

# Gene therapy rising?

**F**ifteen 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.

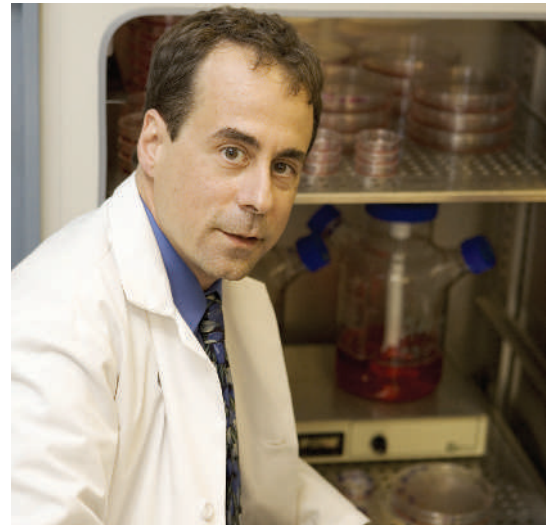
In 2002, hopes dimmed again when two children in a clinical trial for the treatment of X-linked severe combined immunodeficiency (X-SCID), led by Alain Fischer at the Necker Hospital in Paris, developed leukaemia after the retroviral vector integrated itself into or near a gene called *LMO2*. One child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

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.**

**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 haemophilia 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



