Journal of Stem Cell Research

Genesis-JSCR-6(1)-69
Volume 6 | Issue 1
Open Access
ISSN: 2582-8797

Advances in Gene Therapy for Respiratory and Renal Diseases

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Citation: Ferreira DP, Silvaa ALD and Morales MM. Advances in Gene Therapy for Respiratory and Renal Diseases. J Stem Cell Res. 6(1):1-23.

Received: February 17, 2025 | **Published**: February 28, 2025

Abstract

Background: Respiratory and kidney diseases pose substantial challenges to global health, contributing significantly to morbidity and mortality worldwide. Current therapies for these diseases often focus on managing symptoms and decelerating disease progression, but they often fall short in addressing the genetic and molecular roots of these conditions. Gene therapy, which involves correcting or modifying genetic material to treat or prevent disease, has emerged as a promising approach for targeting both respiratory and kidney conditions.

Methods: This review explores the recent advances in gene therapy that apply to respiratory and kidney disorders, with emphasis on innovative nanotechnology for gene delivery, emerging therapeutic targets, and the hurdles that must be overcome for clinical translation.

Conclusion: The increasing number of efficient and safe gene therapy products highlights the significant therapeutic potential of this approach, offering durable and targeted solutions for treating respiratory and renal diseases. Ongoing advancements in delivery technologies and research efforts are crucial for overcoming current challenges and translating these therapies into widespread clinical applications.

DOI: *https://doi.org/10.52793/JSCR.2025.6(1)-69*

Keywords
Gene therapy; Kidney disease; Respiratory diseases; Monogenic diseases; Recombinant adeno-associated viral vectors; AAV-based therapies; Adeno-associated virus.

Abbreviations

- **AAT:** alpha-1 antitrypsin
- **AATD:** alpha-1 antitrypsin deficiency
- **AAV:** adeno-associated virus
- **CF:** cystic fibrosis
- **CFTR:** cystic fibrosis transmembrane conductance regulator
- **CKD:** chronic kidney disease
- **COPD:** chronic obstructive pulmonary disease
- **Cas9:** CRISPR-associated protein 9
- **CRISPR:** clustered regularly interspaced short palindromic repeats
- **ESKD:** end-stage kidney disease
- **FDA:** US Food and Drug Administration
- **FEV1:** forced expiratory volume in 1 second
- **HSCs:** hematopoietic stem cells
- **IPF:** idiopathic pulmonary fibrosis
- **LNPs:** lipid nanoparticles
- **PH1:** primary hyperoxaluria type 1
- **PKD:** polycystic kidney disease
- **rAAV:** recombinant adeno-associated viral vectors
- **siRNA:** small interfering RNA
- **TGF-β:** transforming growth factor beta
- **UABCs:** upper-airway basal stem cells

Introduction

Respiratory diseases such as cystic fibrosis (CF), asthma, and chronic obstructive pulmonary disease (COPD), as well as kidney diseases such as chronic kidney disease (CKD) and polycystic kidney disease (PKD), affect millions worldwide. These conditions impose significant global health and economic burdens, and existing treatments primarily manage symptoms rather than address the root causes [1,2].

Gene therapy offers a groundbreaking approach to treating these disorders by directly targeting genetic mutations and molecular dysregulations, aiming to halt or reverse disease progression instead of merely alleviating symptoms. This paradigm shift holds significant promise for treating a wide range of conditions, particularly rare diseases with limited or no therapeutic options under standard care [3]. As clinical trials validate its efficacy and regulatory approvals increase, gene therapy is transitioning from experimental to mainstream, offering hope for diseases previously deemed untreatable [4].

Mechanisms of Gene Therapy

Gene addition and genome editing

Early gene therapy strategies focused primarily on gene addition, whereby a functional copy of a defective gene is introduced to restore its normal function. This approach has shown success in treating specific monogenic diseases, such as severe combined immunodeficiency due to adenosine deaminase deficiency, inherited retinal dystrophy caused by RPE65 mutations, spinal muscular atrophy type I, β-thalassemia, hemophilia A and B, and Duchenne muscular dystrophy [5].

Although effective, gene addition therapy is limited to recessive disorders, because it does not correct dominant mutations or modify existing genes [6]. To address these limitations, advancements in genome editing technologies have revolutionized the field of gene therapy by allowing precise alterations directly at the DNA level. Tools such as zinc-finger nucleases, transcription activator-like effector nucleases, and the widely known CRISPR–CRISPR-associated protein 9 (Cas9) system are now at the forefront of therapeutic innovation [7]. These approaches work by introducing a DNA double-strand break at the specific location of the disease-causing mutation, enabling the repair process through non-homologous end joining or homology-directed repair pathways [8, 9]. Such precision is particularly beneficial for treating dominant monogenic disorders, where simply adding a wild-type gene copy would not be effective.

A notable advancement within the CRISPR–Cas9 system is base editing, a method in which Cas9, an RNA-guided DNA endonuclease, is fused to a cytidine or adenine deaminase enzyme. This innovative configuration enables precise base pair conversions, such as converting adenine to inosine (interpreted by the cell as guanine) or cytidine to uridine, facilitating targeted genetic modifications without the need for double-strand breaks [10]. Another significant breakthrough is prime editing, a technique that uses a Cas9 nickase combined with a specialized prime editing guide RNA, allowing precise insertions, deletions, or nucleotide substitutions without double-strand breaks [11]. These advancements in genome editing enhance precision and safety, minimizing the risks associated with traditional CRISPR-induced cuts [12]. On November 16, 2023, the UK Medicines and Healthcare Products Regulatory Agency approved exagamglogene autotemcel as the first genome editing-based therapy for severe sickle cell disease and transfusion-dependent β-thalassemia, marking a milestone in clinical gene editing [13, 14].

Delivery systems

A crucial factor in the success of gene therapy is the safe and efficient delivery of therapeutic genetic material into target cells. This can be achieved using either viral or non-viral (synthetic) vectors [15].

Viral vectors leverage naturally evolved mechanisms to efficiently target cells, enter them, and transport genetic material to the nucleus, where gene expression occurs. These vectors have been engineered from viruses such as adenovirus, adeno-associated virus (AAV), and lentivirus to optimize DNA or RNA delivery [16].

Recombinant adeno-associated viral vectors (rAAV) are widely favored in gene therapy due to their low immunogenicity and ability to achieve long-term gene expression without integrating into the host genome [17].

Advances in rAAV technology, such as tyrosine-mutant capsids, have further enhanced their efficiency by reducing ubiquitin/proteasome-mediated degradation and increasing transduction rates. For example, in preclinical studies, a Y733F-mutant AAV8 vector demonstrated efficient delivery of pigment epithelium-derived factor to mouse lungs, achieving high transgene expression without adverse effects [18]. Similarly, tyrosine-mutant AAV9 vectors improved pulmonary transgene delivery by 30% compared with their wild-type counterparts and reduced inflammatory responses [19]. A study with AAV8 capsids reported that a single tyrosine mutation enhanced transduction efficiency while preserving lung mechanics and safety in murine models [20].

Studies conducted by our group have further explored the potential of AAV vectors for pulmonary applications. Tyrosine-mutant rAAV vectors demonstrated enhanced transduction in CF bronchial epithelial cells, overcoming intracellular trafficking barriers [21]. Repeated administration of rAAV5 to murine airways did not induce inflammatory, mechanical, or morphometric changes, supporting its safety profile, although a decrease in transgene expression was observed over time [22]. Conversely, rAAV2 induced a discrete inflammatory response in preclinical models, particularly after the second dose, with increased airway and parenchymal cellularity and alveolar collapse. These effects diminished over time [23]. Despite its safety, AAV2 was less efficient than AAV8 and AAV9 in pulmonary gene delivery. These findings highlight the importance of serotype selection and capsid optimization to maximize efficacy and safety in pulmonary gene therapy.

Several AAV-based therapies have demonstrated clinical success, leading to US Food and Drug Administration (FDA) approvals. Alipogene tiparvovec (Glybera), approved in the European Union in 2012 (but withdrawn in 2017), was an AAV1-based therapy targeting lipoprotein lipase deficiency through lipoprotein lipase gene delivery [24]. Voretigene neparvovec (Luxturna), approved in 2017, uses AAV2 to deliver the RPE65 gene to treat RPE65 mutation-associated retinal dystrophy [25]. Another AAV-based therapy, onasemnogene abeparvovec (Zolgensma), approved in 2019, uses AAV9 to treat spinal muscular atrophy by delivering the *SMN1* gene [26]. Etranacogene dezaparvovec (Hemgenix), approved in 2022, utilizes AAV5 to transfer the FIX-Padua gene to address hemophilia B [27]. Valoctocogene roxaparvovec (Roctavian) gained FDA approval in 2023 for hemophilia A, relying on AAV5 to deliver the Factor VIII gene [28]. Eladocagene exuparvovec (Upstaza), approved in the European Union in 2022, is the first gene therapy designed for direct delivery to the brain. It uses an AAV2 vector to deliver a functional DDC gene, addressing aromatic L-amino acid decarboxylase deficiency by restoring neurotransmitter levels and improving motor function [29]. As this review was being written in November 2024, this therapy was also approved by the FDA under the US trade name Kebilidi, further expanding its availability [30].

Adenoviral vectors are commonly used for their ability to efficiently infect a wide range of cells and their relatively large cargo capacity, despite their high immunogenicity [31]. Gendicine is one such therapy, approved in China in 2003, and used to treat head and neck squamous cell carcinoma. This therapy uses adenovirus type 5 to deliver the p53 gene, a critical tumor suppressor [32]. Another product, H101 (Oncorine), also based on adenovirus type 5, is approved in China for treating head and neck, liver, and esophageal cancers. It specifically targets cancer cells that lack the E1B gene, which is essential for viral replication in normal cells [33]. Alferminogene tadenovec or Ad5FGF-4 (Generx), which delivers fibroblast

growth factor-4 via adenovirus type 5, is undergoing clinical trials (NCT02928094) to assess its efficacy for coronary artery disease [34].

Betibeglogene autotemcel (Zynteglo), approved in the European Union in 2019 and the United States in 2022, is a milestone in gene therapy for β-thalassemia. This therapy utilizes a lentiviral vector to insert a functional β-globin gene into hematopoietic stem cells, enabling patients to produce normal hemoglobin levels [35]. Elivaldogene autotemcel (Skysona), FDA-approved in 2022, is a gene therapy for early cerebral adrenoleukodystrophy, utilizing lentiviral vectors to modify hematopoietic stem cells (HSCs) and restore the production of functional ABCD1 protein, mitigating neurologic damage [36]. Atidarsagene autotemcel (Libmeldy) was approved by the FDA in 2024 for treating metachromatic leukodystrophy, a rare neurodegenerative disorder. This therapy corrects the deficiency of the ARSA gene, preventing toxic sulfatide accumulation in the nervous system and slowing disease progression [37]. In cancer immunotherapy, CAR T-cell therapies such as tisagenlecleucel (Kymriah) (approved in 2022) and axicabtagene ciloleucel (Yescarta) (approved in 2017) use lentiviral vectors to modify patient T cells, equipping them with chimeric antigen receptors that enhance their ability to target and eliminate cancer cells [38].

Although effective for gene delivery, viral vectors have several drawbacks that limit their use. One major issue is immunogenicity, which can trigger host immune responses that reduce the vector's effectiveness and complicate repeat treatments. There is also the risk of insertional mutagenesis, particularly with integrating vectors such as lentiviruses, which cause unintended genetic modifications, potentially leading to oncogenesis. In addition, the limited cargo capacity of viral vectors restricts their application to therapies requiring large genes [31]. Furthermore, pre-existing immunity to common viruses can reduce their effectiveness in some patients [39]. Other challenges include high production costs, potential transgene silencing, and off-target effects [40].

Alternatively, synthetic vectors such as nanoparticles, especially polymer-based and lipid nanoparticles (LNPs), have emerged as powerful tools for the delivery of gene therapy. They offer several advantages, including reduced immunogenicity, higher flexibility in targeting, and the ability to carry larger genetic cargoes, such as CRISPR-Cas9 systems and a wide range of therapeutic agents [41,42]. They also avoid the risk of genome integration, making them safer in some contexts. Furthermore, nanoparticles are easier to produce at scale, which lowers costs and increases accessibility to gene therapies [43].

One notable example is on pattro (Patisiran), which uses LNPs to deliver small interfering RNA (siRNA) to the liver for the treatment of hereditary polyneuropathy of transthyretin amyloidosis. Approved by the FDA in 2018, onpattro silences the TTR gene, effectively reducing amyloid deposits [44,45]. Similarly, givlaari (Givosiran), approved in 2019, uses LNPs to target ALAS1, alleviating symptoms of acute hepatic porphyria [46]. Another product, leqvio (Inclisiran), approved in 2021, utilizes LNPs to lower low-density lipoprotein cholesterol by inhibiting *PCSK9* with siRNA [47]. The well-known mRNA COVID-19 vaccines from Pfizer-BioNTech and Moderna also rely on LNPs to deliver mRNA, encoding the spike protein of SARS-CoV-2, providing immunity against the virus [48]. Fitusiran, an investigational LNP-based therapy for hemophilia A and B, uses siRNA to reduce antithrombin levels and enhance thrombin production to prevent bleeding episodes. During its phase 3 clinical trial (NCT03754790), 66% of participants reported no bleeding episodes over 9 months, although mild liver complications and two instances of blood clots

were observed as side effects. The FDA, which granted Breakthrough Therapy Designation to fitusiran for hemophilia B with inhibitors in December 2023, is expected to issue its approval decision by March 2025 [49].

Gene Therapy for Respiratory Diseases

Respiratory diseases have long been attractive targets for gene therapy due to the relative ease of delivering treatments directly to the lungs through nebulizers or aerosols [50]. Among these, monogenic disorders such as CF stand out as particularly promising candidates because of their well-characterized genetic basis. CF results from mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene, causing the production of thick, sticky mucus that impairs the function of the lungs and digestive system [51]. The primary gene therapy approach for CF involves replacing the defective CFTR gene.

Early clinical trials utilizing viral vectors, such as AAVs and lentiviruses, have shown potential. However, efficiency in delivering genetic material to airway epithelial cells and achieving significant correction levels remains challenging.

In 2003, Flotte et al. reported the first human trial using rAAV for the treatment of CF in 25 patients with mild to moderate lung disease. The rAAV-CFTR vector (tgAAVCF) was delivered at varying doses to the nose and lungs. Several adverse events occurred, but most were attributed to pre-existing CF conditions or procedural effects, with only one serious event potentially linked to the vector. Minimal vector shedding was noted, and neutralizing antibodies were detected in patients who received the highest doses. Gene transfer was observed only in later cohorts with low-level transfer [52].

Recent clinical trials, such as the ongoing phase 1/2 study of 4D-710 (NCT05248230) from 4D Molecular Therapeutics, offer a novel approach to addressing these issues. This therapy uses a modified AAV capsid variant designed for enhanced targeting of lung cells and carries a CFTR transgene variant optimized for clinical efficacy (CFTRΔR). Administered via aerosol, the treatment has demonstrated encouraging safety profiles and dose-dependent improvements in pulmonary function. The study is expected to progress to a phase 2 dose expansion stage by late 2024, with an estimated completion date of January 2030.

In light of the limitations associated with viral vectors, advances in non-viral delivery systems, particularly nanoparticles, have emerged as safer and more versatile alternatives [53].

A phase 2b trial (NCT01621867) evaluated the efficacy of non-viral CFTR gene therapy in patients with CF, using plasmid DNA encoding the CFTR gene complexed with a cationic liposome (pGM169/GL67A), delivered via nebulization every 28 days for 1 year. The study included patients aged 12 years or older with 50%–90% predicted forced expiratory volume in 1 second (FEV1) and any combination of CFTR mutations. One hundred forty patients were randomly assigned to either gene therapy or placebo (saline), with stratification by FEV1, age, trial site, and inclusion in a mechanistic sub study. At the 12-month follow-up, the pGM169/GL67A group showed a modest but statistically significant improvement in FEV1 (3.7%, 95% confidence interval, 0.1–7.3; p=0.046) compared with placebo, reflecting stabilization of lung function in the gene therapy group versus decline in the placebo group, with no significant difference in treatment-related adverse events [54]. Although the findings demonstrate the potential of monthly gene

therapy to stabilize lung function, further enhancements in efficacy and response consistency are necessary before clinical application, and these results encourage the advancement of potent gene transfer vectors into early-phase trials.

CRISPR-Cas9 technology has emerged as a promising tool for directly correcting CFTR mutations at the DNA level. Preclinical studies have demonstrated the successful use of CRISPR to correct CFTR mutations in both cell cultures and animal models, bringing hope for a permanent cure for CF in the future [55].

A study used Cas9 complexed with MS-sgRNA, delivered by AAV6, to correct the DF508 mutation in upper-airway basal stem cells (UABCs) and human bronchial epithelial cells from patients with CF, achieving 30%–50% allelic correction and 20%–50% restoration of CFTR function in differentiated airway cells. Corrected UABCs maintained their ability to differentiate when embedded on a porcine small intestinal submucosal membrane, supporting the potential of genetically corrected autologous stem cell transplants for CF treatment. The findings offer a platform for further optimization of UABC transplantation into the airways as a therapeutic approach for CF [56].

Unlike monogenic disorders, diseases influenced by a combination of genetic and environmental factors are more challenging to treat; respiratory conditions such as asthma and COPD are examples of multifactorial diseases.

Chronic Obstructive Pulmonary Disease

COPD is a progressive lung condition characterized by persistent breathing difficulties due to airflow obstruction. It primarily encompasses two main conditions: chronic bronchitis and emphysema, although patients often exhibit features of both [57]. COPD is usually caused by long-term exposure to irritants such as cigarette smoke, air pollution, or occupational hazards (e.g., dust and chemicals). Over time, these irritants damage the lungs and airways, leading to inflammation, excess mucus production, and narrowed airways, making it hard for air to flow in and out of the lungs [58].

Emphysema

Emphysema refers specifically to damage to the alveoli, the tiny air sacs in the lungs where gas exchange occurs. In emphysema, the walls of the alveoli weaken and eventually rupture, reducing the surface area available for oxygen and carbon dioxide exchange. This loss of elasticity in the lungs causes air to become trapped, making it difficult to fully exhale, leading to shortness of breath [59]. Emphysema is often linked to smoking but can also be caused by genetic factors, such as a deficiency in the enzyme alpha-1 antitrypsin (AAT), which can cause early-onset emphysema [60, 61].

AAT is a protein that protects the lungs from damage caused by enzymes such as neutrophil elastase. A deficiency of this protective protein (AATD) permits unregulated damage to the alveoli, resulting in emphysema. Gene therapy for AATD involves delivering a functional copy of the AAT gene to lung cells, allowing them to produce the protective protein and prevent further damage [62]. AAVs or lentiviral vectors are often used to deliver the gene to targeted cells.

Based on a previous trial using rAAV1-CB-hAAT vector, which provided sustained normal M-AAT expression for more than a year in patients with AATD (NCT00430768) [63], a phase 2 clinical trial (NCT01054339) was conducted using the same vector, but produced by a herpes simplex virus-1 helper

system to increase transgene expression. This trial involved intramuscular injections of the vector at doses of 6.0×10^{11}, 1.9×10^{12}, and 6.0×10^{12} vector genomes (vg)/kg, administered to nine individuals with AATD (three patients per dose). The serum levels of M-AAT were dose-dependent, peaking at a tenfold increase by day 30 compared with the phase I trial, and remained increased for at least 90 days. However, these levels did not achieve the target therapeutic threshold of >570 g/mL. The vector was well tolerated with no serious adverse events reported; although immune responses were noted against the AAV vector, there was no response to the AAT transgene [64]. A subsequent follow-up revealed that AAT expression remained sustained for 5 years after intramuscular injections, which was later attributed to the presence of AAV1 capsid-specific regulatory T cells at the injection site. In addition, some improvement in disease-related neutrophil deficiencies was observed [65].

Although augmentation therapies are encouraging, improvements in vector design and delivery methods are necessary to reach therapeutic AAT levels in serum and achieve meaningful functional benefits [66].

In July 2024, Intellia Therapeutics, Inc. received approval from the UK's Medicines and Healthcare Products Regulatory Agency to commence a phase 1/2 clinical trial for NTLA-3001 (NCT06622668), a CRISPR/Cas9-based gene therapy aimed at delivering a functional SERPINA1 gene to restore therapeutic levels of the AAT protein with a single dose. The trial will involve up to 30 adult patients with lung disease related to AATD and will start with a dose-escalation phase to determine the optimal dosage, followed by a dose-expansion phase for confirmation. Key objectives include evaluating the safety, tolerability, pharmacokinetics, and pharmacodynamics of NTLA-3001, with a specific focus on adverse events, dose-limiting toxicities, immune responses, and vector shedding. The trial is expected to be concluded by May 2030.

Another innovative gene editing therapy for AATD is BEAM-302 (NCT06389877), which focuses on targeting the liver to make precise corrections to the PiZ mutation, a single nucleotide changes prevalent among patients with severe homozygous AATD. BEAM-302 uses an adenine base editor specifically designed to convert A to G at the PiZ mutation site. The therapy is delivered using LNPs and is anticipated to decrease the accumulation of mutated AAT in the liver and the circulation of defective AAT, while simultaneously increasing levels of functional AAT in the bloodstream. By correcting the PiZ mutation at its natural genomic location, BEAM-302 aims to restore normal AAT function even during periods of infection, a benefit that current augmentation therapies do not provide. The safety, pharmacodynamics, pharmacokinetics, and efficacy of BEAM-302 are being assessed in an open-label, dose-escalation phase 1/2 clinical trial, which includes both a dose exploration phase and a subsequent dose-expansion phase to determine the optimal dosage for future pivotal studies. The treatment was initiated for the first patient enrolled in this trial in June 2024.

Gene editing carries inherent risks, such as off-target effects whereby unintended regions of the genome may be modified, potentially resulting in harmful mutations. There is also the possibility of immune reactions to the Cas9 protein, leading to adverse side effects. Moreover, the long-term effects of these genetic modifications are not yet fully understood, which raises ethical concerns, particularly with germline editing [67]. To mitigate the risks associated with permanent genomic changes, recent strategies for treating AATD are focusing on gene silencing technologies, including siRNA [68] and antisense oligonucleotides [69], which target messenger RNA (mRNA) to modulate protein expression [70].

Wave Life Sciences has developed WVE-006, an RNA editing therapeutic aimed at correcting the disease-causing RNA mutation responsible for AATD. By restoring the functional M-AAT protein and lowering harmful Z-AAT levels, WVE-006 addresses both lung and liver complications associated with AATD. The ongoing first-in-human phase 1 trial (NCT06186492) is assessing its safety, tolerability, and pharmacokinetics in healthy participants. This study involves a single subcutaneous ascending dose followed by multiple doses to optimize future dosing for patients with AATD. WVE-006's innovative GalNAc-conjugated A-to-I RNA editing oligonucleotides use ADAR (adenosine deaminases acting on RNA) enzymes to edit RNA, enhancing protein expression and altering disease pathways, marking a breakthrough in RNA therapeutics [71].

Gene therapy for emphysema extends beyond targeting the SERPINA1 gene or mRNA and includes strategies to reduce inflammation and promote lung tissue regeneration. Approaches to silence genes implicated in oxidative stress and inflammation, such as nuclear factor erythroid 2-related factor 2 or tumor necrosis factor alpha, show promise in minimizing lung damage and slowing disease progression [72–75]. Enhancing the expression of protective genes, such as those encoding antioxidant enzymes, is another avenue under investigation. For instance, introducing genes that boost superoxide dismutase activity or other antioxidant molecules may help mitigate oxidative damage commonly observed in patients with COPD [76].

Additional strategies include suppressing the activity of harmful enzymes, such as neutrophil elastase, to prevent excessive tissue destruction [77] and increasing the expression of growth factors (e.g., vascular endothelium growth factor) to stimulate lung repair and regeneration [78]. By leveraging gene therapy to promote healing processes and inhibit destructive pathways, researchers aim not only to slow the progression of emphysema but also to potentially restore damaged lung tissue [79].

Multifactorial diseases and their complexities make designing and implementing effective treatment strategies for these conditions significantly more difficult. In addition, the respiratory system poses unique challenges for gene delivery due to the mucosal barriers and the need for targeted delivery to specific cell types in the lung [80].

Asthma

Asthma is one of the most common chronic pulmonary disorders, affecting more than 330 million people worldwide and this figure is expected to exceed 400 million by the end of 2025 [81]. Asthma is an immunologic disorder triggered by the interaction between environmental and genetic factors, resulting in hyper-excessive mucus production, airway inflammation, and smooth muscle contraction. Therapies with inhaled corticosteroid agents, short- and long-acting β-agonists, anticholinergic agents, and combination therapy of inhaled corticosteroids and longer-acting β-agonists are the mainstay therapies following the global initiative for asthma guidelines. However, it is incurable despite decades of collective efforts to prevent, diagnose, and treat the disease promptly due to the challenges associated with pulmonary delivery of drugs and the complex anatomic construction of the respiratory tract; mucociliary clearance and macrophages rapidly phagocytose inhaled drug particles, limiting their deposition at the lung target [82].

Inhalation is the most straightforward method of administration for the delivery of therapeutics, including gene therapy, to the lung. However, the mucus gel layer covering the lung airways is a critical barrier that hampers the widespread distribution and long-term retention of inhaled therapeutics within the lungs [83].

To overcome these difficulties, in 2014, da Silva et al. developed compacted DNA nanoparticles delivering a thymulin analog, a nanopeptide with anti-inflammatory and antifibrotic properties, preventing airway remodeling by reducing inflammation and fibrosis in a murine asthma model [84]. In 2020, the same authors advanced to mucus-penetrating nanoparticles, overcoming the airway mucus barrier for more effective delivery [85]. The 2014 study focused on prevention, whereas the 2020 approach reversed established asthma pathology, normalizing chronic inflammation, fibrosis, and lung mechanics 20 days after treatment with a single dose.

In 2024, Tu et al. generated RNA nanoparticles with mannose decorated EV-miR-511-3p (Man-EV-miR-511-3p), which could penetrate the airway mucus barrier and target lung macrophages, polarize macrophages into M2, and suppress allergic airway inflammation [86].

Silver nanoparticles can also significantly inhibit the highly expressed reactive oxygen species in the lungs of asthmatic mice and attenuate antigen-induced airway inflammation and hyperresponsiveness. The outstanding antioxidant capacity of silver nanoparticles holds great promise for treating asthma. In addition, silver nanoparticles made outstanding contributions to the formation of airway scaffolds. The airway scaffolds constructed by silver nanoparticles with antiproliferative activity and cisplatin improved the surface function of traditional scaffolds [87].

Although some progress has been made, more economical and simpler experimental methods are needed to alleviate the dilemma of asthma treatment and set up clinical trials as early as possible.

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is another chronic lung disease marked by progressive scarring of lung tissue. The cause of IPF is unknown, but smoking, environmental exposure, and genetics may contribute. IPF typically affects older adults and worsens over time, leading to shortness of breath, chronic dry cough, and fatigue [88]. Although there is no cure, medications such as pirfenidone and nintedanib can slow disease progression and lung transplantation may be considered in severe cases [89, 90]. Gene therapy for lung fibrosis, including IPF, is an emerging area of research. The goal is to target the underlying causes of fibrosis by delivering therapeutic genes to lung cells. Approaches include modifying the genes or mRNAs involved in fibrosis pathways [91, 92].

SRN-001 is an innovative siRNA therapy targeting IPF. Approved by Australia's Human Research Ethics Committee, this phase 1 trial (NCT05984992) involves a randomized study with 24 healthy volunteers across four dose groups. SRN-001, developed using the Self Assembled Micelle inhibitory ribonucleic acid (SAMiRNA, siRNAgen Therapeutics) platform, uses siRNA to downregulate AREG (amphiregulin) mRNA, a growth factor responsible for fibroblast proliferation and transition into myofibroblasts during fibrosis. Preclinical data show that it effectively reduces fibrosis in lung, kidney, and liver models with a strong safety profile. This first-in-human clinical trial aims to assess the safety, tolerability, and pharmacokinetics

of SAMiRNA technology [93]. After phase 1a, siRNAgen Therapeutics plans to seek FDA approval for expanded trials in the United States.

In addition, researchers at Yale University have developed a next-generation microRNA-29 (miR-29) mimic, MRG-229, designed to inhibit fibrotic processes at a molecular level [94]. Building on previous findings with MRG-201 that reduced fibrosis in animal models [95], this updated compound includes modifications for enhanced stability and cellular uptake. Preclinical models have demonstrated MRG-229's effectiveness in reducing fibrosis markers and improving lung function [94]. The compound is expected to move forward into clinical trials as an innovative therapeutic option for patients with IPF, providing a targeted approach that aims to reduce fibrosis directly within lung tissue.

Another promising approach for treating IPF involves a modified DPP4 inhibitor, CMR316, designed for targeted lung regeneration by activating alveolar epithelial stem cells critical for lung repair. A phase 1 trial (NCT06589219) that began in August 2024 is assessing the safety, tolerability, and pharmacokinetics of CMR316 in both healthy participants and patients with IPF. This three-part trial delivers single and multiple ascending doses via nebulizer, allowing for lower and localized dosing that minimizes the side effects associated with traditional DPP4 inhibitors [96]. Such advancements signal a shift toward therapies that not only slow disease progression but actively promote the repair and regeneration of lung tissue.

Gene Therapy for Kidney Diseases

Chronic kidney disease

CKD is a progressive condition characterized by the gradual loss of kidney function, leading to the accumulation of waste products and toxins in the body, causing a range of health problems. It is commonly caused by diabetes, hypertension, or other underlying conditions [97, 98]. Although not typically caused by single-gene mutations, CKD has been linked to genetic factors that influence inflammation, fibrosis, and oxidative stress [99]. CKD currently affects between 11% and 13% of the global population, with increasing mortality rates and projections to become the fifth leading cause of death by 2040 [100, 101]. Current treatments focus on symptom management, and end-stage kidney disease (ESKD) relies on dialysis or kidney transplantation, which, although extending life expectancy, place a heavy burden on patients and offer limited improvements in quality of life, highlighting the need for advanced long-term treatment options [102, 103].

Gene therapy as a potential treatment for CKD

Gene therapy for kidney diseases faces several challenges due to the organ's complex structure and biological characteristics. The kidney's intricate anatomy, with specialized regions such as the glomerulus, proximal and distal tubules, and collecting ducts, complicates targeting specific cell types. Achieving efficient and targeted gene delivery is challenging because many viral vectors lack specificity for key kidney cells, such as podocytes or tubular cells. In addition, the glomerular filtration barrier excludes particles larger than 50 kDa, posing a significant obstacle to conventional gene delivery systems, such as AAVs [104, 105]. Moreover, the dense extracellular matrix in the renal tubules impedes tissue penetration, making it difficult for vectors to reach target cells. Maintaining sustained gene expression is another obstacle; the continuous turnover and immune responses in the kidneys can disrupt long-term expression. Thus, gene therapy has fallen behind in treatments targeting the kidney [101].

Although no kidney gene or cell therapies have yet been approved, several experimental treatments are currently being tested in preclinical or early clinical trials. In parallel, challenges posed by the kidney's complex structure and filtration barriers are being addressed by alternative strategies, including targeting extra-renal systems for treating kidney diseases [101].

Although CKD is typically driven by a combination of genetic and environmental factors, monogenic kidney diseases, such as PKD, congenital nephrotic syndrome, cystinuria, Alport syndrome, and Fabry disease, are particularly well-suited for gene therapy approaches [106].

Polycystic Kidney Disease

Nanotechnology and gene therapy are promising frontiers in the treatment of PKD, a genetic disorder characterized by the growth of numerous cysts in the kidneys, leading to impaired function and eventual kidney failure. PKD is primarily caused by mutations in the PKD1 or PKD2 genes, which affect the structure and function of kidney cells. Current treatments focus on managing symptoms and delaying disease progression, but the advent of nanotechnology and gene therapy opens new avenues for targeted and potentially curative approaches [107].

This therapeutic strategy offers innovative solutions for drug delivery in PKD. Nanoparticles can be engineered to deliver therapeutic agents directly to kidney cells, improving drug efficacy while minimizing systemic side effects. For instance, nanoparticles coated with ligands specific to receptors on renal cells can selectively target the affected tissues. This approach not only enhances the concentration of drugs in diseased areas but also reduces the required dosage, thereby mitigating potential toxicity. Furthermore, nanocarriers can be loaded with multiple drugs, allowing combination therapies to be administered in a single delivery system [108].

Gene therapy is another transformative approach for PKD, focusing on correcting the genetic mutations responsible for the disease. Using advanced tools such as CRISPR-Cas9, scientists can precisely edit the PKD1 or PKD2 genes, potentially halting or reversing cyst formation [109]. Viral vectors, such as AAVs, are often used to deliver these genetic tools directly to kidney cells. Although still in experimental stages, preclinical studies have demonstrated the potential of gene therapy to restore normal cell function and slow disease progression, offering hope for a long-term cure [110].

The combination of nanotechnology and gene therapy may further enhance treatment outcomes in PKD. For example, nanoparticles can be used to deliver CRISPR-Cas9 components or other genetic tools directly to the kidneys. This non-viral delivery system addresses some of the safety concerns associated with viral vectors, such as immune responses and off-target effects. In addition, nanotechnology can improve the stability and bioavailability of genetic materials, ensuring their effective delivery and uptake by target cells [111].

Despite these advancements, significant challenges remain in translating nanotechnology and gene therapy for PKD into clinical practice. These include optimizing the specificity of delivery systems, ensuring long-term safety, and addressing ethical and regulatory concerns. However, continued research and collaboration across disciplines have the potential to overcome these barriers. By leveraging the

synergistic potential of these technologies, the future of PKD treatment could shift from symptom management to precise and personalized therapies, fundamentally transforming patient outcomes [112].

Cystinuria

Cystinuria is an autosomal recessive disorder that impairs the kidneys' ability to reabsorb certain amino acids, especially cystine, leading to its buildup in urine. This excess cystine, which is poorly soluble, crystallizes to form stones in the kidneys, ureter, and bladder. These stones often cause intense pain, hematuria, frequent urinary infections, and, over time, may contribute to kidney damage and CKD if untreated [113]. Management focuses on reducing cystine levels through increased hydration, diet adjustments, and medications to enhance cystine solubility; severe cases may require surgery to remove stones [114]. The autosomal recessive nature of cystinuria and its well-characterized genetic basis, linked to mutations in the SLC3A1 and SLC7A9 genes, which code for subunits of trans-epithelial transporters for the amino acids, makes it a promising candidate for gene therapy. Targeted gene delivery to the proximal tubule could restore partial cystine transport and prevent stone formation [115–117].

A CRISPR/Cas9-engineered albino mouse model of cystinuria was developed to mimic human disease, exhibiting increased urinary cystine levels, cystine crystals, and bladder stones. These Slc3a1 tyrosinase mutant mice are a valuable platform for testing the efficacy of gene therapy, allowing researchers to track gene delivery, expression, and restoration of transporter activity in vivo. This model is an important tool for evaluating gene therapy interventions in cystinuria [118].

Fabry Disease

Fabry disease is a rare genetic disorder caused by mutations in the *GLA* gene, which leads to a deficiency of the enzyme α-galactosidase A (α-GAL A). This enzyme is essential for breaking down a fatty substance called globotriaosylceramide (Gb3), which, without α-GAL A, accumulates in cells, particularly in the kidneys, heart, nervous system, and skin [119]. Over time, this buildup can impair kidney function, leading to CKD. Without treatment, Fabry disease and CKD progress, potentially advancing to kidney failure [120].

A phase 1/2 clinical trial (NCT06270316) is assessing the safety, tolerability, and preliminary efficacy of AMT-191, an investigational gene therapy for male adults with classic Fabry disease. AMT-191 is designed as a single-dose, intravenous therapy using AAV5 to deliver the gene for α-GAL A to the liver, where it promotes liver-specific enzyme expression. The study will examine two dose levels: 6.0×10^{13} genome copies (gc)/kg for the low-dose cohort and 3.0×10^{14} genome copies/kg for the high-dose cohort, each with three participants, for dose-limiting toxicity assessment. The goal of AMT-191 is to sustainably increase plasma levels of GLA, offering a potentially long-term therapeutic effect for Fabry disease.

In a pilot study (NCT02800070) investigating autologous stem cell transplantation for Fabry disease, five adult males with type 1 Fabry disease received HSCs transduced with a lentivirus vector containing the α-GAL A gene. The therapy resulted in near-normal α-GAL A levels within 1 week and stabilization of CKD in all but one patient up to 33 months post-infusion. The non-myeloablative regimen using intravenous melphalan showed no serious adverse events linked to the investigational product. Reductions in plasma and urine Gb3 and globotriaosylsphingosine (lyso-Gb3) were observed. At follow-up, one patient is nearly 3 years post-infusion, and three patients have discontinued enzyme replacement therapy, indicating promising long-term outcomes [121].

A phase 1/2 clinical trial (NCT03897361) is evaluating the safety and efficacy of genetically modified HSCs to express the defective gene (CTNS) in another lysosomal storage disorder, cystinosis; this gene encodes the lysosomal cystine transporter, cystinosin. The trial involves modifying HSCs with a lentiviral vector to express functional cystinosin (CTNS-RD-04), followed by re-infusion of the modified cells in patients with cystinosis. Early results indicate that the therapy restores cystinosin production, lowers cystine levels, and improves developmental scores, with a favorable safety profile [122]. These findings suggest that gene therapy may provide a long-term solution by targeting the underlying cause of cystinosis and preventing cystine accumulation.

Alport syndrome

Alport syndrome is a genetic disorder that primarily affects the kidneys, ears, and eyes. It is most commonly associated with mutations in the COL4A3, COL4A4, and COL4A5 genes responsible for producing type IV collagen [123]. In the kidneys, type IV collagen mutations weaken the glomerular basement membrane, a structure critical for the filtering function of glomeruli. This leads to glomerulosclerosis, proteinuria, hematuria, and, eventually, CKD and ESKD [124]. Current treatment focuses on managing symptoms and slowing kidney decline. Research into gene therapies aims to deliver the correct version of the COL4A5 gene [125]. Yamamura et al. [126] report promising results with exon-skipping therapies. Using antisense oligonucleotides to skip specific truncating variants in exon 21 of COL4A5, researchers were able to restore triple-helix collagen formation and improve kidney pathology in mouse models. Treated mice showed prolonged survival and the integrity of the glomerular basement membrane was restored. This approach has the potential to treat severe Alport syndrome, particularly in males with X-linked disease.

Primary Hyperoxaluria

Primary hyperoxaluria is a metabolic disorder that leads to excessive oxalate production, recurrent kidney stones, and progressive CKD. It has been effectively targeted by iRNA-based therapies such as lumasiran (Oxlumo) and nedosiran (Rivfloza) [127, 128]. Lumasiran, approved in 2020, targets *HAO1* mRNA in hepatocytes to lower glycolate oxidase levels, reducing glyoxylate availability and significantly decreasing oxalate production in patients with primary hyperoxaluria type 1 (PH1) [129, 130]. Nedosiran, approved in 2023, degrades *LDHA* mRNA in liver cells to reduce lactate dehydrogenase A levels, effectively decreasing oxalate synthesis across all three subtypes of primary hyperoxaluria (PH1, PH2, and PH3) [131]. These siRNA therapies present significant advancements in addressing the genetic causes of oxalate-driven kidney disease, offering targeted and effective treatments to prevent renal damage and improve patient outcomes [132].

Kidney fibrosis

Kidney fibrosis is a progressive condition characterized by the accumulation of extracellular matrix components, resulting in scarring and impaired kidney function. It is often caused by chronic conditions such as diabetes, hypertension, and autoimmune diseases. Because persistent kidney injury activates maladaptive repair mechanisms, excessive deposition of the extracellular matrix disrupts the kidney's architecture, leading to glomerulosclerosis and tubulointerstitial fibrosis. These changes significantly impair kidney filtration and are the final common pathway in all forms of CKD, ultimately progressing to ESKD [133]. Current treatments primarily focus on managing the underlying causes of fibrosis, such as

blood pressure control and proteinuria reduction. There are no effective therapies to directly target the fibrosis process [134].

Although direct antifibrotic gene therapies are not yet available, ongoing research shows promise for future treatments targeting the molecular drivers of fibrosis [135]. Current strategies focus on using gene and RNA-based therapies to disrupt the fibrotic cascade, particularly by inhibiting key pathways such as transforming growth factor beta (TGF-β) signaling, crucial for activating fibrosis-driving cells [136, 137].

Viral vectors (e.g., adenovirus) have been utilized to deliver genes such as Smad7, an antagonist of TGF-β1–Smad signaling, and IκB-α, an inhibitor of the inflammatory transcription factor NF-κB, effectively reducing renal fibrosis in rat models [138, 139]. Similarly, AAV vectors have been used to deliver antifibrotic and anti-inflammatory cytokines genes, including hepatocyte growth factor and interleukin-10, which have shown promising results in diminishing fibrosis and inflammation in rodent models of kidney disease [140,141]. In addition to viral vectors, non-viral gene delivery systems, including polyethylenimine nanoparticles, lipid-polymer hybrid nanoparticles, and cationic gelatin nanoparticles, have shown potential for treating renal fibrosis [136]. Studies using polyethylenimine nanoparticles have successfully delivered siRNA targeting paired box2 (PAX2) and microRNA-146a to inhibit TGF-β1 and NF-κB pathways, respectively, reducing kidney fibrosis induced by unilateral ureteral obstruction in mice [142, 143]. Gelatin nanoparticles, derived from collagen, have also been used to deliver TGF-β receptor siRNA and plasmid DNA expressing matrix metalloprotease to modulate fibrosis in kidney models, showing positive effects in reducing fibrotic changes [144, 145].

Epigenetic mechanisms, notably cytosine methylation and histone modifications, also play a regulatory role in the progression of CKD. Changes in methylation have been shown to correlate with altered expression of fibrosis-related genes and histone modifications are linked to fibrosis in diabetic kidney disease [146]. These epigenetic insights open doors for the discovery of novel biomarkers and epigenetic-based therapeutic strategies.

Advancements in kidney gene therapy have focused on developing precise, efficient, and safe delivery platforms that can target diverse renal cell populations. Viral vectors, such as those being developed by Purespring Therapeutics and Ninevah Therapeutics, leverage tissue-specific promoters and rAAV capsid engineering to selectively target renal cells, including podocytes in conditions such as autosomal dominant polycystic kidney disease [101]. Non-viral delivery methods, such as nanoparticles smaller than 8–10 nm, offer promising alternatives by bypassing the glomerular filtration barrier, enabling repeated dosing, and minimizing immune responses [147, 148]. Advanced preclinical models provide a more accurate assessment of kidney development and disease, enabling better evaluation of gene therapy efficacy for various kidney conditions. For instance, in vitro kidney disease models, such as CRISPR-Cas9-engineered organoids derived from human pluripotent stem cells with PKD1 and PKD2 knockouts, provide valuable insights into the pathogenesis of PKD and serve as a platform for studying molecular interactions involved in the disease. In addition, they have potential for advancing organogenesis, which could help address the shortage of transplantable kidneys [149]. In a groundbreaking procedure, researchers at Harvard Medical School and Massachusetts General Hospital successfully transplanted a genetically edited pig kidney into a human, marking a significant milestone in addressing the global shortage of human kidneys for transplant. The kidney, modified using CRISPR-Cas9 to enhance compatibility with humans and reduce

infection risks, was transplanted into a 62-year-old patient with end-stage kidney failure. The transplant showed immediate success as the pig kidney began producing urine, offering hope for the future of xenotransplantation. Although long-term outcomes remain uncertain, this procedure could potentially reduce the need for dialysis and improve organ availability, offering a promising approach to address kidney failure [150].

Conclusions

Gene therapy is emerging as a transformative approach for treating respiratory and renal diseases by addressing their genetic and molecular root causes. Advances in innovative delivery platforms, including viral vectors and nanoparticles, have shown promise in overcoming key physiologic obstacles such as respiratory mucus layers and the renal glomerular filtration barrier. The ability to precisely target specific cell populations, along with the development of enhanced delivery technologies, remains pivotal for achieving optimal therapeutic outcomes. The approval of numerous gene and RNA-based products for genetic disorders underscores the progress in this field. Robust animal models and ongoing clinical trials continue to validate the therapeutic potential of gene therapies, with the potential to provide durable and possibly curative treatments for these life-changing conditions. Continued research to address the challenges related to delivery efficiency, immunogenicity, scalability, and safety is essential to translate these promising therapies into widespread clinical use.

Funding sources

Supported by the Brazilian Council for Scientific and Technological Development (CNPq), Rio de Janeiro State Research Foundation (FAPERJ), Coordination for the Improvement of Higher Education Personnel (CAPES), Department of Science and Technology – Brazilian Ministry of Health (DECIT/MS), and the National Institute of Science and Technology for Regenerative Medicine/CNPq and National Institute of Science and Technology for Gene Therapy/CNPq.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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