophilia. Unfortunately,

a month after treatment, this subject developed high levels of the liver enzyme transaminase, and two weeks later, FIX levels dropped to about 3% of normal. The subject experienced no obvious symptoms related to the rise in liver enzyme; however, possible liver toxicity poses a major concern, as many people with hemophilia have already suffered liver damage from hepatitis. Because of the issues with this patient, the trial has been put on hold by the Food and Drug Administration. Researchers believe the hold will be lifted shortly and the two final subjects can be treated. In previous trials with

adenovirus, liver disturbances occurred, but human and animal studies with AAV have always produced a clean bill of health. "None of what we saw in this patient could have been predicted from the preclinical studies," says Mark Kay of Stanford University Medical Center, one of the key scientists involved in developing the AAV treatment. The recent events with AAV surprised scientists, but also served as a reminder that animal studies can never provide the complete picture. "At some point," Kay said, "you have to move forward into clinical trials." Data from the final two patients will hopefully shed more light on the future of liver-directed gene transfer with AAV. 

Do the 5:

- 1 Get an annual comprehensive checkup at a hemophilia treatment center.
- 2 Get vaccinated—Hepatitis A and B are preventable.
- 3 Treat bleeds early and adequately.
- 4 Exercise to protect your joints.
- 5 Get tested regularly for blood-borne infections.

NHF NATIONAL PREVENTION PROGRAM

Key steps today for giant strides tomorrow.

Collaborating with the CDC, chapters, associations, HTC's, and the community to prevent or reduce the complications of bleeding disorders.

