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Adenoviral Vectors in Gene Therapy: A Detailed Overview

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ABSTRACT

Adenoviral vectors (AdVs) represent one of the most extensively researched platforms in the realm of gene therapy, providing advantages such as high transduction efficiency, large transgene capacity, and broad tropism. This review provides a detailed and structured overview of AdVs, highlighting their biology, gene delivery mechanisms, clinical applications, and challenges limiting their broader therapeutic applicability. The study also explores recent progress in vector engineering, such as rare serotypes, capsid modifications, third-generation vectors, as well as strategies for immune modulation and toxicity reduction. AdVs are used in therapies for genetic disorders, oncology, and vaccinology, alongside innovations such as CRISPR-Cas9, nanotechnology, and artificial intelligence design. Nevertheless, persistent hurdles, including vector immunogenicity, hepatotoxicity, scalability, and the lack of durable expression, prevent widespread clinical use. This review consolidates current knowledge and presents a future perspective on how AdVs may evolve as powerful, adaptable, and precise tools in modern gene therapy. By contextualizing strengths and unresolved challenges, this work aims to give researchers and clinicians a balanced foundation for evaluating their future roles in translational medicine. ***DOI: 10.22034/IBJ.30.1.16***

Keywords: Adenoviridae, Genetic therapy, Oncolytic virotherapy, Transgene

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1. INTRODUCTION

Gene therapy is an emerging frontier in modern medicine, enabling the correction of genetic defects, modulation of disease pathways, and precise delivery of therapeutic agents[1]. It depends on the transfer of genetic material into target cells via specialized delivery systems known as vectors[2]. These vectors, viral and non-viral platforms, are crucial components in gene therapy[3]. Thus, the design and choice of vectors are central to therapeutic success in this field.

Adenovirus (Ad), a DNA virus, was first isolated in 1953 by Rowe et al. in adenoid tissue cell cultures, which have a distinguished history in research due to their unique properties[4]. Collectively, their high transduction efficiency, large genomic capacity (up to 37 kb of exogenous DNA), and decades of clinical exploration (since early 1990s trials) provide extensive data for improvement. However, challenges like immunogenicity and transient expression limit their long-term therapeutic utility. The ongoing importance of AdV is evident from its wide range of applications, including the treatment of monogenic diseases, oncology, and vaccine development. Improvements in vector engineering and new insights into host-vector interactions are expanding their potential while addressing long-standing limitations. This constant interaction between innovation and challenge makes AdVs a key focus for research and development. Taken together, these features make AdVs powerful but imperfect tools, with efficiency balanced by immunogenicity and short-lived expression, driving ongoing innovation.

Previous reviews have provided valuable insights into either the molecular engineering of Ads or their clinical performance in specific applications. Yet, these perspectives often remain fragmented, with molecular

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design principles, immune interactions, and translational outcomes treated in isolation. As a result, readers are left without a cohesive view of how improvements at the molecular level translate into tangible therapeutic benefits or how clinical setbacks inform future design.

The present review addresses this gap by offering a narrative, non-systematic review that explicitly connects Ads biology, vector engineering, and therapeutic applications within a unified framework. Unlike prior reviews, we integrate discussions of capsid modifications, genome streamlining, and host–immune interactions with their implications for safety, efficacy, and manufacturability. Particular emphasis is placed on emerging data from 2015 to 2025, while also incorporating landmark earlier studies where necessary to provide conceptual grounding.

The review is organized as follows: Ad biology relevant to vectorization (Section 3); detailed vector structures and gene delivery processes (Sections 4 and 5); advantages and limitations (Sections 6 and 7); recent improvements (Section 8); clinical and preclinical applications (Section 9); and future perspectives and testable hypotheses (Section 10). These sections critically synthesize existing data and provide an overview of the current status and prospects of AdVs in gene therapy, offering a framework for evaluating their translational trajectory (Fig. S1).

2. MATERIALS AND METHODS

This review provides a comprehensive overview of Adenoviral vectors (AdVs) used in gene therapy. A structured but non-systematic approach was applied to identify and select relevant literature.

2.1. Search strategy

A thorough search was performed in PubMed, Web of Science, ScienceDirect, and Google Scholar, using both Medical Subject Headings (MeSH) and free-text terms related to AdVs and gene therapy. The primary keywords included “Gene Therapy”, “Adenovirus”, and “Adenoviral Vectors”. Additional search terms included “Adenoviral vectors process”, “Mechanism”, “Applications” (e.g., cancer), “Advantages and Challenges”, and “Innovations in Vector Design”. The search covered articles published between 2000 and 2025, with a focus on recent advances reported after 2015. A few landmark studies before 2000 (e.g., early clinical trials and Ad discovery papers) were selectively included to provide historical context and conceptual grounding.

2.2. Selection criteria

Only peer-reviewed original research articles, reviews, and clinical trial reports written in English were included. Non-peer-reviewed works, articles unrelated to AdVs, and studies focusing exclusively on other viral vectors were excluded.

2.3. Data synthesis

Data from the selected studies were extracted and organized based on the following categories: Adenovirus and Its Structure, Adenoviral Vectors, Gene Delivery Process, Advantages, Challenges, Improvements, Clinical and Preclinical Applications, and Future Directions. The aim was to provide an integrative, descriptive analysis that critically connects structural, mechanistic, and translational findings, rather than a systematic synthesis.

3. ADENOVIRUS

Ad is a transmissible (via direct inoculation to the conjunctiva, a fecal-oral route, aerosolized droplets, or exposure to infected tissue or blood) DNA virus characterized by the presence of >88 serotypes in seven species[5]. A remarkably resilient virus, widely prevalent among human and animal populations, can survive for extended durations outside a host and exhibits year-round endemic (sporadic and epidemic) characteristics. Incubation time is usually 2 to 14 days (about two weeks) after exposure to the virus[6]. The virus can infect multiple organ systems; however, most infections are asymptomatic. Ad infections affect individuals of all ages, including neonates. The symptoms of Ad infection include nasal congestion, rhinitis, cough, difficulty breathing, and pneumonia. Additional symptoms may encompass fever, fatigue, muscle aches, headaches, abdominal pain, swollen lymph nodes in the neck, eye infection, sore throat, earache, vomiting, diarrhea, and abdominal pain. The diagnosis of Ad is more effective when specimens are collected early. Appropriate specimens include nasopharyngeal swabs, throat swabs, sputum, tracheal aspirates, bronchoalveolar lavage fluid, conjunctival swabs, stool or rectal swabs, urine, blood, cerebrospinal fluid (CSF), and unfixed tissue samples. Seroreactivity to Ad is also common but limited in acute clinical settings. Adenoviral antigen assays, such as direct fluorescent antigen and enzyme immunoassay, are crucial for diagnosing epidemic keratoconjunctivitis, adenoviral respiratory disease, pharynx-conjunctivitis, and enteritis. Polymerase chain reaction is used with high specificity to identify Ad in various specimens. Serotyping is primarily utilized within the realms of epidemiology and research. Specific serotypes of enteric Ad have been seen in stool specimens using electron microscopy. These non-cultivatable enteric Ads are best detected by antigen assay. The Ad has been identified using electron microscopy and immunohistochemical techniques. Ad

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infections typically do not require specific treatments, as they are self-limiting in individuals with a normal immune response. Antiviral medications such as cidofovir, ribavirin, ganciclovir, and vidarabine have managed these infections for immunocompromised patients. No commercially available vaccine has been approved by the FDA for public use. Severe morbidity and mortality associated with Ad infections are uncommon in immunocompetent individuals. However, rare complications, such as meningoencephalitis and pneumonitis, can increase the risk of mortality. Notably, severe Ad infections have been documented in immunocompromised patients, including transplant recipients and individuals with inherited or acquired immunodeficiency states. Additionally, morbidity and fatalities resulting from pronounced host inflammatory responses have been observed in previous gene vector trials. The virus can be engineered to remove its replicative capacity by removing essential genes. Specific genes can be inserted into the virus to repair defective metabolic, enzymatic, or synthetic pathways in the host. Similarly, suicide gene systems that convert nontoxic systemically delivered prodrugs to active chemotherapeutic agents have been delivered via AdVs directly into cancer cells. Nevertheless, as may be anticipated, one of the significant challenges in viral gene therapy is the immune response elicited by the viral vector. Ads can infect many cell types, including proliferating and quiescent cells, potentially targeting various tissue types and diseased cell lines. Ad is known to be oncogenic in rodents but not in humans. For detailed information, please refer to the National Institutes of Health (NIH) guidelines.

3.1. Adenovirus structure

Ads are medium-sized (90–100 nm), non-enveloped virions with an icosahedral capsid structure, with three primary proteins: Hexon (the main capsid protein, arranged in a hexagonal pattern and occupies the faces to form the outer shell of the virus), Penton base (12 trimetric pentons with its attached fiber protein, located at the outward vertices of the icosahedron for cell entry and include an RGD motif for interacting with integrins during endosomal escape), and fiber (binds to the coxsackievirus-adenovirus receptor (CAR) on host cells facilitating attachment and entry, protruded from the penton base and is responsible for binding to specific receptors on host cells)[7,8]. This virus comprises approximately one million amino acid residues and has an estimated molecular weight of around 150 MDa[9].

3.2. Adenovirus genome structure

Ad genomes are long, linear, non-segmented, double-stranded DNA that spans approximately 26,163 to 45,063 Kbp and encompass 23 to 46 protein-coding genes required for replication and the production of structural proteins[10]. Their genome has special ends called inverted terminal repeats (ITRs) at both ends, which help it replicate, and a packaging signal near the left end, within the E1 region. The ITRs, up to 150 bp in length, enable circularization and act as DNA replication origins, facilitating primase-independent DNA synthesis. Based on transcription timing, the Ad genome is divided into early regions (E1 to E4), which initiate processes such as gene activation, and late regions (L1 to L5), which construct the outer shell of the virus[11]. On the one hand, in the early transcriptional regions, E1 is crucial for initiating the viral replication cycle and regulating gene expression, and E2 is involved in DNA replication and encoding proteins necessary for this process. E3 contributes to immune evasion, thereby aiding the virus in avoiding host defenses, and E4 contributes to cell cycle regulation and viral gene expression, enhancing viral replication. On the other hand, late transcriptional regions are expressed after the onset of viral DNA replication and encode the structural proteins necessary for assembling new virus particles, such as hexon, penton base, and fiber[12]. The genome also contains genes for proteins involved in DNA packaging, such as IVa2, 52K, and L1, as well as core proteins like V, VII, X, and the terminal protein TP.

4. ADENOVIRAL VECTORS

4.1. AdV genome

AdVs are modified Ads (replication-defective) competent in delivering therapeutic genes to the human genome. In the first generation of AdVs, the modification includes the removal of the E1 region, which prevents the virus from replicating to enhance safety. Afterwards, therapeutic genes are inserted into its place under an appropriate promoter. However, the ITRs are retained to maintain vector packaging capability, ensuring the vector can be packaged into virions. Using the first-generation vectors in 293 cell lines necessitates complementation, as these cell lines provide the E1 functions required for viral replication[13]. In some cases, the E3 is also removed to create additional space for the insertion of therapeutic genes[14]. In second-generation vectors, beyond the deletion of the E1 region, these vectors have further deletions in either the E2 or E4 region to reduce toxicity and immune response, aiming to enhance safety and efficacy[15]. The vector DNA remains episomal in the host cell nucleus, avoiding the risk of insertional mutagenesis. Similarly, this setup enables vectors to enter various cell types, delivering and transducing therapeutic genes without causing disease.

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4.2. Modified AdV genome structure

AdV, like gutless or high-capacity vectors, have almost all viral genes removed, retaining only the ITRs and the packaging signal. This structure enables them to transcode up to 37,000 base pairs while concurrently reducing the probability of activating the defense system. Nevertheless, production requires helper viruses or cell lines to provide the necessary viral proteins for replication and packaging. Moreover, oncolytic vectors are designed to replicate in the cancer cells and kill them selectively, with modifications often involving placing the E1 gene under the control of a tumor-specific promoter or making the virus sensitive to cancer cell-specific conditions[16]. Other types, such as capsid-modified vectors, have altered capsid proteins to change the tropism of the vector and/or evade the host immune system. In these cases, fiber proteins are modified to target specific cell receptors, often through chimerization with fiber proteins from other serotypes. All in all, modified AdVs encompass a variety of additional alterations aimed at improving specific properties, such as reduced immunogenicity, increased transgene capacity, or enhanced targeting[17].

5. GENE DELIVERY PROCESS

In gene therapy, delivering the therapeutic genetic material to the cells of an organism is crucial. The delivery has several steps as described in the following sections.

5.1. Attachment

The attachment mechanism involves specific interactions between viral proteins and host cell receptors. The viral fiber coat protein binds to CAR, a transmembrane protein expressed on the host cell, facilitating the main interaction (Fig. 1). This binding is crucial for infection, as CAR serves as the primary receptor for many Ad serotypes, particularly Ad type 5 (Ad5), which is commonly used in vector development. In addition to the fiber-CAR interaction, the penton base

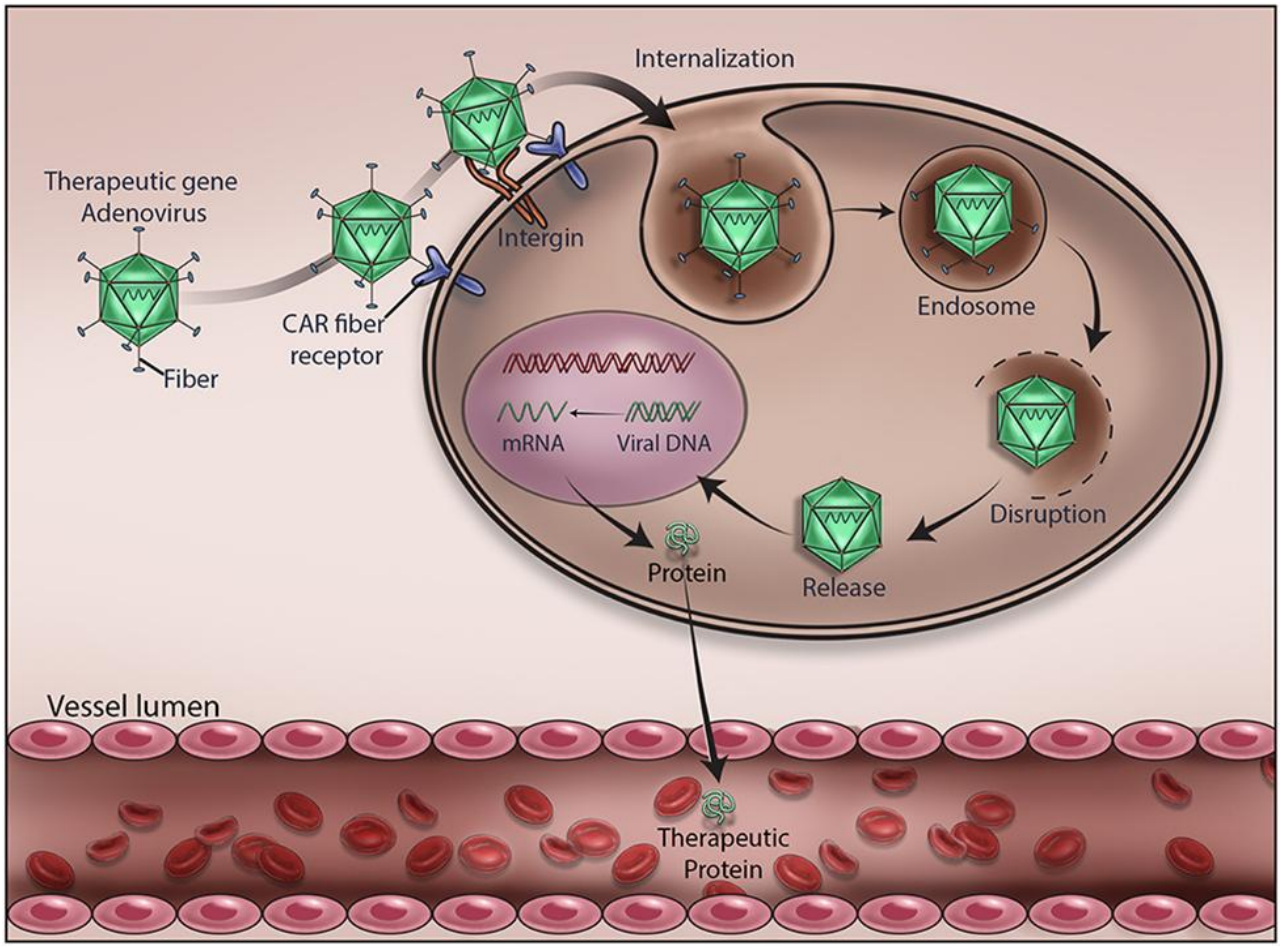

Fig. 1. Mechanism of AdV-mediated delivery of a therapeutic DNA. Figure adapted under the Creative Commons Attribution 4.0 International License (CC BY 4.0)[22].

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binds to cell-surface integrins, such as αvβ3 and αvβ5, enhancing attachment and internalization. The penton base contains an RGD motif that mediates integrin binding, stabilizing the vector on the cell surface for endocytosis. This dual interaction—fiber with CAR and penton base with integrins—ensures efficient attachment and is a key feature of AdV tropism[18]. The attachment step involves binding and determines the ability of the vector to transduce specific cells. CAR appears on various epithelial and endothelial cells, enabling AdVs to target these cells. However, this broad tropism may cause off-target effects, complicating the design of vectors for therapies like cancer gene therapy or vaccine development. Researchers modify the fiber protein to target alternative receptors, enhancing specificity and counteracting off-target effect. Chimeric vectors with modified fiber proteins target receptors such as CD46 or sialic acid, enhancing attachment to specific cell types. This process aims to improve cancer therapy through tumor targeting and vaccine development for immune activation.

5.2. Internalization

Following receptor binding during the attachment phase, the interaction triggers clathrin-coated pit formation on the cell membrane. These investigations, stabilized by clathrin proteins, facilitate internalization through receptor-mediated endocytosis, efficiently internalizing large particles, like viruses. The clathrin-coated pits invaginate and pinch off as clathrin-coated vesicles containing AdV. These vesicles shed their clathrin coat and mature into early endosomes, membrane-bound compartments that sort internalized materials[19]. This step aligns with a classical endocytic pathway.

5.3. Endosomal escape

This critical step requires the AdV to release its genome into the cytoplasm, preventing degradation and allowing nuclear transport for gene expression. It involves the disruption of the endosomal membrane and the action of specific viral proteins[20]. The endosomal escape mechanism is as follows:

5.3.1. Endosomal maturation and acidification

After internalization, the AdV-containing vesicle matures from an early endosome to a late endosome, with the internal pH decreasing due to the activity of proton pumps. This acidic environment, typically with a pH of around 5, triggers conformational changes in the viral capsid, preparing it for escape[19].

5.3.2. Exposure of capsid protein VI (pVI)

The low pH of the endosome induces partial disassembly of the adenoviral capsid, thereby exposing pVI. pVI is a minor capsid protein facilitating endosomal escape by interacting with the endosomal membrane. It has been proposed that this exposure is instigated by the acidic environment, resulting in the insertion of pVI into the lipid bilayer. Utilizing the cytosolic protein galectin-3 (Gal-3) as an indicator of membrane rupture, it becomes clear that the exposure of pVI and the recruitment of Gal-3 to the ruptured membranes transpire at an early stage, either at or near the cell surface[21].

5.3.3. Membrane rupture and viral release

The interaction of pVI with the endosomal membrane causes the membrane disruption, creating pores or ruptures that allow the AdV to escape into the cytoplasm. This process is facilitated by the lytic activity of pVI, which is believed to be inserted into the membrane and destabilized, leading to lysis.

5.3.4. Cytoplasmic release of viral DNA

Once the endosomal membrane is breached, the adenoviral DNA, along with associated proteins, is released into the cytoplasm. The DNA remains episomal (non-integrated) and is transported to the nucleus for transcription and gene expression. This escape is crucial to prevent degradation by lysosomal enzymes.

5.4. Nuclear transport

5.4.1. Cytoplasmic transport via microtubules

After entering the cytoplasm, the Ad complex, made of capsid proteins, initiates directed, retrograde transport toward the nucleus via the microtubule network of the host cell. Motor proteins, such as dynein, facilitate the movement of the viral complex along microtubules toward their minus ends, which are typically oriented toward the nucleus. The viral capsid proteins may facilitate this process by binding to microtubule-associated proteins or directly interacting with dynein, while microtubule disruption impairs dynein function and reduces nuclear entry[6].

5.4.2. Nuclear pore complex (NPC) entry

Upon reaching the nuclear envelope, the adenoviral DNA must enter the nucleus through the NPC, a large protein structure that regulates the transport of molecules between the cytoplasm and the nucleus. During cytoplasmic transport, the viral capsid partially disassembles, exposing the DNA for entry into the nucleus[23]. Adenoviral DNA is small and linear, allowing it to pass through the NPC without active transport, unlike proteins with nuclear localization signals. The viral core binds to the NPC and releases the viral DNA into the nucleus[24]. Capsid proteins may interact with the NPC to aid this process. The Ad particle disassembles at the NPC, indicating capsid

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disassembly is a part of nuclear entry. The viral complex size may hinder NPC passage, but this is less problematic for AdVs due to their small DNA[6].

5.4.3. Episomal gene expression

Once inside the nucleus, the adenoviral DNA remains an episome, which means it does not integrate into the host genome[24,25]. The viral DNA is transcribed using host cell machinery, leading to the expression of the therapeutic genes. The episomal nature is a key safety feature, reducing the risk of insertional mutagenesis. However, it also results in transient expression, as the DNA can be lost during cell division[26].

5.5. Gene expression

The gene expression process in AdVs involves a series of steps that utilize the machinery of the host cell to transcribe and translate the therapeutic gene into a functional protein. When AdVs genome is inside the nucleus, the gene expression process begins. The therapeutic gene is transcribed by the RNA polymerase II of the host cells, leveraging the transcriptional machinery of the host cell[27]. Some promoters (often a strong viral promoter like cytomegalovirus promoter) ensure high-level expression. The transcribed mRNA is subsequently exported to the cytoplasm, where it is translated into protein by ribosomes, utilizing the translational machinery of the host cell. The produced protein can function within the cell, such as inducing apoptosis in cancer therapy, or being secreted as a vaccine that stimulates immune responses.

6. ADENOVIRAL VECTORS ADVANTAGES

AdVs present several advantages that enhance their suitability for gene therapy applications. Their extensive utilization in numerous clinical trials have generated substantial data regarding their safety and efficacy. AdVs stand out in gene therapy due to their inherent strengths, as summarized in Table 1. These features, evolving through engineering like helper-dependent designs, support diverse applications while addressing vector trade-offs. Advancements emphasize cost-effective scalability for widespread use. The following synthesizes these benefits into core themes.

Table 1. Key advantages of AdVs in gene therapy: features, mechanisms, and therapeutic relevance. Abbreviations: Transfecting Human Embryonic Kidney 293: HEK293

Feature	Mechanism/explanation	Therapeutic relevance/examples
Large transgene capacity	First-generation AdVs (E1/E3 deleted) carry 7.5-8 kb; helper-dependent/gutless vectors only retain ITRs and the packaging signal carry up to 37 kb[29].	Facilitation of the delivery of large genes (e.g., dystrophin for Duchenne muscular dystrophy [DMD]) or multi-gene cassettes
Broad tropism and high transduction efficiency	CAR receptor is widely expressed in dividing and non-dividing cells (epithelial, endothelial, neuronal, hepatocytes, muscle).	Effective across tissues: neurons (Parkinson's), hepatocytes (liver disorders), muscle cells (muscular dystrophy [MD]). Ensures efficient gene delivery and strong therapeutic results
Rapid and high-level gene expression	Viral DNA remains episomal, transcribed by host RNA polymerase II under strong promoters (e.g., CMV)[30].	Ideal for vaccines with SARS-CoV-2 spike, Flavivirus and oncology. Offers rapid/strong protein production; less suitable for chronic disorders
Non-integration into host genome	Episomal persistence prevents chromosomal integration, insertional mutagenesis, and oncogenesis.	Vaccine and transient therapy safety enhancement. Limitation: temporary expression, less suitable for long-term correction
High titer production and scalability	HEK293 cells provides E1 in trans, enabling efficient vector replication and packaging. AdVs can be produced at scale.	Application in mass vaccination (e.g., COVID-19). Thermal stability allows distribution in low-resource regions; needs strict quality control in large-scale production
Versatility across applications	Ability to transduce diverse cells with strong expression and flexible genetic engineering.	Genetic disorders, oncology, and vaccines; An adaptable platform with ongoing improvements

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Table 2. Challenges and limitations of AdVs in gene therapy: mechanisms, outcomes, and mitigation strategies

Challenges	Mechanism/ explanation	Outcomes/ limitations	Strategies to mitigate	Examples / trials (phases)	References
Immunogenicity	Capsid proteins (hexon, penton base, fiber) activate innate/adaptive responses (humoral and cellular); pre-existing antibodies to Ad5 neutralize vectors; T-cell destruction of transduced cells	Clears transduced cells, reduces efficacy/ duration; limits repeated dosing; high seroprevalence hampers applications	Rare serotypes (Ad26/Ad35); gutless vectors; repeated dosing; production complications arise	Cystic fibrosis (CF) trials are limited by the immune response; widespread Ad5 exposure	[31]
Trainset expression	Episomal DNA in the nucleus, lost during cell division; no genome integration	Fades in weeks/months depending on the cell type and proliferation rate; unsuitable for chronic diseases; diminishing returns on redosing	Helper-dependent vectors; extend duration but increase complexity	Expression declines in dividing cells	[32,33]
Off-target effects and specificity	Broad tropism via CAR/integrins; liver preference causes unintended transduction	Toxicity in non-target tissues; narrows therapeutic window; side effects like inflammation	Capsid modifications; CD46 receptor targeting; tissue-specific promoters; trade-off in efficiency	Systemic administration leads to hepatocyte transduction and increases liver enzymes	[34]
Production and scalability	Packaging cell line transfection for E1 complementation; risk of Replication-Competent Adenoviruses (RCAs); regulatory standards	Complex/costly scaling; resource-intensive for global demand; purity/stability issues	Suspension cultures/optimized media; helper systems for advanced vectors	COVID-19 vaccine production challenges	[20]
Toxicity and safety concerns	High doses cause liver inflammation/cytokine storms; organ tropism (spleen/lungs)	Elevated enzymes/hepatotoxicity; risks in immunocompromised; limits dose/efficacy balance	Capsid alterations to reduce tropism; local injection/dose optimization; long-term monitoring	Early trials with liver toxicity	[35]

6.1. Delivery and expression power: capacity, tropism, speed

AdVs deliver complex genetic materials, transduce various cell types (e.g., dividing and non-dividing cells), and enable rapid, high-level gene expression. These features make AdVs beyond other viral vectors.

6.2. Safety and practicality: non-integration, production, adaptability

The episomal delivery method reduces long-term risks and is supported by high-yield manufacturing for global deployment, as seen in recent vaccines. This versatility in fields like oncology and regenerative medicine shows AdVs as a flexible platform, where immunogenicity is both a challenge and an advantage, shaping hybrid innovations in the clinical pipelines. However, transient episomal persistence also limits durability, highlighting the dual nature of AdVs as both safe and short-lived platforms.

7. CHALLENGES AND LIMITATIONS

Despite their advantages, AdVs encounter various challenges that restrict their full potential in gene therapy, as detailed in Table 2. These limitations, often

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due to viral biology, highlight the need for ongoing refinements, like capsid engineering, with trials on immune modulation to improve viability. These are summarized into key themes.

7.1. Immune and expression issues: immunogenicity, transience, and specificity

The immunogenic profile of AdVs poses a core barrier, as capsid activation of macrophages and dendritic cells triggers cytokine release, curtailing efficacy in applications like CF[28]. Coupled with transient episomal expression and off-target tropism, this leads to short-lived effects and unintended tissue impacts, complicating chronic therapies. Ultimately, these interconnected challenges underscore the trade-off between potency and persistence, driving strategies like rare serotypes to balance immune evasion with targeted delivery.

7.2. Practical and safety barriers: production and scalability, and toxicity

Producing high-titer, replication-defective adenoviral vectors remains complex and costly, complicating large-scale clinical trials and commercialization. Toxicity concerns, particularly hepatotoxicity from high doses, further narrow the therapeutic window, especially in vulnerable patients. These production and safety hurdles emphasize the need for optimized manufacturing and dose strategies, positioning AdVs for refined, context-specific use in 2025 protocols.

8. IMPROVEMENTS

Despite these limitations, ongoing research and developments have led to several advancements to improve the safety and efficacy of AdVs.

8.1. Vector engineering: enhancing specificity and capacity

Vector engineering includes new rare serotypes, capsid modifications, and advanced AdV generations, demonstrating that capsid and genome engineering can transform AdVs from transient vectors into stable, disease-specific delivery systems.

8.1.1. Rare serotypes

Rare serotypes (e.g., Ad26, Ad35, and ChAd) broaden tropism and reduce pre-existing immunity prevalent among common types, such as Ad5, thereby improving transduction in seropositive populations[17].

8.1.2. Capsid Modification

Capsid modifications, such as incorporating alternative receptors (e.g., CD46 or desmoglein-2), enable tissue-specific targeting (e.g., hematopoietic cell transduction in blood disorder treatments and cervical cancer), minimizing immunogenicity and off-target effects[36,37]. These chimeric vectors improve specificity but present production and regulatory challenges needing optimization. These modifications minimize innate immune activation, such as pro-inflammatory cytokine release, which can clear transduced cells. Fiber proteins can also be modified to target specific receptors, direct vectors to particular cells, or add shielding to evade the immune system. To illustrate, incorporating peptides that target cancer cells, such as those expressing the epidermal growth factor receptor, can enhance tumor-specific transduction. Utilizing active promoters in only specific cell types ensures that gene expression is restricted to those cells, thereby minimizing off-target effects. For instance, using liver-specific promoters, such as albumin, for hepatic gene therapy can enhance specificity, thereby reducing expression in non-target tissues. This strategy is evaluated in clinical trials for liver-related genetic disorders, improving the therapeutic index (Table 3).

8.1.3. Third-Generation AdVs

Third-generation (gutless or helper-dependent) AdVs carry up to 37 kb of transgenes, removing viral genes to reduce inflammation. These vectors use helper viruses or cell lines for replication, lowering immune detection and enabling prolonged gene expression. However, their production is complex and costly due to sophisticated systems. Preclinical studies show these vectors maintain transgene expression for months, making them suitable for various diseases. Advances in high-capacity platforms enable cost-effective therapies for diseases such as cardiovascular diseases, supporting multiplexed gene editing. These strategies enhance AdVs from transient tools to stable delivery systems, despite large-scale production challenges[38].

8.2. Immune modulation: mitigating host responses

Immunogenicity remains a core barrier, with pre-existing antibodies and innate responses limiting efficacy. Strategies for immune modulation include polyethylene glycol shielding to evade neutralizing antibodies and the incorporation of immunosuppressive elements like CTLA-4 or PD-1 inhibitors into the vector genome. Pharmacological adjuncts, such as rapamycin, corticosteroids, or rituximab, have been refined to reduce adaptive immunity. Emerging methods now utilize CRISPR-Cas9 to edit host immune genes (e.g., APOBEC3G knockdown to resist cytidine deamination) or vector-encoded microRNAs to reduce cytokine storms. AdV modifications for hereditary diseases combine rare serotypes with immune evasion peptides, resulting in reduction in inflammation. These

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approaches enhance the clinical utility of AdVs by improving tolerability, enabling repeated dosing (e.g., in hemophilia), and expanding their application in chronic genetic diseases. Nevertheless, optimization is needed since immune suppression must be balanced against the increased risk of infections. Immune modulation is thus both a mitigation strategy and a key factor in whether AdVs can evolve from single-use tools to durable, repeatable therapeutic platforms[39].

8.3. Toxicity reduction and scalability: toward clinical viability

Hepatotoxicity and insertional risks have prompted toxicity reduction efforts, including liver-detargeting mutations (e.g., hexon hypervariable region alterations) and fiber knob engineering to avoid Kupffer cell uptake. Nanotechnology integrations, such as lipid nanoparticle coatings, further shield vectors and enhance biodistribution. Additionally, direct vector delivery, such as intra-tumoral injections for cancer therapy, reduces systemic exposure and toxicity, minimizing off-target effects. In collaboration with the local administration, determining the optimal dose for efficacy and safety is crucial. Clinical trials employ dose-escalation studies to determine the maximum tolerated dose, reducing toxicity while maintaining therapeutic efficacy. Modifying the vector to lower liver cell affinity reduces hepatotoxicity by removing the

Table 3. Summary of key strategies employed to improve AdV performance, categorized by their underlying mechanisms, representative examples, intended purposes, and potential therapeutic benefits

Strategy	Mechanism	Examples	Purposes	Benefits
New serotypes	Using rare Ad serotypes	Ad26, Ad35, or chimpanzee Ads (e.g., Johnson & Johnson COVID-19 vaccine)	Reduce pre-existing immunity (antibody)	Enhance the efficacy of vectors
Capsid modification	Modifying surface proteins	Hexon and Fiber	Inflammatory responses reduction and altered tropism	Enhance targeting
Using 3rd generation vectors	Removal of viral genes	Kept only the ITRs and packaging signals	Lower immunogenicity	Extend gene expression
Immune modulation	Shielding capsid, Immunosuppressive co-therapy	Co-delivery of rapamycin, IL-10, granulocyte-macrophage colony-stimulating factor (GM-CSF)	Reduce immune clearance	Allow repeated dosing
Minimizing toxicity	De-targeting liver, dose optimization, local delivery	Reduced liver tropism, intra-tumoral injection	Enhance safety, reduce hepatotoxicity	Minimizing side effects, improving therapeutic index
Improving specificity	Specifically promoting tissue	microRNA, albumin	Minimize off-target effects	Allowing for more targeted gene expression
Sustained gene expression	Aiding genome integration, using repeated dose, combining vectors	Hybrid vectors, AdVs + AAVs	Prolong therapeutic gene expression	Extending duration of treatment effects
Simplifying production and scalability	Optimizing cultures, packaging cell lines, and purification	Suspension cultures, PER.C6 cells, chromatography purification	Improve yield	Reducing cost

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CAR binding site or using alternative receptors, like modifying the fiber protein to target other cells[10,20]. For scalability, upstream bioprocessing optimizations using suspension-adapted cell lines (e.g., HEK293 derivatives) have increased yields to 10^{13} viral particles per liter, addressing manufacturing challenges while lowering costs[39]. Developing cell lines (e.g., PER.C6) that produce higher titers of vector with less RCA contamination is crucial to enhance production efficiency, reduce RCA risk, and improve safety and yield. Advances in production methods allow recombinant AdVs to be used more widely in clinical applications (e.g., COVID-19 vaccine)[40]. Techniques such as anion exchange chromatography and ultracentrifugation also enhance purity and scalability, ensuring vectors meet clinical standards. These methods reduce production time and cost, enabling broader application. Hybrid AdV-AAV systems combine high-level expression and high titer of AdVs with persistence of AAVs, showing efficacy in preclinical oncology models. Additionally, AdVs can integrate with the components of retroviruses to facilitate long-term expression. However, this comes with the risk of insertional mutagenesis, which must be carefully managed.

9. APPLICATIONS

Analysis of gene therapy clinical trials data from 2004 to 2023 shows a significant decline in AdV usage. Their prevalence dropped from 26.1% in the 1989-2004 period, dropping to 24.7% in 2007, 23.3% in 2012, and 20.5% in 2017, before reaching a notable low of 14.7% by early 2023[41-45]. This reduction is driven by limitations of AdVs, such as high immunogenicity and transient gene expression, compared to alternative vectors like AAV (from ~2% to over 9%) and lentivirus (from ~3% to ~10%), which offer more safety and durability of gene expression. The decline accelerated, with the largest drop of 5.8% points occurring between 2017 and 2023 (Table 4). However, AdVs remain essential in specific clinical applications due to their high transduction efficiency and suitability for targeted gene delivery in certain vaccine platforms. During this time, three FDA-approved adenoviral gene therapy drugs are manufactured: Gendicine, Oncorine (with an intertumoral delivery system), and Astiladren (with an intravesical instillation delivery system)[46]. Following the analysis of AdV drugs and their utilization trends, the key applications that demonstrate the current utility of these vectors in gene therapy are outlined in the subsequent sections. Improvements in recombinant AdV design and production have expanded their clinical and preclinical applications, from gene therapy and cancer virotherapy to immunotherapy, vaccines, and regenerative medicine[40,47,48].

9.1. Genetic disorder

AdVs have been extensively explored for treating genetic disorders, with early successes like the 1993 CF trial highlighting their potenti[49-52]. However, challenges such as transient gene expression and immune responses require repeated dosing. Advances such as FDA approval for AdV-based therapies in rare diseases highlight their growing impact. Beyond CF, AdVs treat MD, hemophilia, rare conditions like LSDs and alpha-1 antitrypsin deficiency (AATD). For MD, especially DMD, less immunogenic serotypes are gaining interest, while hemophilia trials benefit from CRISPR-Cas9. Ornithine transcarbamylase (OTC) studies enhance hepatocyte targeting, expanding therapeutic options. While early studies faced immune response challenges[28], newer vector designs and CRISPR-Cas9 (known as Clustered Regularly Interspaced Short Palindromic Repeats) delivery improved safety and efficacy through chimeric vectors and tissue-specific promoters. These modifications minimize off-target effects and enhance the duration of gene expression, which is crucial for managing bleeding disorders.

9.2. Cancer therapy

AdVs are used to deliver therapeutic and/or suicide genes directly into cancer cells, restore normal cellular functions, sensitize tumors to other treatments, or even

Table 4. Global overview of gene therapy clinical trials (2004-2023)

Years	Clinical trials (n)	Countries (n)	Total vector uses (n)	Adenovirus uses (n)	Percentage
1989 - 2004	918	24	-	240	26.14
2007	1309	28	1339	331	24.72
2012	1843	31	1882	438	23.27
2017	2597	38	-	532 ± (-1) (+2)	20.50
2023	3900	46	3900	574	14.72

This table summarizes worldwide gene therapy trial activity, highlighting the decline in the use of AdVs over time. The 'n' values represent the number of clinical trials, countries, or vector uses for each year

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force self-destruction[53-55]. They can also deliver genes (e.g., herpes simplex virus thymidine kinase [HSV-TK]) to make cancer cells more sensitive to pro-drugs (e.g., ganciclovir), which, when expressed, convert ganciclovir into a toxic metabolite, causing cancer cell death[56](Table 5). AdVs enhance anti-tumor immune responses[57,58]. Initially, these vectors deliver genes encoding cytokines, such as GM-CSF or IL-2, stimulating immune cell activity within the tumor microenvironment[59]. This strategy is particularly effective when combined with immune checkpoint inhibitors, synergistically amplifying the defense system against cancer[60]. Secondly, they deliver genes encoding immune checkpoint inhibitors, including anti-PD-1 or anti-CTLA-4 antibodies, directly to the tumor niche[61]. This localized delivery minimizes systemic toxicity while maximizing the efficacy of immune checkpoint blockade therapies[62]. Furthermore, oncolytic Ads can induce tumor cell lysis, releasing tumor-associated antigens that prime the immune system for a more robust and targeted anti-tumor response[63-65]. Oncolytic Ads are engineered to selectively replicate in and destroy cancer cells while sparing normal tissues. This approach leverages the natural lytic cycle of Ads but restricts their replication to tumor cells through genetic modification[66]. To illustrate, Oncorine (H101), an RCA that selectively replicates in p53-deficient cancer cells, is approved in China for treating head and neck cancer. Clinical trials that used H101 combined with cisplatin demonstrated better tumor response and survival rates than chemotherapy alone[67]. ONYX-015, also known as dl1520, is another vector designed to replicate in cells with defective p53 pathways, common in many types of cancer. It has been tested in clinical trials for cancers such as head and neck, pancreatic, and colorectal cancers, showing tumor regression and improved patient outcomes in some cases[68] (Table 5).

9.3. Vaccines

AdVs are effective in vaccine development against infectious diseases due to high immunogenicity, infecting dendritic cells vital for immune response, and their large capacity for complex vaccine antigens[69-71]. They deliver genetic materials that encode antigens from pathogens into host cells[72]. This stimulates a robust immune response, making them a cornerstone in modern vaccinology[73]. These vaccines highlight their ability to induce both humoral (antibody) and cellular (T-cell) immune responses, providing comprehensive protection[74]. They are also explored for influenza, respiratory syncytial virus, and Zika virus, providing antigens to induce protective immune responses in preclinical models. Nowadays, next-generation AdVs mitigate immune responses, and integrate mRNA technology to enhance antigen expression[70]. These advancements prioritize global health applications, particularly in the context of Tuberculosis and Influenza, and HIV. Despite being primarily known for vaccine development, these vectors are also being explored for treating established infections, particularly chronic viral infections. However, immune responses and pre-existing immunity to Ad serotypes pose significant challenges.

9.4. Other therapeutic areas

AdVs are explored for treating cardiovascular diseases, which involve compromised blood flow[76-79] (Table 5). Although the past trials did not achieve their primary endpoint, they provided valuable insights into safety and feasibility. Ongoing research focuses on optimizing delivery to cardiac tissues (direct injection into the myocardium), reducing off-target effects, and immunogenicity, as well as establishing long-term efficacy and safety. AdVs in neurological disorders are promising but challenging due to the blood-brain barrier and the immune-privileged nature of the central nervous system (CNS) that removes vector[80,81] (Table 5), Strategies such as direct intracranial injection or vector modifications aim to enhance CNS penetration[82]. AdVs modulate the immune system in autoimmune diseases to induce immune tolerance or suppress autoreactive immune responses[83] (Table 5). Challenges include precisely controlling immune responses to prevent unintended immunosuppression. This issue could increase the risk of infection and exacerbate autoimmune conditions by managing vector immunogenicity. Researchers use rare serotypes and tissue-specific promoters to enhance safety and efficacy (Table 5). These vectors are also studied for tissue regeneration and repair, especially in bone regeneration and wound healing, but are still in the early stages of research (Table 5). Challenges include sustaining gene expression long enough for tissue repair and managing immune responses. In tissue engineering, AdVs combined with biomaterials deliver genes for tissue growth, such as cartilage or skin, but safety concerns and delivery efficiency limit clinical use.

10. EMERGING TECHNOLOGIES AND FUTURE DIRECTIONS

As gene therapy evolves, AdVs are central to discussions on delivery efficiency and safety. This section explores not only established paths but also emerging and theoretical innovations that may define the next generation of AdV-based therapeutics. Future perspectives are detailed in Table S1, highlighting ten emerging directions that are likely to influence research and clinical use.

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Table 5. Comprehensive applications of AdVs

Applications	Genes/deliverables	Mechanisms	Outcomes/benefits	Examples	References
Gene therapy					
CF	CFTR	Delivering the CFTR to the nasal epithelium	Initial correction of ion transport defects	First human trial in 1993, with transient expression	[49-51,84]
MD (esp. DMD)	Dystrophin	Delivery via Ad26/Ad35	Particle muscle function restoration, reduced immunogenicity	Preclinical models	[34,52,85,86]
Hemophilia A, B	Clotting Factors (e.g., VIII, IX)	Delivery via CRISPR-Cas9 with promoters	Improved clotting, minimized off-target effects	Clinical trials	[87-91]
Lysosomal storage disorders (LSDs)[92]					
Mucopolysaccharidosis type I	α-L-iduronidase	Enzyme replacement	Mitigates progressive cellular damage	Preclinical trials	[93]
AATD	AAT	Delivery to hepatocytes	Potential enzyme replacement	Ongoing trials	[94,95]
OTC	OTC	Corrects urea cycle enzyme deficiency in hepatocytes	Reduces ammonia buildup		[96-98]
Cancer therapy					
Tumor suppression	p53, a tumor suppressor gene	Restores p53 function in mutated cells	Induces apoptosis (mutation rate: 31-57% in Lung, 19-43% in Head and Neck cancers)	Lung, head, and neck cancers	[69,71,99-103]
Suicide gene therapy	HSV-TK	Increases the sensitivity of cancer cells to pro-drugs	Selective cancer cell apoptosis; can be combined with Chemotherapy	Glioma, colorectal, melanoma	[57,104-106]
Immunotherapy	Cytokines (GM-CSF, IL-2, anti-PD-1 / CLTA-4)	Boost anti-tumor immunity	Enhances immune response, reduces toxicity	Cervical cancer trial	[37,107,108]
Oncolytic therapy	H101, ONYX-015, armed with GM-CSF / TNF-α	Target cancer cells, amplify immune responses	Selective lysis, immune priming, and combination with radiation	H101 in China, ONYX-015	[67,109-111]

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Applications	Genes/deliverables	Mechanisms	Outcomes/benefits	Examples	References
Vaccines					
Ebola	ChAd3-EBO-Z, Ad26.ZEBOV antigens	Antigen encoding for immune stimulation	High efficacy in clinical trials	2019 approval	[112,113]
COVID-19 (Johnson & Johnson's Ad26.COV2.S)	RNA (encoding the spike protein of SARS-CoV-2)	Delivery with human Ad26	>70% efficacy, single-dose regimen		[114-119]
COVID-19 (Oxford-AstraZeneca)	Spike protein	Delivery with chimpanzee AdV (ChAdOx1)	>70% efficacy, scalability, and effectiveness in low-income countries	ChAdOx1 nCoV-19	[36,120,121]
Influenza	Influenza antigens (multivalent)	Adenoviral-vectored delivery to induce mucosal/systemic immunity	Durable protection against Victoria/Yamagata lineages (>80% efficacy in macaques)	Adenoviral-vectored multivalent vaccine Phase II	[122]
Malaria	Plasmodium antigens	Delivery with the ChAd63-MVA platform	Strong T-cell responses	Phase I/II trials	[123-127]
Flaviviruses (Dengue, Zika, JE)	Flavivirus antigens	Delivery of structural proteins	High-titer neutralizing antibodies, robust T-cell responses		[128]
Hepatitis B, C	Antiviral genes, Immunogens	Enhance antiviral immunity, target infected hepatocytes	T-cell stimulation/antibody responses; cure in chronic cases	TherVacB therapeutic vaccine trials	[129]
Cardiovascular disorders					
Ischemic heart disease	VEGF, FGF	Angiogenesis in ischemic tissues	Improved perfusion, angina alleviation	Euroinject One 2000s	[130]
Peripheral artery disease	VEGF, FGF	Promotes neovascularization	Enhanced blood flow, angina alleviation		[130]
Coronary artery disease	VEGF	Direct myocardial injection	Symptom relief (angina), feasibility insights	Euroinject One; early 2000s	[130,131]

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Applications	Genes/deliverables	Mechanisms	Outcomes/benefits	Examples	References
Neurological disorders					
Parkinson's disease	Glial cell line-derived neurotrophic factor	Protects dopaminergic neurons	Motor function improvement		[132,133]
Alzheimer's disease	Anti-amyloid-beta genes	Enzymatic degradation	Plaque reduction, slowed cognitive decline		[134]
Spinal muscular atrophy	Survival motor neuron 1	Restores SMN protein expression	Corrects motor neuron deficits		[47]
Ocular disorders					
Age-related macular degeneration	Anti-angiogenic genes (e.g., *PEDF*/sFlt-1)	Inhibits VEGF signaling	Reduces angiogenesis		[135-137]
Hematopoietic disorders	Gene therapy in bone marrow	In vivo HSC transduction via capsid-modified HDAd	Potential cell correction		[138]
Autoimmune diseases					
Type 1 diabetes	Proinsulin, regulatory molecules	Induces immune tolerance to insulin-producing β-cells	preventing or reversing the autoimmune attack that destroys β-cells	Preclinical trials	[139-141]
Rheumatoid arthritis	Anti-inflammatory genes, cytokines	Suppresses autoreactive responses	Reduced joint inflammation and synovitis		[142]
Regenerative medicine					
Bone regeneration	Bone morphogenetic proteins	Stimulates osteoblast differentiation	Enhances bone healing in breaks or spinal fusion surgeries		[143-145]
Wound healing	Platelet-derived growth factor, transforming growth factor-beta	Accelerates epithelialization and collagen synthesis	Accelerates chronic wound repair; improved closure	Standard treatments fail (diabetic ulcers)	[143,146]

CFTR: cystic fibrosis transmembrane conductance regulator; JE: Japanese encephalitis virus; VEGF: vascular endothelial growth factor; FGF: fibroblast growth factor; HSC: hematopoietic stem cell; HDAd: helper-dependent

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11. DISCUSSION

AdVs have consistently stood out as high-capacity, rapid-delivery gene therapy tools. Their non-integrating nature and strong transgene expression make them ideal for short-term, high-intensity applications such as vaccines and oncolytic therapies. The success of AdV-based COVID-19 vaccines further solidified their clinical relevance, with over three billion doses administered in the first year of the pandemic[38]. However, persistent challenges, namely, immunogenicity, transient gene expression, and off-target delivery, continue to limit their broader adoption, particularly for long-term or systemic therapies. These vectors evoke strong innate and adaptive immune

responses. This is not merely a limitation, but also a defining feature that must be strategically embraced or mitigated depending on the clinical context. While some advances, such as gutless vectors, capsid engineering, and alternative serotypes, have reduced immunogenicity, none have fully eliminated the risk of immune clearance, particularly upon repeated administration. This matter highlights the need for ongoing immune modulation strategies. Moreover, efforts to improve the durability of gene expression, such as co-delivery with epigenetic modifiers or hybrid systems, reflect a growing interest in adapting AdVs to fill therapeutic niches, traditionally dominated by long-lasting vectors. However, this issue raises a central question: should AdVs compete with AAVs in longevity, or redefine their clinical role around their unique strengths—transient but powerful gene delivery?

From a practical standpoint, AdVs are more scalable and economical to produce than other viral platforms, especially in low-resource settings. These attributes make them strong candidates for global vaccine deployment, rapid response therapies, and tumor-targeted applications where short-term expression is sufficient or even preferred. As the field evolves, AdVs may find their most impactful role not in replacing other vectors, but in complementing them—filling specific, well-defined therapeutic gaps. With continued innovation in targeting, immune modulation, and combination strategies, AdVs remain not just relevant but potentially indispensable in the next era of gene therapy.

12. CONCLUSION

AdVs have demonstrated remarkable versatility in gene therapy, enabling efficient transduction, broad tissue tropism, and scalable production. Their success in vaccine platforms, such as those that occurred during the COVID-19 pandemic, and in oncolytic cancer trials, underscores their practical relevance. However, challenges, including immunogenicity, transient expression, and toxicity, still limit their long-term clinical use. Recent innovations, such as rare serotypes, capsid engineering, helper-dependent systems, and the integration of CRISPR-Cas9 technologies, represent critical steps forward, but not definitive solutions. Emerging technologies, including nanotechnology-based delivery systems and computational vector design, are now redefining how we approach vector personalization and tissue targeting. These trends suggest that AdVs may not need to serve as universal vectors; instead, they could excel in transient, high-potency interventions where rapid gene expression is advantageous. Looking forward, a paradigm shift is needed; rather than seeking to overcome every intrinsic limitation, researchers should embrace AdVs for what they are, short-acting, flexible, and powerful tools. Their role will likely become increasingly specialized, especially in scenarios where durability is less critical, such as vaccine development, oncolytic therapy, or rapid genome editing. In this light, AdVs may serve not as competitors to long-term vectors, such as AAVs or lentiviruses, but rather as complementary tools in combination therapies. As the field matures, synergistic strategies that pair adenoviral systems with biomaterial scaffolds, smart nanoparticles, or targeted promoters may finally realize the long-promised potential of precision gene therapy. To ensure this progress, future research must prioritize clinical translation, manufacturing scalability, and targeted delivery strategies. In doing so, AdVs may secure a lasting niche within the gene therapy toolbox, not as a universal answer, but as a precision catalyst for rapid therapeutic change in both resource-rich and resource-limited settings.

DECLARATION

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No scientific content or interpretations were generated or influenced by AI-assisted technologies.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

All authors reviewed the results and approved the final version of the manuscript.

Authors' contributions

HS and ZM: conceptualization; data curation; formal analysis; investigation; project administration; resources; writing–original draft preparation; writing–review & editing preparation

Data availability

The data that support the findings of this study are available in public domain resources and previously published literature. These data were derived from the

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Competing interests

The authors declare that they have no competing interests.

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Supplementary information

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