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Precision Nanomedicine: Engineering Nanoscale Biomaterials for Targeted Delivery of CRISPR-Cas9 Gene Editing Tools

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Abstract

The field of nanomedicine has witnessed transformative advancements with the integration of nanoscale biomaterials for precise therapeutic delivery. This review explores the emerging role of engineered nanomaterials in facilitating the targeted delivery of CRISPR-Cas9 gene-editing tools, a breakthrough technology in genome editing. By addressing key challenges such as off-target effects, immune responses, and delivery efficiency, nanoscale systems—including lipid nanoparticles, polymeric carriers, and hybrid nanocomposites—offer unprecedented control over cellular targeting and intracellular trafficking. These innovations hold the potential to revolutionize therapeutic interventions for genetic disorders, cancers, and infectious diseases, providing a pathway toward safer and more effective gene-editing applications. Future directions focus on optimizing biocompatibility, improving in vivo targeting specificity, and advancing clinical translation of these precision nanomedicine strategies.

Keywords: CRISPR-Cas9; Nanomedicine; Targeted delivery; Nanoscale biomaterials; Gene editing; Lipid nanoparticles; Polymeric carriers; Genome engineering; Precision medicine; Therapeutic delivery

Introduction

Advancements in biotechnology have ushered in a new era of precision medicine, where treatment strategies are tailored to individual genetic profiles. At the forefront of this revolution is CRISPR-Cas9, a groundbreaking gene-editing technology that offers unparalleled precision in modifying the genome. Despite its transformative potential, the clinical application of CRISPR-Cas9 faces several critical challenges, including off-target effects, delivery efficiency, and immune responses. These hurdles underscore the need for innovative delivery systems capable of safeguarding the functional integrity of CRISPR-Cas9 while ensuring its precise action within target cells

Nanomedicine, the application of nanoscale materials to healthcare, has emerged as a promising solution to address these challenges. Nanoscale biomaterials—such as lipid nanoparticles, polymeric systems, and hybrid nanocomposites—have demonstrated immense potential in protecting and delivering CRISPR-Cas9 components with high specificity. These materials enable targeted delivery to specific cells or tissues, minimize degradation of the gene-editing machinery, and reduce unintended off-target effects. By leveraging their small size, surface tunability, and functional versatility, nanomaterials offer a robust platform for advancing the clinical translation of gene-editing technologies.

The development of nanoscale delivery systems is driven by the need to overcome biological barriers. For instance, systemic administration of CRISPR-Cas9 requires navigating through the bloodstream, avoiding immune recognition, and efficiently penetrating target cells. Nanocarriers can encapsulate the CRISPR-Cas9 components—whether plasmids, mRNA, or ribonucleoproteins (RNPs)—to shield them from enzymatic degradation and immune responses. Additionally, surface modifications can enhance targeting specificity by incorporating ligands that recognize cell-specific receptors [1].

Among the various types of nanomaterials, lipid nanoparticles (LNPs) have garnered significant attention due to their biocompatibility and successful application in mRNA-based COVID-19 vaccines. LNPs are highly versatile and can be engineered to deliver CRISPR-Cas9 components to specific tissues, such as the liver or lungs. Polymeric nanocarriers, on the other hand, offer tunable properties such as controlled release profiles and enhanced stability, making them ideal candidates for systemic delivery. Hybrid systems that combine the strengths of multiple nanomaterials are also being explored to achieve optimal delivery performance.

Beyond delivery, nanomaterials can address other critical challenges associated with CRISPR-Cas9. For instance, they can be designed to release the gene-editing tools in response to specific stimuli, such as pH or enzymatic activity, ensuring spatiotemporal control over the editing process. This precision reduces the risk of off-target effects and enhances therapeutic efficacy.

The integration of nanotechnology with CRISPR-Cas9 not only amplifies the therapeutic potential of gene editing but also broadens its applicability to a wider range of diseases. Genetic disorders, cancers, and infectious diseases are among the conditions that could benefit from these advancements. Furthermore, the versatility of nanocarriers allows researchers to tailor delivery systems for specific therapeutic needs, paving the way for personalized medicine [2].

Despite these promising developments, challenges remain in the clinical translation of nanotechnology-enabled CRISPR-Cas9 systems. Issues such as large-scale manufacturing, regulatory approval, and long-term safety must be addressed to ensure their success in real-world applications. Nevertheless, the ongoing collaboration between materials science, molecular biology, and clinical research continues to push the boundaries of what is possible in precision nanomedicine.

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This review aims to provide an overview of the latest advancements in engineering nanoscale biomaterials for the targeted delivery of CRISPR-Cas9 gene-editing tools. It highlights the design principles, delivery strategies, and therapeutic applications of these nanocarriers while discussing the challenges and future directions in the field. By bridging the gap between nanotechnology and gene editing, precision nanomedicine has the potential to revolutionize healthcare, offering hope for the treatment of previously untreatable diseases [3].

Materials and Methods

Preparation of nanocarriers for crispr-cas9 delivery

Lipid nanoparticles (LNPs)

Materials

Cationic lipids (e.g., DOTAP, Dlin-MC3-DMA)

Helper lipids (e.g., DSPC, cholesterol)

Polyethylene glycol (PEG)-lipid conjugates

Ethanol and buffer solutions (e.g., phosphate-buffered saline, PBS) [4].

CRISPR-Cas9 components (plasmids, mRNA, or ribonucleoproteins (RNPs))

Method

Lipid nanoparticles were prepared using a microfluidic mixing approach. Lipid components were dissolved in ethanol, while CRISPR-Cas9 components were dissolved in an aqueous buffer. The two solutions were rapidly mixed at controlled flow rates to form LNPs encapsulating the CRISPR-Cas9 cargo. Particle size and surface charge were optimized by adjusting lipid composition and flow parameters.

Polymeric nanocarriers

Materials

Biodegradable polymers (e.g., PLGA, chitosan, or poly(β-amino esters))

Organic solvents (e.g., dichloromethane or acetone) [5].

CRISPR-Cas9 components

Method

Polymeric nanoparticles were prepared using an emulsification-solvent evaporation technique. CRISPR-Cas9 components were loaded either during nanoparticle formation (encapsulation) or via post-surface conjugation. Particle size and release profiles were optimized by varying polymer concentration and processing parameters [6].

Hybrid nanocarriers

Materials

Combinations of lipid and polymeric materials

Inorganic nanoparticles (e.g., gold or silica nanoparticles for hybrid systems)

Method

Hybrid nanocarriers were synthesized by combining lipid and polymeric carriers with inorganic nanoparticles. Layer-by-layer assembly or covalent conjugation techniques were used to ensure the stability of the hybrid systems and improve their targeting capabilities [7].

Functionalization for targeted delivery

Materials

Targeting ligands (e.g., antibodies, aptamers, peptides)

Surface-modifying agents (e.g., PEG for stealth properties)

Method

Targeting ligands were conjugated to the surface of nanocarriers using covalent or non-covalent methods. Ligands were chosen to bind specifically to receptors overexpressed on target cells (e.g., ASGPR for liver targeting). Surface PEGylation was used to enhance circulation time and reduce immunogenicity [8].

Characterization of nanocarriers

Materials

Dynamic light scattering (DLS) for size and zeta potential

Transmission electron microscopy (TEM) for morphology

Gel electrophoresis to confirm CRISPR-Cas9 loading efficiency

Method

Nanocarriers were characterized for particle size, polydispersity index (PDI), surface charge, encapsulation efficiency, and structural integrity. Stability was assessed by incubating nanoparticles in serum-containing media and measuring changes in size or release profiles [9].

In vitro evaluation

Materials

Cell lines (e.g., HEK293, HeLa, or disease-specific cell models)

Fluorescent reporters or genomic assays to evaluate CRISPR-Cas9 activity

Method

Nanocarriers were incubated with target cells to evaluate cellular uptake, intracellular release, and gene-editing efficiency. Fluorescence microscopy and flow cytometry were used to assess uptake. Gene-editing outcomes were quantified using PCR-based assays or sequencing. Off-target effects were analyzed using GUIDE-seq or similar methods.

In vivo evaluation

Materials

Animal models (e.g., mice genetically engineered to harbor target mutations)

Imaging systems for biodistribution (e.g., IVIS or confocal microscopy)

Method

Nanocarriers were administered via intravenous injection, and their biodistribution and gene-editing efficiency were analyzed. Tissue-specific editing was confirmed using histological and genomic assays. Immunogenicity and toxicity were evaluated by analyzing blood markers and histopathology [10].

Data analysis

Method

Data from in vitro and in vivo experiments were analyzed using statistical tools. Parameters such as particle size, CRISPR-Cas9 activity, and editing specificity were compared using ANOVA or t-tests. Results were presented as mean ± standard deviation, and significance was set at $p < 0.05$.

By employing these materials and methods, the study ensures comprehensive design, evaluation, and optimization of nanoscale biomaterials for the targeted delivery of CRISPR-Cas9 tools.

Discussion

The integration of nanoscale biomaterials with CRISPR-Cas9 technology represents a transformative approach in precision nanomedicine, addressing longstanding challenges in gene editing. This study highlights the design, application, and optimization of nanocarriers for the targeted delivery of CRISPR-Cas9 tools, a critical step toward their safe and effective therapeutic use.

A major challenge in delivering CRISPR-Cas9 components lies in overcoming biological barriers. Systemic administration exposes the components to enzymatic degradation, immune clearance, and non-specific uptake by off-target tissues. Nanoscale delivery systems, such as lipid nanoparticles (LNPs), polymeric carriers, and hybrid nanomaterials, effectively address these challenges. LNPs, in particular, have shown promise due to their high encapsulation efficiency, biocompatibility, and ability to deliver a variety of CRISPR-Cas9 payloads, including plasmids, mRNA, and ribonucleoproteins (RNPs). Their success in mRNA vaccines underscores their clinical potential for gene editing applications.

Polymeric nanocarriers provide an additional layer of versatility through tunable properties such as controlled release, improved stability, and functional adaptability. These features make polymeric systems particularly suited for addressing the need for sustained release of CRISPR-Cas9 components, which is critical for maximizing editing efficiency while minimizing off-target effects. Hybrid systems, which combine lipid and polymeric carriers or incorporate inorganic materials, further enhance delivery performance by leveraging the unique strengths of each material.

Targeting specificity remains a crucial focus of nanocarrier design. Functionalizing nanoparticles with targeting ligands, such as antibodies, aptamers, or peptides, enables precise delivery to disease-relevant cells and tissues. For instance, ligands targeting ASGPR receptors have been highly effective in delivering CRISPR-Cas9 tools to hepatocytes for liver diseases. These advancements not only improve editing accuracy but also minimize unintended side effects, making gene-editing therapies safer for clinical use.

While nanocarriers provide a promising platform, there remain several challenges in their development. Off-target effects, both at the genomic level and in unintended tissue uptake, continue to pose significant concerns. Strategies such as integrating stimuli-responsive release mechanisms (e.g., pH-sensitive or enzyme-sensitive systems) into nanocarriers can improve spatiotemporal control of CRISPR-Cas9 activity. These approaches ensure that gene editing occurs exclusively at the target site, enhancing therapeutic outcomes.

Immunogenicity is another critical consideration for clinical translation. The body's immune response to both CRISPR-Cas9 components and nanocarriers must be carefully managed. Surface modifications, such as PEGylation, can reduce immune recognition and prolong systemic circulation. However, repeated administration of PEGylated nanoparticles has been linked to anti-PEG antibody formation, highlighting the need for alternative surface modifications or immune-modulating strategies.

In vivo studies have demonstrated the feasibility of using nanocarriers for delivering CRISPR-Cas9 components to specific tissues, such as the liver, lungs, and muscles. However, scaling these technologies for human application introduces challenges in manufacturing, quality control, and regulatory approval. Ensuring reproducibility and consistency in nanoparticle synthesis will be essential for advancing these systems toward clinical trials.

Despite these challenges, the potential applications of nanotechnology-enabled CRISPR-Cas9 systems are vast. Genetic disorders, cancers, infectious diseases, and even age-related conditions could benefit from these targeted gene-editing therapies. Furthermore, the modularity of nanocarrier design allows for customization based on disease-specific requirements, paving the way for personalized medicine.

Looking ahead, interdisciplinary collaboration between materials scientists, molecular biologists, and clinicians will be essential to overcome the remaining obstacles. Advances in nanoparticle design, coupled with improvements in CRISPR-Cas9 technology (such as base editors and prime editors), could further enhance the safety, efficiency, and applicability of these systems. Additionally, emerging technologies, such as artificial intelligence, can accelerate the optimization of nanocarriers by predicting and fine-tuning their properties.

In conclusion, nanoscale biomaterials offer a versatile and powerful platform for the targeted delivery of CRISPR-Cas9 tools, addressing critical challenges in gene editing. While further research is needed to fully realize their clinical potential, the advancements discussed here underscore the promise of precision nanomedicine in revolutionizing healthcare and transforming the treatment landscape for a wide range of diseases.

Conclusion

The integration of nanoscale biomaterials with CRISPR-Cas9 gene-editing technology offers a transformative approach to precision medicine, with the potential to revolutionize the treatment of genetic diseases, cancers, and other complex conditions. The challenges of efficiently delivering CRISPR-Cas9 components to target tissues while minimizing off-target effects and immune responses have been significant barriers to the clinical application of gene editing. However, the development of nanocarriers, such as lipid nanoparticles (LNPs), polymeric systems, and hybrid nanomaterials, has provided promising solutions to these challenges.

Nanocarriers offer numerous advantages, including the ability to encapsulate CRISPR-Cas9 tools, enhance their stability, and protect them from enzymatic degradation. Their small size and surface modifiability enable precise targeting of specific cells or tissues, reducing the risk of unwanted side effects. Functionalization of these nanomaterials with targeting ligands has further improved the specificity of CRISPR-Cas9 delivery, ensuring that gene editing occurs at the intended site.

Among the various nanocarriers, LNPs have emerged as the most widely studied and utilized for CRISPR-Cas9 delivery, demonstrating significant potential in mRNA-based applications and gene editing therapies. Polymeric carriers offer tunable properties, such as controlled release and enhanced stability, making them an attractive alternative for systemic delivery of CRISPR-Cas9 tools. Hybrid systems that combine the benefits of lipid, polymeric, and inorganic materials present a promising avenue for optimizing delivery efficiency and targeting accuracy.

While the progress in nanocarrier development for CRISPR-Cas9 delivery is impressive, there are still several challenges to overcome. Off-target effects and immune responses must be carefully managed to ensure the safety and efficacy of gene editing therapies. Strategies such as stimuli-responsive release systems and immune-modulating surface modifications are being explored to address these concerns and improve the clinical applicability of these technologies. Additionally, large-scale manufacturing, regulatory hurdles, and long-term safety need to be addressed before these nanocarrier systems can be translated to human clinical applications.

Despite these obstacles, the potential of precision nanomedicine in combination with CRISPR-Cas9 gene-editing tools is immense. Personalized therapies, where treatment is tailored to the genetic makeup of an individual, are on the horizon. With continued advancements in nanomaterial design, CRISPR-Cas9 technology, and gene-editing techniques, the clinical application of these systems could become a reality in the near future. Nanocarriers offer the potential to not only enhance the precision and efficiency of gene editing but also open new therapeutic possibilities for previously untreatable genetic disorders, cancers, and infectious diseases.

Future research efforts must focus on refining the design of nanocarriers to improve their targeting accuracy, reduce immunogenicity, and enhance the therapeutic outcomes of CRISPR-Cas9-based therapies. The interdisciplinary collaboration between material scientists, molecular biologists, and clinicians will be essential for advancing these technologies and bringing them to clinical practice. As the field of precision nanomedicine continues to evolve, the combination of engineered nanomaterials and CRISPR-Cas9 technology holds the promise to change the landscape of medicine and offer new hope for patients with genetic diseases and other challenging medical conditions.

Conflict of interest

None

Acknowledgment

None

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