

A black and white portrait of Katherine A. High, an older woman with short, wavy hair, looking slightly to the left. She is wearing a dark top and a pearl necklace. The background is dark.

*PERSPECTIVE & OPINIONS*

# gene therapy: still a contender

— *KATHERINE A. HIGH* —

DESPITE SEVERAL PUBLICIZED INSTANCES OF CANCER IN GENE THERAPY EXPERIMENTS,  
THE ROLLERCOASTER TREATMENT OF GENE THERAPY IN THE MEDIA,  
AND MIXED OPINION ABOUT IT ON THE PART OF THE PUBLIC, THE FIELD IS ALIVE AND WELL,  
SAYS ONE OF ITS LEADERS. PROBLEMS ARE BEING SOLVED, PROGRESS IS BEING MADE,  
AND FINANCIAL SUPPORT IS COMING FROM A WIDER SWATH OF SOURCES.

SEAN KERNAN

Few scientists are as familiar with gene therapy's promises—and obstacles—as HHMI investigator Katherine A. High, who served last year as president of the American Society of Gene Therapy. Once touted as a revolutionary breakthrough, gene therapy has endured intense scrutiny since 1999, when a teenager died in an experiment. Nevertheless, High remains a vocal advocate for fully exploring the field's possibilities. Her own research involves development of gene-therapy techniques to treat hemophilia. She is an attending hematologist at the Children's Hospital of Philadelphia and William H. Bennett Professor of Pediatrics at the University of Pennsylvania School of Medicine.

**HHMI: GENE THERAPY IS OFTEN CALLED A MIXED SUCCESS. HAS THAT STATUS BEEN DEMORALIZING FOR PEOPLE IN THE FIELD?**

**KH:** Gene therapy is as complicated a therapeutic idea as any that researchers have attempted, but if you're intensively involved in the field, you don't feel despair. We're solving problems every day. Five years ago, we could only use gene therapy to cure diseases in mice. Today, we're curing diseases in dogs and cats—and even beginning to treat humans. Researchers in Milan have used gene therapy to successfully treat six kids with a form of severe combined immune deficiency known as ADA-SCID. And China approved the first commercial gene-therapy product, to treat cancerous tumors of the head and neck.

For perspective, consider the history of novel monoclonal antibodies for the treatment of cancer. When I was in medical school in the 1970s there was a lot of hype about them, followed by widespread disappointment during the 1980s when newspapers announced that all the clinical trials were failing. The field then dwindled to fewer scientists, and this core group worked hard to overcome hurdles. Today, monoclonal antibodies are considered a great success, though it's easy to forget that this success was 30 years in the making.

**HHMI: WHAT ARE THE BIG CHALLENGES IN GENE THERAPY NOW?**

**KH:** Immune response to the viral vector is one big challenge. Think of this vector as an envelope and the gene product being delivered to the patient as the letter inside. Too often, that patient's immune system rejects the envelope, and the letter within is never even read. So we're exploring ways to create transient immunosuppression—to shut down a patient's immune system just long enough for the viral vector to degrade, thereby allowing the body full exposure to the gene product inside.

Another challenge is immune response to the

gene-transferred product itself. In this regard, one interesting strategy is to ask: Can we exploit nature's redundancy? Traditionally, gene therapy meant delivering a healthy gene to replace a mutated one. But now we often ask whether we can achieve the same biochemical effect through a different route.

Hemophilia offers one example. The body has at least two biochemical pathways that produce several important blood-clotting factors. The first pathway produces factor VIII and factor IX, but if a hemophilia patient is missing one of them, we don't necessarily try to replace it. Therapy might instead rev up the second biochemical pathway, which relies on factor VII, by generating extra amounts of that factor, which the patient's immune system will accept.

**HHMI: WHAT ARE SOME RECENT ADVANCES?**

**KH:** The ADA-SCID work of Milanese scientists was an important success. These researchers, in clinical trials that began 5 years ago, used a retrovirus to deliver the gene encoding adenosine deaminase (ADA) to six children. Today, all six kids are able to lead normal healthy lives, with no need for treatment and no overt symptoms. This result has been largely ignored in "bad news" stories of gene therapy.

More recently, other researchers have used zinc-finger DNA-binding and -cleaving proteins ["zinc finger" refers to the proteins' shape and composition] to correct errors in a gene that lead to another form of severe combined immune deficiency known as X-linked SCID. That technology for gene correction is promising because it could be adapted into different strategies for fighting many immunodeficiency conditions, including HIV.

And last year scientists published research using a viral vector to loop out the mutant part of the dystrophin protein that's implicated in some forms of muscular dystrophy. Together, these results show that the field is moving forward.

continued on page 63

continued from page 39  
[KATHERINE HIGH]

**HHMI: WHAT IS THE STATUS OF YOUR OWN RESEARCH?**

**KH:** We have cured hemophilia in lab mice and dogs by injecting them with the gene for Factor IX wrapped in a vector called adeno-associated virus (AAV). Over the past few years, however, humans in clinical trials have expressed therapeutic levels of Factor IX for only a few weeks following vector infusion. That's probably because the patients' immune systems killed the cells hosting the inserted gene. To overcome this problem, we've been working on transiently suppressing the immune response to the viral vector AAV.

**HHMI: EXPENSIVE GENE-THERAPY RESEARCH NEEDS INDUSTRIAL SUPPORT, BUT DOESN'T INDUSTRY'S IMPATIENCE ADVERSELY AFFECT THE FIELD'S PROGRESS?**

**KH:** Early safety studies have been slow and time-consuming, and that pace indeed tests the patience of some companies, which exist, after all, to make money for shareholders. But as safety issues are resolved, testing proceeds more quickly—and we are now entering that era.

Meanwhile, we're witnessing the dropout of small biotech companies

in gene therapy—and the entry of willing replacements. This shortfall in resources must be addressed by the disease foundations and by federal support for early development of novel therapies.

**HHMI: WHAT IS MOST CHALLENGING ABOUT BEING A LEADER IN GENE THERAPY?**

**KH:** It's in imparting a sense of the field's momentum to outside people such as foundation officers and NIH institute directors, who often remain unaware of our progress after having been saturated with negative media coverage of gene therapy. Poor public perception works against us, translating into reluctant funding agencies and clinical trial participants.

During the year I served as president of the American Society of Gene Therapy, the best thing I did was to lead a stakeholders' conference aimed at answering the question: What's slowing down gene-therapy research? We asked scientists to share 15-minute stories of their recent research, sketching what worked and what didn't. From that, we identified several of the field's key hurdles. One of them is the financing of clinical trials, a lost middle ground when pharmaceutical compa-

nies want to pick up phase III projects and NIH wants to fund early-stage, or phase I, research. Another challenge is the complex regulatory process governing gene-therapy protocols.

Despite these hurdles, though, there is no question that gene therapy ultimately will succeed. We have to walk before we can run. But we're going to get there. ■

-Interview by Kathryn Brown-

# SUBSCRIBE!

## Knowledge. Discovery. Research. Education.

These four key components of HHMI's work also guide and define the mission of the Institute's quarterly magazine, the *HHMI Bulletin*.

Not yet a subscriber to the *HHMI Bulletin*? If you're not receiving your own copy of the *Bulletin*, take a minute now to join our mailing list.

Subscribing is fast, easy and free.

Visit [www.hhmi.org/bulletin](http://www.hhmi.org/bulletin) and follow the instructions there to subscribe online.

While you're online, read the Web edition of the *Bulletin*.

