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Gene Therapy: An Overview

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1. Introduction

A genes are a section of DNA. Found to be physical and functional unit of heredity. Every person has two copies of each gene, one inherited from each parent. They contain the instructions for our individual characteristics – like eye and hair colour. A person's genetic code is responsible for coding proteins which constitutes our physical makeup. A single alteration to this code can result in a favorable effects includes helping organisms adapt to changes in their environment and increase their of survival or reproduction. As well as non-favorable effect includes cancer , cystic fibrosis and many more.

1.1 Brief History of Genes

The term 'gene introduced Wilhelm Johannsen in 1905. The structure of DNA and molecular repository of genetic information was studied by Rosalind Franklin and Maurice Wilkins using X-ray crystallography, 1940s to 1950s. The first time the sequence of a gene: determined by Walter Fiers and his team In 1972.

1.2 What is Mutation?

A Mutation is a change that occurs in our DNA sequence, which is caused by an error in DNA replication or due to environmental factors, such as cigarette smoke and exposure to radiation. Genetic testing can reveal changes in genes(mutations) . There are many methods are used to diagnose mutation which includes Carrier testing.(For people with family history of a genetic disorder — such as sickle cell anemia or cystic fibrosis), Newborn screening, Prenatal testing (for pregnant women), Pre implantation testing before in-vitro fertilization .

1.3 Gene Therapy

Gene therapy involves the insertion of a functioning gene into cells to correct a cellular dysfunction.,

The main purposes of Gene therapy includes:
(a) Gene replacement in genetic diseases;
(b) Destroying malignant cells in neoplastic diseases
(c) Modifying immune responses
(d) Providing trophic molecules
(e) Immunization against infectious diseases.

1.4 Important Mile Stones of Gene Therapy

In **1984** a retrovirus vector system was designed to efficiently insert foreign genes into animal chromosomes.

1990s: The first approved gene therapy clinical research in the US took place on 14 September 1990, at the National Institutes of Health (NIH), under the direction of William French Anderson Four-year-old Ashanti DeSilva received treatment for a genetic defect that left her with ADA-SCID, a severe immune system deficiency. The effects were successful, but temporary.

2002s The modified cancer gene therapy was registered , by Wiley gene therapy clinical trial The approach has shown promising results in the treatment of six different malignant tumors: glioblastoma, cancers of liver, colon, prostate, uterus, and ovary. Sickle-cell disease can be treated in mice.

In 2003 a research team inserted genes into the brain for the first time in China for the treatment of head and neck squamous cell carcinoma.

2006s the successful use of gene therapy to treat two adult patients for X-linked chronic granulomatous disease,

2008s A clinical trial done to cure an inherited blinding disease caused by mutations in the RPE65 gene. Total three trials done. In all clinical trials, patients recovered functional vision without apparent side-effects.

2010: 18-year-old male patient in France with beta-thalassemia major had been successfully treated

In 2011 Neovasculgen was registered in Russia as the first-in-class gene-therapy drug for treatment of peripheral artery disease, including critical limb ischemia;

2013: Researchers reported that two children born with adenosine deaminase severe combined immunodeficiency disease (ADA-SCID) had been treated with genetically engineered stem cells

2014: Clinical trials of gene therapy for sickle cell disease were started on human sample.

2017: The FDA approved 'Tisagenlecleucel' a modified genetic material for acute lymphoblastic leukemia.

2019: The first ever "in body" human gene editing therapy to permanently alter DNA - in a patient with Hunter Syndrome.

The Basic Mechanism of Gene Therapy

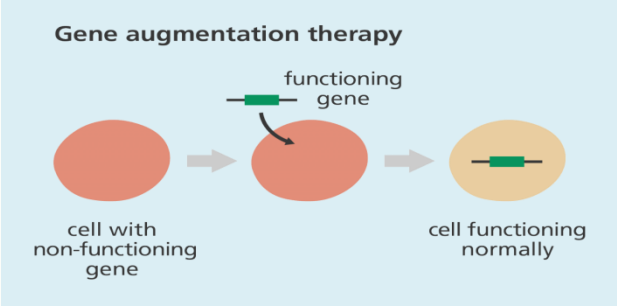
1) Identify the defective gene in a patient suffering from a genetic disease.
2) Prepare and Install cure gene into the DNA of target cells using viral or non viral agent.
3) Allow this modified virus or non viral to infect the cells of the sick patient.
4) The agents insert the therapeutic gene into the patients cells.
5) These infected cells now contain a copy of the missing gene.
6) Symptoms of the genetic disease begin to disappear.

7) The disease is considered / cured.

Techniques Used for Gene Therapy

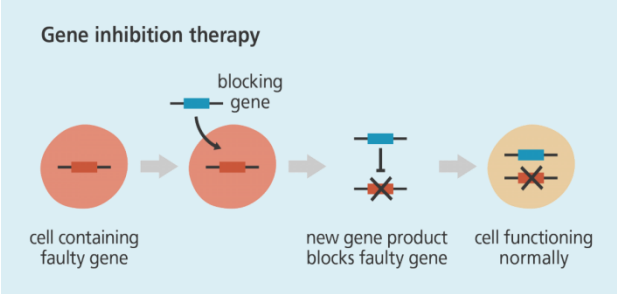
There are several techniques for carrying out gene therapy. These include:

Gene Augmentation Therapy: This is used to treat diseases caused by a mutation .This therapy adds DNA containing a functional version into host cell. After The therapy host cells performs normal function.



Gene Inhibition Therapy

This therapy used to eliminate the activity of a gene that encourages the growth of disease-related cells by eliminating the activity of that faulty gene. Best example is cancer.



Route of Administration of Gene Therapy

The route for inserting a gene therapy depends on the type of tissue under treatment and the mechanism by which the therapeutic gene exerts its effect. Gene therapy for cystic fibrosis, which is a disease affects cells within the lung and airway, in this case the cure genes are may be inhaled. Most therapeutic genes which is used to treat cancer are administered directly into the tumor. Proteins such as factor VIII or IX for hemophilia are also being introduced directly into target tissue where it is produced or stored (the liver).

Human Genome Project

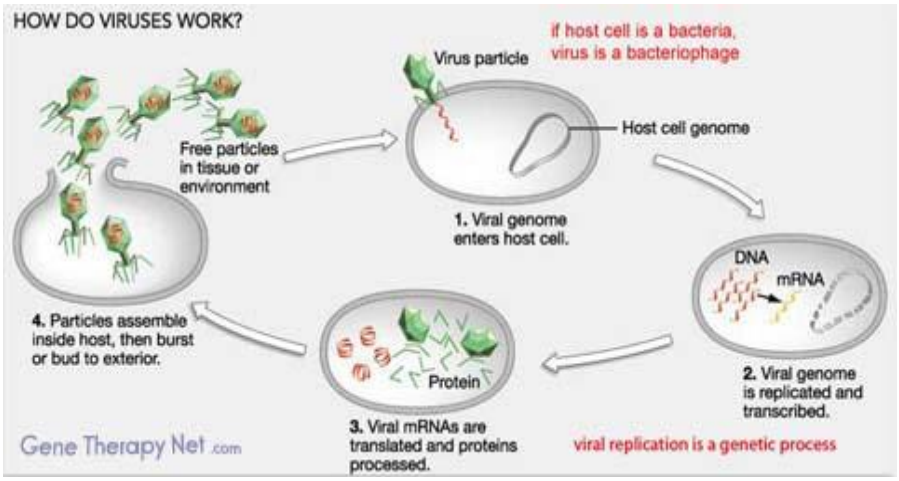
The Human Genome Project (**HGP**) was an international scientific research project with the goal of determining the base pairs of human DNA, and identifying all of the genes of the human genome from both a physical and a functional standpoint. It was a 13-year-long, publicly funded project initiated in 1990 and finished on April 14, 2003. The main benefits includes understand diseases , to prepare medication and accurate prediction of their effects and other energy applications like Agriculture, Animal Husbandry, Bio Processing; Risk Assessment; Bio Archeology, Anthropology And Evolution.

Basic Process: How Does Gene Therapy Work?

A gene cannot be directly inserted into a person's cell. It must be delivered to the cell using a carrier, or vector. Vector systems can be divided into: viral (Vector), non-viral and Nano structured vectors

Viral Agent For Gene Therapy:

Viral vectors have been used in more than 70% of the clinical trials, most commonly used agents are retroviruses, adenovirus, adeno-associated virus, herpesvirus and poxvirus. The Viral agent with genetic material enters the host cells, where it replicates and delivers therapeutic genes to cells using recombinant DNA technologies.



Diseases treated using viral gene therapy includes

a) Gene therapy trials using retroviral vectors to treat X-linked severe combined immunodeficiency.
b) Adenoviruses and Alphaviruses are commonly used for treatment of cancer.
c) Herpes simplex virus tested in glioma, melanoma and ovarian cancer patients.

Non Viral Agent for Gene Therapy

Non-viral methods present certain advantages over viral methods, with simple large scale production and low host immunogenicity. This therapy mainly uses DNA plasmids that can be delivered to the target cells as naked DNA or with different compounds such as liposomes, gelatin or polyamine nanosphere by gene delivery systems which uses

physical and chemical methods.The most common physical methods are microinjection, electroporation, ultrasound, gene gun, and hydrodynamic applications. chemical methods utilize natural or synthetic carriers to deliver genes into cells. Nanotechnology and nucleic acid chemistry that have promising non-viral delivery systems.

Diseases treated using non viral gene therapy includes are CNS disorders and cancer.

Indications: Successful Use Of Gene Therapy

Indications	Gene Therapy Clinical Trials	
	Number	%
Cancer diseases	2004	66.8
Cardiovascular diseases	183	6.1
Gene marking	50	1.7
Healthy volunteers	61	2
Infectious diseases	184	6.1
Inflammatory diseases	15	0.5
Monogenic diseases	350	11.7
Neurological d iseases	53	1.8
Ocular diseases	37	1.2
Others	64	2.1

Cancer is so far the largest category of indications being investigated with 66.8% of the gene therapy clinical trials in this area. The second most popular category of indications is inherited monogenetic disease with 11.7% which includes achondroplasia. adrenoleukodystrophy. Alpha Thalassaemia. Alpha-1-Antitrypsin Deficiency. Alport Syndrome. Amyotrophic Lateral Sclerosis. Beta Thalassemia, followed by infectious diseases (6.1%) example includes tuberculosis, malaria, HIV and influenza and cardiovascular diseases (6.9%) rounding out the top four indications.

2. Challenges in Gene Therapy

Gene therapy is not a new field; it has been evolving for decades. Despite the best efforts of researchers around the world, gene therapy has seen only limited success. The effect of gene therapy for a particular patient depends on multiple factors which includes the disease severity, type of agent used , durability of gene therapy, size and demographic of treatable population, relative efficacy and safety of the drug, medical and patient advocacy support, and the price of treatment.

The Main Challenges In Gene Therapy.

a) **Gene delivery and activation:** Introducing a therapeutic genes into host cells and targeting diseased gene is a crucial success of any gene therapy treatment. Delivering a gene to the wrong tissue would be inefficient, and it could cause health problems for the patient.
b) **Immune response:** An unwelcome immune response by the body against Gene-delivery vectors could cause serious illness or even death. The story of Jesse Gelsinger illustrates this challenge. 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, sparking a much-needed discussion on how best to regulate experimental trials and report health problems in volunteer patients
c) **Disrupting the function of target cells:** It happens, when the therapeutic gene stitches itself into an inappropriate location, disrupting another gene. This happened in two gene therapy trials aimed at treating children with X-linked Severe Combined Immune Deficiency (SCID).Between 1999 and 2006, researchers tested a gene therapy treatment that would restore the function of a crucial gene, gamma c, in cells of the immune system. The treatment appeared very successful, restoring immune function to most of the children who received it. But later, 5 of the children developed leukemia, a blood cancer. Researchers found that the newly transferred gamma c gene had stitched itself into a gene that normally helps regulate the rate at which cells divide. As a result, the cells began to divide out of control, causing leukemia. Doctors treated 4 of the patients successfully with chemotherapy, but the fifth died.
d) **Commercial viability:** Developing a new therapy—including taking it through clinical trials necessary for government approval— is very expensive. And some patients may never be able to afford them.

3. Ethical and Legal Issues: Gene Therapy & Gene Testing

To protect patients from additional distress related to genetic conditions, care providers should be aware of the relevant ethical, legal, issues related to genetics in health care. Since gene therapy involves making changes to the target cell function by bringing changes in gene , sometimes has adverse effect on body hence treating doctor should take an informed consent about therapy.

Informed consent. Informed consent is an important part of the medical-decision making process. For patients considering gene therapy,

Main purpose of this consent is

a) To help ensure that patients understand the risks and benefits of health care choices,
b) The following items should be carefully discussed and understood before consent is obtained:
   - Risks, limitations and benefits of therapy
   - Alternatives to genetic therapy.
   - Details of the way in which the therapy will be performed.
   - cost of treatment.
   - Potential consequences related to results including impact on health.
   - Possible emotional and psychological reactions.
   - Treatment/prevention options .

4. Regulation of Gene Therapy in India

The field of gene therapy is associated with ethical, social and legal considerations and it require additional department for efficient scientific and ethical evaluation. Recently prime minister of India proposed to establish Gene Therapy Advisory and Evaluation Committee (GTAEC) with secretariat at Indian Council of Medical Research (ICMR) under the aegis of Department of Health Research

(DHR), Ministry of Health and Family Welfare, Government of India.

This committee will be composed of a core group of scientists and clinicians who have prior knowledge of gene therapy in clinical trials, as well as representation of the government agencies (ICMR, DGHS, CDSCO, DBT, DST, MCI).

Role of the Gene Therapy Advisory and Evaluation Committee (GTAEC)

a) Rigorously monitoring all first-in-human trials or existing gene therapy in India.
b) Recommendation for all institutions who engaged in development of Gene therapy to establish an Institutional Bio-safety committee (IBSC), constituted as per the Regulations and Guidelines on Bio-safety of recombinant DNA Research and Bio containment 2017.
c) Research involving development of new gene therapy needs to obtain approvals from Institutional Bio-safety committee(IBSC) and Institutional Ethics Committee (IEC)., additional approval from the Institutional Committee for Stem Cell Research (IC-SCR) is required.
d) Gene therapy should have prior approval of Review Committee on Genetic Manipulation.

Gene Therapy Vs Genetic Engineering

Gene therapy involves filling the defective DNA gene with cure gene to improve altered function of target cells or to cure the diseases , Where as genetic engineering is, the artificial manipulation, modification of DNA or other nucleic acid molecules in healthy organisms to enhancement function or characteristics. Gene therapy Is also known as therapeutic genetic engineering .

Gene Therapy: Future Prospective

The goal of gene therapy is to address a disease at its genetic level. The future application of this therapy involves preparation of medicines and vaccines to cure diseases, evaluating the possibility of treating patients with AIDS, cardiopathies, and neurologic diseases. In addition, gene transfer technology has led to innovative vaccine design for the treatment of neoplasias and development of protective immunity against infectious agents.

References

[1] What are genes and why are they important? https://www.medicalnewstoday.com/articles/120574.php
[2] https://www.yourgenome.org/facts/what-is-a-gene
[3] https://en.wikipedia.org/wiki/Gene
[4] What is a mutation? https://www.yourgenome.org/facts/what-is-a-mutation
[5] What is gene therapy? https://www.yourgenome.org/facts/what-is-gene-therapy
[6] https://en.wikipedia.org/wiki/Human_Genome_Project
[7] https://www.ncbi.nlm.nih.gov › pubmed
[8] https://academic.oup.com/cardiovascres/article/91/4/565/348876
[9] https://www.intechopen.com/books/gene-therapy-tools-and-potential-applications/non-viral-delivery-systems-in-gene-therapy
[10] Harrison's PRINCIPLES OF INTERNAL MEDICINE.
[11] Dr. Fauci's and Dr. Longo's Seventeenth Edition
[12] Challenges In Gene Therapy, https://learn.genetics.utah.edu/content/genetherapy/challenges/understanding genetics book
[13] The gene therapy sector is experiencing an acceleration
[14] https://www.risingtidebio.com/what-is-gene-therapy-uses/
[15] Comments/ suggestions invited on Draft National Guidelines for Gene Therapy Product Development and Clinical Trials. Page number (15-18)
[16] http://dbtindia.gov.in/sites/default/files/Call_comments.pdf
[17] GENE THERAPY AND GENETIC ENGINEERING
[18] https://medicine.missouri.edu/centers-institutes-labs/health-ethics/faq/gene-therapy
[19] https://theoncologist.onlinelibrary.wiley.com/doi/full/10.1634/theoncologist.3-4-225