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Gene Therapy

Gene therapy is using "genes as medicine". It is an experimental approach to treating genetic disease where the faulty gene is fixed, replaced or supplemented with a healthy gene so that it can function normally. Most genetic diseases cannot be treated, but gene therapy research gives some hope to patients and their families as a possible cure. However, this technology does not come without risks and many clinical trials to evaluate its effectiveness need to be done before gene therapy can be put to regular medical use.

How is gene therapy done?

To get a new gene into a cell's genome, it must be carried in a molecule called a vector. The most common vectors currently being used are viruses, which naturally invade cells and insert their genetic material into that cell's genome. To use a virus as a vector, the virus' own genes are removed and replaced with the new gene destined for the cell. When the virus attacks the cell, it will insert the genetic material it carries. A successful transfer will result in the target cell now carrying the new gene that will correct the problem caused by the faulty gene.

Viruses that can be used as vectors include retroviruses like HIV, adenoviruses (one of which causes the common cold), adeno-associated viruses and herpes simplex viruses. There are also many non-viral vectors being tested for gene therapy uses. These include artificial lipid spheres called liposomes, DNA attached to a molecule that will bind to a receptor on the target cell, artificial chromosomes and naked DNA that is not attached to another molecule at all and can be directly inserted into the cell.

The actual transfer of the new gene into the target cell can happen in two ways: ex vivo and in vivo. The ex vivo approach involves transferring the new gene into cells that have been removed from the patient and grown in the laboratory. Once the transfer is complete, the cells are returned to the patient, where they will continue to grow and produce the new gene product. The in vivo approach delivers the vector directly to the patient, where transfer of the new gene will occur in the target cells within the body.

Applications of gene therapy

Conditions or disorders that result from mutations in a single gene are potentially the best candidates for gene therapy. However, the many challenges met by researchers working on gene therapy mean that its application is still limited while the procedure is being perfected.

Before gene therapy can be used to treat a certain genetic condition or disorder, certain requirements need to be met:

- The faulty gene must be identified and some information about how it results in the condition or disorder must be known so that the vector

can be genetically altered for use and the appropriate cell or tissue can be targeted.
- The gene must also be cloned so that it can be inserted into the vector.
- Once the gene is transferred into the new cell, its expression (whether it is turned on or off) needs to be controlled.
- There must be sufficient value in treating the condition or disorder with gene therapy - that is, is there a simpler way to treat it?
- The balance of the risks and benefits of gene therapy for the condition or disorder must compare favourable to other available therapies.
- Sufficient data from cell and animal experiments are needed to show that the procedure itself works and is safe.
- Once the above are met, researchers may be given permission to start clinical trials of the procedure, which is closely monitored by institutional review boards and governmental agencies for safety.

Clinical trials for gene therapy in other countries (for example France and the United Kingdom) have shown that there are still several major factors preventing gene therapy from becoming a routine way to treat genetic conditions and disorders. While the transfer of the new gene into the target cells has worked, it does not seem to have a long-lasting effect. This suggests that patients would have to be treated multiple times to control the condition or disorder. There is also always a risk of a severe immune response, since the immune cells are trained to attack any foreign molecule in the body. Working with viral vectors has proven to be challenging because they are difficult to control and the body immediately recognizes and attacks common viruses. Recent work has focussed on potential non-viral vectors to avoid the complications associated with the viral vectors. Finally, while there are thousands of single-gene disorders, the more common genetic disorders are actually caused by multiple genes, which do not make them good candidates for gene therapy.

One promising application of gene therapy is in treating type I diabetes. Researchers in the United States used an adenovirus as a vector to deliver the gene for hepatocyte growth factor (HGF) to pancreatic islet cells removed from rats. They injected the altered cells into diabetic rats and, within a day, the rats were controlling their blood glucose levels better than the control rats. This model mimics the transplantation of islet cells in humans and shows that the addition of the HGF gene greatly enhances the islet cells' function and survival.

In Canada, researchers in Edmonton, Alberta also developed a protocol to treat type I diabetes. Doctors use ultrasound to guide a small catheter through the upper abdomen and into the liver. Pancreatic islet cells are then injected through the catheter into the liver. In time, islets are established in the liver and begin releasing insulin.

Another application for gene therapy is in treating X-linked severe combined immunodeficiency (X-SCID), a disease where a baby lacks both T and B cells of the immune system and is vulnerable to infections. The current treatment is bone marrow transplant from a matched sibling, which is not always possible or effective in the long term. Researchers in France and the United Kingdom, knowing the disease was caused by a faulty gene on the X chromosome, treated 14 children by replacing the faulty gene ex vivo. Upon receiving the altered cells, the patients showed great improvements in their immune system functions. Unfortunately, two of the children developed a form of leukemia several years after the treatment. Further investigation showed that the vector had inserted the gene near a proto-oncogene, which led to uncontrolled growth of the T cells. The clinical trials were put on hold until a safer method can be designed and tested.

Date modified:

2005-11-25