

Gene Therapy: A Veracity or Myth!

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ABSTRACT

Gene therapy is a novel approach to treat, cure, or ultimately prevent disease by changing the expression of a person's gene. 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 favorably 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. Though single gene disorders are best treated than multifactorial disorder; the challenge of developing successful gene therapy for any specific condition is considerable. The problem of 'gene delivery' into the desired tissues is very complex and challenging. Some of the 'vectors' for delivering the working copy of the gene to the target cells include using harmless viruses and non viral vectors. Till date, in gene therapy, only somatic cells and not the germ cells are targeted for treatment. The possible genetic manipulation of the germ cells remains the subject of intense ethical and philosophical discussion. Though some devastation was recorded in gene therapy trial; the potential benefits of new treatments must always be balanced against such risks. In particular, safety will appropriately remain an important consideration as the field of gene therapy evolves. The purpose of this review is to focus on merit and demerit of gene therapy and to provide information about its future prospective.

Keywords: Gene therapy, Myth & Veracity

INTRODUCTION

Gene is the unit of heredity that passed from one generation to the next. They contain instructions for making proteins. Proteins do most of the work in cells. They move molecules from one place to another, build structures, break down toxins, and do many other maintenance jobs for maintaining normal life. Sometimes there is a mutation, a change in a gene or genes. This mutation changes the gene's instructions for making a correct protein, so the protein does not work properly or is missing entirely. Therefore, if genes don't produce the right proteins or don't produce them correctly, a child can have a medical problem called "genetic disorder".

Now-a-days genetic disorder are attempted to treat by a method called Gene therapy. It is an experimental technique that uses genes to treat or prevent disease.¹

The basic principle of this therapy is to transfer and expression of the therapeutic genes in specific target cells.²The most common form of gene therapy involves using DNA that encodes a functional, therapeutic gene to replace a mutated gene. Other forms involve directly correcting a mutation, or using DNA that encodes a therapeutic protein drug (rather than a natural human gene) to provide treatment. In gene therapy, DNA that encodes a therapeutic protein is packaged within a "vector", which is used to get the DNA inside cells within the body. Once inside, the DNA becomes expressed by the cell machinery, resulting in the production of therapeutic protein, which in turn treats the patient's disease.¹

Gene therapy was first planned in 1972, with the authors urging caution before commencing gene therapy studies in humans.³ However, the first FDA-approved gene therapy experiment in the United States occurred in 1990, when Ashanti DeSilva was treated for ADA-SCID, a severe immune system deficiency. The effects were only temporary, but successful.^{1,4}

By January 2014, about 2,000 clinical trials had been conducted or had been approved using a number of techniques for gene therapy.⁵

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Although early clinical failures led many to dismiss gene therapy as over-hyped, clinical successes since 2006 have reinforced new confidence in the promise of gene therapy. These include successful treatment of patients with the retinal disease Leber's congenital amaurosis,^{6,7,8,9} X-linked SCID¹⁰ and ADA-SCID,^{4,11} cystic fibrosis, adrenoleukodystrophy,¹² chronic lymphocytic leukemia (CLL),¹³ acute lymphocytic leukemia (ALL),¹³ multiple myeloma, haemophilia,¹⁴ Parkinson's disease,¹⁵ beta-Thalassemia,^{16,17} and Retinitis pigmentosa.¹⁸ These clinical successes have led to a renewed interest in gene therapy, with several articles in scientific and popular publications calling for continued investment in the field¹⁹ and between 2013 and April 2014, US companies invested over \$600 million in gene therapy. In 2012, Glybera became the first gene therapy treatment to be approved for clinical use in either Europe or the United States after its endorsement by the European Commission.^{20,21} Although there is much expectation for gene therapy, it is still experimental and a dream for future medicine.

HOW GENE THERAPY IS 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. There are various methods of gene therapy as shown in Figure 1.

Of all these challenges, the one that is most difficult is the problem of 'gene delivery' i.e. how to get the new or replacement genes into the desired tissues.²²

To reverse disease caused by genetic damage, researchers isolate normal DNA and package it into a vehicle known as a vector, which acts as a molecular delivering device. Vectors composed of viral DNA sequences have been used successfully in human gene therapy trials. Generally the DNA is incorporated into an engineered virus that serves as a vector, to get the DNA through the bloodstream, into cells, and incorporated into a chromosome.^{23,24} However, so-called naked DNA approaches have also been explored, especially in the context of vaccine development.²⁵

Generally, efforts have focused on administering a gene that causes a protein to be expressed, that the patient directly needs. However, with development of our understanding of the function of nucleases such as zinc finger nucleases in humans, efforts have begun to incorporate genes encoding nucleases into chromosomes; the expressed nucleases

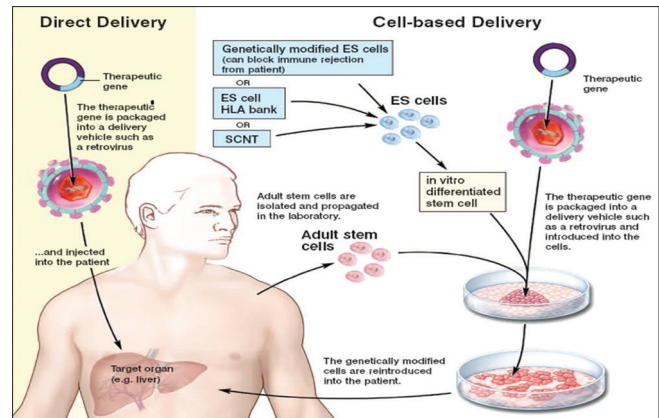


Figure 1: Different methods of Gene delivery
(Ref: <http://imgbuddy.com/chimera-genetics-diagram.asp>)

then "edit" the chromosome, disrupting genes causing disease. From 2014 these approaches have been limited to taking cells from patients, delivering the nuclease gene to the cells, and then administering the transformed cells to patients.²⁶

Researchers continue to optimize viral vectors as well as develop non-viral vectors that may have fewer unpredicted side effects. Non-viral gene delivery involves combining DNA with an agent that permits it to enter a cell non-specifically. DNA that is delivered in this manner is usually expressed for only a limited time because it rarely incorporates into the host cell genome.

Initial efforts in gene therapy focused on delivering a normal copy of a missing or defective gene, but current programs are applying gene delivery technology across a broader spectrum of conditions. Researchers are now utilizing gene therapy to deliver genes that catalyze the destruction of cancer cells or cause cancer cells to revert back to normal tissue. They supply viral or bacterial genes as a form of vaccination or provide genes that promote the growth of new tissue or stimulate regeneration of damaged tissue.

Vectors are the media through which successful gene delivery to a cell can be possible. There is no "perfect vector" that can treat every disorder. Like any type of medical treatment, a gene therapy vector must be customized to address the unique features of the disorder. Part of the challenge in gene therapy is choosing the most suitable vector for treating the disorder.²⁷

Vectors are of two types: Viral & non-viral vectors. A number of viruses have been used for human gene therapy, including adenovirus, retrovirus, lentivirus, herpes simplex virus, vaccinia virus, pox virus, and adeno-associated virus etc.²⁷ The incidence of use of some vectors in different clinical trials is shown in Figure 2.

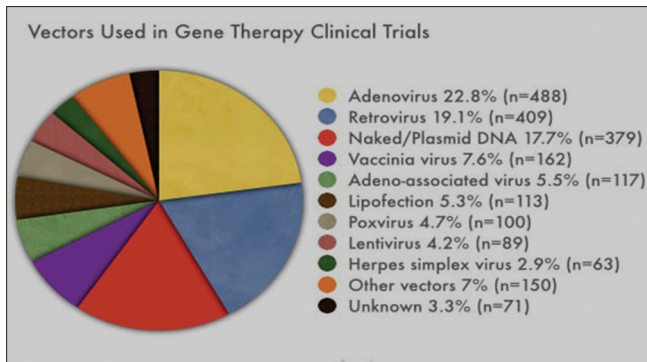


Figure 2: Pie chart showing frequency of Vectors used in different Gene Therapy Clinical Trials
(Ref: www.wiley.co.uk/genmed/clinical)

Viruses may effectively deliver genetic material into a patient's cells, but they have limitations. Some of these limitations can be overcome by using non-viral vectors.¹ In comparison to viruses, nonviral vectors are relatively easy to synthesize, less immunogenic, low in cost, and have no limitation in the size of a gene that can be delivered. One of the disadvantages of non-viral method is its low levels of transfection and expression of the gene; however, recent advances in vector technology have yielded molecules and techniques that approach the transfection efficiencies of viruses. There are several methods for non-viral gene therapy, including the Plasmid, liposomes, oligonucleotides, and inorganic nanoparticles etc.¹

TYPES OF GENE THERAPY

Virtually all cells in the human body contain genes, making them potential targets for gene therapy. However, these cells can be divided into two major categories: somatic cells (most cells of the body) or cells of the germ line (ovum or sperm). In theory it is possible to transform either somatic cells or germ cells.

In somatic gene therapy, the therapeutic genes are transferred into the somatic cells of a patient. Any modifications and effects will be restricted to the individual patient only, and will not be inherited by the patient's offspring or later generations. Several somatic cell gene transfer experiments are currently in clinical trials with varied success. Most of these trials focus on treating severe genetic disorders, including immuno-deficiencies, haemophilia, thalassaemia, and cystic fibrosis. These disorders are good candidates for somatic cell therapy because they are caused by single gene defects. While somatic cell therapy is promising for treatment, a complete correction of a genetic disorder or the replacement of multiple genes in somatic cells is not yet possible. Only a few of the many clinical trials are in the advanced stages.²⁸

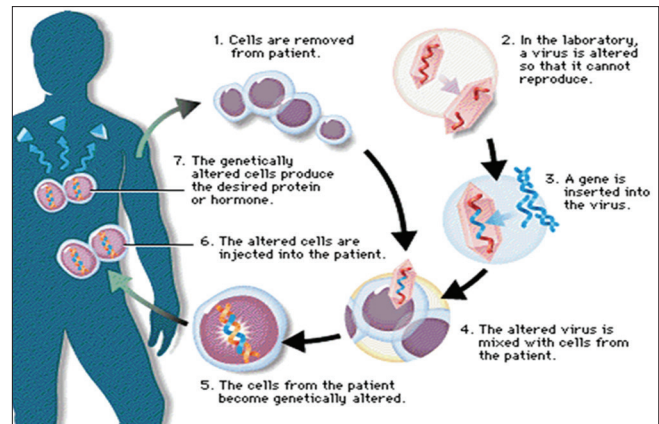


Figure 3: Ex vivo gene therapy
(Ref: <http://pixshark.com/somatic-gene-therapy-diagram.htm>)

Somatic gene therapy can be broadly split into two categories: *ex vivo*, which means exterior (where cells are modified outside the body and then transplanted back in again, as shown in (Figure 3). 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 treated outside the body.

In vivo, which means interior (where genes are changed in cells still in the body). This form of gene therapy is called *in vivo*, because the gene is transferred to cells inside the patient's body as shown in Figure 1.

In the case of germ line gene therapy, germ cells, i.e., sperm or ovum, are modified by the introduction of functional genes, which are ordinarily integrated into their genomes. Therefore, the change due to therapy would be heritable and would be passed on to later generations. This new approach, theoretically, should be highly effective in counteracting genetic disorders and hereditary diseases. However, many jurisdictions prohibit this for application in human beings, at least for the present, for a variety of technical and ethical reasons.^{29,30}

TECHNOLOGY SNAG

Gene therapy poses one of the greatest technical challenges in modern medicine. It is very hard to introduce new genes into cells of the body and keep them working. A good gene therapy is one that will last for long time. Ideally, an introduced gene will continue working for the rest of the patient's life. Unfortunately patients will have to undergo multiple rounds of gene therapy, because of the short-lived nature of gene.

Whenever a foreign object is introduced into human tissues, the immune system is stimulated to attack the invader. The risk of stimulating the immune system in a way that reduces gene therapy effectiveness is always a possibility. Therefore, making repeated round of gene therapy difficult.

Conditions or disorders that arise from mutations in a single gene are the best candidates for gene therapy. Unfortunately, some of the most commonly occurring disorders, such as heart disease, high blood pressure, Alzheimer's disease, arthritis, and diabetes, are caused by the combined effects of variations in many genes and environment. Multigene or multifactorial disorders such as these would be especially difficult to treat effectively using gene therapy.

There may be a chance of inducing a tumor if the DNA is integrated in the wrong place in the genome, for example in a tumor suppressor gene, it could induce a tumor. This has occurred in clinical trials for X-linked severe combined immunodeficiency (X-SCID) patients, in which hematopoietic stem cells were transduced with a corrective transgene using a retrovirus, and this led to the development of T cell leukemia in 3 of 20 patients.^{31,32}

In most gene therapy, viruses is the carrier of choice, present a variety of potential problems to the patient like toxicity, immune and inflammatory responses etc. In addition, there is always the fear that the viral vector, once inside the patient, may recover its ability to cause disease.

Another important issue related to the gene therapy is financial concern: Can a company profit from developing a gene therapy to treat a rare disorder? If not, who will develop and pay for these life-saving treatments? Only a small number of patients can be treated with gene therapy because of the extremely high price. Glybera recently available for lipoprotein lipase deficiency syndrome, needs cost of about \$1.6 million per patient; a most expensive drug in the world was reported in 2013.³³

OVERCOMING OF SOME TECHNOLOGY OBSTACLE

In May 2006 a group of scientists guided by Dr. Luigi Naldini and Dr. Brian Brown from the San Raffaele Telethon Institute for Gene Therapy in Milan, Italy reported a breakthrough for gene therapy in which they developed a way to prevent the immune system from rejecting a newly delivered gene.³⁴ Similar to organ transplantation, gene therapy has been plagued by the problem of immune rejection. So far, delivery of the 'normal' gene has been difficult because the immune system recognizes the new gene as foreign and rejects the cells carrying it. To overcome this problem, they utilized a newly uncovered network of genes regulated by molecules known as microRNAs.

Dr. Naldini's group reasoned that they could use this natural function of microRNA to selectively turn off the identity of their therapeutic gene in cells of the immune system and prevent the gene from being found and destroyed. The researchers injected mice with the gene containing an immune-cell microRNA target sequence, and the mice did not reject the gene, as previously occurred when vectors without the microRNA target sequence were used. This work will have important implications for the treatment of hemophilia and other genetic diseases by gene therapy.³⁴

CALAMITY IN GENE THERAPY

Three patients' deaths have been reported in gene therapy trials, putting the field under close scrutiny. The first was that of Jesse Gelsinger, who had a rare liver disorder, participated in a 1999 gene therapy trial. He died of complications from an inflammatory response shortly after receiving a dose of experimental adenovirus vector. His death halted all gene therapy trials in the United States for a time, flashing a much-needed discussion on how best to regulate experimental trials and report health problems in volunteer patients. One X-SCID patient died of leukemia following gene therapy treatment in 2003.¹ In 2007, a rheumatoid arthritis patient died from an infection in a gene therapy trial; however, a subsequent investigation concluded that the death was not related to her gene therapy treatment.³⁵

MISAPPROPRIATION OF GENE THERAPY

Several uses for gene therapy have been speculated. There is a risk that athletes might abuse gene therapy technologies to improve their athletic performance.³⁶ This idea is known as gene doping and is as yet not known to be in use but a number of gene therapies have potential applications to athletic enhancement.

It has been speculated that genetic engineering could be used to changes in human nature.³⁷ Change in physical appearance, metabolism, and even improve physical capabilities and mental faculties like memory and intelligence, although for now these uses are limited to science fiction. These speculations have in turn led to ethical concerns and claims, including the belief that every fetus has an inherent right to remain genetically unmodified. In contrast parents also hold the rights to modify their unborn offspring to give birth to a baby free from genetic disorder.^{38,39} On the other hand, others have made claims that many people try to improve themselves already through diet, exercise, education, cosmetics, and plastic surgery and that accomplishing these goals through genetics could be more efficient and worthwhile.⁴⁰ This view sees the prevention of genetic diseases as a duty to humanity in preventing harm to future generations.

ETHICAL CONSIDERATION

While the body has about 3.72×10^{13} of cells⁴¹, 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, heart, liver, skin or bone cells, are known as 'somatic cells'.

In gene therapy, only somatic cells are targeted for treatment.^{2,3,42,43,44} 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 offspring. Changes to the somatic cells cannot be inherited and therefore, has no impact on future generations.^{2,3}

The possible genetic handling of the germ cells remains the subject of passionate ethical and rational argument. The strong agreement view at present is that the risks of germ line manipulation far exceed any potential benefit and should not be challenged.

CONCLUSION

Researchers have been working for decades to bring gene therapy to the clinic, yet very few patients have received any effective gene-therapy treatments. But that doesn't mean gene therapy is an impossible dream. Even though gene therapy has been slow to reach patients, its future is very encouraging. Decades of research have taught us a lot about designing safe and effective vectors, targeting different types of cells, and managing and minimizing immune responses in patients. We've also learned a lot about the disease genes themselves. Today, many clinical trials are underway, where researchers are carefully testing treatments to ensure that any gene therapy brought into the clinic is both safe and effective. Despite widespread agreement that it would be ethical to use somatic cell gene therapy to correct serious diseases, there is still uneasiness on the part of the public about this procedure. The basis for this concern lies less with the procedure's clinical risks than with fear that genetic engineering could lead to changes in human nature. Legitimate concerns about the potential for misuse of gene transfer technology justify drawing an ethical line that includes corrective germline therapy but excludes enhancement interventions in both somatic and germline contexts.

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