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Important points

- Gene therapy is 'the use of genes as medicine' involving the transfer of a therapeutic or working copy of a gene into specific cells of an individual in order to repair a faulty gene copy
- The technique may be used to replace a faulty gene, or to introduce a new gene whose function is to cure or to favourably modify the clinical course of a condition
- Gene therapy is still an experimental discipline and much research remains to be done before this approach to the treatment of condition will realise its full potential
  - Gene therapy was used in 2000 by a French research group in the treatment of a form of immune deficiency due to a mutation in a gene located on the X chromosome (Severe Combined Immune Deficiency). When two of the children treated developed leukaemia in 2002 and 2003, caused when the virus used to deliver the therapeutic gene activated a cancer-causing gene, the clinical trials were stopped but have now been resumed only for patients with no other treatment options
- The challenge of developing successful gene therapy for any specific condition is considerable:
  - The condition in question must be well understood
  - The underlying faulty gene must be identified and a working copy of the gene involved must be available
  - The specific cells in the body requiring treatment must be identified and accessible
  - A means of efficiently delivering working copies of the gene to these cells must be available
- The problem of 'gene delivery' ie. how to get the new or replacement genes into the desired tissues, is very complex and challenging. Some of the 'vectors' for the role of delivering the working copy of the gene to the target cells include using harmless viruses and stem cells
- In gene therapy, *only* body (somatic) cells and not the egg or sperm cells (germ cells) are targeted for treatment. Somatic gene therapy treats the individual and has no impact on future generations as changes to the somatic cells cannot be inherited
- The strong consensus view at present is that the risks of manipulation of the genes in the egg or sperm cells far exceed any potential benefit and should not be attempted

What is gene therapy?

Gene therapy is 'the use of genes as medicine'. It involves the transfer of a therapeutic or working gene copy into specific cells of an individual in order to repair a faulty gene copy. Thus it may be used to replace a faulty gene, or to introduce a new gene whose function is to cure or to favourably modify the clinical course of a condition.

The scope of this new approach to the treatment of a condition is broad, with potential in the treatment of many genetic conditions, some forms of cancer and certain viral infections such as AIDS.

Gene therapy remains an experimental discipline however and much research remains to be done before this approach to the treatment of certain conditions will realise its full potential.

The majority of clinical gene therapy trials are being conducted in the United States and Europe, with only a modest number initiated in other countries, including Australia. The majority of these trials focus on treating acquired conditions such as cancer. The only gene therapy that has been approved for routine treatment so far is for a form of cancer which was approved in China in early 2004.

A form of immune deficiency called adenosine deaminase (ADA) deficiency was the first condition to be treated with a gene therapy approach in humans in the early 1990s. It is also the first condition for which therapeutic gene transfer into stem cells (see later) has been attempted in the clinical arena (Candotti F, 2001).

A case study of gene therapy for a genetic condition

Another form of immune deficiency is due to a mutation in a gene located on the X chromosome and is called Severe Combined Immune Deficiency (SCID). This 'X-linked condition' only affects boys (see Genetics Fact Sheet 10 for an explanation of the inheritance pattern of genes located on the X chromosome).

The use of gene therapy in 2000 in the treatment of this condition by a French research group led by M. Cavazzana-Calvo was hailed as the first example of a genetic condition being successfully treated by gene therapy and is a milestone in medical history.

- Seven out of ten infants treated to date have restored immune function. Two of the children treated by the gene therapy however developed leukaemia in 2002 and 2003, caused when the virus used to deliver the therapeutic gene activated a cancer-causing gene (an *oncogene* – see Genetics Fact Sheet 47)
- The clinical trials were halted but have now been resumed only for patients with no other treatment options
- This experience illustrates the need for this therapy to be conducted as part of clinical trials

How is gene therapy carried out?

The challenge of developing successful gene therapy for any specific condition is considerable. The condition in question must

be well understood and the underlying faulty gene identified.

A working copy of the gene involved must be available, the specific cells in the body requiring treatment must be identified and accessible and finally, a means of efficiently delivering working copies of the gene to these cells must be available.

Of all these challenges, the one that is most difficult is the problem of 'gene delivery' ie. how to get the new or replacement genes into the desired tissues. Some of the 'vectors' for the role of delivering the working copy of the gene to the target cells include using:

a) Harmless viruses

One of the most promising methods currently being developed is the use of harmless viruses that can be used to carry genes into cells.

Scientists now have the knowledge and skills to remove the virus' own genes and to replace them with working human genes. These altered viruses can then be used to smuggle genes into cells with great efficiency. When viruses are used in this way they are known as vectors.

Some of these vectors are capable of not only carrying the gene into the cell but also of inserting the gene into the genetic make-up of the cell.

Once in the right location within the cell of an affected person, the transplanted gene is 'switched on'. The transplanted gene can then issue the instructions necessary for the cell to make the protein that was previously missing or altered.

b) Stem cells

Another technique with potential is the use of stem cells in delivering gene therapy. Stem cells are immature cells that can differentiate or develop into cells with different functions.

In this technique, stem cells are manipulated in the laboratory in order to make them accept new genes that can then change their behaviour.

For example, a gene might be inserted into a stem cell that could make it better able to survive chemotherapy. This would be of assistance to those patients who could benefit from further chemotherapy following stem cell transplantation.

Ethical considerations

While the body has many billions of cells, only a very small proportion of these cells are involved in reproduction, the process by which our genes are handed on to future generations. In males these cells are located in the testes and in females, in the ovaries. These special reproductive cells are called '**germ cells**'.

All other cells in the body, irrespective of whether they are brain, lung, skin or bone cells, are known as '**somatic cells**'.

In gene therapy, only somatic cells are targeted for treatment. Therefore any changes to the genes of an individual by gene therapy will only impact on the cells of their body and cannot be passed on to their children. Changes to the somatic cells cannot be passed on to future generations (inherited).

Somatic gene therapy treats the individual and has no impact on future generations.

An example of somatic gene therapy for an inherited condition

Imagine, for example, a little boy with haemophilia, a condition that is caused by a faulty gene that makes his liver unable to make blood clotting factor 8 (see Genetics Fact Sheet 40).

- Gene therapy would involve putting a working copy of the gene which codes for factor 8 into his liver cells so that his liver could then produce adequate levels of factor 8
- While the little boy himself would be cured, the altered genes in his germ cells would remain unchanged and he could still pass the faulty gene on to future generations

Concerns with gene therapy of the egg or sperm cells

The possible genetic manipulation of the egg or sperm cells (germ cells) remains the subject of intense ethical and philosophical discussion.

The strong consensus view at present is that the risks of germline manipulation far exceed any potential benefit and should not be attempted.

Safety considerations

No therapy, established or experimental, is without some associated risk and the potential benefits of new treatments must always be balanced against such risks. The experience with gene therapy for the immunodeficiency condition SCID as described above illustrates the need for this therapy to be conducted as part of clinical trials.

Safety will appropriately remain an important consideration as the field of gene therapy evolves.

Other Genetics Fact Sheets referred to in this Fact Sheet: 10, 40, 47

Information in this Fact Sheet is sourced from:

Candotti F.(2001). Gene therapy for immunodeficiency. *Current Allergy & Asthma Reports*. 1(5):407-415.

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