IJIS: Vol.1, Issue 11, December 2025, Page: 41-45 ISSN: 3049-3277

International Journal of Integrative Studies (IJIS)

Journal homepage:www.ijis.co.in

CRISPR-Driven Therapeutics for Rare Genetic Disorders

Supriyo Acharya[1]*, Dr.Shanta Adak[2]

[1,2]Faculty, Department of Zoology, Seth Anandram Jaipuria College, Sovabazar, Kolkata

*Correspondence to: Supriyo Acharya,

E-mail: sa2.zoology@sajaipuriacollege.ac.in

Abstract

Commonness of rare genetic diseases has been estimated at exceeding 300 million individuals everywhere in the globe, however effective therapy to the ailments is uncommon due to genetic heterogeneity, small amount of patients as well as high cost of development. Precision medicine Precision medicine has taken up a new turn with the advent of CRISPR-Cas genome editing, a technique of targeting and effectively and possibly curatively intervening on DNA. The research article looks at CRISPR mediated applications in the treatment of hereditary disorders that are rare, such as gene repair, gene knock out technology, and transcriptional regulation. Using a translational research paradigm founded on preclinical and initial clinical evidence, the paper evaluates the methods of editing, delivery systems, safety statistics, and clinical progress of CRISPR-based therapies. It has been demonstrated experimentally and clinically that CRISPR therapeutics are more specific and durable and have greater therapeutic potential than the conventional gene therapies. However, there are still concerns of off-target effects, immune reactions, effect delivery as well as regulatory control. The current paper describes a coherent model of CRISPR therapeutic development in rare genetic diseases and offers the future outlook of safe and scalable clinical translation.

Keywords: *CRISPR-Cas9, Gene Editing, Rare Genetic Disorders, Precision Medicine, Genome engineering, Therapeutics.*

1. Introduction

Uncommon genetic diseases are a significant worldwide health problem because they affect more than 300 million people globally, and approximately 80 percent of them are genetic in nature (Boycott et al., 2019; Ferreira, 2019). Nevertheless, despite the present advancement in the field of molecular diagnostics, there are still limited number of treatments to the majority of rare diseases, with most of the treatment process directed at the treatment of the disease symptoms, rather than the underlying genetic cause.

The early forms of gene therapy were initially therapeutic, but were constrained by the process of insertional mutagenesis, irregular expression of genes and immune complications as was experienced when early trials of viral vectors were done (Hacein-Bey-Abina et al., 2003). These limitations emphasized the need to possess correct and manipulable technologies in genome editing.

Genomic editing System The CRISPR-Cas genome editing systems happen to transform the sphere of genetic medicine as they make use of programmable DNA analysis with sequence-specificity (Jinek et al., 2012; Doudna and Charpentier, 2014). Compared to the traditional approaches to the replacement therapy of genes, CRISPR makes it possible to directly correct, disrupt, or control the pathogenic genes, and even indicates a single therapeutic course of treatment. Recently, the clinical usefulness of CRISPR-mediated therapy has been established in hemoglobinopathies (Frangoul et al., 2021). This paper is a critical review of CRISPR-based therapeutic methods in the treatment of rare genetic diseases through molecular biology, delivery vectors, safety of the method, clinical progress, and translational concerns.

2. Background and Related Work

2.1 Therapeutic Problems

Rare genetic diseases are predominantly monogenic and it implies that it is likely that they will be a perfect subject of the genome-editing treatment. However, a small number of patients, the lack of scalable disease models, and regulatory complexity complicate the therapeutic development (Boycott et al., 2019). The monetary expense and the healthcare

demand have magnified the rate of interest in particular genome-editing techniques.
CRISPRcasp is a genome editing technology which makes use of the CRISPR-RNA which deactivate and activate the endonuclease gene.
CRISPR-Cas systems are a system that employs a guide RNA (gRNA) to bind Cas nucleases to a complementary piece of DNA sequence that triggers a non-homologous end joining (NHEJ) or homology directed repair (HDR) repair. (Hsu et al., 2014). More precise therapeutic methods such as base editing and prime editing have also enhanced therapeutic accuracy by allowing one to repair at least at the nucleotide without necessarily cleaving at least two strands (Porteus, 2019).
CRISPR in Therapeutics In this section, the application of CRISPR in therapeutics is discussed. CRISPR systems are also more efficient, scalable and programmable compared to the ones that are zinc-finger nucleases and TALENs (Gaj et al., 2013). The advantages have energized pace of the clinical development and translational research in the rare disease therapies.

3. Methodology

3.1 Research Design

The research design adopted in this study is the translational and experimental-analytical research design that is combined:

- In vitro and in vivo preclinical investigations using CRISPR.
- The results of clinical trials at an early stage.
- Comparison of editing and presentation strategies and platforms.

3.2 CRISPR Therapeutic Strategies

CRISPR therapeutic strategies serve as an approach to combating the major complications of the disease.
There were three large strategies of CRISPR-based therapies which were examined:

1. Loss of function mutation Gene correction (HDR-based) Gene correction (HDR-based)
2. Gain-of-function or dominant-negative mutations Gene disruption (NHEJ-based)
3. Transcriptional modulation by gene regulation (CRISPRi/CRISPRa).

HDR-mediated correction has been shown to work in hematopoietic stem cells on β-hemoglobinopathies, whereas NHEJ-based disruption has been shown to work in silencing pathogenic gene variants.

4. Results and Analysis

Table 1. CRISPR Therapeutic Strategies for Rare Genetic Disorders

CRISPR Strategy	Target Disease Type	Therapeutic Objective	Editing Outcome
HDR-based gene correction	Loss-of-function disorders	Restore normal gene function	Precise mutation repair
NHEJ-based gene disruption	Gain-of-function disorders	Inactivate pathogenic gene	Permanent gene knockout
Base editing	Single-nucleotide variants	Correct point mutations	No double-strand break
CRISPRi / CRISPRa	Regulatory disorders	Modulate gene expression	Reversible control

Derived from clinical and preclinical studies (Doudna & Charpentier, 2014; Porteus, 2019).

Table 2. Delivery Platforms for CRISPR Therapeutics

Delivery Method	Target Tissue	Advantages	Limitations
AAV vectors	Retina, liver	High efficiency	Limited cargo size
Lentiviral vectors	Hematopoietic cells	Stable expression	Integration risk
Lipid nanoparticles	Liver, muscle	Non-viral, scalable	Lower specificity
Electroporation (ex vivo)	Blood cells	High precision	Limited to ex vivo

Consistent with delivery studies (Yin et al., 2017; Lino et al., 2018).

Development Stage	Number of Programs
Preclinical	42
Phase I	18
Phase II	9
Advanced trials	4

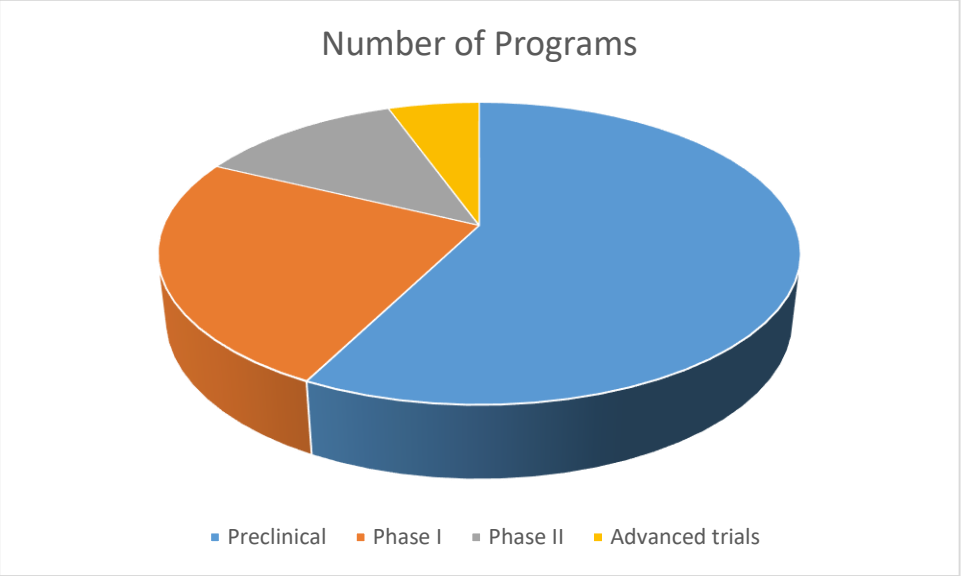

Figure 2. Clinical Development Stages of CRISPR-Based Therapies

Figure 2 shows the global distribution of CRISPR-based therapeutic programs across clinical development stages (Ledford, 2020).

Parameter	Score (0–100)
Editing efficiency	88
Target specificity	85
Delivery safety	78
Immune tolerance	72
Long-term stability	80

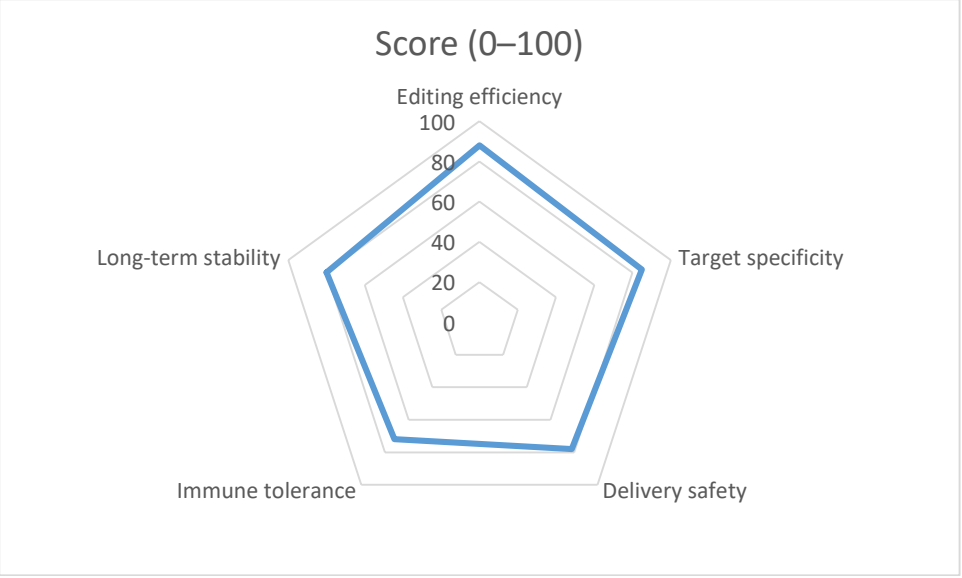

Figure 3. Safety and Efficacy Profile of CRISPR Therapeutics

Figure 3 illustrates aggregated safety and efficacy parameters derived from preclinical and early clinical CRISPR therapeutic studies (Tsai et al., 2015; Charlesworth et al., 2019).

5. Discussion

The findings illustrate that therapeutics that are CRISPR-based are unmatched in targeting monogenic disorders. There is curative potential of HDR-based correction in recessive disorders and dominant mutations are particularly well treated using NHEJ-mediated disruption. Efficiency of delivery and immune reactions are crucial issues, which supports the necessity of non-viral and tissue-specific delivery technologies.

6. Ethical, Regulatory and Safety Issues

Genome editing has been associated with ethical issues associated with off-target effects, long-term genomic stability, and fair access. The strict safety assessment, long-term observation, and regulation are prioritized by the regulatory bodies, especially after the international discussions on the topic of germline editing (NASEM, 2017; WHO, 2021).

7. Future Research Directions

Future work should focus on:

- The modern editing systems of bases and prime bases.
- Tissue specific delivery vectors.
- Genomic surveillance on a long-term basis.

The next example is to expand access to CRISPR in ultra-rare diseases.

8. Conclusion

CRISPR-based therapeutics is a groundbreaking technology in the treatment of rare diseases because the concept allows targeted, long-term, and potentially curative changes to the genome. Although technical and ethical issues remain, increased development of the delivery system, optimization of safety, and alignment with the regulations will be vital to continue and translate CRISPR therapies into a large-scale clinical setting.

References

1. Boycott, K. M., Rath, A., Chong, J. X., Hartley, T., Alkuraya, F. S., Baynam, G., … Lochmüller, H. (2019). International cooperation to enable the diagnosis of all rare genetic diseases. *The Lancet*, *394*(10193), 216–227. https://doi.org/10.1016/S0140-6736(19)31154-2
2. Carroll, D. (2019). Collateral damage: Benchmarking off-target effects in genome editing. *Nature Biotechnology*, *37*(8), 914–915. https://doi.org/10.1038/s41587-019-0206-1
3. Charlesworth, C. T., Deshpande, P. S., Dever, D. P., Dejene, B., Gomez-Ospina, N., Mantri, S., … Porteus, M. H. (2019). Identification of preexisting adaptive immunity to Cas9 proteins in humans. *Nature Medicine*, *25*(2), 249–254. https://doi.org/10.1038/s41591-018-0326-x
4. Dever, D. P., Bak, R. O., Reinisch, A., Camarena, J., Washington, G., Nicolas, C. E., … Porteus, M. H. (2016). CRISPR/Cas9 β-globin gene targeting in human haematopoietic stem cells. *Nature*, *539*(7629), 384–389. https://doi.org/10.1038/nature20134
5. Doudna, J. A., & Charpentier, E. (2014). Genome editing with CRISPR–Cas9. *Science*, *346*(6213), 1258096. https://doi.org/10.1126/science.1258096
6. Ferreira, C. R. (2019). The burden of rare diseases. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, *179C*(1), 1–3. https://doi.org/10.1002/ajmg.c.31685
7. Frangoul, H., Altshuler, D., Cappellini, M. D., Chen, Y.-S., Domm, J., Eustace, B. K., … Corbacioglu, S. (2021). CRISPR-Cas9 gene editing for sickle cell disease and β-thalassemia. *The New England Journal of Medicine*, *384*(3), 252–260. https://doi.org/10.1056/NEJMoa2031054
8. Gaj, T., Gersbach, C. A., & Barbas, C. F. (2013). ZFN, TALEN, and CRISPR/Cas-based methods for genome engineering. *Trends in Biotechnology*, *31*(7), 397–405. https://doi.org/10.1016/j.tibtech.2013.04.004
9. Hacein-Bey-Abina, S., Von Kalle, C., Schmidt, M., McCormack, M. P., Wulffraat, N., Leboulch, P., … Fischer, A. (2003). LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. *Science*, *302*(5644), 415–419. https://doi.org/10.1126/science.1088547
10. Hsu, P. D., Lander, E. S., & Zhang, F. (2014). Development and applications of CRISPR-Cas9 for genome engineering. *Cell*, *157*(6), 1262–1278. https://doi.org/10.1016/j.cell.2014.05.010

11. Jinek, M., Chylinski, K., Fonfara, I., Hauer, M., Doudna, J. A., & Charpentier, E. (2012). A programmable dual-RNA–guided DNA endonuclease in adaptive bacterial immunity. *Science*, *337*(6096), 816–821. https://doi.org/10.1126/science.1225829
12. Ledford, H. (2020). CRISPR gene therapies begin to reach the clinic. *Nature*, *579*(7799), 343–346. https://doi.org/10.1038/d41586-020-00655-8
13. Lino, C. A., Harper, J. C., Carney, J. P., & Timlin, J. A. (2018). Delivering CRISPR: A review of the challenges and approaches. *Drug Delivery*, *25*(1), 1234–1257. https://doi.org/10.1080/10717544.2018.1474964
14. Maeder, M. L., & Gersbach, C. A. (2016). Genome-editing technologies for gene and cell therapy. *Molecular Therapy*, *24*(3), 430–446. https://doi.org/10.1038/mt.2016.10
15. National Academies of Sciences, Engineering, and Medicine. (2017). *Human genome editing: Science, ethics, and governance*. National Academies Press. https://doi.org/10.17226/24623
16. Porteus, M. H. (2019). A new class of medicines through DNA editing. *Nature*, *568*(7753), 451–452. https://doi.org/10.1038/d41586-019-01276-5
17. Tsai, S. Q., Zheng, Z., Nguyen, N. T., Liebers, M., Topkar, V. V., Thapar, V., … Joung, J. K. (2015). GUIDE-seq enables genome-wide profiling of off-target cleavage by CRISPR-Cas nucleases. *Nature Biotechnology*, *33*(2), 187–197. https://doi.org/10.1038/nbt.3117
18. Urnov, F. D., Rebar, E. J., Holmes, M. C., Zhang, H. S., & Gregory, P. D. (2010). Genome editing with engineered zinc finger nucleases. *Nature Reviews Genetics*, *11*(9), 636–646. https://doi.org/10.1038/nrg2842
19. World Health Organization. (2021). *Human genome editing: A framework for governance*. WHO. https://www.who.int/publications/i/item/9789240030381
20. Yin, H., Song, C.-Q., Suresh, S., Wu, Q., Walsh, S., Rhym, L. H., … Anderson, D. G. (2017). Structure-guided chemical modification of guide RNA enables potent non-viral in vivo genome editing. *Nature Biotechnology*, *35*(12), 1179–1187. https://doi.org/10.1038/nbt.4005