



CRISPR-BASED GENOME EDITING AND ADVANCED DELIVERY SYSTEMS: RECENT INNOVATIONS, THERAPEUTIC APPLICATIONS, AND CHALLENGES IN CLINICAL TRANSLATION

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Abstract

CRISPR-based genome editing has emerged as a promising advancement in molecular medicine, offering new opportunities for precise genetic modification and therapeutic development. This narrative review examines recent innovations in CRISPR technologies, advanced delivery systems, therapeutic applications, and challenges associated with clinical translation. Conventional CRISPR-Cas9 systems, base editing, and prime editing are discussed, emphasizing improvements in editing precision, efficiency, and versatility. Advanced delivery strategies, including viral vectors, lipid nanoparticles, polymeric carriers, and engineered virus-like particles, are evaluated for their potential to improve cellular uptake and tissue-specific targeting. Recent therapeutic developments demonstrate the potential of CRISPR-based approaches in treating inherited genetic disorders, cardiovascular and metabolic diseases, cancers, and selected infectious and neurological conditions. Clinical advances in sickle cell disease, β -thalassemia, and transthyretin amyloidosis highlight the growing importance of genome editing in precision medicine. However, off-target modifications, genomic instability, immunogenicity, delivery limitations, manufacturing complexity, and regulatory concerns remain significant barriers to widespread clinical implementation. Emerging innovations involving artificial intelligence, high-fidelity nucleases, optimized prime editors, and personalized delivery platforms may improve therapeutic accuracy and clinical applicability. Continued research, comprehensive safety evaluation, and standardized regulatory frameworks are essential for translating CRISPR-based technologies into effective, accessible, and sustainable treatments. These developments may further expand personalized therapeutic options while supporting responsible clinical adoption across diverse healthcare settings.

Keywords: CRISPR-Cas9; Genome Editing; Base and Prime Editing; Advanced Delivery Systems; Clinical Translation

1. Introduction

Genome editing using CRISPR is one of the greatest developments in the fields of molecular biology, genetic engineering and therapeutic development. The technology will allow precise changes to be made to the DNA sequence which opens up new possibilities for understanding how genes work, fixing mutations associated with diseases and the development of new therapies. CRISPR-Cas systems are used to find a region in the genome to modify, unlike conventional genetic engineering approaches which involve more complex protein engineering and relatively more cumbersome experimental procedures. The simplicity, utility and flexibility of their use have greatly broadened the scope of genome manipulation in biomedical research and clinical use. From primitive natural bacterial defense strategies to advanced genome editing platforms, CRISPR technologies have become indispensable tools in unraveling genetic disorders and driving precision medicine-based therapeutic innovations (Pacesa et al., 2024).

The CRISPR-Cas9 system works by the Cas9 nuclease interacting with a guide RNA that guides the nuclease to a complementary DNA sequence. After target recognition, Cas9 will create a double-strand break that will be fixed by cellular repair processes like non-homologous end joining or homology-directed repair. These repair pathways allow for

more specific disruption or modification of the sequence of targeted genes but may have varying efficiencies and accuracy depending upon cellular conditions. There has been a recent advancement of technologies in genome editing, going beyond the use of DNA cutting, such as base editing and prime editing. Using an engineered Cas9 nickase, a reverse transcriptase and a prime-editing guide RNA, Prime editing allows programmed alterations of nucleotides, insertions, and deletions without the use of the typical double strand breaks of DNA. This method provides more flexibility in genetic modification of the genome for therapeutic applications and is one of the significant developments in achieving precise therapeutic genome modification by correcting disease-associated genetic variations (Chen & Liu, 2023).

The therapeutic promise of these CRISPR technologies has been the focus of much interest due to the large number of human disorders that are known to have mutations and/or pathways that can be targeted for editing. The inherited blood disorders, metabolic diseases, cardiovascular diseases and some cancers are significant areas of investigation. One of the most exciting applications of base editing is its ability to make the desired nucleotide change without creating double-strand breaks, which could limit some of the undesirable genomic changes that occur when using standard editing techniques. A series of experiments have shown that base editing can be used to alter or modify disease genes *in vivo*. For instance, in primates, via genome editing, cholesterol concentrations in the blood were decreased in a sustained manner, a key finding that could support the use of this approach to treat cardiovascular disorders (Musunuru et al., 2021). Moreover, base editing and prime editing provide avenues to provide correction of genetic variants that cannot be corrected by a traditional CRISPR-Cas9 approach (Testa & Musunuru, 2023).

CRISPR technologies are an important milestone in gene therapy as they have become a focus of clinical applications. Previous clinical trials showed that the components of a CRISPR-Cas9 system could be delivered systemically to induce targeted genome modifications in patients with transthyretin amyloidosis, indicating the potential for *in vivo* therapeutic genome modification (Gillmore et al., 2021). Later, the approval of exagamglogene autotemcel for specific patients with sickle cell disease and transfusion-dependent β -thalassemia was a significant milestone in the clinical trial of these CRISPR therapies. There is an *ex vivo* therapy for patients, which involves editing the patient's own hematopoietic stem cells to make more fetal hemoglobin, and less disease. The approval paved the way for the advancement of genome editing beyond experimental studies to clinically viable therapeutic interventions, but there are significant hurdles to consider, such as accessibility, complexity of treatment, and long-term assessment (Hoy, 2024).

While these are encouraging advancements, there are still a number of hurdles to the broad use of CRISPR therapies in the clinic. Safety concerns of off-target modifications and other unintended genome alterations, immunity to the modification, and the variable editing efficiency remain significant challenges (Kalter et al., 2025). Another key challenge for delivery is to ensure that the components of genome editing are delivered to the right tissues, to the right cells, with enough biological activity. Several strategies such as viral vectors, lipid nanoparticles, polymeric nanoparticles and engineered delivery platforms are being explored to overcome these challenges. Despite these advances, regulatory concerns, cost-of-treatment, scalability of manufacturing, cargo stability, and tissue specificity still play roles in the clinical feasibility of these therapies (Khoshandam et al., 2024). The current review focuses on the latest developments in CRISPR-based genome editing and sophisticated delivery systems for genome editing, with a particular emphasis on therapeutic applications, as well as challenges for clinical translation. In particular, the review covers recent advances in genome editing technologies, such as base editing, prime editing and novel CRISPR platforms. It also assesses the performance of these advanced viral and nonviral delivery methods, their impact on improving genome editing efficiency, cellular uptake, and therapeutic targeting. Additionally, the review covers the uses of CRISPR technologies in the treatment of different diseases with key safety concerns, technical challenges and regulatory hurdles to successful clinical application.

2. CRISPR-Based Genome Editing: Mechanisms and Recent Technological Innovations

2.1 Fundamental Mechanisms of CRISPR-Cas Genome Editing

The genome editing technique of CRISPR-Cas relies on programmable nucleases that are able to recognize and modify specific genetic sequences. The standard CRISPR-Cas9 system uses just one-guide RNA to guide the Cas9 enzyme to a target DNA adjacent to a protospacer adjacent motif (PAM). Cas9 creates a targeted double strand break and these breaks are fixed by non-homologous end joining (NHEJ) or homology directed repair (HDR). There are some differences between NHEJ and HDR, with NHEJ often leading to insertions or deletions, while HDR can introduce precise changes when an appropriate repair template is available. But the traditional editing techniques can result in unexpected mutations, inconsistent repair results and genomic rearrangements. With the development of newer CRISPR platforms, the use of modified nucleases and alternative CRISPR editing mechanisms is increasing to increase the precision and widen the therapeutic applications of these tools (Pacesa et al., 2024).

2.2 Base Editing and Prime Editing Technologies

The two methods of targeted genome modification, base editing and prime editing, are important developments. For most of the time, both types of base editors will edit a base pair. Usually, the C–G base pair is edited to T–A, while the A–T base pair is edited to G–C. These technologies involve the use of variants of the Cas proteins and nucleotide modifying enzymes such that substitutions can be made without the need for the conventional double strand DNA cleavage. Prime editing adds these functionalities by combining a Cas9 nickase, reverse transcriptase and prime-editing guide RNA (pegRNA). The pegRNA can specify the target and specify the modification that is desired, such as substitutions, small insertions and deletions. The properties are attractive for inherited genetic abnormalities which can be corrected through prime editing (Fu et al., 2023). It is also versatile as a therapeutic agent, and has the potential to improve the ability to reduce dependence on donor DNA templates in precision gene therapy (Aliciaslan et al., 2025). Figure 1 shows the fundamental mechanisms of the genome editing with CRISPR, such as the guide RNA mediated recognition of the target

genome, the activity of the Cas nuclease, the DNA repair pathways in the cell, base editing, and prime editing.

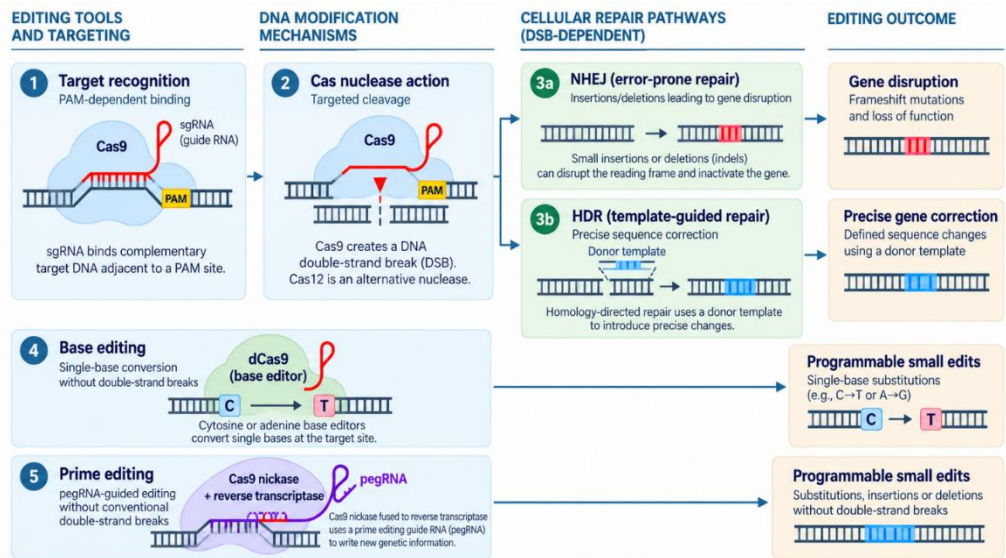


Figure 1. Mechanisms of CRISPR-Based Genome Editing

2.3 Recent Improvements in Genome-Editing Precision and Efficiency

Advances in CRISPR in recent years have been aimed at making the edits more precise and decreasing off-target modifications. The recognition of the target and off-target effects can be enhanced with high fidelity Cas variants and optimized guide RNA sequences, which can also be optimized through molecular engineering. The efficiency of prime editing has also been enhanced through modifications to editor architecture, pegRNA stability, and cellular DNA repair pathways (Zeng et al., 2024). However, the efficiency of editing is dependent on the sequence to be edited, cell type and biological context. For genetic correction to be reproducible, it is therefore important that the design of the pegRNA and the optimization of the editor. These innovations are key to the development of therapies, but it is important that they be tested for their specificity of editing, for sequence changes that may occur in the process, and for possible effects on the cell's responses over time (Godbout & Tremblay, 2023).

2.4 Emerging CRISPR Platforms and Future Innovations

New platforms of CRISPR are broadening genome editing to more than just Cas9-based DNA editing. CRISPR-Cas12 systems have been developed with variations of PAM recognition and DNA-cleavage properties and Cas13 systems direct the cleavage of RNA molecules, and are functional to modify transcripts without permanent mutations in the DNA sequence. New versions of prime editors are also being generated which would boost up the efficiency of the editing and expand compatibility to other genomic targets. The recent technological advances have put greater focus on the application of smaller editing elements, better targeting methods and flexible delivery approaches that are viable for therapeutic application (Jong et al., 2026). These advances could help bring about individualized care for genetic diseases, as the ability to correct genetic variants associated with disease is improved (Li et al., 2025). Table 1 shows the key aspects of traditional and new CRISPR platforms.

Table 1. Comparison of Conventional and Emerging CRISPR-Based Genome-Editing Technologies

Technology	Editing mechanism	Major advantages	Key limitations	References
CRISPR-Cas9	Guide RNA-directed DNA double-strand cleavage	Efficient gene disruption and broad applicability	Off-target cleavage and variable DNA repair outcomes	(Pacesa et al., 2024)
Cytosine base editing	Targeted C→G to T→A conversion	Precise substitutions without conventional double-strand breaks	Bystander editing and restricted conversion types	(Testa & Musunuru, 2023)

Adenine base editing	Targeted A–T to G–C conversion	Precise correction of selected pathogenic variants	PAM restrictions and unintended nucleotide changes	(Musunuru et al., 2021)
Prime editing	Cas9 nickase, reverse transcriptase, and pegRNA-guided editing	Enables substitutions and small insertions or deletions	Variable efficiency and complex editor design	(Zhao et al., 2023)
CRISPR-Cas12	RNA-guided DNA cleavage	Alternative PAM recognition and editing possibilities	Target-dependent activity and delivery challenges	(Pacesa et al., 2024)
CRISPR-Cas13	Programmable RNA recognition and cleavage	RNA targeting without permanent genomic modification	RNA-targeting specificity and delivery limitations	(Pacesa et al., 2024)

3. Advanced Delivery Systems for CRISPR-Based Genome Editing

3.1 Importance of Efficient CRISPR Delivery

Being efficient in delivering CRISPR into the nucleus is a key factor for its successful application. To make the genome editing approach with CRISPR into clinically promising treatments, it is crucial that it is delivered effectively. Components of genome editing are needed to reach the desired tissues, to cross the cellular membranes, to not be trapped or degraded in the cells, and to have high enough activity to modify the desired sequences. Biological barriers, enzymatic degradation, lack of cellular uptake and unintended tissue distribution, however, can diminish the effectiveness of the therapy. Further, the relatively large size of the associated proteins from CRISPR makes it difficult to transport them into the target cells. Thus, the creation of platforms that deliver therapeutic DNA editing to the appropriate tissue, with minimal off-target effects, is an imperative in therapeutic genome editing (Du et al., 2023). The delivery strategies also need to take into account the efficiency of editing and the toxicity and immunogenicity of the product, as well as its long-term safety requirements (Khoshandam et al., 2024).

3.2 Viral Vector-Based Delivery Systems

Viral Vector Based Delivery systems. The genetic transfer of cell by viral vectors is highly explored. Adeno-associated viruses (AAVs) are widely investigated as gene delivery vectors because of their efficient gene transfer capabilities, tissue tropism, and relatively low pathogenicity. However, their limited cargo capacity restricts the delivery of larger CRISPR-based genome-editing components. Lentiviral vectors can carry larger genetic material and can be used to provide a sustained expression over a longer period of time; however, they can have insertional mutagenesis potential. There may be more opportunities for off-target editing as well if the nuclease is expressed for a long period. There are alternative strategies for transient delivery such as engineered viral platforms and nonreplicating virus-like particles. These particles may carry editing protein(s) without the continuous expression of the nucleases encoding genes (Banskota et al., 2022).

3.3 Lipid Nanoparticles and Nonviral Delivery Technologies

Nonviral systems have attracted interest as they appear to be easily formulating, have the potential for scale-up production and repeated administration. Lipid nanoparticles (LNPs) can be used to shield nucleic acids from degradation and to aid in the cellular delivery of nucleic acids via endocytosis. Their composition can be changed to affect their stability, cellular uptake and tissue distribution. There are other delivery methods such as polymer-based nanoparticles, peptides and inorganic nanocarriers. However, there are still several challenges, including the need for the endosomal escape and for a limited organ selectivity, and the formulation associated toxicity. Further development of the engineering of nanoparticles could aid in the release within the cell and tissue-specific targeting, which would facilitate the application in a wide range of treatment (Sioson et al., 2021). Table 2 provides a comparison of the key features of the different delivery platforms.

3.4 Delivery of CRISPR Components as DNA, RNA, and Ribonucleoproteins

CRISPR components can be introduced as plasmid DNA, messenger RNA (mRNA) or ribonucleoprotein (RNP) complexes. Sustained expression can be achieved using plasmidDNA, with the drawback of having a longer nuclease activity. On the other hand, mRNA allows for the production of proteins, while not needing to enter the nucleus. RNP delivery facilitates faster and more convenient editing by introducing preassembled Cas proteins and guide RNAs to limit and shorten exposure to nucleases. These methods vary with respect to stability, cellular processing, length of time it takes

for editing and off-target effects. Therefore, it is crucial to choose an appropriate delivery method to enhance the therapeutic precision (Lin et al., 2022).

3.5 Recent Advances in Tissue-Targeted Delivery Systems

The last few years have focused on organ-specific nanoparticles and delivery vehicles. The delivery of RNP via lipid nanoparticles has been shown to be effective for gene editing in lung tissues, and is under investigation for the potential application of CRISPR/Cas9 in the lungs (Haley et al., 2025). Likewise, lipid nanoparticles have been applied to the experiments of editing cells of the trabecular meshwork, and have been proposed for use in disorders of the eye (Huang et al., 2025). All these advances demonstrate the need for more selectivity in the tissue and delivery to intracellular sites. The various viral and nonviral delivery systems for CRISPR (such as lipid nanoparticles, polymeric-based nanoparticles, and engineered virus-like particles), as well as the cellular uptake, delivery, and targeted delivery of CRISPR to the genome, are shown in Figure 2.

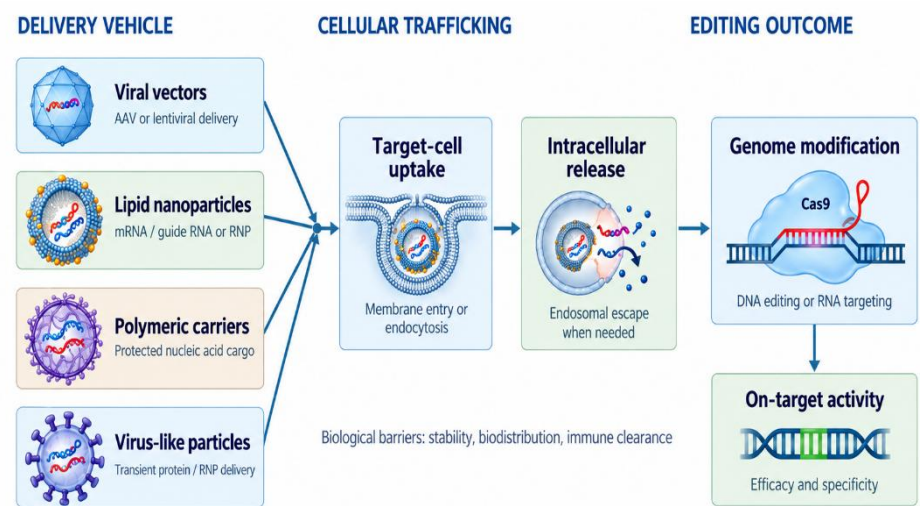


Figure 2. Advanced Delivery Systems for CRISPR-Based Genome Editing

Table 2. Comparison of Viral and Nonviral Delivery Systems for CRISPR-Based Genome Editing

Delivery system	Advantages	Major limitations	References
AAV vectors	Efficient gene transfer; tissue tropism	Limited cargo capacity; immune responses	(Khoshand am et al., 2024)
Lentiviral vectors	Larger cargo capacity; stable expression	Integration risks; prolonged expression	(Du et al., 2023)
Lipid nanoparticles	Flexible formulation; transient delivery	Endosomal escape and organ targeting challenges	(Madigan et al., 2023)
Polymeric nanoparticles	Customizable composition; cargo protection	Variable toxicity and delivery efficiency	(Sioson et al., 2021)
Virus-like particles	Transient protein delivery	Manufacturing and targeting challenges	(Banskota et al., 2022)

4. Therapeutic Applications of CRISPR-Based Genome Editing

4.1 Treatment of Inherited Genetic Disorders

Genome editing using CRISPR has proven to have great therapeutic potential for inherited genetic diseases, like sickle cell disease and β -thalassemia. These disorders are disorders of hemoglobin production, which can be corrected by specific modification of the hematopoietic stem cell. Exagamglogene autotemcel is an ex vivo CRISPR-Cas9-based therapy that disrupts the erythroid-specific enhancer of the BCL11A gene in patients' hematopoietic stem cells. This modification reduces BCL11A expression in erythroid cells, increases fetal hemoglobin production, and helps alleviate the clinical manifestations of sickle cell disease and β -thalassemia. Significant decreases in severe vaso-occlusive crises have been seen in sickle cell disease (SCD) patients (Frangoul et al., 2024). Also, patients with transfusion dependent β -thalassemia (TDT) have been reported to have improved transfusion independence after treatment (Locatelli et al., 2024). More recently, HBG1 and HBG2 promoters were targeted using CRISPR-Cas12a, and offers promising therapeutic results in patients with β -thalassemia (Frangoul et al, 2026).

4.2 CRISPR-Based Therapies for Cardiovascular and Metabolic Diseases

CRISPR technology to treat cardiovascular and metabolic diseases. The in vivo CRISPR-based editing may provide the

opportunity to treat the cardiovascular and metabolic diseases by targeted disruption or correction of disease-associated genes. Liver-directed editing (LDE) has been shown to be feasible for TTR-AMC because investigational CRISPR-Cas9 therapy has resulted in long-lasting decreases in TTR levels in blood plasma (Fontana et al., 2024). CRISPR-mediated KLKB1 disruption has also yielded promising clinical results in hereditary angioedema, making it a possible new therapeutic target to prevent swelling attacks. In addition, CRISPR-mediated KLKB1 disruption has demonstrated promising clinical results in hereditary angioedema, thereby providing a potential therapeutic target to prevent swelling attacks (Cohn et al., 2025). The Hao1 lipid nanoparticles mediated base editing has been shown to have therapeutic effects in an experimental model of primary hyperoxaluria type 1 (Zhang et al., 2024). The results indicate the viability of durable genetic editing but should be further tested for safety and the ability to cure patients, along with other areas of research.

4.3 Applications in Cancer Immunotherapy

Genetic modification of immune cells is a key aspect of cancer immunotherapy using CRISPR-based technologies that is being investigated. Functional properties of CAR T cells can be optimized using gene editing to increase the ability to recognize the tumor cells and avoid unwanted interactions with the tumor cells in the immune system. Multiplex gene modification is clinically feasible as has been shown using base-edited CAR7 T cells, which have been shown to have antileukemic activity in patients with T-cell ALL who have relapsed (Chiesa et al., 2023). Furthermore, using targeted lipid nanoparticles for the delivery of the components of CRISPR-Cas9 has demonstrated experimental therapeutic potential in head and neck cancers (Masarwy et al., 2025). However, there are still several limitations, such as the heterogeneity of the tumor, immune toxicity, and poor delivery.

4.4 CRISPR Applications in Infectious and Neurological Diseases

CRISPR technologies are also being studied on infectious diseases and neurological diseases. CRISPR-Cas13a has the potential to control pathogenic bacterial infections by targeting their RNA and could be an experimental approach to tackle antimicrobial resistance (Kim et al., 2025). A base edit can have a therapeutic effect that lasts for many years in neurological diseases, which involve a defect in the production of abnormal proteins. Experimental gene editing of PRNP in a pre-clinical humanized mouse model of prion disease led to reduction in prion protein expression and increased survival, suggesting potential clinical use, but not yet proven. Experimental editing of PRNP expression in a pre-clinical humanized mouse model of prion disease resulted in increased survival and reduced expression of prion protein, indicating clinical potential, but not proven).

4.5 Recent Clinical Advances and Approved CRISPR-Based Therapies

In recent years, remarkable advances in the clinic have shown the increasing potential for therapeutic applications of CRISPR. Exagamglogene autotemcel is a big regulatory step; investigational treatments are opening new treatment options. There are some encouraging results for patients with sickle cell disease (SCD) who have benefited from the CRISPR-Cas12a editing of fetal hemoglobin (HbF) regulatory regions (Hanna et al., 2026).

The translation of these findings, however, needs to be continually assessed in terms of the durability of the treatment, safety, cost and availability. The therapeutic uses of genome editing—including for hemoglobin disorders, transthyretin amyloid cardiomyopathy, hereditary angioedema, leukemia, prion disease, and primary hyperoxaluria—and the various steps in clinical development are briefly summarized in Figure 3. The main stages of development of therapeutic applications are described in Table 3.

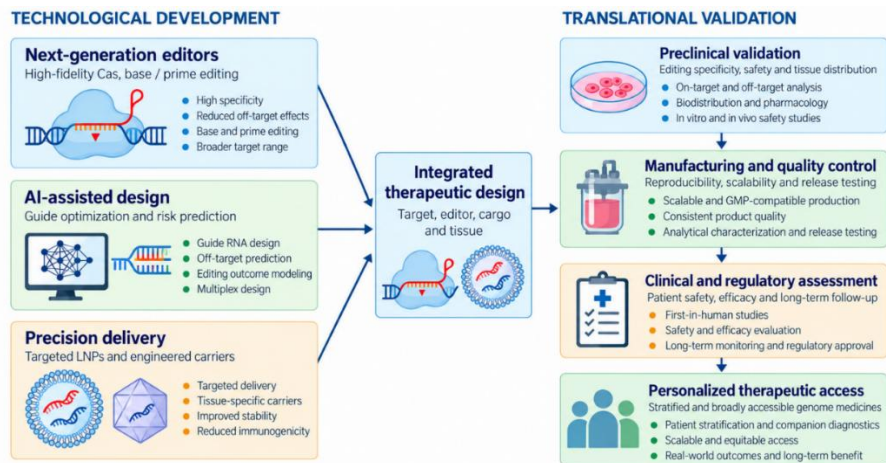


Figure 3. Therapeutic Applications of CRISPR-Based Genome Editing Across Human Diseases

Table 3. Major Therapeutic Applications and Clinical Advances of CRISPR-Based Genome Editing

Disease/application	CRISPR approach	Development stage	References (APA format)
Sickle cell disease	Ex vivo editing to increase fetal hemoglobin	Approved therapy	(Frangoul et al., 2024)

β -Thalassemia	Hematopoietic stem-cell editing	Approved and investigational approaches	(Locatelli et al., 2024)
ATTR cardiomyopathy	In vivo TTR gene disruption	Clinical investigation	(Fontana et al., 2024)
Hereditary angioedema	In vivo KLKB1 gene editing	Clinical investigation	(Cohn et al., 2025)
Leukemia	Base-edited CAR-T cells	Early clinical investigation	(Chiesa et al., 2023)
Primary hyperoxaluria	HAO1 base editing	Preclinical	(Zhang et al., 2024)
Prion disease	PRNP base editing	Preclinical	(An et al., 2025)

5. Challenges in Clinical Translation of CRISPR Technologies

5.1 Off-Target Editing and Genomic Safety

One of the biggest issues to clinical translation of CRISPR-based therapeutic approaches is off-target genome editing. While CRISPR-Cas systems can be used to target DNA for modification, guide RNAs are sometimes able to identify partially complementary sequences, which can lead to non-specific DNA cleavage. These changes can cause mutations, chromosomal rearrangement, large deletions and also changes in the regulation of genes, which might be detrimental. Targeted sequence modification can result in unanticipated changes to the genome as a result of cellular mechanisms that repair the DNA. All these effects are a cause of concern for possible genomic instability, carcinogenic effects and long-term therapeutic safety. Assessment methods, such as whole genome sequencing, targeted deep sequencing and genome-wide off-target detection methods all are, therefore, vital. Additional optimization of the guide RNA, comprehensive safety evaluation and better high-fidelity nucleases could help to minimize unintended modifications before clinical application (Kalter et al., 2025).

5.2 Delivery Efficiency and Tissue-Specific Targeting

An additional challenge for the use of CRISPR in the clinic is the efficient delivery of CRISPR components to target tissues. Biological hurdles such as enzymatic degradation, immune clearance, cellular membranes and restrictions on cellular trafficking need to be overcome by those molecules that are used to alter the genome. Viral vectors are good in delivering cargo to cells but may be limited by size of cargo, immunogenicity and continuous expression of the genes. Nonviral systems, especially lipid nanoparticles, can be used for transient delivery, but have an uneven distribution of nanoparticles across organs. Furthermore, the successful cellular uptake does not always result in efficient endosome escape and/or nuclear localization. In order to increase therapeutic specificity, targeting of ligands, engineering of the composition of the nanoparticles, and delivery system engineering is required. Restrictive tissue penetration and intra-tumor heterogeneity in cancer therapy, for example, might hinder prime-editing strategies (Sen et al., 2023).

5.3 Immunogenicity and Long-Term Therapeutic Safety

The effectiveness and safety of CRISPR-based therapeutic applications may be influenced by immune responses against genome-editing components and delivery vehicles. Pre-existing immunity or treatment-induced immune responses against bacterial Cas nucleases can affect therapeutic efficiency and patient safety. Viral capsids and certain nanoparticle components may also trigger inflammatory reactions, potentially reducing delivery efficiency or limiting repeated administration (Khoshandam et al., 2024). Although transient nuclease exposure may reduce the duration of genome-editing activity, immune reactions and unintended cellular modifications remain possible. Long-term follow-up is particularly important because permanent genomic alterations may produce delayed adverse effects that are not detectable during initial clinical evaluations. Potential concerns include genomic instability, unintended mutations, and the clonal expansion of edited cells (Kalter et al., 2025). Therefore, comprehensive post-treatment monitoring should include genomic stability, treatment durability, immune responses, and possible clonal expansion to ensure the long-term safety of CRISPR-based therapies.

5.4 Manufacturing, Scalability, and Regulatory Challenges

Large-scale manufacturing and regulatory requirements represent significant challenges to the widespread clinical implementation of CRISPR-based therapies. Clinical-grade production requires standardized manufacturing procedures, consistent product quality, and validated testing methods to ensure therapeutic safety and effectiveness (Far et al., 2025). Patient-specific cell therapies involve complex processes, including cell collection, genetic modification, expansion, and quality-control assessments, which increase treatment costs and limit scalability. Regulatory evaluation must address editing accuracy, product consistency, genomic safety, and long-term therapeutic outcomes. Furthermore, differences between ex vivo and in vivo genome-editing approaches introduce additional challenges related to manufacturing, delivery, and clinical assessment (Khoshandam et al., 2024). Developing standardized production systems, cost-effective delivery technologies, and internationally coordinated regulatory frameworks may improve treatment accessibility, manufacturing scalability, and the clinical translation of CRISPR-based therapies.

5.5 Ethical Considerations and Accessibility

Ethical issues continue to be a crucial part of the proper application of CRISPR-based treatments. While somatic genome editing has significant therapeutic potential, the possibility of future generations being affected by the modification, of not allowing the future to decide whether the altered genome is passed on, and the effect on the biology of future generations are also concerns. Access to advanced treatments may also lead to unequal treatment experiences, which could further exacerbate the health care inequities, especially in low-resource countries. The high cost of treatment, the need for specialized equipment and facilities and the reduced access to clinical services may limit access to patients. Transparency of ethical control, equitable treatment policies and ongoing evaluation of clinical benefits and risks are required to implement this responsibly. To realize the potential of the innovations enabled by CRISPR in sustainable healthcare, it is crucial to tackle these concerns in conjunction with technological challenges (Far et al., 2025). The principal translational challenges and corresponding mitigation strategies are summarized in Table 4.

Table 4. Major Challenges in CRISPR Clinical Translation and Potential Mitigation Strategies

Major challenge	Clinical implications	Potential mitigation strategies	References (APA format)
Off-target editing	Unintended mutations and genomic instability	High-fidelity nucleases and genome-wide screening	(Kalter et al., 2025)
Delivery limitations	Inadequate editing in target tissues	Targeted nanoparticles and improved delivery vehicles	(Sen et al., 2023)
Immunogenicity	Inflammation and reduced therapeutic effectiveness	Transient editor exposure and immune monitoring	(Khoshandam et al., 2024)
Manufacturing complexity	High costs and inconsistent production	Standardized manufacturing and quality-control procedures	(Far et al., 2025)
Regulatory and ethical concerns	Delayed approval and unequal access	Long-term surveillance, ethical oversight, and equitable access policies	(Far et al., 2025)

6. Emerging Trends and Future Perspectives

6.1 Development of Next-Generation Genome-Editing Platforms

Future developments of more accurate, effective and versatile genome editing technologies are likely to further shape the future of CRISPR technology. Next generation of high fidelity nucleases are being engineered to better target a sequence while causing less of an unintended modification to the genome. The potential applications of making genetic changes to right the wrongs may be even wider, now that advanced base editors and prime editors can be used to correct more types of genetic mutations without creating a conventional double-strand DNA break. Better editor architecture, guide RNA stability and modulation of DNA repair may help to increase the editing efficiency in various types of cells. Furthermore, there are also smaller CRISPR-associated proteins and RNA editing platforms that could be used for in-cell delivery, and allow for editing of previously inaccessible molecular targets. Even with these advances, there is still a need for standards to be set in terms of consistent editing results as well as genomic security in the long-term. For future investigations, platforms that can be used for complex mutations, with high specificity and therapeutic reliability are important. (Jong et al., 2026).

6.2 Integration of Artificial Intelligence and Precision Delivery Technologies

Artificial intelligence (AI) is expected to play an increasingly important role in optimizing CRISPR-based therapeutic development. Machine learning algorithms can analyze genomic sequences, predict guide RNA efficiency, and identify

potential off-target interactions before experimental validation (Sherkatghanad et al., 2023). AI-assisted computational models may also support the design of improved base editors, prime-editing guide RNAs, and highly specific nuclease variants (Lee, 2023). Furthermore, integrating AI with nanotechnology could facilitate the development of more efficient delivery systems by predicting nanoparticle composition, cellular uptake, and tissue distribution (Dorsey et al., 2024). Advanced lipid nanoparticles, engineered virus-like particles, and targeted polymeric carriers may improve the transport of genome-editing components into specific tissues. However, computational predictions require experimental confirmation, particularly when evaluating biological responses and long-term safety. Combining predictive modeling with high-throughput screening and experimental validation could accelerate the development of reliable genome-editing delivery platforms.

6.3 Personalized Genome Editing and Translational Opportunities

Precision medicine can be useful to patients suffering from rare genetic diseases or mutations, and genome editing could be a good approach for developing personalised therapies. Genomic data from individual patients can help inform the choice of the editing technology, molecular targets and delivery system to be used (Li et al., 2025). Advances in the engineering of stem cells, ex vivo genome editing, and organ-specific nanoparticles could open up new avenues for treating inherited disorders, cancers, neurological diseases, and metabolic diseases (Khoshandam et al., 2024). Moreover, developments in manufacturing technologies and standardisation of quality control could make the development and clinical implementation of treatment easier (Far et al., 2025). This should be integrated into future treatment strategies, which should also include a detailed genomic analysis, risk stratification of the patient and follow-up of treatment response. However, personalized interventions may be limited due to high development costs, complex regulatory requirements and access to healthcare. Cooperative research, appropriate regulatory processes and cost-effective manufacturing methods will thus be essential for successful clinical translation.

7. Conclusion

CRISPR genome engineering is a revolutionary technique in molecular medicine, with great potential in the treatment of genetic diseases, cancers and other complex diseases. The development of genome modification technologies, including the recent advance of CRISPR-Cas9, base editing, and prime editing, has greatly enhanced the precision, versatility, and therapeutic applications of genome modification. Moreover, there are opportunities for targeted and efficient delivery of genome-editing components through the development of advanced delivery systems such as viral vectors, lipid nanoparticles and engineered virus-like particles. Growing relevance in precision medicine is shown by clinical advances that are made in sickle cell disease, β -thalassemia, transthyretin amyloidosis and cancer immunotherapy. Despite these advantages, problems with off-target effects, genomic instability, immunogenicity, tissue-specific delivery and long-term safety remain a limitation to widespread clinical use. The complexity of the manufacturing process, regulatory conditions, treatment accessibility and ethical aspects further affect the accessibility of the treatment. New technologies such as artificial intelligence, high-fidelity nucleases, better prime editors, and delivering the editors to specific cells could help address these challenges. There is a need for extensive evaluation of the safety, enhanced delivery efficacy, standardisation of manufacturing processes and long term clinical studies. For this to become a reality, researchers, clinical practitioners, regulators and biotechnology developers will have to work closely together. The field of genome editing is an area of personalized medicine that is likely to become a more essential part of health care, both in this country and around the world, as technology advances and clinical development of the technology is responsible and safe.

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