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A Review on Gene Therapy: A Narrative Review

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ABSTRACT:
Background: Gene therapy, also called gene transfer therapy, is a 21st century medicine that treats or prevents sickness by means of correcting the underlying genetic problem. Gene therapy strategies permit medical practitioners to deal with a disease by using altering a person's genetic make-up instead of the use of pills or surgery. It offers a personalized approach to treating diseases by targeting the specific genes responsible for the disease. This can increase the effectiveness of treatment and reduce side effects Overall, gene therapy has the potential to transform the way we treat and prevent genetic diseases, offering personalized and potentially curative treatments that could improve the lives of millions of people.
Purpose: This review article aims to collate past and present updated information on gene therapy history, types, issues related to gene therapy and its safety.
Key Words: Gene Therapy, Germline therapy, Somatic Gene Therapy, Ex Vivo Gene Therapy, In Vivo Gene Therapy

I. INTRODUCTION

1 **Genes**

Genes are the essential bodily and purposeful unit of heredity. A gene is an ordered sequence of nucleotides observed in a specific role on a unique chromosome that encodes a particular practical product (i.e., a protein or RNA molecule). Gene is termed as a "biological unit of heredity". Inherited from the parents, it figures out the special characteristics - like the color of the eyes and shade and texture of the hair. They additionally parent out matters like whether the infant will be male or female, the quantity of oxygen the blood can carry, and what the IQ will be. [1]

Genes are composed of lengthy strands of a molecule known as DNA and are in single files inside the chromosomes. The genetic message is encoded by using subunits of the DNA referred to as nucleotides. There are about three billion pairs of nucleotides in the chromosomes of a human cell. Each person's genetic make-up has a special sequence of nucleotides, and this is what makes us special from one another. Scientists accept it as true that every human has about 30,000 genes per cell. A mutation or imperfection in any one of these genes can result in a disease, bodily incapacity or shortened existence span. These mutations can be surpassed from one technology to another, inherited simply like a mother's blond hair or a father's brown eyes. But with gene therapy, the cure or removal of inherited ailments or bodily prerequisites due to these mutations should come to be a reality. [2]

2 **History of Gene Therapy**

The concept of gene therapy arose for the duration of the 1960s and 1970s and is nonetheless in its infancy, which means there is a paucity of reliable, long-term records on the safety and efficacy of this therapy.
In 1972, Theodore Friedmann and Richard Roblin published a paper in Science referred to as "Gene therapy for human genetic disease?" which mentioned Stanfield Roger's suggestion in 1970 that "good DNA" should be used to substitute faulty DNA in humans with genetic disorders.

The first affected person to be dealt with gene therapy used to be a 4-year-old girl treated at the NIH Clinical Center in 1990. She had a congenital disorder known as adenosine deaminase (ADA) deficiency which severely influences immunity and the capacity to fight infections. For the therapy, her white blood cells were taken from her and inserted with the right genes for making ADA and then reinjected into her. This method used to be carried out by Dr. W. French Anderson from the National Heart, Lung and Blood Institute.

In 1985, Anderson and colleague Michael Blease began working collectively to exhibit how cells from human beings with ADA deficiency may want to be modified in tissue culture. They used a retrovirus as a vector to raise the right ADA gene into the cells.

In 1986, they tried transferring the right genes into the bone marrow of animals, however in 1988, located that transferring them to white blood cells was once a great deal greater successful, with

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a dramatic enlarge in the quantity of the right genes being taken up by way of cells.

In 1989, the researchers teamed up with Dr. Steven Rosenberg to check how secure and tremendous the gene remedy would be in most cancer patients. The crew cultured tumor infiltration lymphocytes cells (TIL cells) from human beings with malignant melanoma. A viral vector used to be made that would raise a DNA marker into these cells and these marked cells allowed the researchers to see which TIL cells had been the most fantastic and additionally validated that the engineered virus was once protected for use in humans.

In 1990, the four-year old girl and some other nine-year old girl with ADA deficiency were infused with their very own corrected cells over two years and in 1993, the team used gene therapy to deal with newborn babies with ADA deficiency. The corrected ADA genes had been transferred to immature blood cells bought from the babies' umbilical cords. [3]

3 **Gene Therapy**

Gene Therapy is a novel remedy technique which makes use of genes or brief oligonucleotide sequences as therapeutic molecules, rather than traditional drug compounds. This method is extensively used to deal with these faulty genes which contribute to sickness development. Gene remedy entails the introduction of one or greater overseas genes into an organism to deal with hereditary or sold genetic defects. In gene therapy, DNA encoding a therapeutic protein is packaged inside a "vector", which transports the DNA interior cells inside the body. The ailment is handled with minimal toxicity, by way of the expression of the inserted DNA by means of the mobile machinery. In 1990 FDA for the first time authorized a gene remedy scan on ADA-SCID in the United States after the cure of Ashanti DeSilva. After that, about 1700 medical trials on sufferers have been carried out with several strategies and genes for many diseases.

Many diseases such as ADA-SCID, X-linked SCID, Leber's congenital amaurosis (a retinal disease), Parkinson's disease, a couple of myelomas, continual and acute lymphocytic leukemia, adrenoleukodystrophy have mentioned of profitable scientific trials. But these are nonetheless no longer accredited by means of the FDA. Some different diseases on which gene therapy-based lookup is going on are Hemophilia, Tyrosinemia, Hyperbilirubinemia (Crigler-Nijjar Syndrome), Cystic Fibrosis and many different cancers. After 30 years of lookup and medical trials, solely one product referred to as Glibber received approval in November 2012 which may also be accessible in market in late 2013. It can therapy lipoprotein lipase deficiency (LPLD) an uncommon disorder [4]

The earliest technique of gene therapy, regularly known as gene transfer or gene addition, used to be developed to:

• Introduce a new gene into cells to assist fight a disease.

• Introduce a non-faulty replica of a gene to stand in for the altered replica inflicting disorder

Later research led to advances in gene therapy techniques. A more modern technique, known as genome editing (an instance of which is CRISPR-Cas9), makes use of an extraordinary method to right genetic differences. Instead of introducing new genetic cloth into cells, genome editing introduces molecular equipment to exchange the current DNA in the cell. Genome enhancing is being studied to:

• Fix a genetic alteration underlying a disorder, so the gene can feature properly.

• Turn on a gene to assist combat a disease.

• Turn off a gene that is functioning improperly.

• Remove a piece of DNA that is impairing gene features and inflicting disease.

Gene therapies are being used to deal with a small wide variety of diseases, together with an eye disease known as Leber congenital amaurosis and a muscle ailment referred to as spinal muscular atrophy. Many extra gene cures are present process lookup to make certain that they will be secure and effective. Genome modifying is a promising approach additionally beneath find out about that medical doctors hope to use quickly to deal with problems in people. [5]

4 **Types of Gene Therapy**

There are two basic types of gene therapy that include germline therapy and somatic gene therapy.

4.1 Germline therapy

Germline therapy entails the change of the gene's internal germ or gamete cells, which consist of sperm or ova. Germline remedy would consequently be administered during reproduction, the place the modified gamete cells fuse to shape a zygote. Once fused together, the zygote divides and passes on the modified gene to all different cells of the physique throughout the improvement of

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offspring. In this way, germline remedy alters the genome of future generations to come.

Although theoretically, germline therapy should counteract hereditary diseases, authorities in a range of international locations such as Switzerland, Australia, and Germany restrict the use of germline therapy due to fears on the unknown dangers of this therapy and whether it motives any long-term outcomes in future generations. Germline therapy is extraordinarily expensive, which in addition limits its realistic use.

4.2 Somatic Gene Therapy

Unlike germline therapy, somatic gene therapy entails the insertion of therapeutic DNA into physique cells, as a substitute than germ cells or gametes. This potential that any outcomes of the therapy are restricted to the person being dealt with and are now not inherited with the aid of future offspring.

The field of somatic gene therapy is surrounded via fewer moral problems as in contrast to germline gene therapy. While this may additionally be true, this therapeutic strategy is nevertheless in the preliminary tiers of development.

The first hurdle in somatic gene therapy is the profitable incorporation of the new gene into the genome. In fact, integrating the modified gene into the incorrect phase of the DNA may result in as a substitute than stop disease. In addition to requiring the preferred gene desires to be expressed, the gene expression of the new gene wants to be regulated to stop over-expression that should additionally set off disease. [6]

There are two kinds of somatic gene therapy:

- Ex-vivo – Here the cells are taken out from the physique and grown in the laboratory. These cells are then uncovered to the virus having the preferred gene and then after recombination, the recombinant cells are back to the patient.
- In-vivo – Here the genes are transferred to the cells existing interior the patient's body. [7]

4.2.1 Ex vivo Gene Therapy

In this mode of gene therapy genes are transferred to the cells grown in culture, modified cells are selected, accelerated, and then brought into the patient.

The use of autologous cells avoids immune system rejection of the added cells.

The cells are sourced in the beginning from the affected person to be handled and grown in a way of life earlier than being reintroduced into the same individual.

This method can be utilized to the tissues like hematopoietic cells and pores and skin cells which can be eliminated from the body, genetically corrected outdoor the body and reintroduced into the affected person physique the place they end up engrafted and live to tell the tale for an extended duration suggests a self-explanatory schematic format for ex vivo gene transfer.

4.2.2 In vivo Gene Therapy

In vivo the approach of gene transfer includes the switch of cloned genes directly into the tissues of the patient.

This is carried out in case of tissues whose character cells cannot be cultured in vitro in enough numbers (like brain cells) and/or where re-implantation of the cultured cells in the affected person is no longer efficient.

Liposomes and sure viral vectors are employed for this motive due to the lack of any different mode of choice.

In the case of viral vectors such kinds of cultured cells had been frequently used which have been contaminated with the recombinant retrovirus in vitro to produce modified viral vectors regularly. These cultured cells will be known as vector-producing cells (VPCs). VPCs transfer the gene to surrounding disease cells.

The effectivity of gene transfer and expression figures out the success of this approach, due to the fact of the lack of any way for preference and amplification of cells which take up and specific the overseas gene. [8]

In vivo	**Ex vivo**
Less invasive	More invasive
Technically simple	Technically complex
Vectors introduced directly	No vectors introduced directly
Safety check not possible	Safety check possible
Decreased control over target cell	Close control possible

Table Difference between In vivo Ex vivo Gene Therapy

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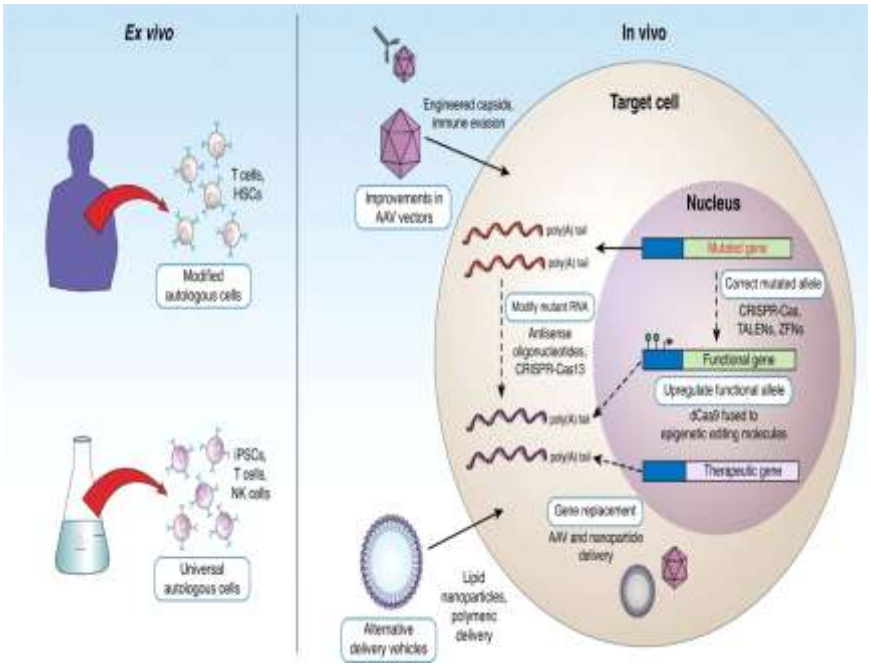

Fig Ex vivo, In vivo

For ex vivo techniques (left panel), autologous cells can be remoted at once from the affected person and genetically modified to elicit a therapeutic effect, whilst allogeneic cells can be produced and effortlessly reachable "off the shelf." In vivo techniques require concentration on unique cells to overexpress a therapeutic gene or right pathological mechanisms to enable purposeful gene expression (dashed arrows). [9]

5 **Gene Therapy Issues**

Gene therapy has been associated with several issues over the last few decades. One of the key problems is the lack of understanding about the long-term consequences of the therapy and the subject is fraught with ethical issues.

The Weismann barrier is an essential precept put ahead by using August Weismann that says hereditary data need to move from genes solely ever to cells of the physique and in no way vice versa to make sure it is no longer fed again to germline or gamete cells (sperm and ova).

In other words, if an individual has gone through gene therapy whereby the DNA content material of their body cells has been changed, there need to be no way that the inserted gene can be transferred to the gametes. If this rule is no longer followed, the remedy should lead to heritable differences in the genome that may want to be handed on to future generations, alternatively than the consequences being restricted to one person.

Other challenges confronted in the subject of gene therapy include:

Most gene therapies are short-lived which means sufferers want to endure a couple of treatments. Therapeutic DNA wants to be purposeful in the long-term and the cells having it want to be long-lived and secure if the therapy is going to provide an everlasting cure. However, subject integrating the DNA into the genome blended with the truth that many cells divide so unexpectedly skill long-term advantages are troublesome to obtain and repeated redress are needed.

Disorders arising from one gene mutation are the most promising candidates for gene therapy however a lot of the most frequent problems such as diabetes, coronary heart disorder and arthritis are induced with the aid of a combination of altered genes making them specifically challenging to deal with

The body's immune system can reply to the modified vectors and disrupt the effectiveness of gene therapy. The immune system's consciousness of overseas our bodies additionally capacity repeated remedy can emerge as problematic.

Use of the viral vectors can also pose a risk to patients in a variety of ways by triggering toxic, immune or inflammatory reactions or through the virus itself recovering its ability to cause disease once inside the body.

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There is a risk of inducing tumor growth, a concept referred to as insertional mutagenesis; if the inserted DNA is incorrectly placed, such as in a tumor suppressor gene, then a tumor may form.

Three deaths have occurred during gene therapy trials. One of the most notable was the death of 18-year-old Jesse Gelsinger during a trial conducted at the University of Pennsylvania in 1999. Gelsinger was treated for a deficiency in the enzyme ornithine transcarboxylase, a condition where the liver is unable to metabolize ammonia. He died four days after the therapy due to a severe immune reaction to the viral vector used to transport his corrected genes. [10]

6 **Safety of Gene Therapy**

The first gene therapy trial was run more than thirty years ago. The earliest research confirmed that gene therapy ought to have serious health risks, such as toxicity, inflammation, and cancer. Since then, researchers have studied the mechanisms and developed multiplied strategies that are much less probable to cause hazardous immune reactions or cancer. Because gene remedy strategies are fantastically new, some dangers may additionally be unpredictable; however, scientific researchers, institutions, and regulatory companies are working to make sure that gene remedy research, scientific trials, and accepted redress are as secure as possible.

Comprehensive federal laws, regulations, and recommendations assist protect humans who take part in research studies (called clinical trials). The U.S. Food and Drug Administration (FDA) regulates all gene therapy products in the United States and foreign places research in this area. Researchers who desire to check a strategy in a scientific trial need to first attain permission from the FDA. The FDA has the authority to reject or suspend clinical trials that are suspected of being hazardous for participants.

The National Institutes of Health (NIH) also performs a good-sized position in making sure the safety of gene therapy research. NIH offers recommendations for investigators and establishments (such as universities and hospitals) to comply with when conducting clinical trials with gene therapy. These guidelines state that clinical trials at establishments receiving NIH funding for this kind of research should be registered with the NIH Office of Biotechnology Activities. The protocol, or plan, for every clinical trial is then reviewed by using the NIH Recombinant DNA Advisory Committee (RAC) to determine whether it raises medical, ethical, or safety problems that call for further dialogue at a RAC public meeting.

The Institutional Review Board (IRB) and the Institutional Biosafety Committee (IBC) must approve every gene therapy clinical trial before it can be carried out. An IRB is a committee of scientific and scientific advisors and customers that reviews all research inside an institution. An IBC is a team that reviews and approves an institution's hazardous research studies. Multiple tiers of contrast and oversight make sure that safety concerns are a pinnacle precedence in the planning and carrying out of gene therapy research.

The clinical trial technique takes place in three phases. Phase I studies decide if a cure is safe for humans and pick out its side effects. Phase II studies determine if the remedy is effective, which means whether it works. Phase III research examines the new therapy to the current remedies available. Doctors favor recognizing whether the new cure works higher or has fewer aspects results than the standard treatment. The FDA reviews the outcomes of the clinical trial. If it finds that the advantages of the new treatment outweigh the side effects, it approves the therapy, and physicians can use it to deal with a disorder.

Successful clinical trials have led to the approval of a small variety of gene therapies, inclusive of therapies to deal with inherited problems like spinal muscular atrophy and Leber congenital amaurosis. [11]

7 **Advantages of Gene Therapy**

1) Germ-line gene therapy gives a genuine cure, and not truly palliative or symptomatic treatment.
2) Germ-line gene therapy may additionally be the sole positive way of addressing some genetic diseases.
3) By stopping the transmission of disorder genes, the cost and chance of somatic cell therapy for more than one generation is avoided.
4) Medicine needs to reply to the reproductive health wants of potential parents at chance for transmitting serious genetic diseases
5) The scientific community has a right to free inquiry, inside the bounds of suitable human research.

8 **Disadvantages of Gene Therapy**

1) Germ-line gene therapy experiments would contain too much scientific uncertainty and medical risks, and the long-term outcomes of such therapy are unknown.

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2) Such gene therapy would open the door to tries at altering human characteristics not related with disease, which may want to worsen issues of social discrimination.
3) As germ-line gene therapy includes research on early embryos and influences their offspring, such research really creates generations of Un consenting research subjects.
4) Gene therapy is high-priced and will by no means be price fine enough to benefit excessive social priority.
5) Germ-line gene therapy would violate the rights of next generations to inherit a genetic endowment that has not been deliberately modified [12]

II. CONCLUSION:

In the future, genetic therapies may be used to prevent, treat, or cure certain inherited disorders, such as cystic fibrosis, alpha-1 antitrypsin deficiency, hemophilia, beta thalassemia, and sickle cell disease. They additionally may also be used to deal with cancers or infections, which include HIV. Genetic therapies that are presently authorized by the FDA are available for humans who have Leber congenital amaurosis, an uncommon inherited condition that leads to blindness. CAR T-cell therapy external link is FDA authorized for humans who have blood cancers, such as acute lymphoblastic leukemia (ALL)external link and diffuse massive B-cell lymphoma.

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