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EXOME ENGINEERING IN PRECISION MEDICINE: CRISPR-BASED THERAPEUTIC STRATEGIES FOR GENETIC DISEASES AND CANCER

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ABSTRACT

Exome engineering represents an emerging genome-editing strategy that focuses specifically on protein-coding regions of the genome where the majority of disease-associated mutations occur. Targeted modification of these regions provides an opportunity to directly correct pathogenic variants responsible for inherited disorders and cancer. Recent advances in genome-editing platforms, particularly CRISPR/Cas9, base editing, and prime editing technologies, have significantly improved the precision and efficiency of gene modification. Parallel progress in delivery systems has also accelerated the translation of gene editing into clinical applications. Among these systems, exosomes have attracted increasing attention as natural nanocarriers capable of transporting gene-editing components across biological barriers while minimizing immune responses. In oncology, exome-level analysis has facilitated the identification of tumor-specific mutations and neoantigens, enabling more precise therapeutic approaches such as adoptive cell therapy and personalized immunotherapies. In particular, cancers such as oral squamous cell carcinoma may benefit from targeted editing of driver mutations including TP53, KRAS, and EGFR. Despite these advances, challenges related to delivery efficiency, off-target effects, scalability, and regulatory oversight remain significant barriers to clinical translation. Continued developments in artificial-intelligence-assisted genomic analysis and improved delivery technologies are expected to accelerate progress in this field. This review uniquely integrates exome-targeted genome editing with emerging exosome-based delivery systems, providing a focused perspective on their combined therapeutic potential. Collectively, these advances position exome engineering as a promising and evolving strategy in precision medicine with significant clinical potential.

Keywords: *Precision gene editing; CRISPR/Cas9; Exosome based delivery; Cancer immunotherapy; Personalized medicine, Cancer genomics*

1. INTRODUCTION

Cancer develops as a consequence of genetic alterations that disrupt the normal regulation of cellular growth, division, and survival (Carlberg & Velleuer, 2021). These mutations frequently occur within the exome, the portion of the genome that encodes proteins. Although the exome represents only a small fraction of the human genome, it contains the majority of disease-causing variants responsible for many inherited disorders and cancers(Marwaha et al., 2022).

Because pathogenic mutations are enriched within protein-coding sequences, strategies that specifically target these regions have gained increasing attention. Exome engineering refers to genome-editing approaches that selectively modify coding regions in order to repair pathogenic variants or disrupt genes involved in disease progression(Ross et al., 2020). By focusing on the most functionally relevant segments of the genome, this strategy aims to improve therapeutic precision while reducing unintended genomic alterations.

Recent breakthroughs in gene-editing technologies have transformed the possibilities for targeted genomic manipulation. The CRISPR/Cas9 system allows researchers to introduce site-specific DNA modifications with remarkable efficiency(Doudna & Charpentier, 2014; Kantor et al., 2020; Zou et al., 2023). In cancer research, these tools have been used to investigate and potentially correct mutations in genes such as KRAS, TP53, and EGFR, which play central roles in tumor development and therapeutic resistance (Hasbullah & Musa, 2021; SV et al., 2024).

However, the clinical success of genome editing depends not only on editing accuracy but also on the ability to deliver gene-editing components safely to target cells. Emerging delivery platforms, including lipid nanoparticles and extracellular vesicles such as exosomes, have shown significant promise(Albertsen et al., 2022; Elliott & He, 2021) . Exosomes are nanoscale vesicles naturally released by cells that can transport proteins, RNA, and other biomolecules between cells(Elliott & He, 2021). Their intrinsic biocompatibility and ability to cross biological barriers make them attractive candidates for delivering gene-editing systems in vivo(Aslan et al., 2024; Zhang et al., 2023).

Another important development is the integration of exome sequencing with immunotherapy. Whole-exome sequencing enables identification of tumor-specific mutations that produce neoantigens, which can guide personalized immunotherapies such as adoptive T-cell therapies (Schumacher & Schreiber, 2015; Wang & Cao, 2020).

This review examines the technological foundations of exome engineering, explores its applications in genetic diseases and cancer therapy, summarizes ongoing clinical developments, and discusses the ethical and technological challenges that must be addressed for successful clinical implementation.

2. Technological Foundations of Exome Engineering

2.1 Gene Editing Technologies

Modern exome engineering relies on several genome-editing technologies capable of introducing precise genetic modifications.

CRISPR/Cas9. The CRISPR/Cas9 system, derived from bacterial immune defense mechanisms, enables targeted DNA cleavage guided by programmable RNA molecules(Kantor et al., 2020). Following cleavage, endogenous DNA repair pathways can be exploited to introduce gene disruptions or correct pathogenic mutations.

Base Editing. Base editors allow direct conversion of individual nucleotides without generating double-strand breaks, improving editing precision and reducing unintended genomic damage(Anzalone et al., 2019; Kantor et al., 2020).

Prime Editing. Prime editing enables targeted insertions, deletions, and nucleotide substitutions without requiring donor DNA templates, offering a versatile and highly precise editing approach(Anzalone et al., 2019).

Together, these tools provide a flexible platform for correcting disease-associated mutations within protein-coding regions of the genome.

2.2 Delivery Strategies

Efficient delivery of gene-editing components remains a central challenge in therapeutic genome editing(Hsu et al., 2014).

Viral Vectors. Viral vectors such as adeno-associated virus and lentivirus have traditionally been used for gene delivery because of their high transduction efficiency(Li & Samulski, 2020). However, immune responses and insertional mutagenesis remain potential safety concerns.

Electroporation. Electroporation is widely used for ex vivo editing applications, where electrical pulses temporarily permeabilize cell membranes to enable nucleic acid delivery(Young & Dean, 2015).

Lipid Nanoparticles. Lipid nanoparticle platforms have gained considerable attention due to their success in mRNA vaccines and their potential for delivering CRISPR ribonucleoprotein complexes (Albertsen et al., 2022).

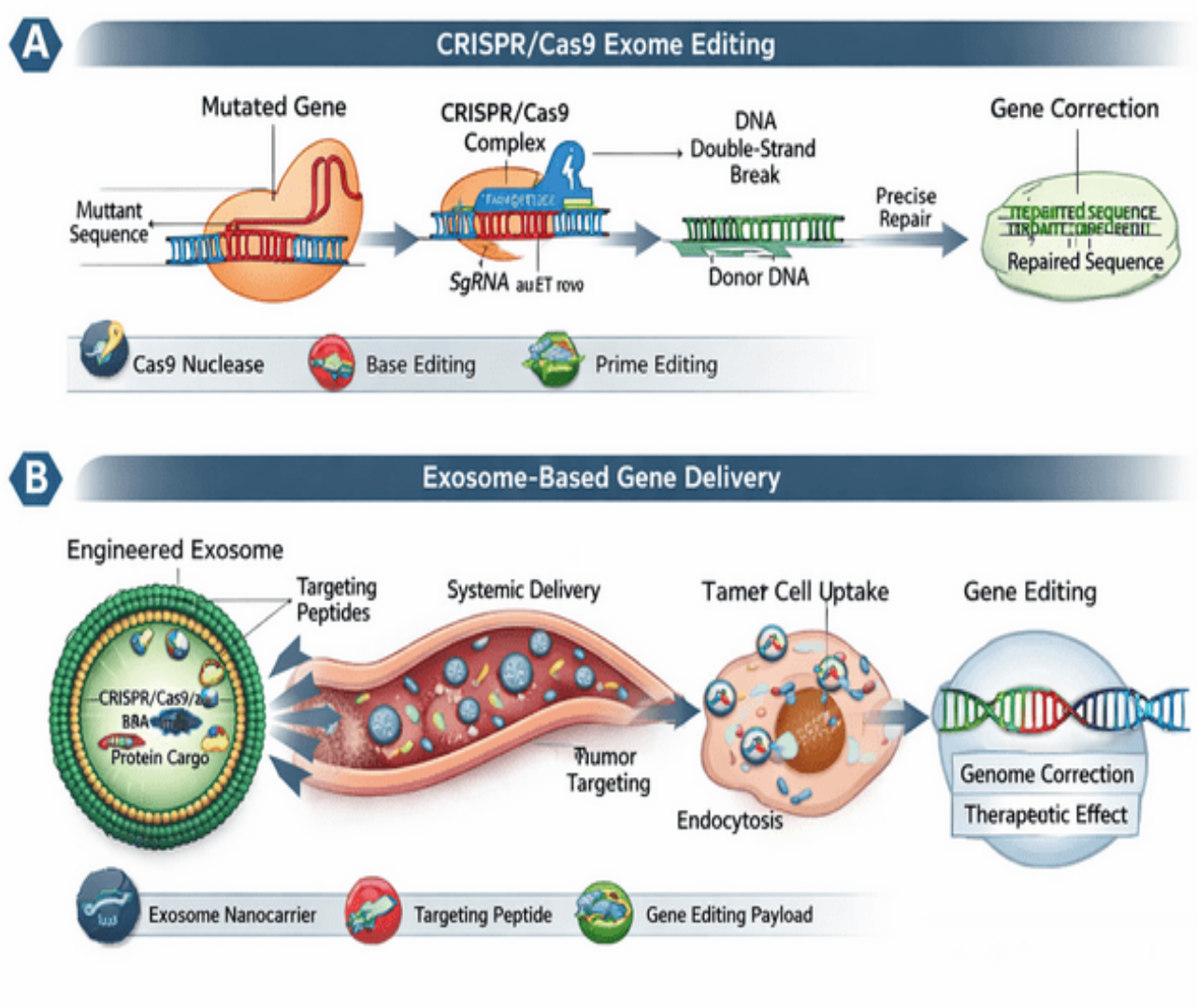

Figure 1. Comparison of delivery platforms for genome-editing therapeutics.

(A) Viral vector-mediated delivery of CRISPR components showing efficient gene transfer but potential risks of immune responses and insertional mutagenesis. (B) Lipid nanoparticle systems delivering nucleic acids or CRISPR ribonucleoproteins with high cargo capacity and

reduced immunogenicity. (C) Exosome-based delivery platforms enabling natural cell targeting and improved biocompatibility for therapeutic genome editing. Created by the authors.

2.3 Exosomes as Natural Delivery Vehicles

Exosomes are small extracellular vesicles secreted by most cell types and play key roles in intercellular communication(Elliott & He, 2021). Their biological origin and inherent stability make them promising candidates for therapeutic delivery systems.

Exosomes possess several advantages for gene-editing delivery. They exhibit low immunogenicity, can transport nucleic acids and proteins, and are capable of crossing biological barriers such as the blood–brain barrier(Elliott & He, 2021). These properties enable them to function as natural nanocarriers capable of delivering CRISPR components to target tissues(Aslan et al., 2024; Dara et al., 2024).

Researchers are also developing engineered exosomes with improved targeting capabilities. Approaches include genetic modification of donor cells, electroporation-based cargo loading, chemical surface modification, and hybridization with nanoparticle systems to increase therapeutic payload capacity(Aslan et al., 2024; Zhang et al., 2023).

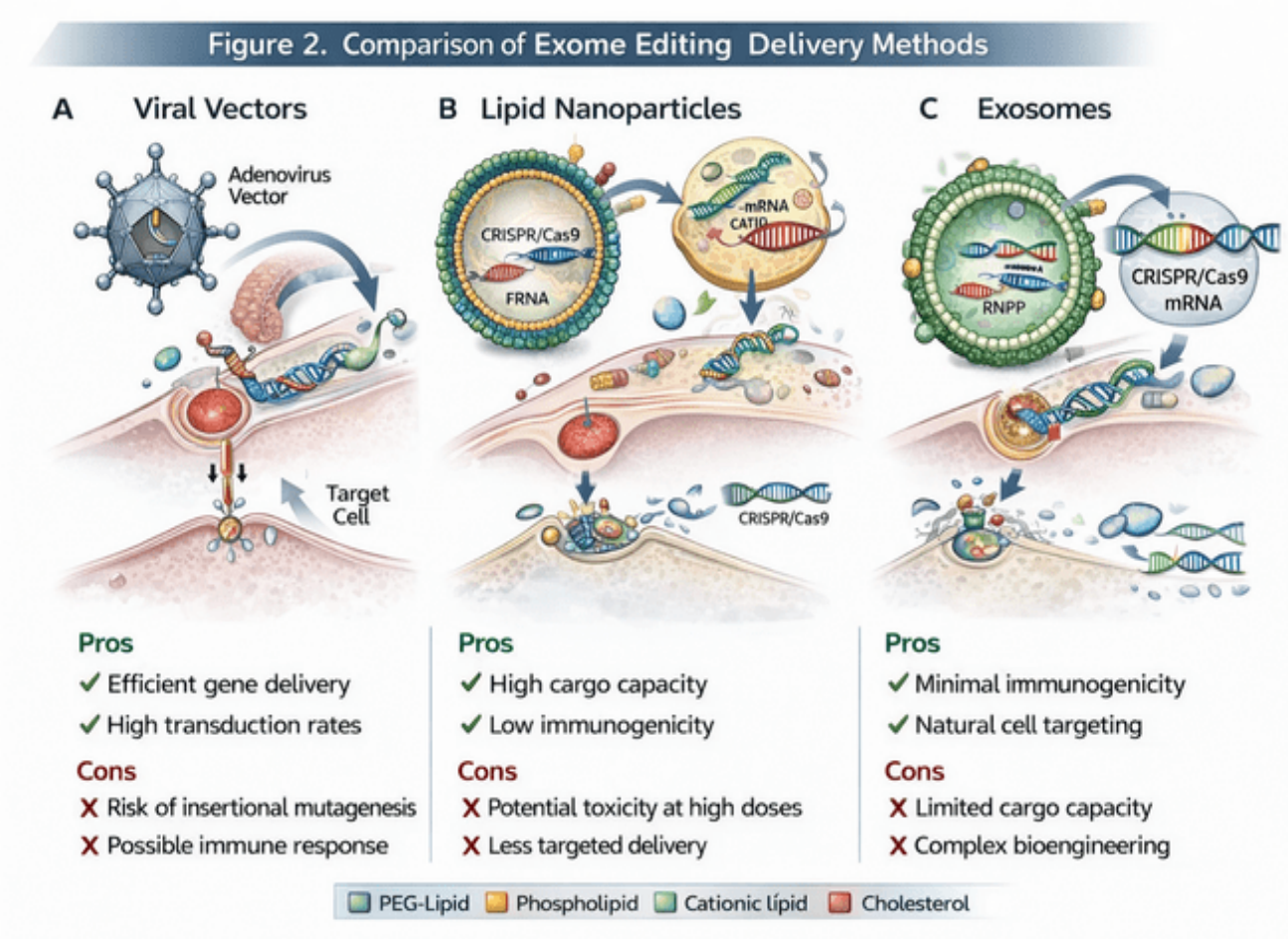

Figure 2. CRISPR-based exome editing and exosome-mediated gene delivery. A) CRISPR/Cas9-mediated mutation correction. (B) Exosome-based delivery of gene-editing systems to target cells. Created by the authors.

2.4 Ex Vivo and In Vivo Editing Approaches

Genome editing therapies can generally be divided into two primary strategies.

Ex Vivo Editing. In this approach, cells are removed from a patient, genetically modified in vitro, and then reintroduced into the body. This strategy is widely used in immune-cell-based therapies such as CAR-T cells(Wang & Cao, 2020).

In Vivo Editing. In contrast, in vivo editing delivers gene-editing components directly to tissues using delivery vehicles such as viral vectors, nanoparticles, or exosomes (Volodina & Smirnikhina, 2025).

3. Applications in Genetic Diseases

Many inherited diseases arise from single-gene mutations, making them attractive targets for genome-editing therapies(Ross et al., 2020). By correcting pathogenic variants directly within their native genomic context, exome engineering offers the potential for durable therapeutic effects.

Cystic Fibrosis. Genome editing strategies targeting CFTR mutations have demonstrated promising results in airway epithelial cells(King et al., 2020).

Duchenne Muscular Dystrophy. CRISPR-mediated editing of the dystrophin gene has been explored as a strategy to restore functional protein expression in muscle tissue(Shi et al., 2024).

Sickle Cell Disease. Editing of the HBB gene or regulatory pathways controlling fetal hemoglobin production has produced encouraging therapeutic outcomes in experimental and clinical studies (Frangoul et al., 2021; Janoudi et al., 2025).

These examples demonstrate how genome editing technologies initially developed for genetic diseases are increasingly being adapted for oncology applications.

4. Applications in Cancer Therapy

Cancer therapy is rapidly transitioning from generalized treatments toward personalized and targeted strategies(Hibshman, 2024; Huang et al., 2025) . Exome engineering contributes to this shift by enabling the precise modification of oncogenic mutations and identification of tumor-specific neoantigens.

In cancers such as oral squamous cell carcinoma, editing driver mutations in genes including TP53, PIK3CA, and CDKN2A may inhibit tumor progression or restore drug sensitivity(SV et al., 2024).

Genome editing can also enhance immunotherapy. Whole-exome sequencing enables identification of tumor-specific neoantigens that guide adoptive cell therapy approaches(Wang & Cao, 2020). Furthermore, CRISPR can modify immune cells by removing inhibitory checkpoint receptors such as PD-1, thereby enhancing anti-tumor immune responses(Shams et al., 2025).

5. Clinical Development and Current Trials

Several clinical trials are currently evaluating genome editing technologies in cancer therapy. Early trials involving CRISPR-engineered T cells have demonstrated promising safety profiles and preliminary evidence of therapeutic activity(Shams et al., 2025; Stadtmauer et al., 2020).

In some studies, engineered T cells targeting tumor antigens while lacking inhibitory checkpoint receptors have shown enhanced persistence and anti-tumor activity. Additional trials are exploring engineered immune cells against solid tumors such as pancreatic cancer and mesothelioma(Klampatsa et al., 2021).

Large-scale genomic sequencing initiatives have also demonstrated that treatment strategies guided by genomic profiling may improve clinical outcomes compared with conventional therapies(Schumacher & Schreiber, 2015; Tiwari et al., 2025; Topol, 2019).

6. Ethical, Legal, and Social Considerations

Despite significant advances, genome editing technologies raise important ethical and regulatory concerns(Hsu et al., 2014). Ensuring safety remains a priority, particularly with respect to potential off-target mutations and unintended genomic alterations.

The development of standardized manufacturing and quality-control protocols is also essential for

emerging delivery platforms such as exosome-based therapeutics(Wang et al., 2024).
Artificial intelligence is increasingly used to support genomic analysis, biomarker discovery, and prediction of treatment responses(Zhang et al., 2024). Machine learning techniques have shown promise in identifying cancer-derived exosomes and improving early disease detection(Zhang et al., 2024).
However, integration of advanced technologies into healthcare systems also raises questions related to data privacy, equitable access to treatment, and regulatory oversight.

7. Future Perspectives and Challenges

Although exosome-mediated gene editing holds substantial promise, several challenges must be addressed before widespread clinical translation becomes feasible(Cheng & Kalluri; Hsu et al., 2014). Biological variability among patients may influence exosome composition, targeting efficiency, and therapeutic outcomes(Minocha & Sardana, 2023).
Large-scale production and standardization of exosome isolation and purification remain major technical challenges. In addition, the relatively short circulation time of exosomes in the bloodstream may limit therapeutic efficiency.
Advances in nanotechnology, synthetic biology, and artificial intelligence are expected to address many of these limitations and accelerate the development of next-generation precision therapies.

Conclusion

Exome engineering represents a powerful strategy for addressing genetic diseases and cancer by targeting mutations within protein-coding regions of the genome. Advances in CRISPR-based genome editing technologies have dramatically improved the precision and flexibility of genetic modification(Doudna & Charpentier, 2014; Kantor et al., 2020; Zou et al., 2023). At the same time, emerging delivery platforms, particularly exosome-based systems, offer promising solutions for safely transporting gene-editing components into target tissues(Aslan et al., 2024; Zhang et al., 2023).
The integration of genome editing with immunotherapy and personalized genomic analysis has the potential to transform modern therapeutic strategies(Schumacher & Schreiber, 2015; Wang & Cao, 2020). Although challenges related to delivery efficiency, scalability, and regulatory oversight remain, ongoing technological innovation continues to advance the field.
With further development, exome engineering may become a central component of precision medicine, offering new therapeutic possibilities for diseases that were previously considered untreatable.

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