

Gene Therapy for Cancer: Questions and Answers

Key Points

- Gene therapy is an experimental treatment that involves introducing genetic material into a person's cells to fight or prevent disease (see Question 2).
- Researchers are studying gene therapy for cancer through a number of different approaches (see Question 3).
- A gene can be delivered to a cell using a carrier known as a "vector." The most common types of vectors used in gene therapy are viruses (see Question 4).
- The viruses used in gene therapy are altered to make them safe; however, some risks still exist with gene therapy (see Questions 5 and 6).
- A clinical trial using gene therapy must be approved by at least two review boards at the scientists' institution, as well as by the U.S. Food and Drug Administration and the National Institutes of Health Recombinant DNA Advisory Committee (see Questions 9 and 10).
- The Ethical, Legal, and Social Implications (ELSI) Research Program was established in 1990 to identify, analyze, and address the implications of human genetics research (see Questions 11 and 12).

1. What are genes?

Genes are the biological units of heredity. Genes determine obvious traits, such as hair and eye color, as well as more subtle characteristics, such as the ability of the blood to carry oxygen. Complex characteristics, such as physical strength, may be shaped by the interaction of a number of different genes along with environmental influences.

Genes are located on chromosomes inside cells and are made of deoxyribonucleic acid (DNA), which is a type of biological molecule. Humans have between 30,000 and 40,000 genes. Genes carry the instructions that allow cells to produce specific proteins, such as enzymes.

To make proteins, a cell must first copy the information stored in genes into another type of biological molecule called ribonucleic acid (RNA). The cell's protein synthesizing machinery then decodes the information in the RNA to manufacture specific proteins. Only certain genes in a cell are active at any given moment. As cells mature, many genes become permanently inactive. The pattern of active and inactive genes in a cell and the resulting protein composition determine what kind of cell it is and what it can and cannot do. Flaws in genes can result in disease.

2. What is gene therapy?

Advances in understanding and manipulating genes have set the stage for scientists to alter a person's genetic material to fight or prevent disease. Gene therapy is an experimental treatment that involves introducing genetic material (DNA or RNA) into a person's cells to fight disease. Gene therapy is being studied in clinical trials (research studies with people) for many different types of cancer and for other diseases. It is not currently available outside a clinical trial.

3. How is gene therapy being studied in the treatment of cancer?

Researchers are studying several ways to treat cancer using gene therapy. Some approaches target healthy cells to enhance their ability to fight cancer. Other approaches target cancer cells, to destroy them or prevent their growth. Some gene therapy techniques under study are described below.



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- In one approach, researchers replace missing or altered genes with healthy genes. Because some missing or altered genes (e.g., p53) may cause cancer, substituting “working” copies of these genes may be used to treat cancer.
- Researchers are also studying ways to improve a patient’s immune response to cancer. In this approach, gene therapy is used to stimulate the body’s natural ability to attack cancer cells. In one method under investigation, researchers take a small blood sample from a patient and insert genes that will cause each cell to produce a protein called a T-cell receptor (TCR). The genes are transferred into the patient’s white blood cells (called T lymphocytes) and are then given back to the patient. In the body, the white blood cells produce TCRs, which attach to the outer surface of the white blood cells. The TCRs then recognize and attach to certain molecules found on the surface of the tumor cells. Finally, the TCRs activate the white blood cells to attack and kill the tumor cells.
- Scientists are investigating the insertion of genes into cancer cells to make them more sensitive to chemotherapy, radiation therapy, or other treatments. In other studies, researchers remove healthy blood-forming stem cells from the body, insert a gene that makes these cells more resistant to the side effects of high doses of anticancer drugs, and then inject the cells back into the patient.
- In another approach, researchers introduce “suicide genes” into a patient’s cancer cells. A pro-drug (an inactive form of a toxic drug) is then given to the patient. The pro-drug is activated in cancer cells containing these “suicide genes,” which leads to the destruction of those cancer cells.
- Other research is focused on the use of gene therapy to prevent cancer cells from developing new blood vessels (angiogenesis).

4. How are genes transferred into cells so that gene therapy can take place?

In general, a gene cannot be directly inserted into a person’s cell. It must be delivered to the cell using a carrier, or “vector.” The vectors most commonly used in gene therapy are viruses. Viruses have a unique ability to recognize certain cells and insert genetic material into them.

In some gene therapy clinical trials, cells from the patient’s blood or bone marrow are removed and grown in the laboratory. The cells are exposed to the virus that is carrying the desired gene. The virus enters the cells and inserts the desired gene into the cells’ DNA. The cells grow in the laboratory and are then returned to the patient by injection into a vein. This type of gene therapy is called *ex vivo* because the cells are grown outside the body. The gene is transferred into the patient’s cells while the cells are outside the patient’s body.

In other studies, vectors (often viruses) or liposomes (fatty particles) are used to deliver the desired gene to cells in the patient’s body. This form of gene therapy is called *in vivo*, because the gene is transferred to cells inside the patient’s body.

5. What types of viruses are used in gene therapy, and how can they be used safely?

Many gene therapy clinical trials rely on retroviruses to deliver the desired gene. Other viruses used as vectors include adenoviruses, adeno-associated viruses, lentiviruses, poxviruses, and herpes viruses. These viruses differ in how well they transfer genes to the cells they recognize and are able to infect, and whether they alter the cell’s DNA permanently or temporarily. Thus, researchers may use different vectors, depending on the specific characteristics and requirements of the study.

Scientists alter the viruses used in gene therapy to make them safe for humans and to increase their ability to deliver specific genes to a patient’s cells. Depending on the type of virus and the goals of the research study, scientists may inactivate certain genes in the viruses to prevent them from reproducing or causing disease. Researchers may also alter the virus so that it better recognizes and enters the target cell.

6. What risks are associated with current gene therapy trials?

Viruses can usually infect more than one type of cell. Thus, when viral vectors are used to carry genes into the body, they might infect healthy cells as well as cancer cells. Another danger is that the new gene might be inserted in the wrong location in the DNA, possibly causing harmful mutations to the DNA or even cancer.

In addition, when viruses or liposomes are used to deliver DNA to cells inside the patient's body, there is a slight chance that this DNA could unintentionally be introduced into the patient's reproductive cells. If this happens, it could produce changes that may be passed on if a patient has children after treatment.

Other concerns include the possibility that transferred genes could be "overexpressed," producing so much of the missing protein as to be harmful; that the viral vector could cause inflammation or an immune reaction; and that the virus could be transmitted from the patient to other individuals or into the environment. Scientists use animal testing and other precautions to identify and avoid these risks before any clinical trials are conducted in humans.

7. What major problems must scientists overcome before gene therapy becomes a common technique for treating disease?

Scientists need to identify more efficient ways to deliver genes to the body. To treat cancer and other diseases effectively with gene therapy, researchers must develop vectors that can be injected into the patient and specifically focus on the target cells located throughout the body. More work is also needed to ensure that the vectors will successfully insert the desired genes into each of these target cells.

Researchers also need to be able to deliver genes consistently to a precise location in the patient's DNA, and ensure that transplanted genes are precisely controlled by the body's normal physiologic signals.

Although scientists are working hard on these problems, it is impossible to predict when they will have effective solutions.

8. The first disease approved for treatment with gene therapy was adenosine deaminase (ADA) deficiency. What is this disease and why was it selected?

ADA deficiency is a rare genetic disease. The normal ADA gene produces an enzyme called adenosine deaminase, which is essential to the body's immune system. Patients with ADA deficiency do not have normal ADA genes and do not produce functional ADA enzymes. ADA-deficient children are born with severe immunodeficiency and are prone to repeated serious infections, which may be life-threatening. Although ADA deficiency can be treated with a drug called PEG-ADA, the drug is extremely costly and must be taken for life by injection into a vein.

ADA deficiency was selected for the first approved human gene therapy trial for several reasons:

- The disease is caused by a defect in a single gene, which increases the likelihood that gene therapy will succeed.
- The gene is regulated in a simple, "always-on" fashion, unlike many genes whose regulation is complex.
- The amount of ADA present does not need to be precisely regulated. Even small amounts of the enzyme are known to be beneficial, while larger amounts are also tolerated well.

9. How do gene therapy trials receive approval?

A proposed gene therapy trial, or protocol, must be approved by at least two review boards at the scientists' institution. Gene therapy protocols must also be approved by the U.S. Food and Drug Administration (FDA), which regulates all gene therapy products. In addition, trials that are funded by the National Institutes of Health (NIH) must be registered with the NIH Recombinant DNA Advisory Committee (RAC). The NIH, which includes 27 Institutes and Centers, is the Federal focal point for biomedical research in the United States.

10. Why are there so many steps in this process?

Any studies involving humans must be reviewed with great care. Gene therapy in particular is potentially a very powerful technique, is relatively new, and could have profound implications. These factors make it necessary for scientists to take special precautions with gene therapy.

11. What are some of the social and ethical issues surrounding human gene therapy?

In large measure, the issues are the same as those faced whenever a powerful new technology is developed. Such technologies can accomplish great good, but they can also result in great harm if applied unwisely.

Gene therapy is currently focused on correcting genetic flaws and curing life-threatening disease, and regulations are in place for conducting these types of studies. But in the future, when the techniques of gene therapy have become simpler and more accessible, society will need to deal with more complex questions.

One such question is related to the possibility of genetically altering human eggs or sperm, the reproductive cells that pass genes on to future generations. (Because reproductive cells are also called germ cells, this type of gene therapy is referred to as germ-line therapy.) Another question is related to the potential for enhancing human capabilities—for example, improving memory and intelligence—by genetic intervention. Although both germ-line gene therapy and genetic enhancement have the potential to produce benefits, possible problems with these procedures worry many scientists.

Germ-line gene therapy would forever change the genetic makeup of an individual's descendants. Thus, the human gene pool would be permanently affected. Although these changes would presumably be for the better, an error in technology or judgment could have far-reaching consequences. The NIH does not approve germ-line gene therapy in humans.

In the case of genetic enhancement, there is concern that such manipulation could become a luxury available only to the rich and powerful. Some also fear that widespread use of this technology could lead to new definitions of "normal" that would exclude individuals who are, for example, of merely average intelligence. And, justly or not, some people associate all genetic manipulation with past abuses of the concept of "eugenics," or the study of methods of improving genetic qualities through selective breeding.

12. What is being done to address these social and ethical issues?

Scientists working on the Human Genome Project (HGP), which completed mapping and sequencing all of the genes in humans, recognized that the information gained from this work would have profound implications for individuals, families, and society. The Ethical, Legal, and Social Implications (ELSI) Research Program was established in 1990 as part of the HGP to address these issues. The ELSI Research Program fosters basic and applied research on the ethical, legal, and social implications of genetic and genomic research for individuals, families, and communities. The ELSI Research Program sponsors and manages studies and supports workshops, research consortia, and policy conferences on these topics. More information about the HGP and the ELSI Research Program can be found on the National Human Genome Research Institute (NHGRI) Web site at <http://www.genome.gov> on the Internet.

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Related NCI materials and Web pages:

- National Cancer Institute Fact Sheet 2.11, *Clinical Trials* (<http://www.cancer.gov/cancertopics/factsheet/Information/clinical-trials>)
- National Cancer Institute Fact Sheet 7.2, *Biological Therapies for Cancer: Questions and Answers* (<http://www.cancer.gov/cancertopics/factsheet/Therapy/biological>)
- *Taking Part in Cancer Treatment Research Studies* (<http://www.cancer.gov/clinicaltrials/Taking-Part-in-Cancer-Treatment-Research-Studies>)

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