



postnote

June 2005 Number 240

GENE THERAPY

In 2003 the Government pledged £50 million over three years to harness the potential of developments in genetics for the benefit of NHS patients. £10 million of this has been earmarked for gene therapy research and development. This briefing introduces gene therapy, outlines the potential benefits for patients and examines current regulatory and technical issues.

What is gene therapy?

Gene therapy involves the introduction of genetic material into a cell to treat disease. Many of the conditions treated in this way are genetic diseases that occur when genes malfunction (see box 1). A common approach in gene therapy is to identify a malfunctioning gene and supply the patient with functioning copies of that gene. Other approaches include switching specific genes on or off, introducing genes to kill cancer cells, to suppress tumours by inhibiting the blood supply, or to stimulate the immune system to attack certain types of cells. Whichever approach is used, the aim of gene therapy is to introduce therapeutic material into the target cells, for this to become active inside the patient and exert the intended therapeutic effect. At present, gene therapy is still at the clinical research stage.

The UK Clinical Trials Regulations 2004 prohibit gene therapy on reproductive (germ line) cells; it can only be carried out on non-reproductive (somatic) cells. Germ line gene therapy can potentially cause changes in a patient, including harmful effects that could be passed on to future generations. It is therefore currently considered unacceptable for both ethical and safety reasons.

Administering gene therapy

Successful gene therapy requires that the:

- genetic malfunction/nature of a disease is understood;
- therapeutic material can be delivered to the target cells in the affected tissue or organ;
- therapeutic material is active for the intended duration and delivers the intended benefit to the target cells;
- harmful side effects, if any, are manageable.

Box 1 Genes, proteins and genetic disease

- A gene contains the set of instructions that a cell needs to produce a particular gene product (usually a protein).
- Proteins are large molecules that perform various essential functions in the body.
- Genetic diseases are caused by malfunctioning gene(s). Malfunctions can be inherited, occur at birth or be randomly acquired due to environmental or lifestyle factors, such as exposure to toxins.
- Single gene disorders, such as Cystic Fibrosis (CF) affecting 0.04% of the UK population, are caused by a single gene malfunctioning and are usually inherited.
- Complex genetic diseases, such as Parkinson's disease, cancer or cardio-vascular diseases, result when environmental factors cause malfunctions in genes, or combine with the presence of one or more malfunctioning genes. These diseases have a genetic component, but are not necessarily inherited.

Therapeutic material can be delivered to the target cells in two main ways. First, it can be inserted into cells from the affected tissue outside the body, and these cells then returned to the body. Second, it can be delivered directly into the body at the required site. Either way a 'delivery vehicle' called a vector is used to get the therapeutic material to the patient's target cells. Vectors are most commonly based on modified viruses, because these can target and enter cells efficiently (box 2). To date, some 70% of gene therapy trials approved in the UK have involved viral vectors.

UK regulation of clinical gene therapy

UK regulatory bodies

The Clothier Committee on the Ethics of Gene Therapy in 1992 recommended that gene therapy be limited to life threatening disorders. Researchers wanting to use gene therapy in clinical trials must obtain approval from the:

- Gene Therapy Advisory Committee (GTAC), set up in 1993, is the UK national ethics committee for gene therapy clinical research under the Clinical Trials Regulations 2004. GTAC assesses the ethical acceptability of gene therapy research proposals taking

account of the scientific merits and potential benefits and risks. It comprises specialists in medicine and science as well as lay members. GTAC also advises ministers on developments in gene therapy, networks with regulators worldwide and keeps itself informed on new developments in the field.

Box 2 Viral vectors used in gene therapy trials

Viral vectors are most commonly used, as viruses have evolved a way to deliver their genes to specific human cells. Vectors can be rendered harmless by removing viral genes and replacing them with therapeutic genes. Some types of viral vectors include modified versions of the following:

- pox viruses that normally cause pox diseases (used in 20% of UK trials approved since 1993);
- adenoviruses that, unmodified, are responsible for mild respiratory infections, such as colds (20% of UK trials);
- retroviruses that normally cause disease in mice but that can also infect human cells (16% of UK trials);
- herpes viruses that can affect the skin and nervous system (used in 10% of UK trials);
- lentiviruses, a type of retrovirus that normally causes HIV/AIDS (1% of UK trials).

- Medicines and Healthcare Products Regulatory Agency (MHRA), established in 2003 as the licensing authority for clinical trials in the UK. MHRA is the UK's competent authority for regulating medicinal products and devices.

Clinical trials

Ninety-six trials involving patients have been approved in the UK since 1993. Of these, 72% were for cancer, 13% for single-gene disorders and 7% for vascular disease.

The majority were 'Phase I' clinical trials to evaluate the safety of a proposed gene therapy with small numbers of very ill patients, for whom no other treatment options existed. For instance, some early CF trials had 16-18 patients. If Phase I is successful, a trial may be repeated with a larger group of patients in Phase II, to assess therapeutic activity in very ill patients. Even at this stage, a successful outcome cannot be attributed solely to the efficacy of the gene therapy. Efficacy can only be established in a Phase III clinical trial, involving more (perhaps up to a few hundred) patients. To date, three UK gene therapy trials – one for HIV and two for glioma (a type of brain cancer) – have progressed to Phase III.

Marketing approval

No form of gene therapy has yet advanced to become a licensed treatment in the UK. Any commercial marketing of a gene therapy product would require a marketing licence from the European Medicines Agency (EMA). As a human medicinal product of biological origin, gene therapy medicinal products for marketing in one or more of the EU member states must receive approval via the EMA's centralised marketing procedure. This is a well-established procedure for biological therapeutic products, such as recombinant therapeutic proteins. To assess each application for marketing authorisation, the EMA appoints a rapporteur and a co-rapporteur from two member states. The application is then assessed on the basis of quality, safety and efficacy of the product.

Issues

Gene therapy is only used to treat very serious diseases. While the first clinical trials focused mainly on single-gene disorders, more recent trials have looked at complex diseases such as cancer. Such trials offer hope for cancer patients but are at an early stage. The experience of 12 years and nearly a hundred UK trials in gene therapy has produced significant successes. But it has also highlighted questions about effectiveness, safety, durability and the likely commercialisation of gene therapy. These are discussed below.

Technical considerations

Gene delivery

Successful gene delivery is not easy or predictable, even for single-gene disorders. For example, although the genetic basis of CF is well known, the presence of mucus in lungs makes it physically difficult to deliver genes to the target lung cells. Delivering genes for cancer therapy may also be complicated where the disease may be in several sites. Gene therapy trials for X-chromosome-linked severe combined immuno-deficiency (X-SCID) however, have been more successful. In this case, the genetic basis of the disease is well-understood and the therapeutic material can be delivered using the established procedure of bone marrow transplant. A viral vector has been used to introduce functioning copies of the gene whose malfunction causes X-SCID into blood-producing stem cells from the patient's bone marrow. These are then transplanted back into the patient. In most cases the modified bone marrow successfully supplied the missing gene product, and the patients are able to lead normal lives.

Durability and integration

Some gene therapy approaches aim to achieve a long-term effect. Where such durability is required the therapeutic material must remain functional for the intended duration or gene therapy may not achieve long-term benefits. Two possible ways of achieving this are to use multiple rounds of gene therapy, or to integrate therapeutic genes so they remain active for some time.

Integrating therapeutic DNA into the target cells' genetic material, while long-lasting, raises concerns over possible undesirable side effects. For instance, this approach has been used in trials to treat babies with X-SCID syndrome. In UK trials, 7 babies responded well to gene therapy and remain healthy. However, 3 of those in a similar French trial went on to develop leukaemia-like symptoms. A possible explanation is that the therapeutic material might have integrated where it could affect another gene to produce rapid growth of cancerous cells. Researchers are thus investigating ways of achieving long-term therapeutic effects without integration, for instance by using stable, non-integrating, vectors.

Other approaches seek more immediate effects, where integration of therapeutic DNA into the target cells is not the aim. For instance, in gene therapy to treat cancer, the aim may be to use 'suicide' genes to kill cancerous cells as quickly as possible.

Immune response

When a viral vector is used to deliver gene therapy, the body may recognise it as 'foreign' and mobilise the immune system to attack it. In cancer, triggering such an immune response may be the aim of the gene therapy. In other cases, immune responses may reduce the efficacy of gene therapy, causing the patient to stop responding after a few applications or inducing serious side-effects. Further, an enhanced response to vectors encountered previously may make it difficult to give repeat applications of gene therapy.

Safety of vectors

Worldwide, more than 3,000 patients with serious diseases have been treated using experimental gene therapies since 1990. To date, there have been just two fatalities that have been directly attributable to such treatments. Nevertheless, a small minority of cases have raised potential concerns. For instance, the use of viral vectors has been suggested as a factor in the death of a US gene therapy patient and the cases of leukaemia-like symptoms after X-SCID gene therapy trials in France.

Animal research may also provide important information on vector safety. Following recent reports of a pre-clinical study, where mice developed liver tumours after exposure to one particular vector, GTAC published an open letter drawing attention to potential safety concerns. Further the UK Health and Safety Executive issued information and interim advice on containment. These steps were taken in case these observations affected any pre-clinical or clinical studies planned or in progress outside the UK; they do not appear to affect any current or previous UK trials.

Uncertainty

While GTAC and MHRA make every effort to maximise patient safety, uncertainties remain. The range of explanations that have been advanced to account for leukaemia-like symptoms in the French X-SCID gene therapy trial, illustrate the difficulties faced by regulatory bodies. These explanations include problems with the integration of the therapeutic material, an immune response to the vector, a family history of cancer, and pre-existing infections and other problems symptomatic of immune deficiency.

Regulatory challenges

Gene therapy research on children

Conducting medical research with children raises difficult issues. To date, very few gene therapy trials have involved babies or children, but this may change (see box 3). There may be good clinical reasons to involve children in gene therapy trials. For instance, some diseases progressively worsen with age, and the best chances of positive outcomes often lie with interventions at an early stage. CF is a case in point. It is irreversible after a certain stage of deterioration of the lungs, so it is only possible to stabilise (rather than improve) a 30 year old patient's condition using conventional treatments. Gene therapy for CF may thus work best in the early years of life. In such cases, researchers are required to

demonstrate the therapeutic necessity of using children in a gene therapy trial.

Box 3 Gene therapy research on children

In future, more gene therapy trials may involve children due to developments such as

- The Government has recently awarded £900,000 to the Institute of Ophthalmology at University College London for gene therapy research on childhood blindness.
- The DH has awarded £2.5 million to further research into gene therapy for CF. One of the projects being funded is specifically intended to support research into gene therapy for children with CF.

Obtaining informed consent for a child to take part in a clinical trial is legally complex and there is ongoing debate in the UK on this issue. GTAC's guidelines on writing patient information leaflets include guidance on how to communicate information to the child. The Medical Research Council (MRC) has also published an ethics guide for medical research involving children.

Accountability, openness and transparency

GTAC and MHRA adopt a case-by-case approach to safety issues. For instance, following reports of leukaemia-like illness in three patients in a French X-SCID trial, GTAC and the MHRA's Committee on Safety of Medicines made joint recommendations to the Department of Health (DH). While such an approach is welcomed by researchers, groups such as GeneWatch have been critical of a lack of transparency in the UK's gene therapy regulation. For instance, it points out that GTAC holds its meetings for evaluation of research proposals in private. Furthermore, MHRA publishes details of clinical trial authorisation applications in a database accessible only to competent European regulatory bodies, the EMEA and the Commission.

GTAC argues that it publishes minutes of meetings and an annual report, but has to preserve independence in evaluation, protect patient privacy and, in later phases of trials, ensure commercial confidentiality. MHRA believes that confidentiality encourages the reporting of sensitive information relating to public health concerns. All NHS funded trials must be registered in a publicly accessible database. Industry has also announced voluntary measures on registering Phase III and further clinical trials.

Resources

96 gene therapy trial applications have been approved in the UK since 1993. However, as investment in research grows, the number of trial applications could also grow in the next few years. This could have resource implications both for GTAC and MHRA.

Future regulatory challenges

As the science of gene-based medicines evolves, new technologies and new therapies will emerge. For instance, RNAi is a method of 'silencing' genes to prevent the formation of unwanted protein. MRC is investing in basic research into the therapeutic potential of RNAi. At

present, GTAC and MHRA review the use of emergent technologies in clinical trials on a case-by-case basis.

New interventions combining gene therapy with other approaches such as stem cell therapy are emerging. For instance, bone marrow stem cells are already used in some gene therapy trials. While bone marrow transplants are an established practice, it is possible that in the longer-term, gene therapy trials could involve stem cells derived from embryos. Such developments may pose new challenges to the regulatory system, which currently regulates gene therapy and embryonic stem cell research separately. The House of Lords Stem Cell Committee¹ considered ways of regulating new stem cell therapies and identified a number of options. These included expanding the remit of GTAC to take on this role, or establishing a new regulatory body based on the GTAC model. DH has noted that it will consider the need for further oversight in this area in the light of any new developments.

Future prospects and expectations

Research

In its 2003 White paper, the Government committed £10 million for research into single gene disorders and safety of vectors, as well as to enable access for public sector researchers to high standard gene therapy vector production facilities². In 2004, the Government awarded £0.5 million for haemophilia, £1.6 million for Duchenne Muscular Dystrophy, £0.9 million for childhood blindness and £1 million for research into long-term safety of some techniques used for gene therapy. In addition, MRC funds basic science such as vector development and delivery methods in cell lines and animal models. Public funding of gene therapy research is supplemented by funding from research foundations and charities. Over the last five years, the Wellcome Trust has provided £4.8 million for non-clinical gene therapy research aimed at several inherited and acquired diseases. Cancer Research UK (CR-UK) is also currently funding nine gene therapy research projects.

While patient groups are largely satisfied with the current disease-led approach to gene therapy research, researchers have called for more research into vector safety, delivery techniques, molecular causes of diseases, and uncertainty of outcomes.

What happens next?

Opinions vary as to how soon commercial gene therapy products will be on the market. For instance, CR-UK believes that gene therapy presents realistic opportunities for new ways to treat cancer, but not for the next 10-15 years. The Genetic Interest Group, a national alliance of patient organisations, does not expect that working therapies for a wide-range of diseases will emerge in the near-term, but suggests that research will contribute to the knowledge of vectors, insertion and delivery techniques, and safety. Such understanding will be critical to the development of potential gene therapies.

However a number of gene therapy products may be in the pipeline. For instance, a UK firm, Ark Therapeutics, has two gene-based medicines in late stage clinical trials; it currently aims to apply to market these in 2007. The first ever recombinant gene therapy to obtain marketing approval was 'Gendicine', a gene-based medicine for treating head and neck cancer. This was approved for use in China in late 2003 by the Chinese State Food and Drug Administration³.

As noted earlier, any gene therapy products will have to be assessed through the EMEA's centralised procedure. While well-established for other biological therapeutic products, this procedure has not yet been used for gene therapy products. If the UK regulator (the MHRA) is not appointed as the Rapporteur or Co-rapporteur, it will still review the data provided by the applicant company and provides inputs into the process of authorisation through the Committee for Human Medicinal Products (CHMP).

Overview

- Gene therapy can potentially treat diseases such as CF, cancers, heart disease and HIV infection. To date, no gene therapy clinical trial has given rise to the development of a commercial treatment in the UK.
- While industry considers commercial gene therapy likely for some cancers in the next few years, others suggest it may be 10 to 15 years before gene therapies are widely available.
- Potential issues with gene therapy include effective delivery, longevity of the therapy and safety concerns.
- Gene therapy clinical trials in the UK are regulated by GTAC and MHRA. MHRA is also responsible for regulating medicinal gene products in the UK.
- The regulatory system considers all gene therapy research proposals on a case-by case basis, taking ethical and scientific factors into account. Some have called for more open and transparent assessments.
- Technical developments may necessitate changes to the current regulatory framework, which has separate arrangements for therapies derived from human genes, stem cells, cells and tissues.

Endnotes

- 1 Report from the House of Lords Select Committee Stem Cell Research, HL 83(i), February 2002.
- 2 *Our Inheritance, Our Future*, Department of Health, June 2003
- 3 *The Story of Gendicine: The Story behind the First Gene Therapy*, Biopharm International, May 2004.

POST is an office of both Houses of Parliament, charged with providing independent and balanced analysis of public policy issues that have a basis in science and technology. POST is grateful to Shefaly Yogendra for researching this briefing note, and to all contributors and reviewers. For further information on this subject, please contact Peter Border at POST.

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The Parliamentary Office of Science and Technology, 7 Millbank, London SW1P 3JA; Tel: 020 7219 2840; email: post@parliament.uk

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