NIH BACKGROUNDER

Gene Transfer

What is human gene transfer research?

Human gene transfer is the process of transferring genetic material (DNA or RNA) into a person. This experimental technique is being studied to see whether it could treat certain health problems by either compensating for defective genes, prompting the body to make a potentially therapeutic substance, or triggering the immune system to fight disease. This type of experimentation is sometimes called "gene therapy" research.

Why is NIH supporting human gene transfer research?

NIH is supporting this research because it may lead to treatments for a number of serious diseases and disorders. Human gene transfer may help people with genetic disorders, particularly those conditions that result from inherited errors in a single gene (for example, sickle cell anemia, hemophilia, and cystic fibrosis). It may also hold promise for diseases with more complex origins, like cancer and heart disease. Human gene transfer is also being studied as a possible treatment for certain infectious diseases, such as AIDS.

How do scientists transfer genes into people?

Scientists often transfer genes into people by harnessing the ability of viruses to gain entry into cells in the course of infection. They remove genes that cause disease from the virus, then add new genes in the hope that the viruses will infect the desired cells and deliver the new genes to them. Another method of transferring genes is to mix them with microscopic bubbles of fatty molecules (lipids) called liposomes, which, once injected into the body, can carry them into cells. After the genes have been transported into cells, they will hopefully become activated and have a positive effect.

Has human gene transfer cured any diseases yet?

No disease has yet been cured by human gene transfer. Since 1990, when the first human gene transfer experiment was performed, more than 500 gene transfer studies have been registered with the NIH. These studies are contributing greatly to improving scientists' understanding of human gene transfer. However, since they are mostly in the early stages of development, very few have resulted in actually improving the health of study participants.

However, in 2000, researchers in France reported that gene transfer had positive results in two infants with a type of inherited immune deficiency. In this instance, their bone marrow stem cells were collected and given new genes. The modified stem cells were then put back into the infants, allowing the production of normal immune cells. The experiment has shown positive results, and presently, the infants are living normally. Their health will continue to be monitored closely. In 2002, scientists in Italy also reported a beneficial effect from gene transfer in patients with a different form of immune deficiency known as adenosine deaminase (ADA) deficiency.

Gene transfer studies conducted in animals and humans indicate that this technology also has promise for other diseases and disorders. Examples include reducing bleeding episodes in patients with a type of hemophilia and promoting the growth of new blood vessels in patients with blocked blood vessels in the heart.

Will human gene transfer cause changes that will be passed on to offspring?

Thus far, human gene transfer has only been directed toward "somatic" cells, the non-reproductive cells in the human body. The studies are purposely designed so that the transferred genes stay within the somatic cells and are not passed on to the next generation through the reproductive cells (eggs or sperm). Because of technical challenges, safety issues, and most importantly, ethical concerns, it is not yet feasible or desirable to try to transfer genes into human reproductive cells.

What are the health risks involved with human gene transfer research?

Like other forms of medical research, human gene transfer has risks that vary based on the nature of the disease and the specific procedure being performed. Two possible risks include inflammation (swelling) around the injection site or, more seriously, a severe immune reaction to the virus used to deliver the gene or to the substance a gene may produce. It is possible that the newly inserted gene could disrupt an important gene in the cell and predispose the cell to cancer

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http://www.nih.gov/news/backgrounders/genetransferbackgrounder.htm

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or other abnormalities. An adverse reaction could also occur if a gene or its product reaches not only the intended cells but also other cells in the body that researchers hadn't intended to be affected. There is a chance that the gene may be inadvertently introduced into reproductive cells, and could thus be passed on to future generations. Scientists use extensive laboratory work, animal testing, and safety measures to assess and attempt to minimize these risks.

How will sequencing the human genome affect human gene transfer?

Knowing the details of our genetic makeup (the human genome) will help scientists find and understand genes involved in health and disease. This knowledge is key to developing strategies for using gene transfer to correct various diseases and disorders.

How is human gene transfer research regulated?

Two Federal agencies provide special oversight of human gene transfer research. The Food and Drug Administration (FDA) authorizes and regulates all human gene transfer clinical trials conducted in the U.S. FDA has information about their role at http://www.fda.gov/cber/infosheets/genezn.htm.

The NIH, through its Office of Biotechnology Activities, also oversees this field, requiring researchers to follow certain scientific and ethical principles and to comply with safety reporting requirements. These requirements are set forth in the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (see http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html. All institutions that receive NIH funding for basic and clinical recombinant DNA research must ensure that all research conducted at or sponsored by the institution complies with the *NIH Guidelines.*

These institutions must establish an Institutional Biosafety Committee (IBC), which is responsible for ensuring that recombinant DNA research is conducted safely and in accordance with the *NIH Guidelines*. In addition, most institutions conducting research involving humans must have an Institutional Review Board (IRB) to ensure that the research complies with Department of Health and Human Services regulations for the protection of human subjects.

An integral component of NIH's oversight is the Recombinant DNA Advisory Committee (RAC). The NIH convenes this advisory committee to conduct in-depth review and public discussion of the scientific, safety, and ethical issues associated with selected gene transfer protocols. The RAC review process also focuses on emerging policy issues in recombinant DNA research.

More information about the NIH system of oversight can be found at http://www4.od.nih.gov/oba.

When will therapies from human gene transfer research be available?

Human gene transfer products, like all medical products, must be studied in several phases before the FDA can approve them for use by the public. Most gene transfer trials registered with the NIH have been phase I studies that investigate safety. Only thirteen percent have been phase II studies, which assess both safety and effectiveness and generally involve more subjects. Less than one percent of the trials (four) have progressed to phase III studies, which test for effectiveness using large numbers of subjects.

No human gene transfer product has yet been approved for medical use by the FDA. Given the research that must yet be done, gene transfer products are not expected to be available to patients in the immediate future.

What's next?

Gene transfer is a relatively new technology that still faces many technical challenges. The body's immune system, for example, can make it difficult to deliver a foreign substance into cells, a major technical hurdle. Researchers are investigating ways to enhance the effectiveness of gene delivery methods to increase the likelihood that genes will reach their target cells and that they will work properly once they are there.

As technology advances, scientists, policy-makers and the public are closely following the progress of human gene transfer research and studying the safety and ethical issues in this field. Their collaborative efforts will help human gene transfer advance safely and ethically toward fulfilling its promise.

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