CRISPR/Cas9 Applications in Therapeutics: Clinical Implications and Future Perspectives

Hetal J Modi[1], Dr Rashmi C Patel[2]

[1]Assistant Professor at Sardar Patel Institute of Applied Science, Bakrol

[2]Environment Expert Real Enviro Solutions Pvt. Ltd

ABSTRACT

CRISPR/Cas9 genome-editing technology has revolutionized molecular medicine by enabling precise, efficient, and cost-effective genetic modifications. Its applications in therapeutics range from monogenic disorders, oncology, and infectious diseases to potential use in regenerative medicine. This review explores the current clinical applications of CRISPR/Cas9, discusses challenges including off-target effects, delivery strategies, and ethical considerations, and highlights the future potential for integrating CRISPR-based therapies into personalized medicine.

Keywords: CRISPR/Cas9, Gene Editing, Therapeutics, Monogenic Disorders, Clinical Applications, Precision Medicine

1. Introduction

Genetic disorders, cancers, and certain infectious diseases remain major global health challenges despite advances in conventional therapeutics. Traditional drug therapy often manages symptoms rather than addressing underlying genetic causes.

CRISPR/Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated protein 9) offers a precise genome-editing tool that can modify, delete, or insert specific DNA sequences. Since its adaptation in mammalian systems in 2013, CRISPR/Cas9 has shown immense potential in therapeutic interventions. The system relies on a guide RNA (gRNA) that directs the Cas9 nuclease to a specific DNA sequence, enabling targeted gene modification.

2. Literature Review

CRISPR/Cas9 has been applied in:

- **Monogenic Disorders:** Clinical trials targeting sickle cell disease, β-thalassemia, and cystic fibrosis have demonstrated promising outcomes by correcting pathogenic mutations in patient-derived cells.
- **Oncology:** CRISPR-engineered T cells and CAR-T therapies are being developed to enhance anti-tumor immunity and overcome resistance mechanisms.
- **Infectious Diseases:** CRISPR systems have been explored for viral genome disruption in HIV, hepatitis B, and cytomegalovirus.
- **Regenerative Medicine:** CRISPR-mediated gene correction in induced pluripotent stem cells (iPSCs) enables potential tissue regeneration and organ repair.

Key studies include:

- Frangoul et al., 2021 – CRISPR-based therapy for sickle cell disease.
- Stadtmauer et al., 2020 – CRISPR-engineered T cells for refractory cancers.
- Yin et al., 2016 – In vivo genome editing using lipid nanoparticles.

3. Methodology

A narrative review was conducted using PubMed, Scopus, and Web of Science databases (2014–2025). Keywords included "CRISPR therapeutics," "gene editing clinical trials," "monogenic disorders CRISPR," and "precision medicine genome editing." Clinical trial registries were also reviewed to identify ongoing human studies.

4. Therapeutic Applications

4.1 Monogenic Disorders

CRISPR/Cas9 enables correction of single-gene mutations responsible for diseases like sickle cell anemia, β-thalassemia, Duchenne muscular dystrophy, and cystic fibrosis. Ex vivo editing of patient hematopoietic stem cells followed by autologous transplantation has shown durable correction.

Table 1 (Suggested):

Disease	Gene Target	Editing Strategy	Clinical Status
Sickle Cell Disease	HBB	Ex vivo correction	Clinical trial
β-Thalassemia	HBB	Ex vivo CRISPR editing	Clinical trial
Cystic Fibrosis	CFTR	Ex vivo gene correction	Preclinical

4.2 Oncology

CRISPR/Cas9 enables engineering of immune cells for targeted anti-cancer therapy:

- **CAR-T Cells:** CRISPR-mediated modifications enhance efficacy and reduce immunogenicity.
- **Oncolytic Therapy:** Targeting tumor suppressor pathways and oncogenes to sensitize tumors to therapy.
- **Drug Resistance Reversal:** Knockout of resistance-associated genes improves chemotherapy outcomes.

4.3 Infectious Diseases

CRISPR-based antiviral strategies disrupt viral genomes or latent reservoirs:

- HIV proviral DNA excision
- HBV genome targeting
- Antiviral RNA-targeting CRISPR systems (Cas13) for RNA viruses

5. Challenges and Limitations

1. **Off-target effects:** Unintended edits may result in genomic instability.
2. **Delivery systems:** Safe and efficient delivery to target tissues remains a hurdle; viral vectors, lipid nanoparticles, and ex vivo editing are common strategies.
3. **Ethical concerns:** Germline editing raises significant moral and societal debates.
4. **Immunogenicity:** Host immune responses against Cas proteins can reduce efficacy.
5. **Regulatory barriers:** Long-term safety and approval pathways are still evolving.

6. Future Perspectives

- **In vivo genome editing:** Direct delivery of CRISPR components to patients without ex vivo manipulation.
- **Precision medicine integration:** Combining pharmacogenomics with CRISPR therapies for highly personalized treatment.
- **AI-assisted CRISPR design:** Machine learning models predict off-target effects and optimize gRNA efficiency.
- **Combination therapies:** CRISPR plus immunotherapy or conventional drugs for synergistic effects.

7. Conclusion

CRISPR/Cas9 holds transformative potential in therapeutics across genetic, oncologic, and infectious disease domains. While challenges exist in delivery, off-target effects, and ethics, ongoing research, clinical trials, and technological advancements indicate a promising future. Integrating CRISPR with precision medicine strategies may redefine modern clinical therapeutics.

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