



# NHF Gathers Top Gene Therapy Experts

## A Report from the 4th Workshop

Last April at the Salk Institute for Biological Studies in La Jolla, California, approximately 80 scientists and clinicians from academic institutions, pharmaceutical companies and government agencies spent two marathon days presenting and listening to reports on advances in gene therapy. Five different approaches to treating hemophilia made their way into the clinic. Three studies are winding down, while two are gearing up. With those studies in progress, research in the laboratory still continues. Scientists are developing new modes of delivering the corrective gene, and they are trying to understand how and why inhibitors interfere with treatment. Researchers are improving and expanding existing gene therapy strategies, hoping to offer patients a cure for hemophilia.

The workshops began in 1996, at a time when several academic and industrial groups were working on gene delivery systems and testing them in hemophilic dogs with mixed, but limited success. The workshops, organized by Inder Verma, PhD, Glenn Pierce, PhD, MD, Katherine High, MD, Gilbert C. White II, MD, and Michael Coyne, MD, have allowed scientists to debate the best strategies, and have given NHF the broad framework on which to focus future research funding. Dr.

Verma, one of four recipients of NHF's Researcher of the Year award in 1999, has had a long-standing interest in hemophilia and is widely regarded as one of the top scientists who started the field of gene therapy.

"I am so impressed with the fact that you all come together and share information, when in fact you're competing with one another," was one of many encouraging comments voiced by patient representatives at the 4th workshop on Gene Therapies for Hemophilia. Some of the talks may lead to further collaborations, while others may sharpen competition. Whatever the outcome, everyone present admired the

Editor's Note: Although many refer to the current studies as gene therapy, technically, a more accurate term would be gene transfer. This is because the gene is transferred by one or another mechanism into the cell, and the studies are not really therapy.

spirit of cooperation with which scientists have gathered each year, resulting in tremendous progress in the field.

The recent tragedy of Jesse



*Mark Skinner,  
Glenn Pierce, PhD, MD,  
and Inder Verma, PhD*

BY JUDY BERLFEIN

Gelsinger's death (See sidebar below) has overshadowed gene therapy research this past year. His death coincided closely with the initiation of the first three gene therapy clinical trials for hemophilia. Great pause was taken at the time to rigorously evaluate the safety of the studies. Today, those trials are wrapping up, and researchers are hinting at further plans to test their therapies on a wider scale.

The three studies that are in their final stages have passed the safety test with high marks. Chiron Corporation used a retroviral vector to carry the factor VIII (FVIII) gene; Transkaryotic Therapies, Inc employs a non-viral plasmid approach carrying the FVIII gene for patients with hemophilia A; and Avigen, Inc., working with teams from the Children's Hospital of Philadelphia and Stanford University have injected adeno-associated viral (AAV) vector ferrying the factor IX (FIX) gene into the muscle. In each study, patients reported no more than minor side effects. In the two trials using viral vectors, investigators concluded that risk of transmission to offspring is very low, citing the absence of vector in semen.

These studies, referred to in the research world as "phase I," are designed specifically to examine safety at increasing dose levels. However, all investigators offered bits of evidence for potential effectiveness. In each study, a few subjects showed small gains in factor levels, the highest being 6% of normal. One subject retained



Katherine High, MD,  
and Mark Kay MD, PhD

some expression for a full year. In addition, some patients also stated that bleeding episodes had decreased along with their

need for replacement factor.

"Clearly, expression of around 1% clotting factor in only some of the subjects in each clinical study cannot be considered a cure. However, the fact that each of the three studies had some patients with a little clotting factor detectable, plus the finding of decreased clotting factor usage by some of the patients, points a clear pathway toward improving gene delivery sufficiently to produce a cure," emphasized Glenn Pierce, PhD, MD, president-elect of NHF.

While these three trials are winding down, two additional studies are gearing up. One is similar to the muscle trial in that the AAV vector is being used to transport the gene for FIX. The desired site of infusion, though, is different. The vector, developed by the Kay/High group and Avigen, Inc., a gene therapy company in Northern California, will be administered to the liver, the natural site of factor production, rather than the muscle. The second trial, sponsored by Genstar Therapeutics Corporation of San Diego, California, will also target the ►

**JESSE GELSINGER** died during a gene therapy trial at the University of Pennsylvania in September of 1999. He did not have hemophilia, but he suffered from ornithine transcarbamylase deficiency, a rare metabolic disorder. After receiving a high dose of an early-generation adenoviral vector, he developed liver, kidney and lung failure, and, consequently, he passed away. His death is currently believed to be related to his underlying liver dysfunction related to his condition. There were many reasons for his death, including his underlying disease and the fact that the investigators didn't follow proper procedures in conducting the clinical trial.



► liver, using a “guttated” adenoviral vector carrying the gene for FVIII, though the vector will be administered intravenously.

Although five different approaches to treating hemophilia have now made their way into the clinic, the pre-clinical phase of research is by no means complete. As Dr. Philip Noguchi, (See article on page 18) director of the Division of Cellular and Gene Therapies at the Food and Drug Administration, said, “No matter how straightforward we think the disease is, it becomes more complicated as we gain more basic knowledge.” Researchers are still improving and expanding existing models, hoping one day to offer patients a cure for hemophilia. They are exploring the use of viral and non-viral methods of correcting the gene defect in patients with hemophilia. Techniques are also being developed for turning these newly-introduced genes on and off at will allowing greater control of factor synthesis.

While clinical and preclinical studies proceed successfully, the issue of inhibitors continues to lurk in the background. Researchers have not detected inhibitor development in any of the clinical studies to date, but the concern that gene therapy may trigger inhibitor development has not gone away. To that end, a portion of the workshop each year has been devoted to understanding the basics of immunology. This year, several researchers presented discussions on inducing tolerance. Polly Matzinger, of the National Institute of Allergy and Infectious Diseases, and Bianca Conti-Fine, of the University of Minnesota, presented evidence for a simple method of achieving tolerance (elimination of the immune response to factors VIII or IX). Frequently, inhibitors develop in individuals who have a complete deletion of the gene encoding



*Polly Matzinger and her dog, Lily Llanferian*

the factor. Because their immune systems have not seen factor previously, the cells mount an immune reaction when faced with it. Based on that information, Matzinger and Conti-Fine propose the following approach: Expose the subject to the “foreign” protein by either feeding it orally or administering it nasally. Conti-Fine has tried this technique

in mice and has shown that the mice don’t develop inhibitors when the protein is later injected into the bloodstream. Matzinger is pursuing the same strategy with sheep. She plans to feed factor to sheep and test for an immune response. If sheep confirm the theory, hemophilic dogs will follow. “It’s a completely noninvasive and cheap way to handle the problem,” Matzinger said.

Following presentations by scores of scientists, one could easily become lost in details and technical issues, forgetting the real concern at hand—a cure for bleeding disorders. At the end of the workshop, this was quickly brought back into focus when a panel of patient representatives offered their perspectives on the state of gene therapy. “I come away each year impressed by how much you’ve learned, but also impressed by how much you don’t know,” commented Steven Faust, an NHF board member who has lived with hemophilia for nearly 40 years. Faust reminded scientists, “We would like to participate in clinical trials, but we don’t have a compelling reason to do so.” (See sidebar on page 37.) Existing treatment ►► TO | 37

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*President-Elect Glenn Pierce, PhD, MD*



► is adequate in many ways. He clearly sees the challenge that researchers face in developing gene therapy for hemophilia. "You have the power to bring us a wonderful gift," Faust added. "And yet, you have the power also to bring devastation. It's a precarious balance you have to walk." Other consumers voiced similar concerns to maintain vigilance as clinical research progresses, while expressing hope that these

technologies will lead to the absence of bleeding for months or years, in short, the elusive cure.

The workshop was best summed up by Dr. Inder Verma, who concluded, "These early studies show the potential for gene therapy to cure genetic diseases like hemophilia. This is a tremendously exciting time for investigators working on hemophilia gene therapy, but many questions remain to be answered."

### Desire & Need

The following is an excerpt from an editorial written by Steven Faust to be published in an upcoming issue of *Molecular Therapy*.

Unlike some diseases, hemophilia has a treatment that works relatively well—factor replacement therapy, the safest of which is recombinant. To ensure safety in gene therapy, we can be somewhat more insistent about protections than subjects with no alternative effective therapy, such as with cystic fibrosis. So, do we people with hemophilia want to help cure a disease that has painfully crippled many of us? Yes! Do we desire to prevent the crippling of our young hemophilic compatriots? Absolutely! Are we quite frustrated with sticking our veins time after time until our arms are scarred with tracks? Clearly! Do we yearn to help lead to a curative gene therapy for other diseases such as diabetes or cystic fibrosis, et al.? A resounding affirmative! Will we do so at any cost or risk? From this writer's perspective, no. We are a community that has "been burned," which means researchers must be careful so as to not allow us



*Steven Faust*

to be burned again. Simply, it is proceeding with all due concern, respect and empathy as possible.

What will the hemophilia community support? I believe that I can properly speak for much of the community sentiment when I say that we embrace and enthusiastically participate in research trials that carefully balance, and make clearly known to human subjects, the risks and benefits of a particular gene therapy protocol. This would mean exhausting all tools possible for research observation before insertion of gene therapy into a human subject. It would mean delineating to potential subjects what is known as well as not known about a specific model. We can support any trial that respects the recent memory of those with hemophilia and our determined hope for a better future. ☺

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*Inder Verma, PhD*

