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GENE THERAPY: AN OVERVIEW

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ABSTRACT

The ability to form site-specific modifications to the human genome has been an objective in medicine since the popularity of the gene because the basic unit of heredity. Thus, gene therapy is known because the ability of genetic improvement through the correction of altered (mutated) genes or site-specific modifications that focus on therapeutic treatment. This therapy became possible through the advances of genetics and bioengineering that enabled manipulating vectors for delivery of extrachromosomal material to focus on cells. One of the most focuses of this system is that the optimization of delivery vehicles (vectors) that are mostly plasmids, nanostructured or viruses. The viruses are more often investigated thanks to their excellence of invading cells and inserting their genetic material. However, there's great concern regarding exacerbated immune responses and genome manipulation, especially in germ line cells. In vivo studies in in vegetative cell showed satisfactory results with approved protocols in clinical trials. These trials are conducted within the us, Europe, Australia and China. Recent biotechnological advances, like induced pluripotent stem cells in patients with liver diseases, chimeric antigen receptor T-cell immunotherapy, and genomic editing by CRISPR/Cas9, are addressed during this review.

KEYWORDS: Gene therapy, Genetic Vectors, Gene transfer.

INTRODUCTION

The concept of gene therapy was proposed within the early 1970s. In the past few years, gene therapy has come to the central stage worldwide. The ability to form local modifications within the human genome has been the target of drugs since the knowledge of DNA because the basic unit of heredity. Gene therapy is known because the capacity for gene improvement by means of the correction of altered (mutated) genes or site-specific modifications that have therapeutic treatment as target. Further on, different strategies are described, which are often used for this purpose.[1] Currently, gene therapy is an area that exists predominantly in research laboratories, and its application is still experimental.[2] Most trials are conducted within the US, Europe, and Australia. The approach is broad, with potential treatment of diseases caused by gene disorders (cystic fibrosis, hemophilia, dystrophy, and red blood cell anemia), acquired genetic diseases like cancer, and certain viral infections, such as AIDS.[3] One of the foremost often used techniques consists of recombinant deoxyribonucleic acid technology, during which the gene of interest or healthy gene is inserted into a vector, which may be a plasmodial, nanostructured, or viral; the latter is the most often used due to its efficiency in invading cells and introducing its genetic material. On a few gene therapy protocols are summarized, approved and published for clinical use, exemplifying the disease, the target, and the type of vector used. Although several protocols are successful, the gene therapy process remains complex, and lots of techniques need new developments. The specific body cells that require treatment should be identified and accessible. A way to effectively distribute the gene copies to the cells must be available, and the diseases and their strict genetic bonds need to be completely understood.[4] There is also the important issue of the target cell type of gene therapy that currently is subdivided into two large groups: gene therapy of the germline and gene therapy of somatic cells. The modifications are hereditary and expire to subsequent generations. Any modification and any effects are restricted only to that patient and are not inherited by future generations.[5,6] Although genes get tons of attention, it is the proteins that perform most life functions and even structure the bulk of cellular structures. When genes are altered so that the encoded proteins are unable to carry out their normal functions, genetic disorders can result.[7]

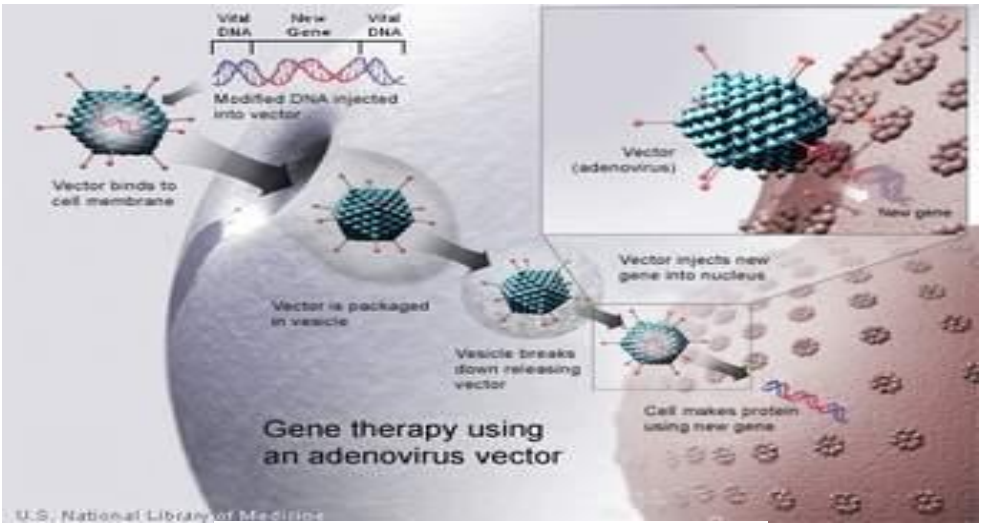

Fig. 1: Gene therapy using an adenovirus vector.

History and Future Of Gene Therapy

The patient was treated on 14th September 1990, at National Institutes of Health's Clinical Center (NHICC), Bethesda, Maryland. Dr. W. French Anderson and his colleagues at the clinic, administered the proceedings. White blood cells were extracted from the body. After the implantation of genes that produce ADA, the cells were transferred back to the patient body. Considerable improvement within the system of the girl was noticed. This trial of gene therapy continued on various diseases. The patients with skin cancer, melanoma was treated by means of gene therapy.

Advantages Of Gene Therapy[8,9]

1. Gene therapy offers a true cure, and not simply palliative or symptomatic treatment.
2. Gene therapy may be the only effective way of addressing some genetic diseases.
3. By the transmission of prevention of disease genes, the expense and risk of somatic cell therapy for multiple generations is avoided.
4. Drug are responds to the reproductive health needs of prospective parents at risk for transmitting serious genetic diseases.
5. Scientific community has a right to free inquiry, within the bounds of acceptable human research.

While the development of germ-line gene therapy techniques will undoubtedly place some embryos at risk in the laboratory, once the successful techniques are developed, the therapy could help parents and researchers avoid the moral dilemma of disposing of "defective" embryos in the lab if the embryos could be repaired.

Disadvantages of Gene Therapy[8,9]

1) Gene therapy experiments would involve too much scientific uncertainty and clinical risks, and the long-term effects of such therapy are unknown.
2) Such gene therapy would open the door to attempts at altering human traits not associated with disease, which could exacerbate problems of social discrimination.
3) As germ-line gene therapy involves research on early embryos and effects their offspring, such research essentially creates generations of un-consenting research subjects.
4) Gene therapy is very expensive, and will never be cost effective enough to merit high social priority.
5) Gene therapy would violate the rights of subsequent generations to inherit a genetic endowment that has not been intentionally modified.

The ethical issues posed by both somatic and germ-line gene therapies are international in scope. The documents listed below serve to demonstrate the variety of reactions to gene therapy, and to illuminate the complexity of this continuing public debate.

Types of Gene Therapy[10]

1) Somatic gene therapy, involves introducing a "good" gene into targeted cells with the end result of treating the patient - but not the patient's future children because these genes do not get passed along to offspring. In other words, even though some of the patient's genes may be altered to treat a disease, the likelihood remains that the same disease will affect the patient's children. This is the form of gene therapy that is being done at most genetics' laboratories throughout the world.

2) Germ line gene therapy, entail injecting foreign genes into fertilized eggs or in sperms producing cells, which will then pass any genetic changes to future generations as well. However, although it has potential for preventing inherited disease, this form of gene therapy is extremely controversial and currently very little research is being done in this area, both for technical and ethical reasons.

Target Cells For Gene Therapy[11]

1) Peripheral blood lymphocytes
2) Haemopoietic stem cells
3) Fibroblasts

4) Hepatocytes
5) Keratinocytes
6) Skeletal muscle myoblasts
7) Airway epithelial cells
8) Vascular endothelial cells
9) Tumor cells

Methods For Gene Therapy[12]

1) Physical
a) Direct injection of DNA
b) Liposome-mediated DNA transfer
c) Calcium phosphate transfection-
d) Electroporation
2) Retrovirus vectors
3) Other viral vectors
4) Targeted gene transfer via receptors
5) Artificial chromosomes
6) Site-directed recombination
7) Activation of genes of related function.

In most gene therapy studies, a "normal" gene is inserted into the genome to replace an "abnormal," disease-causing gene. A carrier molecule called a vector is used to deliver the therapeutic gene to the patient's target cells. Currently, the most common vector is a virus that has been genetically altered to carry normal human DNA. Viruses have evolved a way of encapsulating and delivering their genes to human cells in a pathogenic manner. Scientists have tried to take advantage of this capability and manipulate the virus genome to remove disease-causing genes and insert therapeutic genes.[13]

Vectors In Gene Therapy[14,15]

The different types of viruses used as gene therapy vectors is given below-

- **Retroviruses** - A class of viruses that can create double-stranded DNA copies of their RNA genomes. Genome copy can be integrated into the chromosomes of host cells. Human immunodeficiency virus (HIV) is a retrovirus.
- **Adenoviruses** - A class of viruses with double-stranded DNA genomes that cause respiratory, intestinal, and eye infections in humans. The virus that causes the common cold is an adenovirus.
- **Adeno-associated viruses** - A small class, single-stranded DNA viruses that can insert their genetic material at a specific site on chromosome 19.
- **Herpes simplex viruses** - A class of double-stranded DNA viruses that infect a particular cell type, neurons. The Herpes simplex virus type 1 is a common human pathogen that causes cold sores.

Approaches Of Gene Therapy[16]

1. Gene modification
- Replacement therapy
- Corrective Gene therapy

2. Gene transfer
- Physical
- Chemical
- Biological

3. Gene transfer in specific cell line
- Somatic gene therapy
- Germ line gene therapy

4. Eugenic approach (gene insertion)

Applications of Gene Therapy

Gene therapy is likely to have the greatest success with diseases that are cause by single gene defects. By the end of 1993, gene therapy had been approved for use on such diseases as severe combined immune deficiency, familial hypercholesterolemia, cystic fibrosis, and Gaucher's disease. Most protocols to date are aimed toward the treatment of cancer; a few are also targeted toward AIDS. Numerous disorders are dis-cussed as candidates for gene therapy: Parkinson's and Alzheimer's dis-eases, arthritis, and heart disease. The Human Genome Project, an ongoing effort to identify the location of all the genes in the human genome, continues to identify genetic diseases.[17,18]

Eve Nichols describes the criteria for selection of disease for human gene therapy[19]

1) The disease is an incurable, life-threatening disease;
2) Organ, tissue and cell types affected by the disease have been identified
3) The normal counterpart of the defective gene has been isolated and cloned
4) The normal gene can be introduced into a substantial sub fraction of the cells from the affected tissue; or that introduction of the gene into the available target tissue, such as bone marrow, will somehow alter the disease process in the tissue affected by the disease.
5) The gene can be expressed adequately (it will direct the production of enough normal protein to make a difference
6) Techniques are available to verify the safety of the procedure**.**

Future Aspect of Gene Therapy

- Nanotechnology + gene therapy yields treatment to torpedo cancer. March, 2009. The School of Pharmacy in London is testing a treatment in mice, which delivers genes wrapped in nanoparticles to cancer cells to target and destroy hard-to reach cancer cells [BBC article].
- Results of world's first gene therapy for inherited blindness show sight improvement. 28 April 2008. UK researchers from the UCL Institute of Ophthalmology and Moorfield's Eye Hospital NIHR Biomedical Research Centre have announced results from the world's first clinical trial to test a revolutionary gene therapy treatment for a type of inherited blindness.
- Researchers at the National Cancer Institute (NCI), part of the National Institutes of Health, successfully reengineer immune cells, called lymphocytes, to target and attack cancer cells in patients with advanced metastatic melanoma. This is the first time that gene therapy is used to successfully treat cancer in humans. See New Method of Gene Therapy

Alters Immune Cells for Treatment of Advanced Melanoma (August 30, 2006).

- Gene therapy is effectively used to treat two adult patients for a disease affecting non lymphocytic white blood cells called myeloid cells. Myeloid disorders are common and include a variety of bone marrow failure syndromes, such as acute myeloid leukemia. The study is the first to show that gene therapy can cure diseases of the myeloid system. See Gene Therapy Appears to Cure Myeloid Blood Diseases in Groundbreaking International Study (March 31, 2006).
- University of California, Los Angeles, research team gets genes into the brain using liposomes coated in a polymer call polyethylene glycol (PEG). The transfer of genes into the brain is a significant achievement because viral vectors are too big to get across the "blood-brain barrier." This method has potential for treating Parkinson's disease. See Undercover Genes Slip into the Brain (March 20, 2003).
- RNA interference or gene silencing may be a new way to treat Huntington's. Short pieces of double-stranded RNA (short interfering RNAs or RNAs) are used by cells to degrade RNA of a particular sequence. If an RNA is designed to match the RNA copied from a faulty gene, then the abnormal protein product of that gene will not be produced. See Gene Therapy May Switch off Huntington's (March 13, 2003).
- New gene therapy approach repairs errors in messenger RNA derived from defective genes. Technique has potential to treat the blood disorder thalassemia, cystic fibrosis, and some cancers. See Subtle Gene Therapy Tackles Blood Disorder (October 11, 2002).
- Researchers at Case Western Reserve University and Copernicus Therapeutics are able to create tiny liposomes 25 nanometers across that can carry therapeutic DNA through pores in the nuclear membrane, Sickle cell is successfully treated in mice.

CONCLUSION

According to gene therapy different types of genetic disorder are cured. In case of cystic fibrosis, Diabetes, AIDS, Hepatitis melanoma, Alizhmer, Parkinson's diseases etc. In case of Parkinson's disease one trial is done Neurologic a biotech company announced that they have successfully completed its landmark Phase I trial of gene therapy for Parkinson's Disease. Twelve patient study with four patients in each of three dose escalating cohorts. All procedures were performed under local anesthesia and all 12 patients were discharged from the hospital within 48 hours of the procedure, and followed for 12 months. Primary outcomes of the study design, safety and tolerability, were successfully met. There were no adverse events reported relating to the treatment.[15] Steps involved in treatment of Parkinson's disease. In case of diabetes gene therapy also play a good role. Replacing a mutated gene that causes disease with a healthy copy of the gene. Inactivating, or "knocking out," a mutated gene that is functioning improperly. Introducing a new gene into the body to help fight a disease.

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