Pharmedico Publishers
International Journal of Pharmaceutical Science and Medicine
ISSN (Online): 2584-1610
Volume 1, Issue 1 (2023): 32-36
http://dx.doi.org/

REVIEW ARTICLE

EMERGING TRENDS IN GENE THERAPY: APPLICATIONS AND CHALLENGES

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Article History
Received: 02 September 2023
Revised: 07 November 2023
Accepted: 08 December 2023
Published: 25 December 2023

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ABSTRACT: Gene therapy is a field that is changing quickly and has a lot of potential for treating a wide range of diseases that people are born with or get over time. This article is a review of recent developments in gene therapy and how it might be used to treat different medical conditions. It looks at the different ways gene therapy can be done, such as with viral and non-viral vectors, genome-editing tools like CRISPR-Cas9, and RNA-based therapies. The article talks about the problems and limits that researchers and doctors face when trying to use gene therapy successfully. These include immune responses, off-target effects, and ethical concerns. Also, it shows how the future of gene therapy as a transformative medical intervention is being shaped by ongoing clinical trials and regulatory issues.

Key Words: Gene therapy; Viral vectors; Genome editing; RNA-based therapies; Clinical trials; Ethical considerations.

INTRODUCTION:

Gene therapy is a new way of treating and preventing diseases that is changing the way genetic material is used. In the past few years, it has made a lot of progress, thanks to better gene delivery systems and genome editing technologies [1]. This article talks about recent changes in how gene therapy is used and the problems that researchers and clinicians have to deal with. It talks about different kinds of gene therapy and how they might be used to treat genetic diseases, cancer, neurological conditions, and heart diseases. It also talks about problems like immune responses, off-target effects of genome editing, ethical concerns, and the ability to make more of something. Gene therapy has a lot of potential to change modern medicine and offer personalised treatments for diseases that were once untreatable [2].

GENE THERAPY APPROACHES:

Gene therapy is a broad term for many different ways to treat or prevent diseases by putting therapeutic genetic material into the body [3]. Here are the main ways gene therapy is used:

1. Viral Vectors: Viral vectors are changed viruses that carry therapeutic genes to cells that need them. Some common ways viruses spread are:

- **Adeno-Associated Viruses (AAV):** AAVs are small, non-disease-causing viruses that can integrate into the genome of the host cell and turn on genes for a long time [4].
- **Lentiviruses:** Lentiviral vectors are made from HIV and can efficiently deliver genetic material to both cells that are dividing and cells that are not dividing. This makes them useful for a wide range of applications [4].
- **Retroviruses:** Retroviral vectors can add their genetic material to the genome of the host cell, which makes stable gene expression possible [4].

2. Non-viral Vectors: Non-viral vectors are an alternative to viral vectors, and they usually involve sending genetic material directly to the target. Examples of common non-viral vectors are:

- **Naked DNA:** Plasmid DNA is put directly into target cells, but because it doesn't have the viral envelope, it isn't as good at transferring genes [5].
- **Liposomes:** Therapeutic genes are wrapped up in lipid-based nanoparticles, which makes delivery more efficient and keeps the payload from breaking down [5].
- **Nanoparticles:** Engineered nanoparticles, which are often made of polymers, deliver genes to target cells efficiently, making gene therapy work better [5].

3. Genome Editing Technologies: Genome editing lets DNA sequences in the genome be changed in a very specific way. CRISPR-Cas9 is the most well-known tool for editing the genome, but there are also:

- **Zinc Finger Nucleases (ZFNs):** ZFNs are made up of engineered DNA-binding domains that are linked to a nuclease. This makes it possible to cut specific parts of DNA [6].

- **Transcription Activator-Like Effector Nucleases (TALENs):** TALENs use TAL effector proteins to find certain DNA sequences and edit genes [6].

4. RNA-based Therapies: Small RNA molecules are used in RNA-based therapies to control how genes are turned on and off. There are two main ways to use RNA:

- **RNA Interference (RNAi):** Small interfering RNAs (siRNAs) or short hairpin RNAs (shRNAs) are used to turn off disease-causing genes [7].

- **Antisense Oligonucleotides:** These molecules bind to specific mRNA sequences to change how a gene is expressed or make an exon skip more likely [7].

Depending on the medical condition and cells being treated, each gene therapy method has its own pros and cons. As gene therapy keeps getting better, the combination of these methods could lead to new ways to treat diseases and personalised treatments for many of them. Before wide use, though, there needs to be a lot of research and clinical testing to make sure it is safe and works [8].

APPLICATIONS OF GENE THERAPY:

Gene therapy has shown that it could be used to treat a wide range of health problems. Some of the most important uses are:

Genetic Disorders:

Gene therapy gives people with genetic diseases caused by changes in certain genes hope. Gene therapy has been used to try to help people with diseases like cystic fibrosis, sickle cell disease, haemophilia, and muscular dystrophy. The goal is to add functional genes or fix the bad genes that cause these diseases. This could provide long-term relief or even a cure [9].

Cancer Treatment:

Gene therapy is changing the way cancer is treated by using new methods. As a way to fight cancer, scientists are making oncolytic viruses that can only infect and kill cancer cells. Also, Chimeric Antigen Receptor T-cell (CAR-T) therapy involves changing a patient's T-cells so that they express CARs, which specifically target and kill cancer cells. Targeted gene delivery is also being looked into as a way to improve the delivery of therapeutic agents directly to tumour sites while reducing the effects on healthy cells [10].

Neurological Disorders:

Neurological disorders are hard to treat because the central nervous system is so complicated. But gene therapy shows promise for diseases like Spinal Muscular Atrophy (SMA), which is a genetic disorder of the nerves and muscles. Gene replacement therapy for SMA has been very successful. Gene therapy research is also being done for neurodegenerative diseases like Parkinson's and Alzheimer's, with the goal of slowing the progression of the disease or bringing back lost function [11].

Cardiovascular Diseases:

Gene therapy is making progress in dealing with cardiovascular diseases, which are still the leading cause of illness and death around the world. When a person has heart failure, gene therapy tries to help the heart heal and grow new cells by giving them genes that promote tissue growth or improve heart function. Gene therapy can also be used to fix or lessen the effects of genetic defects that cause inherited heart conditions caused by specific gene mutations [12]. In each of these situations, gene therapy can be used to treat diseases at the genetic level in a way that is unique to each person and may be able to cure them. Even though a lot of progress has been made, problems like immune responses, off-target effects, and finding the best way to deliver the drug still need to be solved. Still, the constant improvements in gene therapy show that it has a lot of potential to change medical treatments and make patients' lives better in the future [13].

CHALLENGES AND LIMITATIONS:

Even though gene therapy has a lot of potential, there are some problems and limitations that need to be solved before it can be used safely and effectively. Some of the most important ones are:

Immune Responses:

The immune response of the host to the viral vectors used to deliver genes is a big problem in gene therapy. When viral vectors are brought into the body, the immune system may see them as foreign invaders and respond to them as such. This can cause the viral vectors to be destroyed before the therapeutic genes can reach the target cells, making the treatment less effective. Researchers are working hard on ways to avoid or change the immune response of the host, like changing the viral vectors to make them less immunogenic [14].

Off-Target Effects and Safety Concerns in Genome Editing:

Genome editing technologies like CRISPR-Cas9 could change specific genes in a very precise way. But one big worry is the possibility of off- target effects, which happen when genetic changes happen in places other than the ones that were meant. Effects that aren't meant to happen could have unintended effects and put people's safety at risk. Researchers are always improving CRISPR-Cas9 and other tools for editing the genome to make them more specific and reduce their side effects [15].

Ethical Considerations:

Gene therapy raises a lot of ethical questions, especially when it is used on germline cells (eggs or sperm) or early embryos.

Germline editing, which involves making changes to the genome that are passed down from generation to generation, has huge effects on future generations. Concerns about ethics include the possibility of unintended effects, the need for germline editing for medical reasons, and the effects on the diversity of human genes. In gene therapy research and clinical trials, it is very important to make sure that informed consent and ethical review processes are in place [16].

Manufacturing and Scalability Challenges:

Another problem is making gene therapy products on a large scale. Viral vectors, tools for editing the genome, and RNA-based therapies need to be made with care to make sure they are safe, pure, and consistent. It is important to make sure that gene therapy production can be scaled up to meet what could be a very high demand as gene therapy becomes more popular. Getting gene therapies to patients and making them affordable and accessible is also hard from an economic point of view because it is hard to control the costs of making them and increase production [17].

It is important to deal with these problems and limitations if gene therapy is to be taken from the experimental research stage to real-world clinical applications. As the field continues to change, researchers, clinicians, regulatory authorities, and ethical committees will need to work together to make sure that gene therapy is used to its fullest potential while minimising risks and ethical concerns. By solving these problems, gene therapy could change the way medicine is done and give hope to people with diseases that couldn't be treated before [18].

CLINICAL TRIALS AND REGULATORY LANDSCAPE:

Gene therapy has come a long way over the years, and many clinical trials have been done to test how safe and effective it is at treating different diseases. In the sections that follow, we'll talk about clinical trials for gene therapy, the regulatory environment, and pricing and reimbursement issues [19].

Overview of Promising Gene Therapy Trials and Recent Breakthroughs:

Gene therapy is being tested in more and more clinical trials for a wide range of diseases. Here are some recent breakthroughs and trials that look promising:

- **Hemophilia Gene Therapy:** Several clinical trials have shown that delivering the missing or broken clotting factor genes could be an effective way to treat haemophilia. This would significantly cut the number of bleeding episodes and improve the quality of life for patients [20].

- **CAR-T Cell Therapy for Cancer:** CAR-T cell therapy has been very effective at treating some types of leukaemia and lymphoma. It has led to long-lasting remissions in patients who did not respond to other treatments [21].

- **Spinal Muscular Atrophy (SMA) Treatment:** Gene replacement therapy for SMA has led to big improvements in how babies with this terrible neuro-muscular disorder move and how long they live [22].

- **Gene Therapy for Inherited Blindness:** Patients with certain inherited diseases of the retina have been able to see better in clinical trials [23].

These breakthroughs and ongoing clinical trials show how gene therapy could change the way we treat diseases that were hard or impossible to treat before [24].

Regulatory Approval and Oversight of Gene Therapy Products:

Health officials carefully watch how gene therapy is regulated to make sure that patients are safe and that the treatments work. Gene therapy products are reviewed by regulatory agencies like the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and other agencies around the world based on rigorous preclinical data and results from clinical trials. Before they can be sold commercially, gene therapy products must pass strict tests of their safety, quality, and effectiveness. The long-term safety and effectiveness of gene therapy products are still being checked after they have been approved [25].

Pricing and Reimbursement Considerations for Gene Therapies:

Gene therapies are a new area of medicine, and they often require a lot of money for research and development. Because of this, gene therapies tend to cost a lot of money. When setting prices, the costs of innovation must be balanced with the possible benefits to patients and society. Gene therapies can be hard for patients to get because they cost a lot up front. Talking about how to pay for them is important to make sure that everyone who needs it can get it. Payers, healthcare systems, and pharmaceutical companies all work together to figure out how to make gene therapies more affordable and look into new ways to pay for them [26]. As gene therapy keeps getting better, regulations will change to fit the unique qualities of these life-changing treatments. Collaboration between researchers, clinicians, regulators, patient advocacy groups, and payers is still needed to get through the regulatory challenges and help gene therapies develop in a responsible way and become more accessible. Gene therapy has the potential to be a game-changing medical treatment, giving hope to people with hard-to-treat diseases that were once thought to be untreatable. This can be done through continued research, improvement, and regulation [27].

FUTURE PERSPECTIVES:

Potential Impact of Gene Therapy on the Future of Medicine:

Gene therapy has a huge chance to change the future of medicine by giving us new ways to treat diseases. It can give

targeted and precise treatments for a wide range of diseases, focusing on the genetic causes instead of just treating the symptoms. As research on gene therapy moves forward and technology improves, it is likely to become a standard part of medical care. This new way of thinking has the potential to cure diseases that can't be cured right now, improve the quality of life for patients, and make living with chronic conditions easier [28].

Emerging Research Areas and Novel Applications: Gene therapy is a field that is always changing, and new areas of research are opening up new possibilities. Researchers are looking into how to use gene-editing technologies to treat diseases that aren't caused by genes. This could change how infectious diseases, autoimmune diseases, and other conditions are treated. Gene therapies are also being looked into for diseases that come with getting older, which gives us hope for treating conditions that come with getting older. Also, gene therapy could be used as a preventive medicine, with early interventions that could reduce genetic risks and stop diseases from happening [29].

Integrating Gene Therapy with Other Treatment Modalities for Improved Outcomes: Integrating gene therapy with other types of treatment could improve the effectiveness of treatment. Traditional cancer treatments like chemotherapy and radiation therapy can work better when they are combined with gene therapy. By focusing on certain genetic factors, gene therapies can also help with regenerative medicine by making it easier for tissues to heal and grow back. Also, applications of precision medicine could lead to personalised gene therapies that are based on the genetics of each patient. This would make treatments work better and have fewer side effects [30].

CONCLUSION:

In short, gene therapy has the potential to change the medical field by providing targeted treatments for diseases that are both inherited and acquired. Its growing importance is shown by the fact that clinical trials have been successful and it may be able to treat diseases that were once incurable. But problems like immune responses, off-target effects, and ethical concerns need to be dealt with before it can be used safely. If we can get past these problems, we can start a new era of precision medicine that will offer personalised treatments and better outcomes for patients all over the world.

ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: Nil

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How to Cite this article:
Jamali M. Emerging trends in gene therapy: applications and challenges. International Journal of Pharmaceutical Science and Medicine 2023; 1(1): 32-36.