

Gene therapy: great expectations?

Unrealistic expectations may overshadow genuine advances and focus attention more on failures

For many years, scientists and clinicians have sought to harness the power of genes for treating disease. The potential for gene therapy to cure otherwise untreatable conditions, and to offer a completely new strategy where conventional medicine has limited efficacy, has attracted huge interest and investment of time and money from both academic and commercial biotechnology sectors. The field of gene therapy has therefore grown rapidly. However, unrealistic expectation has overshadowed genuine advances and focused attention more on clinical failures and unnecessary mistakes. Only recently, federal law enforcement officials announced a substantial settlement with the University of Pennsylvania after the death of a patient in a gene therapy trial in 1999. Consequently, gene therapy has been viewed with suspicion, and the tight regulatory control on the conduct of clinical studies has to some extent restricted progress. But is the frequently cited accusation that gene therapy has failed to deliver in the clinical arena justified, or is it another manifestation of unrealistic expectation?

At the start of the 1990s, the first clinical trials of gene therapy were attempted for an inherited severe combined immunodeficiency (SCID) caused by deficiency of the intracellular enzyme adenosine deaminase (ADA).¹⁻⁴ In the absence of definitive treatment, SCID of any molecular type is usually fatal within the first year of life, although patients with ADA deficiency can be supported by administration of exogenous bovine enzyme. Even so, this is often only partially effective, and is extremely expensive. The rationale for the development of gene therapy for SCID therefore derives from the severity of the illness, the inadequacy of conventional therapy, and the considerable morbidity and mortality associated with stem-cell transplantation, particularly from a mismatched donor.

Efficacy in these early studies was limited, but a decade further on, gene transfer technology and cell handling protocols had been refined sufficiently to produce real clinical benefit. Four recent studies have demonstrated highly effective gene therapy for the X-linked form of SCID (SCID-X1) and ADA deficiency, using retroviruses to deliver the therapeutic genes into haemopoietic stem cells *ex vivo*⁵⁻⁸ (also Gaspar and Thrasher, unpublished data). Bearing in mind the outcome and adverse effects of conventional therapy, these are remarkable results and the first clear indication that gene therapy can offer a cure for some human diseases. In a few patients, including one reported in this issue of the *Journal* (page 458),⁹ the treatment has failed, indicating that there is more to learn about the effective dose of corrected cells and the potential for host factors to influence immune cell development.¹⁰

Many different types of vector have been tested in laboratory experiments to deliver therapeutic genes, and their effectiveness is largely determined by the host and tissue type. For stable gene transfer to dividing cells, such as haemopoietic cells, the new genetic material has to be retained through cell division and passed on to daughter cells. Although retroviruses are highly effective for this, their dependence on chromosomal integration brings with it the risk of inadvertent gene activation or inactivation. Having initially achieved successful immunological reconstitution, three

patients with SCID-X1 (out of a total of 18 SCID-X1 and seven ADA-deficient patients treated to date) developed T cell lymphoproliferative disease about 3 years after the gene therapy procedure.¹¹ In two of these patients, the enhancer sequences in the retroviral vector, which are responsible for effective transgene expression, had activated the *LMO-2* proto-oncogene. There are likely to be other factors that contributed to cell transformation, but they have not yet been defined. It is therefore unclear whether all patients are at significant risk, or whether this is restricted to a few with SCID-X1.

All this makes decision-making by regulatory authorities very difficult, as it would be unfortunate to withdraw potentially life-saving therapy from patients who have few rational alternatives. It is also difficult for families faced with deciding whether to participate in a new therapy with proven curative potential but an element of uncertainty in the longer term. In light of the third adverse event reported earlier this year, regulatory authorities in both France and the United States have put ongoing SCID-X1 studies on hold, although the US Food and Drug Administration have preserved the potential to treat patients in whom allogeneic transplantation has failed. Having considered all options, UK authorities have allowed trials to continue as before, with case-by-case review. This response seems to offer the most flexibility, as patients in whom conventional therapy is judged to be of very high risk can continue to benefit from gene therapy. Importantly, it also empowers families to participate, with informed consent, in the decision-making process. The Australian position is outlined in this issue of the *journal* (page 441).¹²

Fortunately, it is likely that much can be done to improve efficiency and safety of current protocols, and these developments are expected to enter clinical trial quite soon. The design of vectors used for gene delivery is clearly important, and modifications are possible that limit the risks of mutagenesis, such as incorporation of DNA and RNA insulator sequences in integrating vectors; use of self-inactivating vectors in which the powerful viral enhancer sequences are deleted; or targeting of safe regions in the genome.

Ultimately, the development of homologous recombination or gene repair to accurately correct genetic mutations, or the construction of mitotically stable extrachromosomal vectors, would obviate many of these problems, but current technologies are inefficient.

The potential for gene therapy to treat human disease is clear, and the clinical evidence is beginning to emerge. The time between concept and delivery of therapeutic success is really no different from that of other significant medical advances, and the continuing occurrence of side effects associated with established approaches, such as organ and bone-marrow transplantation, should not be forgotten. Undoubtedly, similar strategies will be applied to other severe conditions, but also to a larger number of non-lethal conditions associated with significant disability. In this latter case, the risks of therapy have to be more clearly defined in biologically relevant model systems. The expectation that this exciting new therapeutic modality will produce major immediate effects in the absence of either predictable or unexpected adverse events is

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unrealistic. More than ever, human clinical trials are necessary to establish the efficacy of gene therapy and to inform future technological development.

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