REVIEW

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Recent Trends in Gene Therapy for Treatment of Diseases, Disorders and Conditions

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ABSTRACT

Gene therapy, driven by advances in genetic engineering and molecular biology, offers a powerful approach to treating diseases by modifying genetic material within a patient's cells. Techniques involving the insertion, deletion, or alteration of genes target the root causes of illness. While viral and non-viral vectors have improved gene delivery, challenges in targeting specific cells and tissues persist. To address this, nanomedicine has introduced nanoparticle-based delivery systems that enhance precision and efficiency. This approach holds promise for treating a range of hereditary and acquired diseases, though further clinical development is needed to fully realize its potential.

KEYWORDS: Gene therapy, Advanced Gene Editing Technologies, Therapeutic Applications, clinical trials, genome, mutation, replication, advanced therapy.

INTRODUCTION

Gene Therapy for Cancer Treatment

Gene therapy is becoming a vital tool in cancer treatment. As of late 2009, over 60% of global gene therapy trials were focused on cancer, highlighting its potential in managing this complex disease. (1) One major approach involves oncolytic viruses, which are designed to target and kill cancer cells without harming healthy tissue. These viruses, whether natural or engineered, deliver specific genes into tumor cells, leading to their destruction. Another promising method is gene replacement therapy. This strategy restores the function of damaged tumor-suppressor genes like *p53*. For example, China approved Gendicine in 2003—a viral vector carrying the *p53* gene—for treating certain cancers. Cancer remains the second leading cause of death worldwide, with millions of lives lost each year. Its resistance to treatment stems from its genetic instability and complex environment. Gene therapy offers a targeted, innovative approach that could improve future outcomes.(2)

Gene transfer therapy introduces specific genes into cancer cells or nearby tissues, offering a novel approach to treatment. (3) Various genes have been studied for this purpose, including suicide genes that trigger cell death, anti-angiogenesis genes that block blood vessel growth, and stasis genes that halt cell division.(4) Delivery methods include viral vectors—most commonly non-replicating adenoviruses and non-viral techniques like electroporation and DNA coatings. The choice of delivery system depends on how long the gene needs to be active and how precisely it must target cells. For instance, short-term expression is enough for HSV-tk suicide genes, while long-term expression is essential for anti-angiogenic genes like sFLT-1, often delivered using transposon-based plasmids.(5)

Despite early challenges in achieving effective and targeted

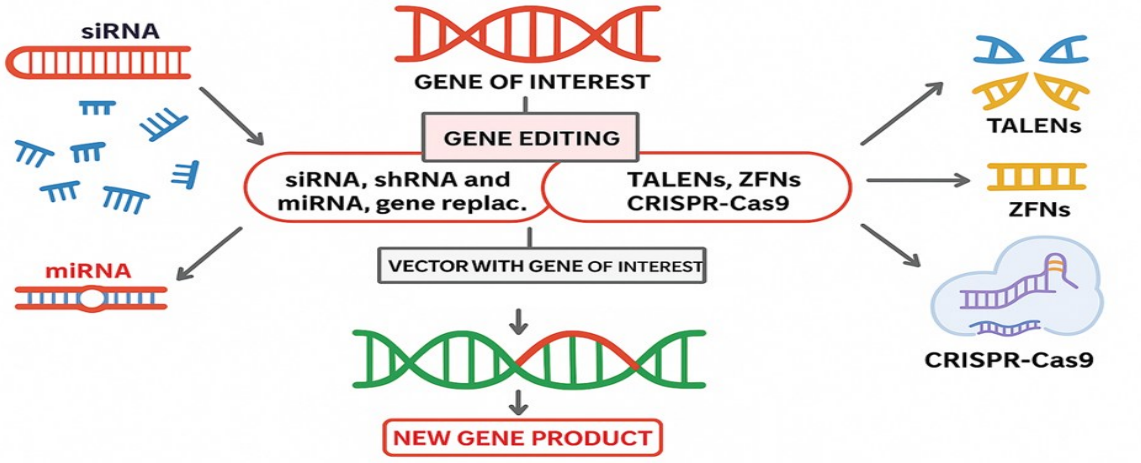

Figure 1: Formation of New Gene Product

gene delivery, preclinical studies have shown success in treating solid tumors in organs such as the prostate, lungs, and pancreas. However, issues like gene silencing, off-target effects, and risks of inserting DNA into harmful genomic regions remain concerns—especially with systems like retrotransposons, which may disrupt essential genes. Techniques like the Sleeping Beauty transposon have improved gene insertion accuracy, as seen in glioma models. Additionally, nucleic acid-based therapies using siRNA, miRNA, and CRISPR aim to suppress harmful genes or restore tumor suppressors. (6) Many of these strategies—including CAR-T cell therapy and tumor microenvironment (TME) targeting—are now central in modern clinical cancer treatment.(7)

Clinical Trials of Gene Therapy in Cancer

Due to the wide range of applications, it's difficult to list every gene transfer treatment. However, several promising therapies are in advanced clinical trials, highlighting the potential of this approach.(8) One notable technique involves using replication-incompetent adenoviruses to deliver the HSVtk gene into tumor cells, followed by treatment with ganciclovir.(8) This antiviral remains inactive until metabolized by HSVtk, ensuring targeted cell death in cancerous tissue. In a phase I trial for glioblastoma, this method improved median survival from 39 to 56 weeks, marking a significant step forward in gene-based cancer therapy.(3-5)

Another widely studied strategy involves restoring the *p53* gene using adenoviral vectors. Since *p53* mutations are found in over half of human cancers and are often linked to aggressive growth, replacing the faulty gene can trigger tumor suppression and apoptosis. INGN 201, a vector carrying the functional *p53* gene, has shown encouraging results in early-phase trials for bladder, prostate, ovarian, and brain cancers. It is now being tested in a phase III trial for advanced head and neck melanoma, showing continued progress in gene therapy's clinical application.(2-9)

FUTURE DIRECTION

Gendicine, approved by China in 2003, remains the only gene transfer therapy to receive regulatory approval globally. This modified adenovirus delivers the *p53* gene to treat head and neck squamous cell carcinoma. Since its approval, hundreds of patients in China have received the therapy, with some undergoing multiple injections. While large-scale trial results are still awaited, Gendicine represents a major milestone in the clinical application of gene transfer technology.(2)

The potential of gene transfer extends far beyond current approvals. It not only introduces entirely new treatment methods but also enhances traditional therapies. By targeting the genetic drivers of cancer, gene transfer enables more personalized and precise approaches. Recent studies in cancers like pancreatic cancer and glioblastoma have shown promising survival benefits. Continued innovation in gene delivery systems and expression cassettes is expected to improve outcomes, pushing the boundaries of cancer treatment and bringing long-term control or even cures closer to reality.(10-11)

Gene Therapy in Spinal Muscular Atrophy &Duchenne Muscular Dystrophy

Gene therapy offers a promising treatment for life-limiting neuromuscular disorders such as Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA).(12) These conditions are caused by the loss or reduction of a single gene's function. Gene replacement therapy aims to deliver a healthy copy of the faulty gene called a transgene so that cells can produce the missing protein. For blood and immune-related disorders, this is often done *ex vivo* by collecting the patient's hematopoietic stem cells, modifying them with a viral vector to carry the transgene, and reintroducing them so that future cell generations carry the corrected gene.(13) In contrast, treating neuromuscular diseases requires targeting non-dividing muscle and nerve cells, making in vivo gene therapy more suitable. In this approach, the transgene is packaged into a viral vector and delivered directly into the patient. The virus enables the therapeutic gene to be expressed inside the target cells without needing to integrate into the DNA. This method allows for sustained protein production in long-lived cells, which is essential for managing chronic neuromuscular conditions.(14)

Gene Therapy in Spinal Muscular Atrophy & Understanding Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a genetic disorder marked by progressive, symmetrical muscle weakness and atrophy, primarily affecting proximal muscles more than distal ones. It results from degeneration of motor neurons in the anterior horn of the spinal cord and lower brainstem. The most common form is caused by biallelic loss-of-function mutations in the *SMN1* gene, making SMA the leading genetic cause of infant death, with an estimated incidence of 8 per 100,000 live births.(12-15)

SMN1 is located on chromosome 5q13.2, which is why this form is also called 5q SMA. In about 94% of cases, patients

have homozygous deletions of exon 7, though other variants like nonsense, frameshift, splice site, and missense mutations have also been identified. Before the development of therapies that modify disease progression, SMA was classified into subtypes based on age of onset and severity of symptoms.(16)

In May 2019, the FDA approved onasemnogene abeparvovec-xioi, the first systemically delivered in vivo gene therapy for spinal muscular atrophy (SMA). This one-time intravenous treatment delivers *SMN* complementary DNA via a self-complementary AAV9 (scAAV9) vector, using a cytomegalovirus enhancer/chicken-beta-actin hybrid promoter for high expression. AAV9's ability to cross the blood-brain barrier and effectively target motor neurons makes it ideal for SMA. Its self-complementary design allows rapid gene expression without relying on host cell synthesis, which is crucial since motor neurons are non-dividing and long-lived.(17-18)

Preclinical trials in SMA mouse models showed dramatic improvements in survival—from a median of 15.5 days to over 250 days—when treatment was administered early, particularly on postnatal day 1. Delayed treatment showed reduced efficacy, likely due to AAV9 sequestration by maturing astrocytes. In clinical trials, all 15 infants with SMA Type 1 who had two *SMN2* copies and received the therapy between 0.9 and 7.9 months of age achieved event-free survival. In contrast, only 8% of untreated historical controls survived without long-term ventilatory support by 20 months, demonstrating the therapy's significant benefit.(19)

The clinical practice of gene therapy for Spinal Muscular Atrophy

Newborn screening for SMA has significantly improved early intervention, especially with gene therapy. Although SMA was added to the U.S. universal newborn screening panel in 2018, its nationwide implementation remains limited. Onasemnogene abeparvovec-xioi is approved for children under two without end-stage disease, but early trials focused on infants with two copies of *SMN2*. Confirmatory genetic testing is essential before treatment, along with screening for anti-AAV9 antibodies, as individuals with titers above 1:50 are ineligible. Cardiac monitoring through troponin I levels is also recommended. The therapy is administered intravenously over 60 minutes, followed by a 30-day course of prednisolone, with dosage adjustments based on lab results.(20-21)

Adverse effects can include elevated liver enzymes and vomiting, and the treatment carries a black box warning for potential liver injury. To limit viral exposure, caregivers and patients should practice strict hygiene and wear gloves for several weeks post-treatment. Although the viral vector does not cause disease, exposure may lead to immune sensitization against AAV9. Breastfeeding was restricted in early trials due to the possible transfer of maternal antibodies. Routine vaccines can be given at least one week before therapy, but live vaccines should be delayed until four weeks after steroid tapering.(22)

Gene Therapy in Duchenne Muscular Dystrophy & Understanding Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a severe, X-linked disorder caused by mutations in the *dystrophin* gene, leading to progressive muscle degeneration. It typically presents with early signs such as calf enlargement, waddling gait, delayed motor milestones, and use of the Gowers maneuver. DMD often results in loss of ambulation before age 13, while its milder counterpart, Becker muscular dystrophy (BMD), shows a broader phenotypic range. Diagnosis is confirmed through genetic testing, including exon deletion/duplication analysis and sequencing. Around 60–70% of cases involve exon deletions, with out-of-frame mutations usually resulting in severe DMD and in-frame deletions leading to milder BMD symptoms.(23)

Dystrophin provides structural stability to muscle cell membranes, and its absence causes muscle damage, fatty replacement, and poor regeneration.(24) DMD affects approximately 1 in 5,000–6,000 live male births and leads to multisystem complications due to both the disease and long-term corticosteroid use.(25) Cardiac involvement, including cardiomyopathy and conduction defects, along with respiratory insufficiency and gastrointestinal dysfunction, are common. The disease also affects bone health and growth, often resulting in short stature, obesity, and low bone mineral density. Orthopedic issues like scoliosis and contractures further complicate mobility.(26)

Additionally, neurodevelopmental and psychological challenges, such as ADHD, learning disabilities, autism, and mood disorders, are more frequent in DMD patients. Emotional distress is also common among caregivers. Due to the complex, multisystem nature of the disease, effective management requires a coordinated, multidisciplinary approach that includes neurology, cardiology, pulmonology, orthopedics, and mental health support to optimize patient outcomes and quality of life.(27-28)

Gene transfer for children with Duchenne Muscular Dystrophy.

Gene replacement therapy for Duchenne muscular dystrophy (DMD) aims to address the genetic defect by introducing a

functional copy of the dystrophin gene, often using AAV vectors. Modified micro-dystrophins, mimicking milder Becker muscular dystrophy mutations, have shown promise despite early trials failing to produce detectable expression due to vector limitations and immune responses. A recent phase 1/2a trial in four children demonstrated high micro-dystrophin expression, reduced creatine kinase levels, and improved motor function within a year, with only mild, temporary side effects like elevated liver enzymes. Additionally, surrogate gene therapies using AAV to upregulate utrophin or B4GALNT2 have shown encouraging preclinical results, but their clinical efficacy in children with DMD remains under investigation.(29)

Gene Therapy for Parkinson's disease:

Clinical trials for Parkinson's disease (PD) have explored three gene therapy strategies: delivering the gene for glutamic acid decarboxylase into the subthalamic nucleus, using neurturin to protect dopaminergic neurons in the putamen, and enhancing dopamine synthesis by boosting L-dopa conversion. Early trials in humans have shown encouraging outcomes for these approaches, offering hope for more targeted therapies in neurodegenerative diseases.(30)

Understanding complex or multifactorial diseases remains a challenge due to their origins in a combination of genetic and environmental influences, including diet, drug exposure, and pollutants. These conditions, such as type II diabetes, obesity, asthma, and coronary artery disease, often involve numerous genes, each contributing modestly, making inheritance patterns difficult to track. Despite this complexity, genome-wide association studies (GWAS) have successfully identified genetic markers tied to many such disorders.(31)

Parkinson's disease (PD) is the second most prevalent progressive neurological disorder, affecting around one million people in the United States. It occurs in about 1% of individuals over the age of 65, with roughly 50,000 new diagnoses annually. While no clear gender bias has been established, PD's clinical presentation is well defined, typically involving resting tremors, bradykinesia (slowness of movement), and balance impairment. These motor symptoms are primarily due to the degeneration of dopaminergic neurons in the nigrostriatal pathway.(32)

In the clinical setting, PD is considered both a movement disorder and a form of neurodegenerative pathology. A key hallmark is the presence of Lewy bodies abnormal aggregates of protein within neurons which are believed to contribute to dopamine neuron loss. Research in animal models suggests that, beyond the nigrostriatal system, dopaminergic activity in the striatum may also play a role in PD expression, indicating broader involvement within the brain's motor and reward systems.(33)

Though there is no cure for Parkinson's disease (PD), treatments such as dopamine agonists and levodopa can significantly ease motor symptoms. However, their long-term effectiveness and side effects remain debated. Fetal nerve tissue transplants have shown promise but yielded mixed results in clinical trials. Gene therapy has emerged as a promising alternative, particularly with glial cell-line derived neurotrophic factor (GDNF) delivered via lentiviral vectors, which have demonstrated neuroprotective effects in non-human primates. Similarly, tyrosine hydroxylase gene delivery has shown long-term dopamine restoration in animal models, offering potential for human application.(34)

Parkinson's pathology is complex, involving multiple environmental and genetic factors. Age remains the most consistent risk factor, with oxidative stress and mitochondrial dysfunction playing major roles. Mechanisms such as the oxidation of MPTP to MPP+ by MAO-B, and the generation of toxic peroxynitrite through nitric oxide pathways, contribute to neuronal damage. Additionally, misfolded α-synuclein and mutations in UCHL1 or parkin promote the formation of Lewy bodies. These cumulative molecular disruptions lead to progressive neuron loss, highlighting the need for early intervention.(35)

Gene Therapy for HIV

Gene therapy involves modifying genetic material to treat diseases. The first clinical trial in humans was conducted over two decades ago by Blaese and colleagues.(36) Since then, promising results have emerged, such as in the treatment of Leber's congenital amaurosis. Despite this progress, gene therapy still faces significant scientific and regulatory challenges before it can become a widely accepted and safe treatment. Currently, the U.S. FDA has not approved any gene therapy products for general commercial use, and most human applications remain experimental.(37)

While HAART has significantly improved life expectancy and quality of life for HIV-positive individuals, it is not without drawbacks. The therapy must be maintained for life, involves complex dosing schedules, and may cause side effects. Continuous monitoring of viral load and drug resistance is also required, and patients remain vulnerable to opportunistic infections. These limitations underscore the need for alternative

therapies, such as gene-based treatments, to offer more durable solutions.(38)

The recent announcement of an HIV cure has reignited interest in gene therapy as a pathway to achieving long-term, drug-free control of the virus. One promising approach involves genetically modifying hematopoietic stem cells (HSCs) and CD4+ T cells to block HIV entry. A major breakthrough occurred when an HIV-positive leukemia patient received an allogeneic stem cell transplant from a donor with a homozygous CCR5Δ32 mutation an alteration that renders cells resistant to HIV infection. Following the transplant, the patient remained HIV-free with undetectable viral levels and reduced HIV-specific antibodies, suggesting a potential cure. The unique HIV-resistant traits of individuals with the CCR5Δ32 mutation have inspired several gene therapy strategies aimed at replicating this protection in the broader population. Experimental efforts focus on blocking HIV entry, especially targeting CCR5, using techniques that mimic natural resistance. Encouraging results from early-stage trials show partial protection from HIV, suggesting a future where gene editing might offer durable, curative outcomes for patients without relying on lifelong antiretroviral therapy. (39)

CONCLUSION

Recent advances in gene therapy, including CRISPR-Cas9, base editing, and viral vector systems, have transformed the treatment of genetic and chronic diseases like sickle cell anemia, beta-thalassemia, and certain cancers. Emerging mRNA-based and in vivo gene editing approaches also show promise for conditions such as muscular dystrophy and neurodegenerative disorders. While challenges like immune reactions, off-target effects, cost, and ethical issues remain, ongoing research is steadily improving safety and efficacy. Gene therapy offers a potential shift from drug-based treatments to targeted, long-term solutions with fewer side effects, paving the way for wider clinical use and commercial viability in precision medicine.

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