KOZAKIEWICZ, Julia, OKOŃSKA, Aleksandra, KOŚCIELECKI, Kamil, KALISZ, Agnieszka, SKORULSKA, Iwona, MĄCZEWSKA, Klaudia, DŁUGOZIMA, Patrycja, GRZESZCZUK, Paulina, GRYWIŃSKA, Weronika, and GŁOWACKA, Aleksandra. Gene Therapy: A Revolution in Medicine or a Risky Game with our DNA?. Quality in Sport. 2025;39:58956. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2025.39.58956
https://apcz.umk.pl/QS/article/view/58956

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 19.02.2025. Revised: 27.02.2025. Accepted: 07.03.2025. Published: 07.03.2025.

Gene therapy: A revolution in medicine or a risky game with our DNA?

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ABSTRACT

Introduction: The aim of this review is to provide an overview of the applications of gene therapies in various diseases and to highlight areas where further research is needed.

Materials and methods: A review of chosen literature in the PubMed database was conducted, using the following keywords: „gene therapy", "SMA", "DMD", "Parkinson's Disease", "Huntington's disease"

Summary: Gene therapy can be useful in a variety of medical conditions, including Parkinson's disease, pulmonary hypertension, Wiskott-Aldrich syndrome, spinal muscular atrophy (SMA), Huntington's disease, Duchenne muscular dystrophy (DMD), and chronic pain management. Different gene therapy approaches, such as viral vector delivery, CRISPR-Cas9 gene editing, exon-skipping therapy, and antisense oligonucleotides (ASOs), have demonstrated potential in treating these diseases.

Conclusions: Gene therapy represents a groundbreaking advancement in medicine, offering hope for diseases that were once considered untreatable. Clinical trials have demonstrated encouraging outcomes in treating neurodegenerative and genetic disorders. Future developments in gene editing tools, improved vector systems, and targeted delivery methods will be crucial in enhancing the efficacy of gene therapy.

Keywords: „gene therapy", "SMA", "DMD", "Parkinson's Disease", "Huntington's disease"

Introduction

Gene therapy is an innovative treatment method that involves inserting or modifying genetic material into a patient's cells to treat or prevent disease. Rather than treating the symptoms of a disease, gene therapy aims to address its cause by changing the way the body's cells function. Gene therapy usually introduces improved genetic material that can:

replace a damaged or missing gene - in the case of genetic diseases such as cystic fibrosis, hemophilia [1] or muscular dystrophy, where the patient has a defect in one of the genes. Fix a defective gene - in situations where a mutation in a gene leads to the production of an abnormal protein that causes a disease or introduce a new gene - which can produce the missing protein or substances that help treat the disease. Methods of delivering genes to cells may include: Viral

vectors- the use of modified viruses that can insert genes into human cells [2]. Non-viral methods such as nanoparticles, liposomes or electroporation, where DNA is introduced into cells using physical or chemical technologies. [3,4] Gene therapy is particularly promising for the treatment of genetic diseases, cancer, and in some cases of viral infections (such as HIV) [5] However, this form of treatment is still in clinical trials, and its efficacy and safety are still being thoroughly tested. Although gene therapy has great potential, it also comes with challenges, such as: cost, safety, long-term efficacy. Despite these difficulties, gene therapy is one of the most exciting areas of modern medicine, offering hope for treating previously incurable diseases.

The aim of this article is to provide an overview of the latest advancements, mechanisms, and applications of gene therapies in various medical fields, to explore new technologies, innovative delivery methods, and potential future directions in gene therapy and to highlight areas where further research is needed, helping guide future studies. To find relevant articles, we conducted a literature review of the latest works available in bibliographic databases such as PubMed, Google Scholar, and Web of Science. We used the following keywords and their combinations: „gene therapy", "SMA", "DMD", "Parkinson's Disease", "Huntington's disease". Based on the collected data and relevant literature, this work will serve as a foundation for advancing understanding of gene therapy.

Parkinson's Disease

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder, affecting an estimated 5.8 million people worldwide. [6] It is characterized by a gradual and asymmetric onset of motor symptoms, including muscle rigidity, gait disturbances, hypokinesia, and tremors, along with a range of non-motor symptoms such as cognitive impairment, emotional disturbances, sleep abnormalities, and autonomic dysfunction. [7] The primary driver of PD's motor symptoms is the progressive loss of dopaminergic neurons in the substantia nigra, leading to disrupted neuronal activity within the basal ganglia–thalamocortical circuit. [8] Current treatment strategies focus on dopamine replacement therapy, which, while effective in managing symptoms, is associated with side effects and does not slow disease progression. As neurodegeneration progresses, the efficacy of pharmacological treatments is reduced. Gene therapy is emerging as a promising avenue for improving therapeutic outcomes. Glucosylceramidase (GCase), an essential lysosomal enzyme encoded by the GBA1 gene,

facilitates the breakdown of glucosylceramide (GluCer) into glucose and ceramide. A deficiency in GCase activity leads to the accumulation of GluCer, glucosylsphingosine (GluSph), and other glycolipids, triggering cellular toxicity and inflammation.[9] Mutations in GBA1 are found in approximately 5% to 25% of PD patients, with up to 30% of carriers developing PD by the age of 80. [10,11] Gene therapy approaches using adeno-associated virus (AAV) vectors to deliver a functional GBA1 gene have demonstrated therapeutic efficacy in various PD animal models. [12-14] Adeno-associated viruses (AAVs) are classified into serotypes based on their capsid characteristics. Within the brain, viral vector particles can travel between regions through different pathways: anterograde transport, where cells in areas receiving projections from the injection site are transduced; retrograde transport, where cells in regions projecting to the injection site are transduced; or a combination of both. The specific transport mechanism is influenced by the serotype and, in preclinical studies, by the species being transduced. [15] Ongoing clinical studies are now exploring whether increasing GCase activity could slow or halt the progression of PD. [16] Moreover with the advent of CRISPR-Cas9 technology, gene editing has become a theoretical possibility for targeting genetic mutations associated with familial Parkinson's disease (PD). This system, which utilizes "clustered regularly interspaced short palindromic repeats" (CRISPR) along with the Cas9 endonuclease, enables the induction of double-stranded DNA breaks, allowing for precise genetic modifications. [17,18] Mutations in several genes, including parkin, LRRK2, SNCA, PINK1, DJ-1, VPS35, DNAJC13, and CHCHD2, have been linked to familial forms of PD. [19] A potential therapeutic approach involves the delivery of CRISPR-Cas9 constructs via brain region-specific injections in adult patients to correct mutations responsible for localized disease pathology. [20] Therapeutic approaches for gene replacement or supplementation in neurodegenerative brain disorders are continuously evolving, driven by advancements in understanding key aspects of the underlying molecular pathophysiology.

Pulmonary Hypertension

Pulmonary hypertension (PH) is a progressive, complex, fatal disease with multiple etiologies. Hyperproliferation and resistance to apoptosis of cells contribute to the pathogenesis of pulmonary vascular bed remodeling leading to the development of pulmonary hypertension. The development of safe and effective gene therapies will restore or reduce the expression of genes, generally involved in the etiology of the disease. Recent advances in genetic approaches have led to the discovery of genes and genetic loci responsible for the predisposition or onset

of PH. The introduction of exogenous genetic material into vascular cells offers great hope for treatment. Various gene delivery strategies, including intranasal, intravenous, endotracheal instillation or aerosol, have previously been used but have been characterized by low efficiency and difficulty in overcoming obstacles due to the pulmonary-air barrier, the pulmonary-blood-barrier, the inflammatory response and limited duration . [21] Achieving precise delivery of genetic material to specific sites of the pulmonary vasculature in the multidimensional structure of complex lung tissue is another aspect of successful gene therapy and remains an unmet goal. [22]

Wiskott-Aldrich Syndrome

Wiskott-Aldrich syndrome is an X-chromosome-associated disease characterized by thrombocytopenia, eczema, immune deficiency and increased risk of autoimmune diseases and cancer. The disease has its basis in mutations in the WASp gene that lead to impaired or abolished expression of the WAS protein (WASP), a hematopoietic regulator of actin cytoskeleton remodeling. Ex vivo gene therapy (GT) is a valuable therapeutic alternative. Compared with allogeneic hematopoietic stem cell transplantation (HSCT) , GT is an autologous procedure that carries a negligible risk of rejection or graft-versus-host disease and does not require immunosuppression .Thirty-four patients with WAS were treated worldwide, with a median follow-up of 3.3 to 7.8 years, depending on the center . Three of the 34 patients died from diseases unrelated to the GT product. No serious adverse events occurred and no treated patient developed clonal selection, insertional mutagenesis, leukemia or replication-competent LV to date. All surviving patients (31 of 34 [91%]) showed sustained multilineage gene-corrected cell engraftment, with higher gene labeling and WASP expression in T cells and other lymphoid cellsAll patients showed improvement or resolution of eczema. Platelet counts improved variously after GT, but remained below normal in most patients.The improvement in thrombocytopenia resulted in protection from major bleeding, and no need for transfusions or thrombopoietin agonists.GT has proven to be an effective treatment for WAS.Available data from recent clinical trials of GT show the safety and efficacy of this therapeutic approach in the short to medium term; however, much time and research must pass for gene therapy to be recognized as a safe and effective form of treatment. [23]

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterized by the progressive weakening and atrophy of proximal skeletal muscles due to lower motor neuron degeneration. The condition affects approximately 1 in 10,000 to 20,000 live births, with a carrier frequency ranging from 1 in 40 to 1 in 70 in the general population. [24] SMA is caused by mutations in the SMN1 and SMN2 genes. According to the first report by Lefebvre et al., a complete absence of SMN1 (homozygous deletion) was identified in 226 out of 229 SMA patients (98.7%), regardless of their clinical subtype, while intragenic mutations in SMN1 were found in 3 patients (1.3%). [25] The severity of symptoms varies based on the number of SMN2 gene copies, ranging from severe neonatal muscle weakness with respiratory failure—often resulting in death before the age of two—to mild proximal lower limb weakness in adulthood. Traditionally, spinal muscular atrophy (SMA) has been categorized into Types 0 to 4. However, these classifications are evolving due to the implementation of newborn screening programs and the early, presymptomatic use of SMN-restoring therapies. [26] The loss of SMN1 function leads to the degeneration of alpha motor neurons, which are responsible for controlling voluntary muscle movements. The survival motor neuron (SMN) protein plays a critical role in spliceosome assembly and ribonucleoprotein biogenesis. Recent research has expanded its known functions to include mRNA trafficking, local translation, cytoskeletal regulation, endocytosis, and autophagy. Consequently, SMN protein deficiency disrupts the homeostasis of motor neurons, contributing to disease progression. [27] Onasemnogene abeparvovec, marketed as Zolgensma, is a gene therapy approved by the U.S. Food and Drug Administration (FDA) for treating SMA in pediatric patients under the age of two. This therapy is administered as a single-dose, preservative-free intravenous infusion of a non-replicating, self-complementary adeno-associated virus 9 (AAV9) vector, which crosses the blood-brain barrier. Zolgensma delivers a functional copy of the SMN1 gene under the control of a cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB). One of its adeno-associated viral (AAV) inverted terminal repeats (ITRs) has been engineered to facilitate the formation of a double-stranded transgene, ensuring efficient transcription. By restoring normal SMN protein levels, this therapy helps maintain cellular homeostasis and supports motor neuron function. [28] Zolgensma demonstrated strong efficacy in clinical trials, achieving a high response rate and significant symptom improvement. [29-32] In terms of safety, trial results primarily indicated

elevated liver transaminase levels, necessitating the use of prednisolone alongside onasemnogene abeparvovec. [29,33,34]

Pain Treatment

Pain treatment is extremely important, as pain has a huge impact on a person's quality of life. Chronic pain not only leads to physical suffering, but can also cause psychological problems, such as depression or anxiety, and prevents normal functioning at work, in the family and in society. It is worth noting that opioid use disorder contributes to hundreds of deaths per day, so gene therapy may be an alternative to chronic pain pharmacotherapy in the future. There are various gene therapy strategies, including ASOs, small interfering RNA (siRNA), optogenetics, chemogenetics, and CRISPR, and their delivery methods targeting primary sensory neurons and non-neuronal cells, including glia and chondrocytes. Targeting peripheral and central nociceptive neurons is a key point of gene therapy. [35] However, this carries some limitations because the path of pain development is very complicated and complex.

Huntington’s Disease

Huntington's disease is a disease of the nervous system with a genetic basis, in which the main symptoms are chorea, dementia and personality disorders. The course of the disease is progressive and leads to irreversible changes in the brain.The cause is an autosomal dominant mutation in the huntingtin gene.

The occurrence of toxic intranuclear aggregates is considered to be the most important pathogenetic factor in the symptoms of Huntington's disease. Causal treatment is currently not possible,therefore, many patients put their hope in new treatment methods, especially gene therapy. Tominersen is an antisense oligonucleotide that interacts with mutant huntingtin RNA and induces their degradation. However, the study with this molecule was discontinued due to indications of an unfavorable benefit-risk ratio. AMT-130 is a DNA sequence encoding miRNA that is delivered to target cells using an adenovirus (AAV). The consequence is a reduction in huntingtin synthesis. The first results obtained in a group of patients confirm the safety of this treatment method. After several months, a 53.8% reduction in mutant huntingtin was observed in treated patients in the cerebrospinal fluid.

PTC518 and Branaplam are splicing modulating molecules. [36] It is worth remembering that the huntingtin protein performs important physiological functions in the nervous system. Therefore, lowering huntingtin levels too much may cause side effects. Another issue that

carries certain limitations is the location of the pathomechanisms of this disease, i.e. in the striatum and cerebral cortex - areas of the brain where the motor and cognitive symptoms of the disease probably arise. Therefore, gene therapy should be strictly targeted at these areas. Currently, many clinical trials are underway which give hope for finding an effective method of treating Huntington's disease.

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is one of the most prevalent inherited neuromuscular disorders (NMDs) in children, with an estimated incidence of 1 in 3,500 to 5,000 newborn boys. It is characterized by the early onset of progressive muscle weakness, motor delays, and eventual loss of ambulation. DMD is caused by mutations in the dystrophin gene, leading to either the complete absence or structural abnormalities of the dystrophin protein. Without functional dystrophin, the integrity and function of myofibers are compromised, disrupting normal muscle growth and development. [37] Since the dystrophin gene is located on the X chromosome, DMD primarily affects male children, while females typically remain asymptomatic carriers. [38] Due to its large size, the dystrophin gene is highly susceptible to mutations, including deletions (~60%), duplications (~6%), translocations, and point mutations, many of which disrupt the reading frame, leading to the production of truncated and nonfunctional dystrophin proteins. However, in some cases, the reading frame can be restored, allowing the synthesis of partially functional dystrophin. [39] Exon-skipping therapy is a promising strategy for treating approximately 60% of DMD patients. To date, four antisense oligonucleotide (ASO) therapies based on phosphorodiamidate morpholino oligomer (PMO) chemistry have received FDA approval. These include ExonDys-51 (targeting exon 51), VyonDys-53 and Viltolarsen (targeting exon 53), and AmonDys-45 (targeting exon 45). However, these treatments result in only modest dystrophin production, with levels increasing by approximately 0.4% to 5% after prolonged treatment. [40] Another therapeutic approach involves small-molecule drugs targeting nonsense mutations. Ataluren, an orally available compound that promotes ribosomal readthrough of premature stop codons, has been evaluated in two randomized, double-blind, placebo-controlled trials. While these trials did not meet the primary endpoint of improving the 6-minute walk test (SMWT) over 48 weeks compared to placebo, they demonstrated a clear trend toward therapeutic benefit, with a 29-meter improvement in SMWT distance and enhanced performance in timed functional tests in the ataluren-treated group. [41,42] So far ataluren developed by PTC Therapeutics was

conditionally approved in the European Union in 2014 for the treatment of ambulatory nonsense mutation DMD patients aged 5 years and older. [43] The effectiveness of Ataluren treatment is influenced not only by disease severity but also by the patient's age at the start of therapy. A 2018 study found the greatest improvement in a patient who began Ataluren therapy at the age of five. [44] Additionally, the treatment response was evaluated in a 25-year-old symptomatic female carrier of DMD with a nonsense mutation in the dystrophin gene. The patient received Ataluren at a dose of 2250 mg/day, reporting subjective improvements in well-being and strength. The patient experienced enhanced motor function, including regaining the ability to walk without support. [45]

Summary and conclusions

Gene therapy represents a revolutionary approach in modern medicine, offering significant promise for treating various genetic, neurodegenerative, and rare diseases. The research presented in this paper highlights the advancements in gene therapy applications, including its potential for conditions such as Parkinson's disease, pulmonary hypertension, Wiskott-Aldrich syndrome, spinal muscular atrophy, chronic pain, Huntington's disease and Duchenne muscular dystrophy. Several key conclusions can be drawn from the findings. Gene therapy has shown considerable success in addressing the root causes of genetic disorders. Approaches such as viral vector delivery, CRISPR-Cas9 gene editing, and exon-skipping therapies have demonstrated the ability to restore or correct defective genes, offering hope for conditions that were previously considered untreatable. Clinical trials and experimental treatments have provided encouraging results. For example, adeno-associated virus (AAV)-based gene therapy in Parkinson's disease has demonstrated neuroprotective effects, while Zolgensma, a gene therapy for spinal muscular atrophy, has proven to be highly effective in preserving motor function and improving survival rates. Similarly, gene therapy for Wiskott-Aldrich syndrome has shown sustained correction of genetic defects with long-term benefits. Long-term safety and efficacy data are still being collected for many therapies. Advances in gene editing tools, such as CRISPR-Cas9, open new avenues for precise genetic modifications, particularly in neurodegenerative diseases. Furthermore, improved vector design, tissue-specific targeting, and novel delivery methods will likely enhance the efficacy and safety of gene therapy in the coming years. Research in non-viral delivery systems and optimized genome integration strategies may address current limitations. While challenges remain, the progress in this field underscores the potential of gene therapy as a groundbreaking tool in personalized medicine.

Disclosure

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Receiving funding - no specific funding.

All authors have read and agreed with the published version of the manuscript.

Financing statement

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflict of interest

The authors deny any conflict of interest.

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