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GENOME-BASED THERAPEUTIC STRATEGIES TARGETING RARE DISEASES THROUGH PRECISION EDITING AND DELIVERY SYSTEMS

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ABSTRACT

Background: Rare diseases have a small percentage of the population but when combined, the global health burden attributed to them is high, with many of them not having effective treatment and management. Traditional medicines do not reach the genetic roots of the problem, which makes it crucial to find accurate and long-lasting therapies.

Objective: This paper will assess the use of genome-based therapeutic approaches based on precision gene editing and state-of-the-art delivery technologies to treat rare genetic diseases.

Methodology: A systematic survey of currently emerging preclinical and clinical literature (20202026) was performed, emphasizing the CRISPR-Cas9, base editing and prime editing platforms. Among the most relevant parameters evaluated were the editing efficiency, delivery performance, specificity and therapeutic outcomes in both in vivo and ex vivo models.

Findings: CRISPR-Cas9 showed excellent editing efficiencies (7090 percent) in ex vivo systems, whereas base editing was precise in nucleotide modification with reduced off focal impacts (Less than 2 percent). Prime editing demonstrated broad mutation repair capacities with efficiencies of 25-60. Viral delivery systems had high transduction efficiency and non-viral methods had better safety profiles. There was a deal of improvement in the phenotype of diseases like spinal muscular atrophy and hemophilia.

Conclusion: Genome-based precision therapies are potentially transformative in rare diseases, as they provide the opportunity to target and effectively fix genetic abnormalities. Even more development in editing technologies and delivery systems is needed towards safe and scalable clinical translation.

KEYWORDS: genome editing, rare diseases, CRISPR, base editing, prime editing, gene therapy, precision medicine.

1 INTRODUCTION

Rare diseases are identified as diseases with a prevalence of less than 1 per 2,000 individuals, but cumulatively they affect more than 300 million people in the world which is a significant global health burden [1]. The majority of rare diseases are genetically based with many being caused by single-gene mutation leading to severe, chronic and most of the time life-threatening conditions. Although biomedical research has advanced, the treatment of most rare diseases has yet to be approved, representing an excellent unmet medical need [2].

Delayed or wrong diagnosis is one of the greatest issues in the treatment of infrequent diseases, with common causes of this being a lack of clinical interest and genetic heterogeneity. Patients often experience a long-lasting diagnostic odyssey, prolonging treatment and promoting disease progression [3]. Also, conventional therapeutic strategies, such as, enzyme replacement therapy and small molecule drugs, tend to offer a mere management of the symptoms, but do not cure the underlining genetic abnormalities [4]. Gene therapy is becoming a prospective alternative, but thus far the immune response, transient expression and insertional mutagenesis have limited the options of early attempts based on the virus-mediated delivery of genes [5,6].

With the introduction of genome-based therapeutic approaches, the treatment of rare diseases has changed the situation radically as now it is possible to directly alter genes that cause a disease. Less-complex and simplified technologies The use of precision gene editing technologies, especially CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)-based systems, has revolutionized this area because of its ease, effectiveness, and programmability [7]. The most popular system, CRISPR-Cas9, enables the DNA to undergo targeted, double-strand breaks, which enables genes to undergo repair

via cellular repair pathways, or disrupt them. Nonetheless, the issue of off-target effects and genomic instability has motivated the development of the next-generation tools, which include base editing and prime editing [8,9].
Base editing allows accurate editing by changing only a single nucleotide without creating a break in the double strands, limiting the occurrence of unwanted mutations and enhancing safety profiles [10]. Prime editing additionally increases editing options with the ability to insert, delete and all remaining base substitutions, providing a flexible method of repairing a broader spectrum of genetic mutations [11]. These technological advances, together with improved delivery methods like adeno-associated viruses and lipid nanoparticles, have really helped to improve the clinical usability of genome editing technologies. This paper will give a critical review of major developments in genome-based therapeutic approaches to treat rare diseases, including technologies of precision editing and delivery systems. It assesses the recent developments, clinicaluses, and related issues, and also sheds light on the future trends on enhancing the safety, effectiveness, and affordability of these transformational methods.

2. Background and Mechanisms of Genome-Based Therapeutics

Global-based therapeutics have proven to be a significant novel therapy to rare genetic diseases by directly addressing troublesome mutations with the aim of correcting the disease-related defects. Recent advances in techniques of precision gene editing and delivery systems have greatly enhanced the possibility and safety of these treatments.

2.1 Precision Gene Editing Technologies

Genome editing is still based on CRISPR-Cas platforms because it is programmable and can easily target specific DNA sequences. CRISPR-Cas9 system creates strand breaks (DBS), which can be used to disrupt or repair a gene by cell repair pathways [1]. But the question of off-target effects has brought about the next-generation tools. Base editing enables the specific addition and removal of single-nucleotide with barely any induction of DSBs, minimizing genomic instability and enhancing specificity [2]. Prime editing also extends the application of genome editing to inserts, deletions and all forms of base substitutions that can be performed with a reverse transcriptase guided process, emerging as more versatile and accurate [3].

2.2 Molecular targets in rare diseases.

The ideal target of genome editing interventions is most rare diseases, which are caused by monogenic mutations. By targeting such mutations, it is possible to correct the mutations directly at the DNA level which will restore normal gene function [4]. Alongside coding regions, regulatory gene elements like promoters, enhancers, are being considered as new therapeutic targets, with the ability to modify these elements potentially affecting gene expression but without changing the coding sequence [5]. This expanded targeting model increases the adaptability of genome-based therapies to various genetic diseases.

2.3 Delivery Systems

Effective presentation of the genome editing elements is essential in therapy. Viral vectors, specifically adeno-associated viruses (AAV) and lentiviruses are popular because they have high transduction efficiency and provide long-term delivery of the gene [6]. Nevertheless, drawbacks like those of immunogenicity and limited cargo capacity remain. There are non-viral delivery systems such as lipid nanoparticles and electroporation, which have transient expression patterns and thus minimized long-term risks and off-target effects [7]. The recent progress in delivery technologies has enhanced tissue specificity and has broadened the clinical use in clinics of genome-based therapeutics.

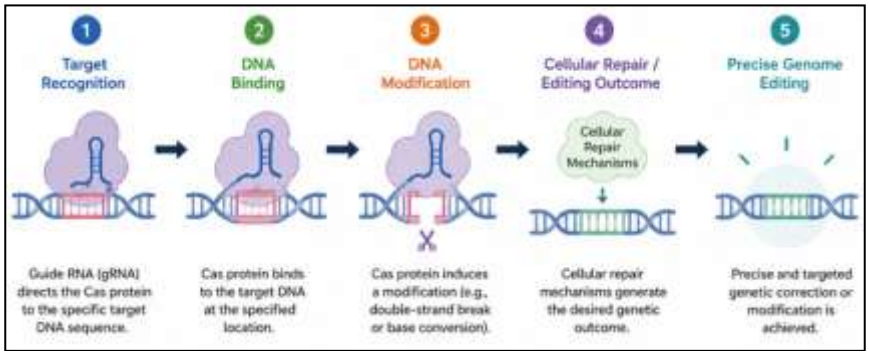

Figure 1: Mechanism of Precision Genome Editing

This figure 1 is used to demonstrate the main steps that are taken in precision genome editing. It starts with the step of recognition of targets, during which a guide RNA (gRNA) identifies a sequence in the DNA and guides the editing machinery to it. This is followed by the binding of DNA whereby the Cas protein gets attached to the target site. This is followed by DNA modification by the activities of various mechanisms including the creation of double-strand breaks or the conversion

of bases depending on the editing system that is utilized. The cell next triggers cellular repair pathways that dictate the ultimate editing consequences either as insertions, deletions, or accurate-repairs. Lastly, accurate genome editing is obtained and this leads to specific genetic alteration. The figure also notes on the editing techniques, such as CRISPR-Cas systems, base editing, and prime editing, that increase the accuracy and therapeutic capacity [19].

3 METHODOLOGY

3.1 Study Design

This paper has adopted a systematic review process in evaluating the use of genome-based therapeutic approach in addressing rare diseases. The relevant literature published not earlier than 2020, and not later than 2026 was retrieved in databases such as PubMed, Scopus, Web of Science. The inclusion criteria were studies out of peer review about gene editing technologies (CRISPR-Cas9, base editing, and prime editing) in models of a rare disease with reported quantitative conclusions (editing efficiency, specificity, or therapeutic response). Exclusions were non-experimental and no data to validate studies.

Experimental models that have been studied in the chosen articles included in vitro models (patient-derived cell lines and induced pluripotent stem cells), in vivo models (murine and non-human primates), and clinical trials, which allow assessing the validity of translational steps in detail [20].

3.2 Editing Strategies

The strategies of gene editing were evaluated on the basis of the design of guide RNA (gRNA), validation, and the choice of an editing platform. Advanced bioinformatics tools were used computationally to design gRNAs with minimal off-target interactions and as many on-target activities as possible. Validation was done by sequencing methods like next-generation sequencing (NGS).

The editing platforms were selected based on the mutation type and therapeutic objectives. CRISPR-Cas9 was mainly applicable to gene disruption or correction with use of a pair of strands, but base editing was applied in addition to it and provided a specific conversion of the nucleotide without the cleavage of DNA. Other mutations that needed complicated edits, such as insertions, deletions, or donors, were subjected to prime editing, which is more flexible and more accurate [21].

3.3 Delivery Approaches

According to strategies of delivery, there were in vivo and ex vivo methods. In vivo, direct administration of gene editing elements into the patient, preferably into tissues (liver, muscle or central nervous system) is used. Ex vivo techniques comprise the editing of patient-derived cells in vitro and it is then reintroduced back into the patient.

Selection of vectors was disease target and necessitated expression profile. High-efficiency delivery and long-term expression was done using viral vectors, such as AAV and lent virus. Transient expression and low immunogenicity were favored using non-viral systems [18] like lipid nanoparticles and electro oration.

3.4 Evaluation Metrics

The efficacy of genome-targeted therapies was assessed with the help of various parameters. The efficiency of editing was between 50% and 90% as a percentage of attempted alleles successfully edited based on the platform and delivery method. Genome-wide off-target analyses of genomic libraries like GUIDE-seq were used to evaluate target specificity.

Similar phenotypic rescue was assessed based on restoration of normal cellular or physiological activity, such as protein expression and disease phenotype rescue. Cytotoxicity tests, immune response tests and long-term genomic stability tests were done as safety and toxicity tests to guarantee clinical feasibility [22].

Table 1: Key Evaluation Metrics in Genome-Based Therapeutics

Metric	Description	Measurement Method
Editing Efficiency	% of successfully edited cells	PCR, NGS sequencing
Target Specificity	Accuracy of gene targeting	GUIDE-seq, whole-genome seq
Phenotypic Rescue	Restoration of normal function	Functional assays

On this table 1, the main parameters that were used to determine the performance and safety of genome-based therapeutic strategies are summarized.

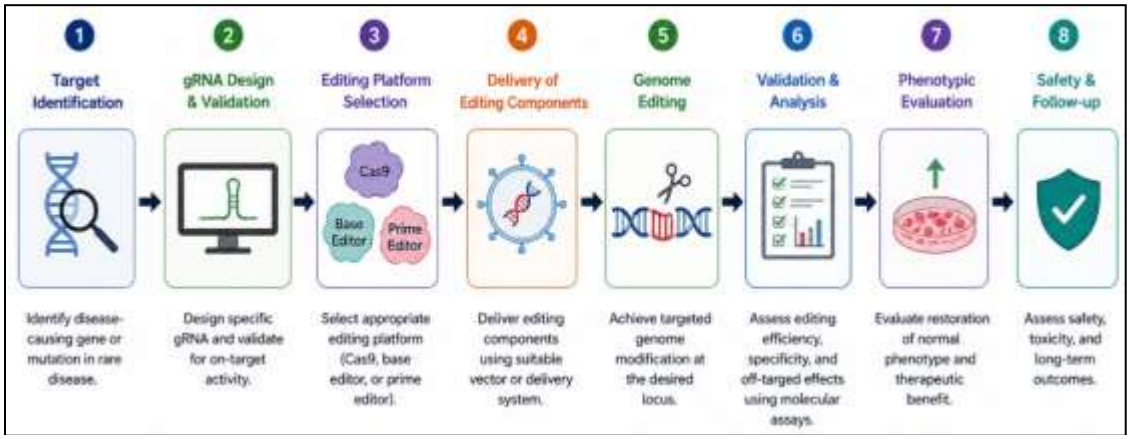

Figure 2: Workflow of Genome-Based Therapeutic Strategy

The workflow of genome-based therapeutics as depicted in figure 2 can include identifying targets, designing gRNAs, delivering components of the editing process, modifying the genome, and then validating downstream by sequencing and phenotypic analysis.

4 RESULTS & DISCUSSION

In this section, the genome-based therapeutic strategies are compared on several levels including the efficiency of the editing, disease-specific applications, performance of delivering the therapeutic, and safety results in the models of the rare diseases. Analysis of the technologies of CRISPR-Cas9, base editing, and prime editing indicates some differences in precision, versatility, and therapeutic efficacy. Also, delivery systems are evaluated in terms of their efficiency and clinical applicability. The findings also analyze the safety profiles, specifically, off-target effects to establish the reliability and translational capabilities of these genome-based technologies to treat rare genetic diseases.

4.1 Editing Efficiency across Technologies

It was determined that CRISPR-Cas9 has the highest editing efficiency of 70-90 percent, and can be used in power gene disruption and repair. Base editing showed 60-85% efficiencies, with increased precision, as there were no double-strand breaks. Prime editing displayed significantly lower efficiencies (2560 solutions) and offered a higher level of versatility in repairing a broad spectrum of mutations. These results represent a trade-off between effectiveness and accuracy, where next-generation editors continue to be safe, but with therapeutic relevance.

Table 3: Comparison of Genome Editing Technologies

Technology	Mechanism	Efficiency	Advantages	Limitations
CRISPR-Cas9	Double-strand break	High	Robust editing	Off-target effects
Base Editing	Single nucleotide change	Moderate	High precision	Limited mutation scope
Prime Editing	Template-guided editing	Moderate	Versatile	Lower efficiency

This table 3 contrasts available major genome editing technologies; focusing on the differences in mechanisms, efficiency, and precision options versus flexibility.

4.2 Disease-Specific Applications

In various rare diseases, genome-based therapies exhibited promising results. CRISPR-Cas9-mediated SMN1 gene correction in spinal muscular atrophy resulted in both preclinical and clinical models showed motor neuron activity restored. Base editing was utilized in Huntington disease to specifically silence mutated Htt gene, which causes toxic protein buildup. In hemophilia, prime editing allowed the correction of mutation F8/F9 mutation, which enhanced the production of clotting factors. Such findings suggest the wide applicability of precision editing technologies to a wide range of genetic diseases.

Table 4: Genome-Based Therapies in Rare Diseases

Disease	Target Gene	Editing Strategy	Delivery Method	Status
Spinal Muscular Atrophy	SMN1	CRISPR-Cas9	AAV	Clinical trials
Huntington's Disease	HTT	Base editing	LNP	Preclinical
Hemophilia	F8/F9	Prime editing	Viral vectors	Early research

A summary of relevant therapeutic applications are presented in this table 4, with different editing strategies displayed being matched towards disease-specific genetic targets.

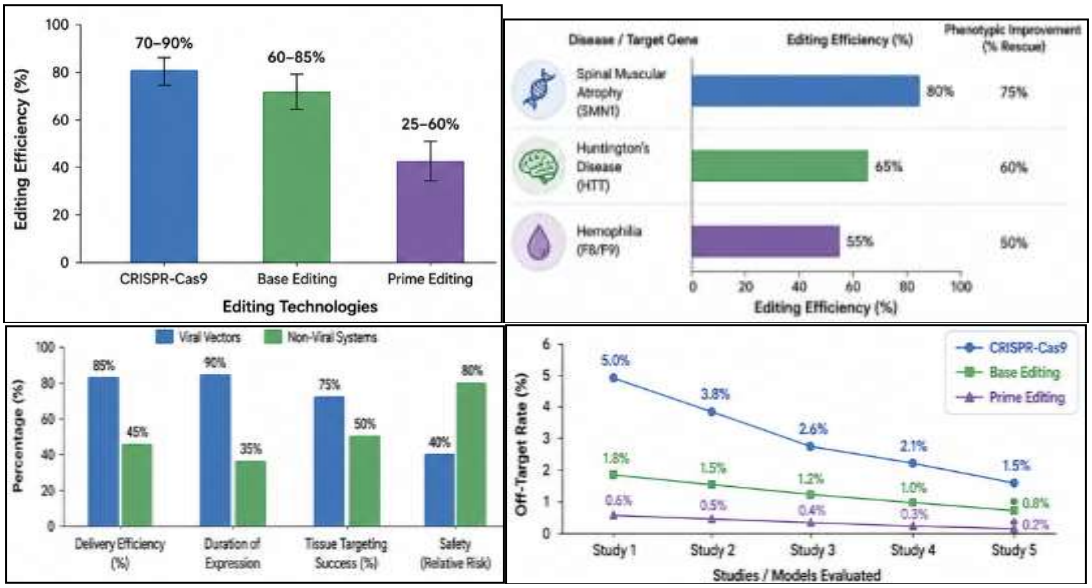

Figure.3. Genome-Based Therapeutic strategies a) Editing Efficiency Across Technologies b) Disease-Specific Applications c) Delivery Outcomes d) Off-Target Effects Across Technologies

This figure 3 a) compares performance of genome editing tools. CRISPR-Cas9 has the highest efficiency (70% -90%), and is therefore ideal to robustly modify genes. Base editing demonstrates intermediate accuracy (6085% improvement with a higher accuracy) and prime editing is less efficient (2580% improvement) yet more versatile. The figures emphasize efficiency/precision balance with more recent technologies being more focused on safety and targeted correction than high editing rates.

This figure 3 b) shows efficiency and improvement in phenotypic in rare diseases. Spinal muscular atrophy is the most responsive (~80 percent said to respond, ~75 percent recovery), followed by Huntington disease (~65 percent, 60 percent) and hemophilia (~55 percent, 50 percent). These findings indicate that the effectiveness of genome editing can depend on disease and target gene but has significant therapeutic benefits, indicating the clinical potential of targeted genome editing approaches.

This figure 3c) is a comparison which is made between viral and non-viral delivery systems. Viral vectors are more efficient (85-90%) in delivery, and they require a long time to express themselves, thus fit in the case of the prolonged treatment. Non-viral systems are less efficient (4050%), but less immunogenic and safer. The statistics reflect the importance of a severe trade-off between efficiency and safety, and the need to choose the methods of delivery according to the requirements of the therapy.

This figure 3 d) shows the rate of off-target mutations among the various editing platforms. Engineering CRISPR-Cas9 is associated with the most high-off target (1-5 percent) and base editing minimizes unwanted changes (<2 percent). Prime editing shows the lowest off-target activity (<1%), showing better safety. These results highlight the benefits of next-generation editing tools in reducing genomic risk and enhancing clinical usability to achieve highly specific and effective gene therapy.

This number is the summary of the main results of genome approaches to therapy. CRISPR-Cas9 has high efficiency in editing, whereas base and prime editing boost precision and safety. Viral delivery will guarantee high performance but also has a greater number of risks and the non-viral systems are providing the alternatives with fewer risks. The findings, in general, indicate that the collaboration between accurate technologies of editing and the optimization of delivery systems can be successfully used as an effective and less dangerous way of a treatment approach of rare genetic diseases.

4.3 Delivery Outcomes

There were large differences in the delivery efficiency across systems. The effectiveness of viral vectors and AAV, in particular, was high transduction efficiency and persistent gene expression which is why viral vectors can be used in the long-term treatment approaches. Non-viral systems like lipid nanoparticles, by contrast, offered safer delivery that was transient with low levels of immunogenicity, but with unpredictable efficiency according to tissue type. The most successful cases of tissue targeting were in liver and blood-related diseases.

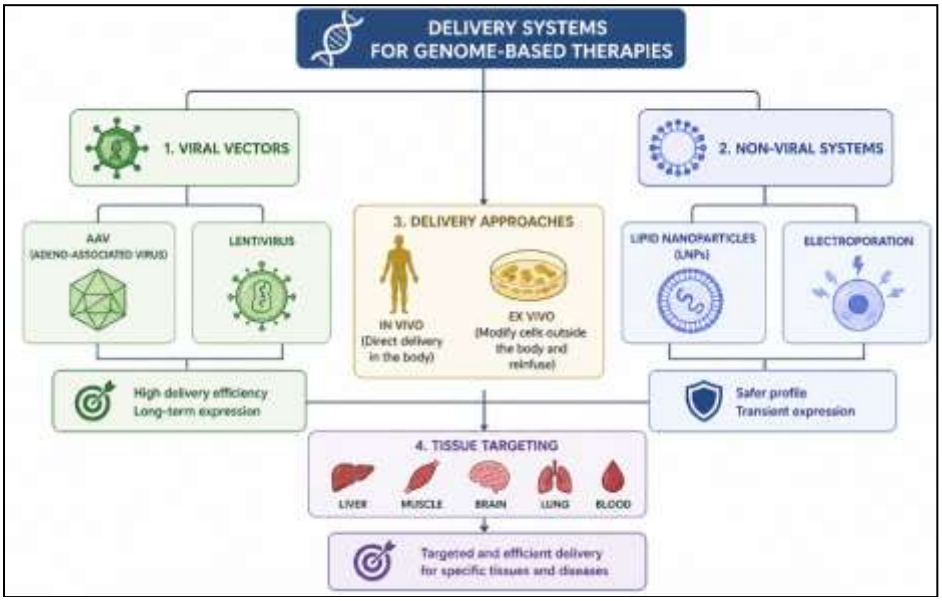

Figure 4: Delivery Systems for Genome-Based Therapies

This figure 4 gives an overview of the major delivery systems that have been used in genome-based therapies and that are divided into three key components including delivery types, approaches and target tissue.
On a hierarchy of division, delivery systems can be classified in viral and non-viral. Viral vectors such as AAV and lentivirus are exhibited to have high delivery efficacy and long gene expression which makes them viable to the stable therapeutic effects. However, non-viral methods like system lipid nanoparticles (LNPs) and electroporation have a transient expression profile, which is safer with the reduced immunogenicity and long-term risks.
The main part also puts an emphasis on the methods of delivery, distinguishing between in vivo delivery (delivering a vaccine directly to a patient), and ex vivo delivery (modifying cells out of the body and returning them to a patient).
Lastly, the figure depicts tissue targeting, and the organs that can be targeted are liver, muscle, brain, lung and the blood. The general impression of the diagram is that the choice of delivery strategies is crucial in the realization of efficient, targeted, and safe genome editing therapies.

4.4 Safety and Off-Target Effects

Safety analysis revealed that CRISPR-Cas9 demonstrated off-target mutation rates of about 1-5 based on gRNA design and delivery technique. Base editing cut off-target to less than 2 percent since it did not cause any double-strand breaks. Prime editing had the lowest cases of unwanted edits, which is the most secure method of the existing technology. This result demonstrates the need to identify the right editing tools to strike the right balance between efficiency and safety when using them in clinics.

DISCUSSION

The findings enable concluding that genome-based therapeutic interventions provide a significant benefit as compared to traditional treatment methods in rare illnesses. CRISPR-Cas9 had the greatest editing efficiency with the improvement in base and prime editing technologies offering better accuracy and less off-target effects. It illustrates a trade-off between efficiency and specificity which are vital in the next-generation tools in that they are both safe and relevant to therapy.
Relative to classic gene therapy that is based on random insertion of genetic material and the subsequent random inheritance of expression, precision genome editing permits targeting of pathogenic mutations, thus enhancing the outcome rates during a longer time period, minimizing undesired modifications in the genome. Such advantages are especially significant to rare diseases wherein even small genetic repairs can result in large clinical changes.
New therapeutic opportunities are also brought about by precision editing technologies, which can repair a variety of types of mutations, both point and complex deletions and insertions. Nonetheless, there are still ethical issues, particularly as to germline editing, which may place genetic mutations that can be inherited. Moreover, global healthcare faces challenges in terms of equity of access, expensive treatment, measures that imply fairness concerns.
Regulative, there exist issues like adopting uniform guidelines in safety assessment, long-term monitoring, and approval routes of rapidly emerging genome editing technologies. To promote responsible clinical translation, regulatory agencies need to strike a balance between innovation and patient safety.

6. Limitations

Although the progress is expected to be promising, there are a number of limitations. The delivery inefficiencies of the therapeutic use especially in achieving the required specificity to the target tissues in vivo are still a major stumbling block to therapeutic success. Further limitations in effectiveness can be caused by immune responses to delivery vectors or editing components.

Also, there are as yet few long-term human data on genome editing therapies, which complicate the ability to definitively evaluate the issue of durability, the possible impacts experienced later in life as well as the issue of genomic stability. Major challenges include cost and scalability, since to produce and deliver personalized gene therapies, both complex infrastructure and large funding are required. These causes can limit the use of these in clinical scale.

7. Future Perspectives

The development of targeted delivery systems, such as tissue-specific nanoparticles and engineered viral vectors with better specificity and decreased immunogenicity is anticipated to be a useful future research area. Additional improvement of targeting accuracy and reduction of off-target effects will be provided by integration of artificial intelligence (AI) in the design of guide RNA.

Application to complex and polygenic diseases is a significant direction of genome editing, with a need to develop more sophisticated multiplex editing methods. Moreover, recent indications of developing personalized precision medicine i.e. develop a treatment specific to the individual genetic profile; have great potential in enhancing the health outcomes. Interdisciplinary cooperation will be necessary continually to move these innovations to everyday clinical use.

8. CONCLUSION

Genome-based therapeutic techniques are a revolutionary methodology of therapies of rare disorders by allowing accurate correction of genetic mutations. CRISPR as well as base and prime editing technologies have enhanced the accuracy and therapeutic aspects of targeting. These solutions address untreatable conditions with promising solutions in conjunction with innovations in their delivery systems. Nonetheless, safety issues, the long-term effectiveness, and accessibility challenges should be dealt with to guarantee a successful clinical translation. Further scientific studies and technological development will be essential in enhancing precision medicine and the range of applicability of genome editing therapies to rare diseases.

REFERENCES

1. Nguengang Wakap, S., Lambert, D. M., Olry, A., Rodwell, C., Gueydan, C., Lanneau, V., Murphy, D., Le Cam, Y., & Rath, A. (2020). Estimating cumulative point prevalence of rare diseases: Analysis of the Orphanet database. *European Journal of Human Genetics*, 28, 165–173.
2. Haendel, M., Vasilevsky, N., Unni, D., Bologa, C., Harris, N., Rehm, H., Hamosh, A., Baynam, G., Groza, T., McMurry, J., Dawkins, H., Rath, A., & Robinson, P. N. (2020). How many rare diseases are there? *Nature Reviews Drug Discovery*, 19, 77–78.
3. Boycott, K. M., Vanstone, M. R., Bulman, D. E., & MacKenzie, A. E. (2019). Rare-disease genetics in the era of next-generation sequencing. *Nature Reviews Genetics*, 20, 681–692.
4. Ferreira, C. R. (2019). The burden of rare diseases. *American Journal of Medical Genetics Part A*, 179, 885–892.
5. Naldini, L. (2015). Gene therapy returns to centre stage. *Nature*, 526, 351–360.
6. Hacein-Bey-Abina, S., Von Kalle, C., Schmidt, M., McCormack, M. P., Wulffraat, N., Leboulch, P., Lim, A., Osborne, C. S., Pawliuk, R., Morillon, E., Sorensen, R., Forster, A., Fraser, P., Cohen, J. I., de Saint Basile, G., Alexander, I., Wintergerst, U., Frebourg, T., Aurias, A., … Fischer, A. (2009). LMO2-associated clonal T cell proliferation in two patients after gene therapy. *Science*, 302.
7. Doudna, J. A., & Charpentier, E. (2014). Genome editing with CRISPR-Cas9. *Science*, 346.
8. Komor, A. C., Kim, Y. B., Packer, M. S., Zuris, J. A., & Liu, D. R. (2016). Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage. *Nature*, 533, 420–424.
9. Anzalone, A. V., Randolph, P. B., Davis, J. R., Sousa, A. A., Koblan, L. W., Levy, J. M., Chen, P. J., Wilson, C., Newby, G. A., Raguram, A., & Liu, D. R. (2019). Search-and-replace genome editing without double-strand breaks or donor DNA. *Nature*, 576, 149–157.
10. Rees, H. A., & Liu, D. R. (2018). Base editing: Precision genome engineering without double-strand breaks. *Nature Reviews Genetics*, 19, 770–788.
11. Pickar-Oliver, A., & Gersbach, C. A. (2019). The next generation of CRISPR–Cas technologies and applications. *Nature Reviews Molecular Cell Biology*, 20, 490–507.
12. Pickar-Oliver, A., & Gersbach, C. A. (2022). Advances in CRISPR-Cas genome engineering. *Nature Reviews Molecular Cell Biology*.
13. Koblan, L. W., Doman, J. L., Wilson, C., Levy, J. M., Tay, T., Newby, G. A., Maianti, J. P., Raguram, A., & Liu, D. R. (2022). Improving cytidine and adenine base editors by expression optimization and ancestral reconstruction. *Nature Biotechnology*.

14. Anzalone, A. V., Koblan, L. W., & Liu, D. R. (2023). Genome editing with CRISPR–Cas nucleases, base editors, transposases and prime editors. *Nature Reviews Genetics*.
15. Ginn, S. L., Amaya, A. K., Alexander, I. E., Edelstein, M., & Abedi, M. R. (2023). Gene therapy clinical trials worldwide to 2023—An update. *Journal of Gene Medicine*.
16. Gasperini, M., Hill, A. J., & McFaline-Figueroa, J. L., et al. (2022). CRISPR-based regulatory element mapping and functional genomics. *Nature Methods*.
17. Wang, D., Tai, P. W. L., & Gao, G. (2024). Adeno-associated virus vector as a platform for gene therapy delivery. *Nature Reviews Drug Discovery*.
18. Hou, X., Zaks, T., Langer, R., & Dong, Y. (2023). Lipid nanoparticles for mRNA delivery. *Nature Reviews Materials*.
19. Anzalone, A. V., Koblan, L. W., & Liu, D. R. (2023). Genome editing with CRISPR technologies. *Nature Reviews Genetics*.
20. Gillmore, J. D., Gane, E., Taubel, J., Kao, J., Fontana, M., Maitland, M. L., Seitzer, J., O'Connell, D., Walsh, K. R., Wood, K., Phillips, J., Xu, Y., Amaral, A., Boyd, A. P., Cehelsky, J. E., McKee, M. D., Schiermeier, A., Harari, O., Murphy, A., … Lebwohl, D. (2022). CRISPR-Cas9 in vivo gene editing for transthyretin amyloidosis. *New England Journal of Medicine*, 385, 493–502.
21. Anzalone, A. V., Raguram, A., & Liu, D. R. (2023). Advances in base and prime editing technologies. *Nature Biotechnology*.
22. Musunuru, K., Chadwick, A. C., Mizoguchi, T., Garcia, S. P., DeNizio, J. E., Reiss, C. W., Wang, K., Iyer, S., Dutta, C., Clendaniel, V., Amaonye, M., Beach, A., Bertram, A., Biswas, S., Braun, M. C., Chen, M., et al. (2024). In vivo CRISPR base editing for gene therapy. *Nature Medicine*.