The future of gene therapy

Balancing the risks and benefits of clinical trials.

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Calculated risk: the use of viral vectors to deliver corrective genes to a patient can cause side effects.

Gene therapy has the potential to treat devastating inherited diseases for which there is little hope of finding a conventional cure. In the late 1990s, our groups in Paris, London and Milan began treating children suffering from rare immune disorders (severe combined immunodeficiencies, or SCIDs). The successful treatment of the first patients was greeted with excitement when it was first reported in 2000 and 2002 (refs 1, 2). Sadly, this euphoria turned to alarm at the end of 2002, when two of the ten children treated in France developed leukaemia-like conditions[3].

In all of these patients, the genetic defect was corrected by inserting a therapeutic gene into a 'disabled' retrovirus, known as a vector. This vector was then used to 'infect' bone-marrow stem cells taken from each patient before being injected back into their bloodstream, where it was hoped they would multiply into normal immune cells. As it turned out, the ability of these viruses to insert themselves into DNA was also responsible for activating a cancer-promoting gene. News of the leukaemia immediately raised concerns about using a therapeutic approach that may cause cancer at such an alarming frequency. Patient safety is, of course, the first and foremost concern of anybody trying to develop a new medical treatment. But it would be unfortunate if the future of gene therapy was decided by emotive issues rather than careful analysis of its risks and benefits.

The leukaemia cases generated enormous interest among scientists, regulators and the general public. Reactions from regulatory authorities in the United States and Europe varied widely (see Box, overleaf). Some asked clinicians to revise the eligibility criteria for future trials and to update procedures for obtaining informed consent from patients, whereas others imposed a general moratorium on trials involving the use of retroviruses. In the United Kingdom, clinical studies were never put on hold, whereas in Italy treatment for individuals was approved during 2003 only when there was an imminent threat to life. The combination of bad press, scepticism from colleagues, and mixed reactions from regulators has effectively thrown the field into recession.

The current 'gene-therapy-causes-cancer' mood and uncertainty about the effects of tighter regulations is discouraging scientists from starting new clinical trials, and scaring investors and the biotechnology industry away from the field. In 2003 leading industrial players either closed their operations (Gene Therapy, Maryland) or redirected their efforts away from retroviral vectors (Cell Genesys, California). This is unfortunate, because in the absence of industrial investment it is unlikely that gene therapy will eventually deliver on its promises.

What can or should be done? As scientists, we are used to learning from crises and developing solutions to emerging problems. But restoring confidence in the future of gene therapy is going to be a tough sell — much of the debate is no longer about scientific concerns. We would like gene therapy to be seen, and treated, as any other experimental therapy, and that means recognizing the successes as well as the failures.

The successes

SCIDs are rare genetic failures in the development of the immune system that are fatal in the first years of life[4]. The patients treated in Italy suffered from adenosine deaminase-deficient (ADA^-) SCID, which means that they lacked an essential enzyme involved in DNA metabolism. The patients treated in France and Britain suffered from X-SCID, caused by a defect in a gene on the X chromosome. For both diseases, transplantation of bone marrow from perfectly matched donors is the treatment of choice, although it is available to less than one in three patients. For the others, transplantation from mismatched donors carries a 75% overall chance of survival, with a 15–20% risk of developing severe immunological complications and a 20–30% risk of early mortality[5].

In the early 1990s, attempts to treat ADA-SCID with gene therapy achieved only partial success, owing to problems in transferring genes into the patients' stem cells. But recent developments in both vector and cell transplantation technology led to the successful treatment of both forms of SCID[1,2]. Of the 18 SCID patients treated so far in Paris, Milan and London, 17 benefited from life-saving reconstitution of their immune functions for up to five years. All these patients are currently alive.

The failures

The optimism generated by what was considered to be the first true success of gene therapy turned into disappointment at the news of the two leukaemia cases. Genetic analysis of the malignant cells showed that in both cases the retroviral vector had inserted into, and activated, an oncogene called *LMO2* that is associated with childhood leukaemia. The activated oncogene was not the only cause of the malignancy, but was most likely the event that triggered it[3].

The leukaemias came as a surprise, partly because none of the preclinical studies had shown any evidence of cancer in animals

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Ready for action: custom-made gene vectors are held for use in a gene-therapy trial.

treated with the same approach. Moreover, although scientists had always considered the possibility that gene insertion would activate oncogenes, no such event had been observed in more than a decade of clinical trials in humans involving large numbers of genetically modified blood cells[6]. The apparently high (15%) risk to X-SCID patients of developing malignant cells suggests that there are specific risk factors for this disease — one possibility being an association between the therapeutic gene and the activated oncogene[3,7]. More research is needed into this question.

The trade-off

The patients who developed the leukaemias received a particularly high number of genetically modified stem cells. The issue of dose is an important one. By considering what we know about the likelihood of retroviruses inserting into active genes and the number of potential oncogenes in the human genome, a recent analysis estimates that up to one in every 10,000 modified cells might harbour a dangerous insertion[8]. Although these predictions need to be checked against actual clinical data, it is likely that the higher the number of cells given to a patient, the higher the probability of receiving one that is potentially malignant. This possibility poses a real ethical dilemma. The effectiveness of gene therapy has been limited for years by inefficient technology. The SCID trials changed that by increasing both gene transfer and cell transplantation efficiency. Scaling back this efficiency might reduce the risk of side effects, but will almost certainly lower the chances of success. Is there a sensible risk/benefit balance in such situations?

After the leukaemia cases occurred, scientists and regulatory authorities called for a halt to clinical experiments. In most countries, trials were allowed to resume after a temporary hold, on the basis that the potential benefits to patients outweighed the risks. Many argued that there is a need to develop new, safer vectors that avoid the problem of oncogene activation, and for more preclinical studies to enable better assessment of the risks. It is hard to disagree with these positions. Research must go on, particularly on vector design. Nevertheless, this work may take many years, and even the best animal model is far from being able to predict all of the possible risk factors when treating patients. This was certainly true in the X-SCID case.

In the meantime, we are left with a life-saving treatment that works for most patients, and several patients with no alternative treatments or with alternatives that carry even higher risks. Gene therapy, just like any other treatment, has side effects, and we have to deal with them — as we would do for any other treatment. Even with the risk of leukaemia, gene therapy is still a much better therapy than mismatched bone-marrow transplantation for SCID patients, and a fair assessment of the risk/benefit ratio should really be the only ethical criterion underlying the decision to use it. Ultimately, when assessing actual risk, there is no substitute for clinical trials on many patients. Delaying these trials would prevent researchers from assessing its full therapeutic potential, postpone its development into an effective therapy, and ultimately affect the right of patients to have access to a better treatment.

Regulatory responses in Europe and the United States

United States

The FDA allows gene-therapy trials for X-SCID if no other therapy is available. Clinical hold on other stem-cell gene-therapy trials may be lifted after case-by-case review.

www.fda.gov/ohrms/dockets/ac/03/minutes/3924M2.doc

United Kingdom

Approved clinical SCID trials are assessed on a case-by-case basis and are ongoing.

www.doh.gov.uk/genetics/gtac/recommendationsGTAC-CSM.PDF

France

After a temporary hold, the French reopened clinical studies for X-SCID in January 2004.

afssaps.sante.fr

Italy

Moratorium on any clinical trial involving the use of retroviruses until 31 December 2003. New ruling is currently awaited.

www.iss.it/sitp/scf1/comu/index.html

Germany

After a temporary hold on all trials involving retroviruses, gene-therapy trials for SCIDs and other diseases restarted in February 2003.

www.bundesaerztekammer.de/30/Ethik/80Themen/85KomSomGen

Europe

No Europe-wide regulations. Although experts argue that stem-cell gene-therapy trials should be allowed for life-threatening disorders after careful risk/benefit evaluation.

www.emea.eu.int/index/indexh1.htm

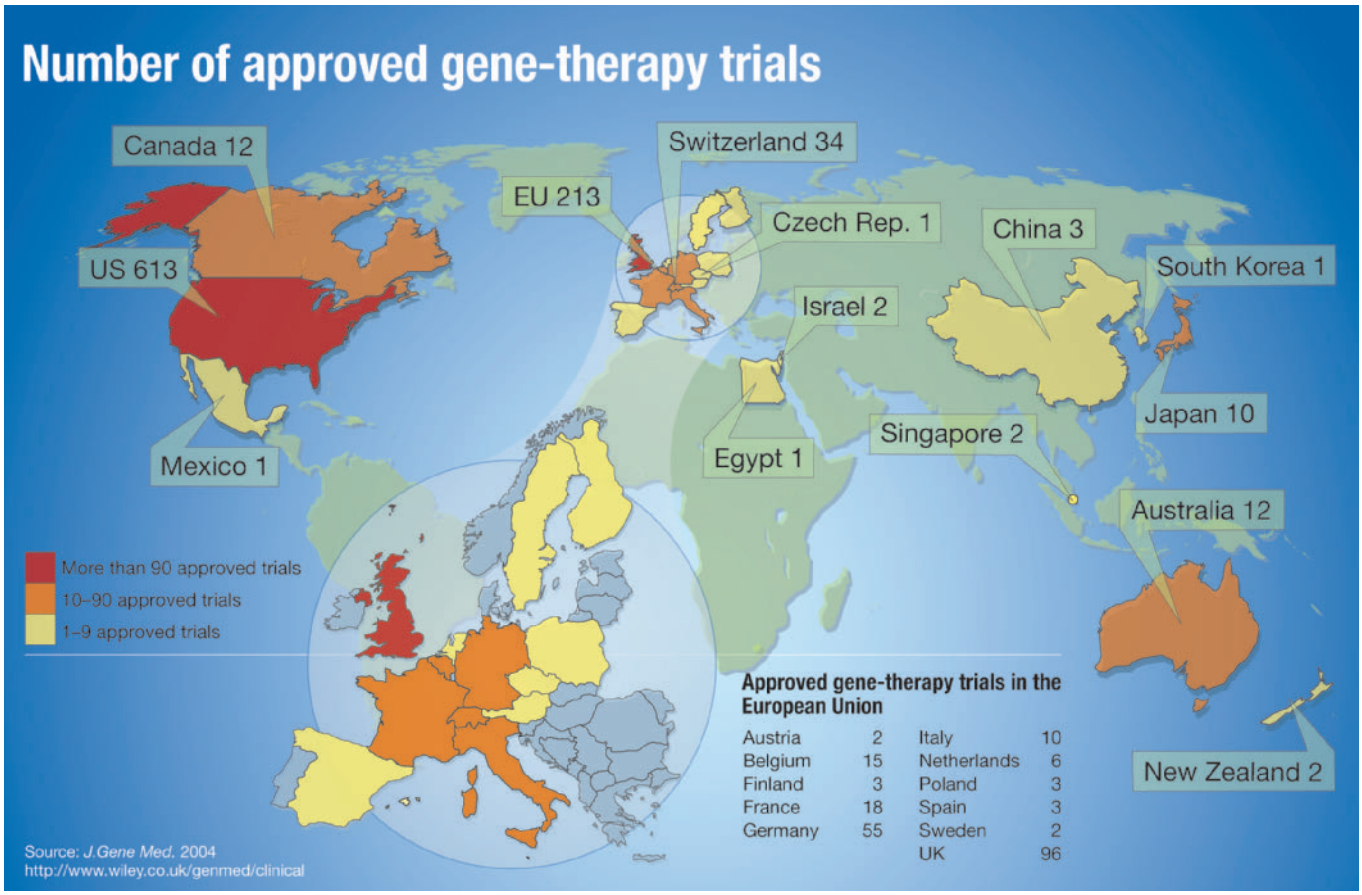
P. MENZEL/SPL

Fresh hope: gene therapy can offer a realistic chance of survival to babies born with severe combined immunodeficiency.

Prediction and monitoring of risks

Decisions on how to carry out further trials are complicated by the availability of technology to analyse genetically modified stem cells before and after they are given to patients. It has been proposed that using such analysis would prevent patients being given potentially malignant cells. Although regulatory authorities in Europe and the United States have not yet demanded this type of monitoring, the jury is still out on the issue. Could such 'molecular monitoring' provide useful information to clinical investigators and reduce the risks to patients?

As discussed above, there could be potentially dangerous gene insertions in all samples of genetically modified cells. Unfortunately, the molecular analysis destroys the cells. So screening all samples before transplantation, as argued by some[9], is technically



impossible — each modified stem cell is unique, and taking 10% of the cells for analysis will tell you nothing about the other 90%. In addition, until we know more about what causes cells to become malignant, there is no evidence that detecting certain insertions would inevitably lead to leukaemia, for example. There are many factors that prevent cells with potentially dangerous insertions from developing into a malignant cell[8], and the risk could vary greatly in different patients and for different diseases.

More realistically, molecular monitoring could be carried out during the follow-up phase of clinical trials. Such analysis could help to estimate the frequency of potentially harmful events, and provide a better risk assessment for future clinical trials. In the case of the French X-SCID patients, retrospective analysis of blood samples taken at regular intervals revealed how clones of the malignant cells grew and proliferated in the patients' blood[3]. This provided a wealth of information on the causes and development of the leukaemia. However, monitoring gene insertions has less value than we would like for predicting and diagnosing cancer in individual patients. For diagnostic purposes, proliferating cell clones cannot indicate cancer alone, which requires other clinical information. We therefore argue that mandatory molecular monitoring would put an unnecessary burden on clinical centres running gene-therapy trials, without significantly reducing the risk of leukaemia. Instead, we recommend systematic archiving of bone marrow and blood samples from all patients undergoing stem-cell gene therapy, to allow retrospective analysis at any time.

Regulatory harmony

The varied responses from regulatory authorities add greatly to the uncertainty surrounding gene therapy. By creating a complex web of different rules in different countries, multicentre clinical trials become harder to plan and execute. Harmonization of legislation among European states, and between Europe and the United States, is urgently needed. Although talks are ongoing between the US Food and Drug Administration (FDA) and the European Medical Evaluation Agency (EMEA) on this point, the picture remains bleak.

The EMEA has no formal jurisdiction over early clinical trials, and individual European countries resist the idea of giving up national authority on this matter. The Gene Therapy Expert Group within the EMEA has done an outstanding job in providing accurate information on the cancer-related risks, and sensible suggestions about the regulatory options[10]. However, unless measures are rapidly taken to harmonize the decision-making process of European states on gene-therapy regulation, it is unlikely that any agreement between the FDA and the EMEA will have the beneficial impact that investigators and industry — and ultimately patients — are waiting for.

Retroviruses are the only clinical tool currently available to introduce a permanent genetic modification into stem cells and to treat life-threatening conditions such as SCIDs. We believe it is essential to find a rational balance between feasibility, safety and efficacy when deciding on the clinical uses of these vectors, as well as when devising suitable regulations and guidelines. ■

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1. Cavazzana-Calvo, M. *et al. Science* **288,** 669–672 (2000).
2. Aiuti, A. *et al. Science* **296,** 2410–2413 (2002).
3. Hacein-Bey-Abina, S. *et al. Science* **302,** 415–419 (2003).
4. Fischer, A. *Lancet* **357,** 1863–1869 (2001).
5. Antoine, C. *et al. Lancet* **361,** 553–560 (2003).
6. Bonini, C. *et al. Nature Med.* **9,** 367–369 (2003).
7. Dave, U. P., Jenkins, N. A. & Copeland, N. G. *Science* **303,** 333 (2004).
8. Baum, C. *et al. Blood* **101,** 2099–2114 (2003).
9. Williams, D. A. & Baum, C. *Science* **302,** 400–401 (2003).
10. http://www.emea.eu.int/index/indexh1.htm

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