Gene therapy rising?

Once hyped, gene therapy still holds promise as an effective method for treating a variety of diseases. On the road to fulfilling that expectation, opportunities exist for young scientists who are excited by a still-emerging field, says **Hannah Hoag**.

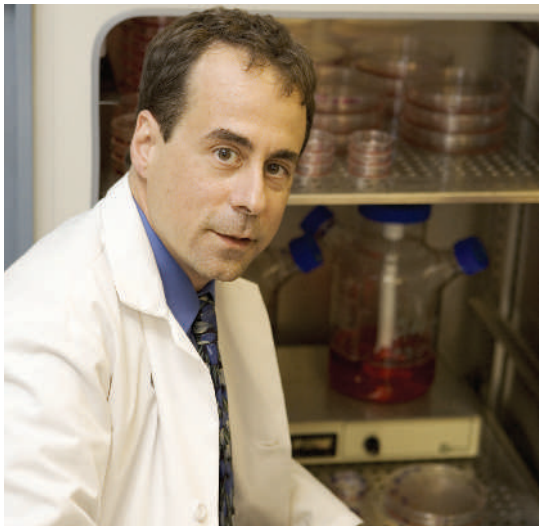
Fifteen years ago, researchers, physicians and most notably the media believed that gene therapy would be the future gold standard of care for single-gene disorders such as cystic fibrosis and haemophilia. Although the concept was simple — the replacement of a faulty gene with one that functions properly — technical and scientific barriers have brought clinical trials to a halt on several occasions, most notably with the death of 18-year-old Jesse Gelsinger in 1999 at the University of Pennsylvania.

In 2002, hopes dimmed again when two children in a clinical trial for the treatment of X-linked severe combined immunodeficiency (X-SCID), led by Alain Fischer at the Necker Hospital in Paris, developed leukaemia after the retroviral vector integrated itself into or near a gene called *LMO2*. One child has since died, and a third child involved in the French trial was reported to have developed leukaemia in January.

Clinical trials have been shut down and restarted repeatedly in the United States and Europe following the disclosure of adverse events. In March, a US Food and Drug Administration (FDA) advisory committee recommended that US gene-therapy trials for X-SCID could resume if the investigators only enrolled patients with no other treatment options. Researchers worry that the restriction will severely limit the number of patients eligible to participate in future trials.

Safety concerns have dampened the enthusiasm formerly lavished on the field. Attendance at the annual meeting of the American Society of Gene Therapy (ASGT) fell to 1,900 last year from a peak of 2,845 in 2002. At a stakeholders' meeting in Arlington, Virginia, in April, gene therapists discussed whether it was possible to revive the field now that new regulatory requirements have made clinical trials even more expensive. Daniel Salomon, a transplant surgeon at the Scripps Research Institute in La Jolla, California, and former head of the FDA advisory panel on gene therapy, cautioned practitioners to pay more attention to the body's immune response to the introduction of foreign vectors (see *Nature* **434,** 812; 2005).

It may face technical challenges, but Theodore Friedman says that gene therapy is slowly beating the odds.



Ready for work: Mark Kay believes that gene therapy offers a lot of exciting opportunities.

At the industry level, some small biotech firms that once pursued gene therapy vigorously are distancing themselves from the field and diverting their energies to more traditional therapies, such as organic chemicals and vaccines. They hope to appease shareholders by refocusing and cutting back on spending. In March, the Seattle-based company Targeted Genetics abandoned its gene-therapy clinical trial for cystic fibrosis. Last month another biotech, Avigen, based in Alameda, California, announced that it would cut short its adeno-associated virus gene-therapy trials for the treatment of haemophila B, after 13 years.

Avigen had long provided funding support for clinical trials to Katherine High, president of the ASGT, and Mark Kay, director of the programme in human gene therapy at Stanford School of Medicine and a founder of the ASGT. "It was taking too long to enrol patients and to do regulatory reviews," explains Kay. The researchers, who are also funded by the National Institutes of Health (NIH), hope to get additional support from the agency to complete the trial.

Flat outlook

Larger and more diversified biotech companies are maintaining programmes, although hiring is flat in many cases. Rich Gregory, head of research at Genzyme in Cambridge, Massachusetts, says that gene therapy has been one of the company's interests for 13 years, but that it receives only a minor portion of the R&D funding, allowing the company to balance the risk of investment in gene therapy with more traditional research activities. But Genzyme has also pursued a variety of vectors. "That has set us apart from many companies," says Gregory.

The field's veterans remain optimistic. There have been important successes: in 2004, 17 children with two forms of SCID were reported to have had their immune systems restored using gene therapy (M. Cavazzana-Calvo and A. Fischer *Lancet* **364,** 2155–2156; 2004).

"These children have been treated. They would have died of their infection but instead they are running

about, playing with their friends and going to school, and rolling around in the dirt — things they wouldn't have been able to do before," says Theodore Friedman, director of the gene-therapy programme at the University of California, San Diego. "The field has made incredible strides. It still has technical and conceptual problems to solve, but they're getting solved."

Other medical technologies have also gone through difficult periods, and gene therapy is no different. "It takes a long time to develop any kind of new therapy," says Ron Crystal of the Sanford I. Weill Medical College of Cornell University in New York. When transplantation medicine began in the 1950s, most of the patients died. "There were moratoriums," says Crystal, "but now transplants are routine."

The challenges are also what attracts young researchers to the field. Kay remembers when he was a graduate student thinking that by the time he had finished his studies and secured a job, all the interesting diseases would already be cured. "The idea of gene therapy was so simple in concept, but the technical and scientific barriers are still there," he says.

Solving these problems is more likely to be done in universities than in industry, so for the near future, at least, jobs may be more abundant in academic labs. Meanwhile, biotech companies will be returning to basics to sort out the field's difficulties and to continue developing new vectors and therapeutic approaches.

"In industry there is a lot of constriction in terms of jobs," says Michael Holmes, of gene-expression company Sangamo BioSciences in Richmond, California. "But academia is alive and well. There is a lot of great research going on."

Healthy funding levels

Federal support for gene therapy remains steady. The NIH spent $391 million on gene-therapy research and $37 million on clinical trials in 2004, a dip from $410 million and $39 million in 2003 that experts believe will be reversed by 2005. For any new biological product to be tested in humans in the United States, an investigational new drug application (IND) must be filed with the FDA; in 2004 there were 245 active gene-therapy INDs and 40 new applications. And foundations that support research into cystic fibrosis, haemophilia and other single-gene diseases continue to fund research into gene therapy.

Vector–host interaction and vector development are two important areas of growth. As the limitations of certain vectors become better understood, they are being strategically paired for specific therapies. "We just have to use them appropriately and learn how to use them better, and a lot of that is basic science," says Crystal. "I think there are a lot of opportunities." Some, like adenovirus, are better for short-term expression of genes, he says, whereas others, such as retroviruses and lentiviruses, provide long-term expression.

Many researchers are developing new vectors and techniques, especially non-viral vectors. "Non-viral vectorology was once considered somewhat outside of the mainstream of gene-transfer technology — but times have changed," writes associate editor Jon Wolff in the March 2005 issue of *Molecular Therapy*. An increasing number of abstracts at the ASGT's meetings are in the non-viral field, opening the door to synthetic lipids and polymers, and nucleic-acid-based methods of silencing genes, including RNA interference.

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Culture of hope: genetically corrected cells may yet be used to cure disease.

WEB LINKS

American Society of Gene Therapy
www.asgt.org
Sangamo BioSciences
www.sangamo.com
National Hemophilia Foundation
www.hemophilia.org

In April, researchers at Sangamo BioSciences showed that zinc-finger nucleases could repair an X-SCID mutation in the *IL2Rγ* gene, with no need for integration into the genome (F. D. Urnov *et al. Nature* doi:10.1038/ nature03556; 2005). "They are able to go in and fix what's wrong and go out without leaving any kind of footprint. It is in its very earliest days, but it is beginning to look like it is going to be possible," says Friedman.

Researchers advise young scientists to think of gene therapy as a discipline of technology, much like gene chips — it is a valuable tool that can be used in all levels of genetic research. Although a subset will apply the techniques and knowledge to clinical medicine, the tools will continue to be used at drug and biotechnology companies as well as universities, and will become more important in stem-cell research as that field matures.

"Although we're in a bit of a trough, it shouldn't discourage people from going into the field," says Kay. "People should move into it now rather than later. There's still a lot of work to do." ■

Hannah Hoag is a science journalist based in Montreal.