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Advancing Medicine: The Potential of Gene Therapy to Treat Genetic Disorders

Noor Fouad Kadhim Al-Shammaa*

Noor Fouad Kadhim Al-Shammaa, ALIraqia University, ORCID ID: https://orcid.org/0000-0002-4517-1538, Iraq.

Corresponding Author: Noor Fouad Kadhim Al-Shammaa
Email: noor.f.kadhim@aliraqia.edu.iq

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ABSTRACT. Since the identification of the gene as the fundamental unit of heredity, the goal of making targeted changes to the human genome has been a key ambition in the field of medicine. Gene therapy refers to the process of enhancing genetic material by correcting mutated genes or making precise alterations at targeted sites for therapeutic purposes. This therapy was made possible by the progress in genetics and bioengineering, which allowed for the use of vectors to transfer extrachromosomal material to specific cells. Gene therapy medications have recently obtained approval in Europe, the United States, and Japan. Gene therapy is an innovative approach that has the potential to cure a wide range of acquired and genetic disorders.

Key words: Gene therapy; Genetic vectors; Germ line gene therapy; Somatic gene therapy; Immune response; Gene delivery; Genetic illness

INTRODUCTION

"James Watson once expressed that used to believe destiny was written in the stars; however, it has become increasingly clear that, to a great extent, destiny lies within genes." Genes, the functional units of heredity, consist of specific sequences of bases that encode instructions for protein synthesis. While genes receive significant attention, proteins carry out most life functions. When genes are altered, the encoded proteins become unable to perform their normal functions, leading to genetic disorders.

The term "gene therapy," which initially referred to "genetic replacement treatment" in the early 1980s, has now broadened its scope to include any procedure that involves gene transfer (Wood and Fry, 1999)

The primary objective of gene therapy is to restore normal protein function by replacing faulty genes with their appropriate counterparts **(**Misra, 2013).

THE AIMS OF THIS WORK

1- Precision Alterations: Researchers aim to make targeted changes to the human genome by correcting mutated genes or introducing precise alterations at specific sites. This approach seeks to enhance genetic material for therapeutic purposes.

2- Clinical Approval and Application: Recent approvals of gene therapy medications in Europe, the United States, and Japan highlight the potential for treating a wide range of acquired and genetic disorders. Researchers strive to advance gene therapy's clinical application and improve patients' lives.

DEFINITION GENE THERAPY

Brief Overview of Gene Therapy

Gene therapy is the process of using genetic material to treat or prevent diseases by modifying the genes within a person's cells.

Gene therapy holds great promise in the treatment of genetic disorders **(**Friedmann and Roblin, 1972). For instance, monogenic diseases of blood cells, such as sickle cell disease or β-thalassemia, were initially seen as ideal candidates for gene therapy due to their well-understood molecular level. The hematologic stem cell, which is the desired recipient for gene therapy, may be readily obtained and subsequently subjected to genetic correction inside a laboratory setting before being reintroduced into the body.

Gene therapy is an innovative approach that shows promise in the treatment of several acquired and hereditary neurologic illnesses, namely those for which the underlying gene deficiency or deletion has been discovered Blömer et al., (1996). The use of genes as therapeutic agents involves the correction of faulty genes that are responsible for hereditary disorders. This can be achieved using one of the following approaches (Miller, 1992; Verma et al., 2005).

General Method of Gene therapy

1.Gene Insertion: The process of inserting a functioning gene into a specified site within the genome to replace a dysfunctional gene. This strategy is frequently employed.

2.Gene Swapping: In this approach, a faulty gene is swapped out for a healthy one through a process called homologous recombination, restoring normal gene function.

3.Gene repair: involves the process of selectively reversing mutations in abnormal genes.

4.Gene expression: can be modified by regulating the extent to which a gene is activated or deactivated **(**Knoell &Yiu, 1998; Ginter, 2000).

Gene therapies: An intricate and versatile approach

Gene treatments function by several techniques, such as the introduction, removal, or modification of genetic information inside the cells of a patient. Let us examine the various options:

Vectors as Transporters: Researchers employ "vectors" to transport genetic material into certain cells. These carriers convey their genetic material. Vectors can be administered directly into the body (in vivo) or introduced to grown cells outside the body (ex vivo). Chimeric antigen receptor T-cells (CAR-Ts), which are genetically engineered cell treatments, exemplify this methodology.

Regulatory Factors to Consider: It's crucial to be aware that gene treatments in Europe are classified as advanced therapy medical products (ATMPs). This classification includes gene treatments, cell therapies, tissue-engineered materials, and integrated products that involve medical devices. Understanding these regulatory factors is key to navigating the field of gene therapies **(**Golchin and Farahany, 2019).

Global Approvals and Development: the U.S. Food & Drug Administration (FDA) approved eight gene treatments.

The European Medicines Agency (2018) approved nine medicines, while three other therapies were with drawn Ronco et al., (2021)

More than 1300 gene treatments were being developed globally, at various stages from preclinical to preregistration. Gene therapy is advancing, providing optimism for the treatment of several ailments **(**Barrett, 2021).

Types of Gene Therapy

Gene therapy may be classified into several types based on the method used to deliver therapeutic genes into the body.

Gene therapy may be classified into two primary categories:

1.**Germline gene therapy** involves the modification of germ cells, such as sperm or egg cells, by adding functional genes that become part of their genome. The effects of this treatment would be heritable and transmitted to subsequent generations. In theory, germline treatment has the potential to mitigate genetic illnesses and inherited problems successfully. Nevertheless, the combination of technological obstacles and ethical concerns makes it improbable that germline treatment will be undertaken in humans in the foreseeable future **(**Matthews and Curiel, 2007).

2.**Somatic gene therapy, a process that** refers to the introduction of therapeutic genes into the somatic cells of an individual, offers a unique approach. The alterations and effects are exclusive to the particular patient, ensuring the safety and individuality of the treatment. These changes will not be passed along to their progeny or future generations, providing a sense of reassurance (Bank, 1996).

ADVANTAGES OF GENE THERAPY

Gene therapy has many advantages compared to traditional hematopoietic stem cell transplantation from suitable donors:

Wide Accessibility: Gene therapy has the potential to be accessible to all patients, as it circumvents the immunological impediments that might result in transplant rejection or graft-versus-host disease.

Technical Challenges: Gene therapy for correcting hemoglobin abnormalities presents significant technological hurdles. In order to be successful, a significant number of hematopoietic stem cells and a strong expression of the β-globin gene in erythrocyte precursors are necessary **(**Parkman, 1986).

DISADVANTAGES OF GENE THERAPY

Gene therapy is a relatively novel technology, and there may be unanticipated risks associated with it. The duration of time required to observe adverse effects is not yet known, and delayed consequences may occur, requiring long-term monitoring in clinical trials. Inadequate comprehension: Detailed studies on the mechanisms and possible difficulties of gene therapy are currently underway, and scientists have not yet completely understood all of the risks.

Safety Considerations: As gene therapy continues to develop, safety remains a critical issue that demands our utmost attention and diligence by Baum et al., (2003)

1. Short-Lived Nature: The effects of gene therapy are frequently transient. In order for gene therapy to become a permanent cure, To achieve lasting therapeutic effects, the introduced DNA in target cells must remain stable and functional. However, long-term benefits are hindered by integrating this therapeutic DNA into the genome, as well as the rapid division of numerous cells. Patients may need multiple rounds of gene therapy, and occasionally, the viral vector fails to elicit the desired response, or the newly introduced gene does not express itself effectively.

2. Immune Response: The immune system, a key player in our body's defense, naturally attacks foreign material that enters human tissues. This natural response can significantly reduce the effectiveness of gene therapy. Furthermore, the immune system's heightened surveillance poses a challenge when it comes to repeating gene therapy, highlighting the need for further research in this area **(**Rochat and Morris, 2002).

3. Problems with Viral Vectors There are three main challenges associated with viral vectors used in gene therapy research. Firstly, viruses can be hazardous to patients. Secondly, they can trigger immunological and inflammatory responses. Lastly, there might be difficulties in controlling and targeting the genes using viral vectors. Furthermore, there is a continuous apprehension that the viral vector may reacquire its pathogenic potential once introduced into the host.

4. Multigenic Disorders: Gene therapy is most effective when targeting single-gene alterations. Regrettably, several prevalent illnesses, including heart disease, hypertension, Alzheimer's disease, arthritis, and diabetes, arise from genetic abnormalities in multiple genes. Treating these illnesses with gene therapy is difficult due to their complex nature involving several genes or factors **(**Walther and Stein, 2000)

5. Insertional mutagenesis: namely the process of inserting genetic material into cells, Geneticists express significant concern about the virus potentially targeting incorrect cells. If DNA becomes integrated into an inappropriate site within the genome, it poses a considerable challenge., such as a gene that suppresses tumor growth, it has the potential to initiate the formation of tumors. During clinical studies conducted for X-linked severe combined immunodeficiency (SCID),

researchers observed this risk. Hematopoietic stem cells modified with a corrected transgene using a retrovirus led to T-cell leukemia development in 3 out of 20 individuals. The reference for this study Durai et al., (2005).

APPLICATION OF GENE THERAPY

Gene therapy may be applied to use gene products that help reduce cellular malfunction or prevent cell death, opening up new possibilities for treatment. This article examines the methods of gene transfer for introducing new proteins into cells using different viral vectors, both in laboratory settings and living organisms, including animal models and human clinical trials. Our main emphasis will be on a novel lentiviral vector, which is a new approach for transferring genes. We will specifically study degenerative illnesses of the central nervous system (CNS) and the model systems associated with the by Blömer et al., (1996)

1. **Monogenic blood cell diseases:** At first, monogenic blood cell disorders like sickle cell disease and β-thalassemia were seen as suitable candidates for gene therapy. Their clearly described molecular pathology and the convenient accessibility to the target cell, the blood stem cell, enables its removal, genetic modification in a controlled environment, and subsequent re-implantation. The reference is from **(**Anderson, 1984).
2. The potential of gene therapy in treating illnesses is becoming increasingly apparent. Recent evidence indicates that gene therapy has the aptitude to target the main causes of several problems, such as malignancies, viral infections, genetic abnormalities, and autoimmune diseases. The treatment strategy seeks to avoid, mitigate, or maybe eradicate these problems (Misra, 2013).
3. **Clinical Gene Therapy:** Gene therapy is presently at the experimental stage, necessitating further studies to comprehend its potential fully. Gene therapy research is primarily conducted in the United States and Europe, with fewer studies occurring in other countries, including Australia.

This technique has a broad range of applications, including prospective therapies for diseases caused by single-gene recessive disorders (such as cystic fibrosis, hemophilia, muscular dystrophy, and sickle cell anemia), acquired genetic diseases like cancer, and specific viral infections, including AIDS **(**Ginter, 2000), This concept is visually depicted in Figure 1, which focuses on the treatment of infectious disorders and monogenic diseases.

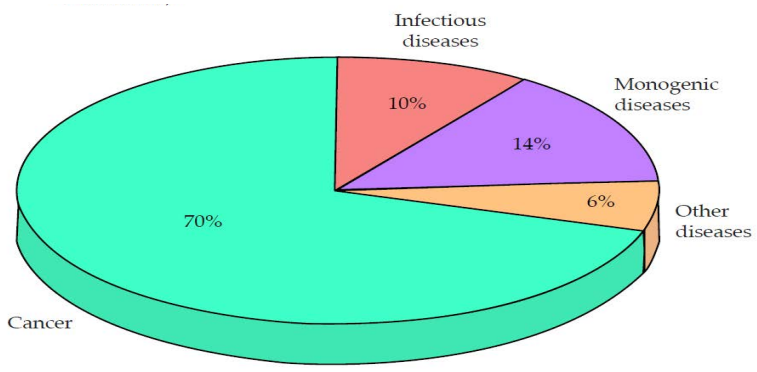

Figure 1. Proportion of protocol for human gene therapy trials relating to various types of diseases.

Additional Gene Therapy Projects: Gene therapy research also aims to tackle conditions like cardiovascular disease, diabetes mellitus, arthritis, and Alzheimer's disease, all of which have a genetic predisposition. The source of this information is **(**Vandendriessche, 2004). (Table 1).

Table 1. A concise overview of authorized clinical gene treatment strategies

Disorders:	The desired outcome or goal.	Specific cells that are the focus of a particular treatment or intervention	Delivery strategy	Countries that have established protocols
Adenosine deaminase (ADA)deficiency	ADA Substitution	Blood cell	Retrovirus	Italy, Netherlands, USA
Alpha-1 Antitrypsin	Deficiency Alpha-1 Antitrypsin Substitution	TherapyRespiratory epithelium is a kind of tissue that lines the respiratory tract.	Liposomes are small spherical vesicles composed of lipid bilayers.	The country referred to as "The United States"
AIDS Hematopoietic	stands for Antigen Presentation and HIV Inactivation.	Blood and Marrow	Retrovirus	The country known as the United States
Immune Function in Cancer	Immune Function Enhancement	Blood, marrow, and tumour can be targeted	using various methods such as retrovirus, liposome, electroporation, and cell-mediated transfer.	Austria, China, France, Germany, Italy, Netherlands, and the United States
Cystic Fibrosis:	Enzyme replacement treatment for CFTR	The respiratory epithelium is a tissue that covers the inner surface of the respiratory system.	Adenovirus is classified as a viral organism, whereas liposome is categorised as a lipid-based method of delivering substances.	The listed countries are the United Kingdom and the United States of America.
Familial hypercholesterolemia.	LDL receptor replacement therapy	Liver Lipoprotein	using Retrovirus	found in the United States.
Gene delivery for Fanconi's Anaemia.	Support Group C is supported	The retrovirus that affects the blood and bone marrow.	using Retrovirus	The country referred to as the United States
Gaucher's disease Therapy	Glucocerebrosidase Substitution	The blood and bon marrow	using Retrovirus	The country referred to as the United States.
Haemophilia B is a condition	that requires Factor IX Replacement.	This treatment involves using Skin Fibroblasts	using Retrovirus	In China, this approach is being studied.
Rheumatoid Arthritis The country referreto as the United States.	can be treated by delivering Cytokines	The Synovium	using Retroviruses.	The country referred to as the United States.

The technique of gene treatment involves a specific approach

The gene therapy procedure is intricate, and several ways need more refinement. The task of creating effective gene therapy for a particular ailment is quite significant. In order to proceed, it is necessary to have a comprehensive understanding of the problem, accurately identify the defective gene responsible, and have access to a fully functional version of the gene. It is necessary to identify and get access to certain cells in the body that need to be treated. It is crucial to have a very effective approach for delivering fully operational copies of the gene to these cells. Moreover, it is essential to possess a comprehensive comprehension of the illnesses and their exact genetic connections **(**Matthews and Curiel, 2007).

The transmission of genes is an essential component of the majority of gene therapy experiments. It involves the introduction of a functional gene into the patient's genome to replace a defective gene that causes illness. The main obstacle is efficiently delivering the novel or substitute gene to the desired cells. In order to do this, researchers employ carrier molecules referred to as vectors**,** by Gardlik et al., (2005)

An ideal gene transfer vector should possess specificity, efficiency in delivering genes of the required size for clinical applications, immune system evasion, and the ability to be purified in large quantities at high concentrations. Upon entering the body, the vector should not elicit an allergic response or provoke inflammation. It is imperative that the medical procedure ensures the safety of both the patient and the surrounding environment. Ultimately, a vector should accurately represent the genetic information for the whole duration of time required, often corresponding to the lifespan of the patient.

Vector transfer has been performed using two methods: ex vivo and in vivo. The citation Romano et al., (1999) is referenced. A more common approach involves using cells derived from the patient. Initially, the customary genes are replicated and inserted into the vector. Next, the cells containing faulty genes from the patient are isolated and combined with the genetically altered vector. Ultimately, the genetically modified cells are reinserted into the patient's body, resulting in the production of the necessary protein to combat the ailment. On the other hand, the latter treatment does not utilise the patient's cells. Alternatively, vectors carrying the whole gene are sent directly into the patient's bloodstream to locate and attach to the specific cells of interest **(**Walther and Stein, 2000)

The future of gene therapy shows potential for closing the divide between clinical dentistry and medicine **(**Misra , 2013). Scientists around the world are striving to eradicate illnesses by targeting their genetic origins. Rather than seeking medications for illness treatment, their objective is to manipulate the genes accountable for these problems. Implementing gene therapy is pursuing this objective. Over time, novel gene-transfer methods, methodologies, approaches, and viewpoints have been created.

Furthermore, the intricate causes of periodontal disease encompass microbial challenges and diverse host immunological responses, which are impacted by both hereditary and environmental factors (Haffajee and Socransky, 1994; Page and Kornman, 1997; Hill, 1965).

CONCLUSION

Gene Therapy for human genetic disease has emphasized the enormous promise of gene therapies to treat genetic illnesses, as well as the significant information gaps at the time. Only in

recent years have scientific advances resulted in a major increase in the number of gene treatments approved for commercialization, improving the lives of individuals suffering from rare genetic illnesses.

Gene treatments can work in various ways, including adding, deleting, or modifying genetic information within a patient's cells. One way is to use vectors as carriers to convey genetic material to target cells. These vectors, which carry genetic material, can be delivered directly into the body (in vivo) or to grown cells outside the body (ex vivo).

Gene therapies, which try to address the underlying cause of an illness at the genetic level, are among the most basic medicines available. They have the potential to profoundly transform the lives of individuals suffering from previously untreatable diseases. The therapeutic promise is greatest for illnesses that can be diagnosed and treated early on before symptoms appear and irreparable damage occurs.

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