RESEARCH PAPER

CRISPR-Compatible Biomaterials: A New Frontier in Gene-Responsive Drug Delivery.

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ABSTRACT

CRISPR-Cas systems revolutionized the prospect of precision medicine by providing a programmable platform for genome engineering. However, safe and efficient delivery of these large, fragile, and immunogenic macromolecular components represents the principal bottleneck to wide clinical translation. While viral vectors raise safety concerns and conventionally used nonviral carriers lack precise control, advanced biomaterials emerged to transform delivery from a passive encapsulation problem into an active, programmable process. A general overview of basic design principles that govern such CRISPR-compatible biomaterials is given within this review. Critically analyzing this field, major findings are summarized thereafter, starting with the key design principles-like biocompatibility, surface chemistry, and the engineering of endosomal escape and nuclear targeting mechanisms. Distinct classes of materials presently employed for this purpose are analyzed, ranging from polymeric nanocarriers over clinically advanced LNPs, inorganic carriers, and localized hydrogel scaffolds to bio-inspired hybrid systems. Other key findings relate to the strategic comparison of delivering CRISPR components in their various molecular forms-that is, pDNA, mRNA, or preassembled RNP complexes-along with their expanding therapeutic applications in oncology, genetic disorders, and regenerative medicine. At the end, technological convergence meets the key translational challenges that must be overcome with AI-driven computational design accelerating carrier optimization. The synergy between advanced materials science and gene editing discussed herein thus forms one key step toward intelligent, responsive, and personalized therapeutics.

Keywords: CRISPR-Cas systems, biomaterials, gene delivery, nanocarriers, non-viral delivery, precision medicine

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INTRODUCTION

The gene-editing era has significantly changed with the discovery of CRISPR and its enzymatic component. From the original description as an adaptive immune response of bacteria, the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas system became a highly accurate programmable tool with capabilities to target and edit almost any genetic sequence. It is fast becoming the backbone for the next generation of therapeutics, diagnostics, and functional genomics [1]. These include the use of CRISPR–Cas9 and, more recently, its derivatives such as Cas12, Cas13, and base or prime editing systems. These have enabled unprecedented specificity in DNA and RNA sequence modulation during the last decade [2]. While indeed efficient, conventional viral vectors are associated with risks of immunogenicity, limited packaging capacity, and insertional mutagenesis [3]. Non-viral strategies are safer alternatives, which include lipid nanoparticles, polymers, and inorganic carriers. However, these mostly lack control over cargo stability, release kinetics, and intracellular trafficking [4].

Accordingly, biomaterials have emerged to form a critical interface between molecular gene editors and physiological barriers. Biomaterial systems, including polymeric nanocarriers, lipid-based formulations, hydrogels, and hybrid nanostructures, can structurally protect CRISPR cargos while enabling site-specific release through tunable chemical and physical properties [5]. Recently developed stimuli-responsive biomaterials, responsive to pH, redox potential, or enzymatic activity, now enable spatiotemporal regulation of gene-editing events within targeted tissues. This level of design flexibility transforms biomaterials from passive carriers into active players in therapeutic modulation [6].

Apart from material engineering, computational and AI-driven design has recently further accelerated developments within CRISPR-compatible systems [7]. Altogether, the obtained knowledge renews the concept of drug delivery from static encapsulation toward intelligent, adaptive, and responsive gene delivery platforms.

This review covers recent advances relating to CRISPR-compatible biomaterials, with a focus on the major design principles, classes of materials, and modes of delivery for CRISPR components, including plasmid DNA, mRNA, and ribonucleoprotein complexes. Safety, regulatory, and translational considerations of CRISPR-based therapies are also discussed. By bridging gene editing and materials science, CRISPR-compatible biomaterials represent a defining step toward programmable and personalized medicine, offering new ways of treating genetic, oncologic, and degenerative diseases.

2. CRISPR–Cas Systems: Mechanism and Features

In essence, CRISPRs are an advanced adaptive immune system present in bacteria and archaea, and their Cas proteins are associated with it. This natural defense

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mechanism evolved to detect, record, and destroy the genetic material of invading bacteriophages [8]. An overview of biomaterial-mediated CRISPR delivery, including key biological barriers and intracellular trafficking steps, is illustrated in Figure 1.

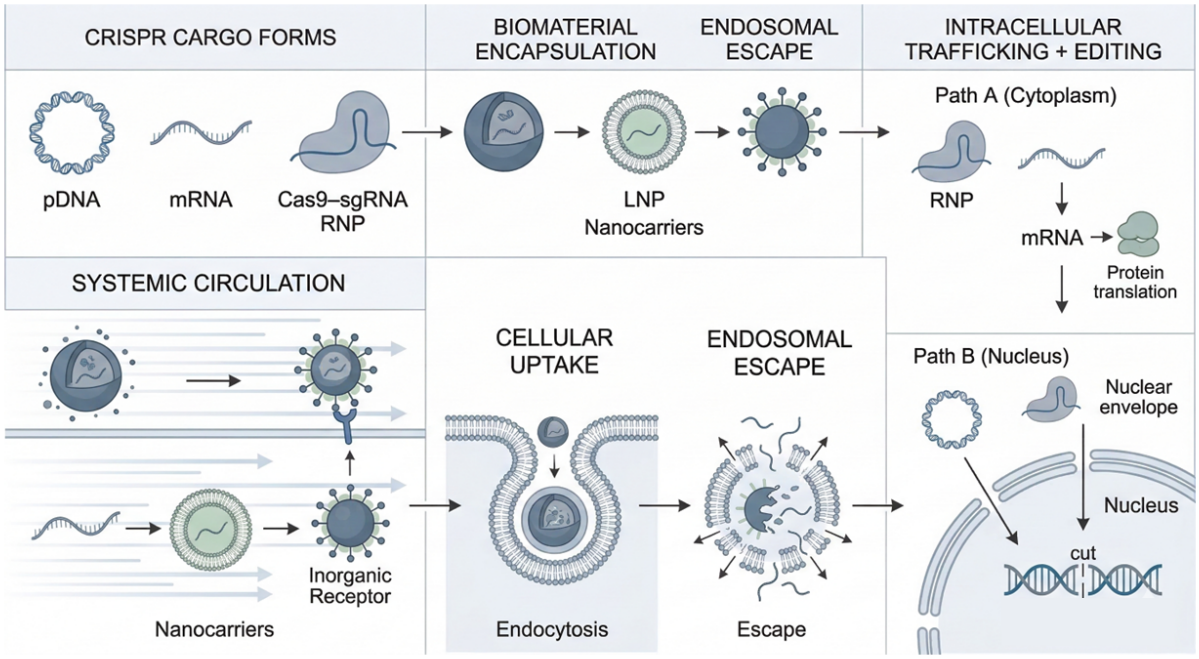

Figure 1. Biomaterial-mediated CRISPR delivery and intracellular trafficking pathways.

2.1. Mechanistic Overview of CRISPR–Cas9, Cas12, and Cas13 Systems

The mechanism of action varies slightly between Cas classes, but the central principle of guide-RNA-directed cleavage remains consistent. The most widely adopted nuclease, Cas9, forms a complex with a single-guide RNA (sgRNA) and scans the genome for a specific 20-nucleotide target sequence [9]. Upon binding, and contingent on the presence of an adjacent Protospacer Adjacent Motif (PAM), its two nuclease domains (HNH and RuvC) create a precise double-strand break (DSB). Cas12 proteins, like Cas12a, offer distinct advantages; they recognize a different, T-rich PAM, which expands the range of targetable sites. They also introduce a 'staggered' DSB instead of a blunt one and can process their own guide RNAs, simplifying multiplexed editing [10]. Quite different from DNA editing, Cas13 is a programmable RNase. Guided to a target mRNA, it cleaves the target and engages in extensive 'collateral cleavage' of other nearby RNA molecules [11].

2.2. Structure and Function of gRNA and Cas Protein Complexes

The functional unit of the CRISPR system is the ribonucleoprotein (RNP) complex-a precise partnership between the Cas protein and its gRNA. Cas protein is the molecular 'scissors,' an endonuclease that provides the enzymatic machinery for cleavage [12]. gRNA is a synthetic RNA molecule, usually ~100 nucleotides, containing a scaffold region which binds and correctly orients the Cas protein and a user-defined ~20-nucleotide 'spacer' sequence [13]. This spacer is complementary to the specific DNA or RNA target; thus, it guides the Cas protein to a unique location within the genome. The fidelity of this gRNA-target hybridization is the very basis of programmability and precision in CRISPR [14].

2.3. Therapeutic Potential and Current Clinical Applications

The most clinically advanced approach is that of *ex vivo* editing: cells from a patient, for instance, hematopoietic stem cells, are gathered, then treated with genome editing in a lab, and readministered [15]. This strategy recently achieved the first-ever regulatory approval of a CRISPR-based therapy, Casgevy, which reactivates fetal hemoglobin to treat sickle cell disease and beta-thalassemia. This *ex vivo* approach is also revolutionizing cancer immunotherapy via the complex engineering of CAR-T cells [16,17]. The more challenging frontier is represented by *in vivo* therapy, where the CRISPR machinery is administered directly into the body as a drug. Pioneering clinical trials are in progress using LNP-mediated intravenous delivery to the liver for the treatment of transthyretin amyloidosis and subretinal injection for genetic forms of blindness [18].

2.4. Barriers in Delivery, Stability, and Immune Response

The CRISPR RNP complex is a large, highly anionic macromolecule incapable of passively diffusing across the cell's lipid membrane. Once inside the cell, it must then escape the endosome, which would otherwise degrade it, and for DNA-targeting Cas, traffic into the nucleus to reach the genome [19]. Moreover, the components are inherently unstable: RNA is rapidly degraded by nucleases abundant in serum and the cytoplasm. Perhaps the greatest single hurdle is immunogenicity [20]. As bacterial proteins, Cas

nucleases are potent immunogens; due to previous infections, many humans possess pre-existing T-cells and antibodies against common Cas proteins, such as those from S. pyogenes Cas9. This leads to rapid clearance, therapeutic failure and risks a dangerous inflammatory response [21].

3. Design Principles of CRISPR-Compatible Biomaterials

Biomaterials for CRISPR-Cas delivery are designed based on the optimization of their physicochemical and biological properties, thus offering a way to accomplish efficient, safe, and targeted genome editing [22]. Besides efficiently encapsulating and protecting the fragile CRISPR components, the effective material should be able to surmount complex biological barriers and reach either the target cell's nucleus or cytoplasm [23]. Compatibility with degradability, physicochemical tunability, efficiency in intracellular trafficking, and finally stimulus responsiveness that allows controlled release are the most prominent design aspects governing functionality in these systems [24].

3.1. Biocompatibility, biodegradability, and non-immunogenic design

Biomaterial vectors for CRISPR delivery should be cytocompatible and possess minimal immunogenicity for safe *in vivo* applications. Surface chemistry, degradation by-products, and interactions with cell membranes define the biocompatibility of the biomaterial vectors [25]. Biodegradable polymers like PLGA, chitosan, and hyaluronic acid derivatives are used because they degrade into nontoxic metabolites cleared through natural pathways [26,27]. In contrast, nondegradable or inorganic nanocarriers, such as gold and silica nanoparticles, maintain structural stability but require surface functionalization with PEGylation or zwitterionic layers to minimize protein adsorption and immune activation [28,29]. The introduction of stealth modifications, such as PEG chains, may prolong systemic circulation and reduce recognition by the reticuloendothelial system, thereby improving biodistribution and accumulation at the target site [30].

3.2. Role of Surface Charge, Molecular Weight and Hydrophilicity

The fine-tuning of surface charge, molecular weight, and hydrophilicity has always been at the heart of the balance between delivery efficiency and biosafety. In general, a moderate positive surface charge in the range of +10 to +30 mV of zeta potential allows for electrostatic binding of negatively charged CRISPR components and promotes cellular uptake via endocytosis. However, excess cationic charge disrupts the cell membrane and induces cytotoxicity [31]. The molecular weight of the polymeric carrier influences complex stability and degradation rate, since high-molecular-weight polymers may form stable complexes and have much slower clearance [32]. The hydrophilic–hydrophobic ratio impacts the solubility and interaction with serum proteins, whereby hydrophilic surfaces resist opsonization but hydrophobic domains favor membrane fusion and endosomal escape [33].

3.3 Engineering Endosomal Escape and Nuclear Targeting

Following internalization, CRISPR components need to escape from endosomal compartments to reach their functional sites in the cytoplasm or nucleus. Failure to achieve timely endosomal release results in lysosomal degradation and loss of activity [34]. Materials incorporating proton-sponge polymers, including polyethyleneimine or polyhistidine, fusogenic peptides, or pH-responsive linkages induce osmotic swelling or membrane fusion under acidic endosomal conditions, thereby promoting escape. Besides, nuclear localization is an important requirement for plasmid- or DNA-based CRISPR constructs [35]. This could be achieved by conjugation of NLS to Cas proteins or through biomaterials designed to exploit intracellular redox gradients and enzymatic triggers for targeted release. Smart trafficking designs enable precise intracellular localization with a minimum of off-target exposure [36].

3.4 Stimuli-Responsive and Self-Assembled Delivery Systems

Recent advances have described the use of stimulus-responsive and self-assembled biomaterials for dynamic, context-dependent CRISPR delivery. These systems change either their structure or release kinetics in response to physiological stimuli, such as pH, temperature, redox potential, or reactive oxygen species, or respond to externally applied triggers including light and ultrasound [36–38]. Self-assembly nanostructures formed via electrostatic, hydrophobic, or hydrogen-bonding interactions allow modular encapsulation of Cas proteins, sgRNA, and auxiliary molecules within a single platform. Modularity also enables co-delivery approaches and synchronized intracellular release [39]. Moreover, it allows the addition of targeting ligands or bio-inspired coatings, for example, exosome membranes or cell-derived vesicles, that can enhance tissue specificity and biocompatibility. Together, these adaptive materials form the next generation of CRISPR carriers capable of spatiotemporally controlled genome editing [40].

4. Classes of Biomaterials for CRISPR Delivery

Efficient and safe delivery of CRISPR components is one of the most important determinants to achieve successful genome editing, especially for therapeutic approaches. Biomaterial-based nanocarriers represent adaptable platforms that protect nucleic acids or RNP complexes, while enhancing cellular uptake and facilitating spatiotemporally controlled release. The diversity in available materials, ranging from polymers and lipids over inorganic to hybrid constructs, allows tailored solutions for a wide range of biological and clinical needs [41]. The major classes of biomaterials and their distinct structural and functional characteristics are summarized in Figure 2.

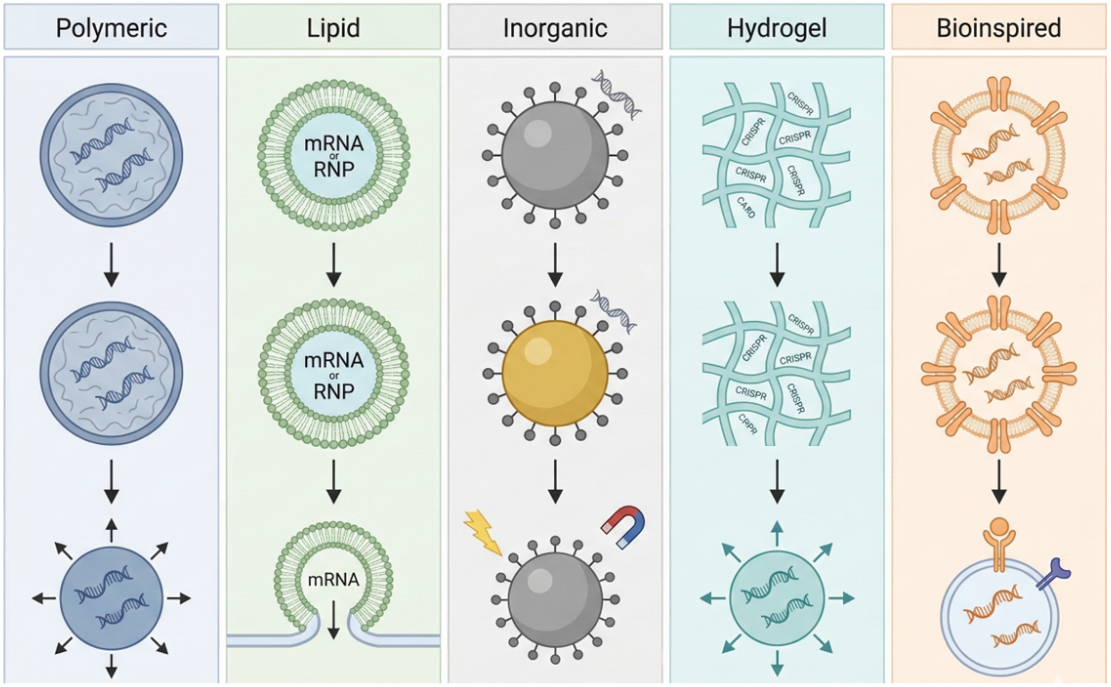

Figure 2. Classes of biomaterials for CRISPR delivery and their functional mechanisms.

4.1. Polymeric Nanocarriers: PLGA, PEI, Chitosan, PEGylated Polymers

Polymeric systems offer tunable physicochemical properties, with a generally established safety profile for gene delivery. Among the most studied are PLGA nanoparticles, which present biocompatibility and controlled degradation to allow sustained release of either plasmid DNA or Cas-sgRNA complexes [42]. The cationic polymer PEI promotes nucleic acid condensation and allows endosomal escape by means of a proton sponge effect through its amine groups' buffering capacity. Still, due to its intrinsic cytotoxicity, modified PEI and PEG-conjugated derivatives with lower toxicity and improved stability have been developed [43]. Chitosan, being a natural polysaccharide, thus joins biodegradability with mucoadhesive and mild cationic properties. This makes it particularly appealing for mucosal and pulmonary CRISPR delivery. PEGylation increases the circulatory half-life and reduces opsonization, improving the systemic biodistribution of the CRISPR cargos [44].

4.2. Lipid-Based Systems: Cationic Liposomes, Lipid Nanoparticles

The clinically most advanced class of nanocarriers for nucleic acid delivery involves lipid-based nanocarriers, including cationic liposomes and LNPs. Because of their amphiphilic architectures, they can easily encapsulate CRISPR mRNA, plasmid DNA, or RNPs with high efficiency, protecting them against enzymatic degradation and facilitating their endosomal escape through membrane fusion [45]. Development of ionizable lipid chemistry using tertiary amine-containing lipids, which are cationic at endosomal pH, has significantly improved both transfection efficiency and tolerability. LNPs have been especially successful in hepatic gene editing, where *in vivo* delivery of Cas9 mRNA and sgRNA led to high on-target activities and transient expression that minimizes off-target effects. Further optimization of the lipid composition, including cholesterol and PEG–lipid ratios, enables superior organ selectivity and lower immunogenicity [46].

4.3 Inorganic Nanocarriers: Gold, Silica, Calcium Phosphate

Inorganic nanoparticles confer structural rigidity, high surface area, and facile functionalization, hence allowing for certain advantages in CRISPR component delivery. Gold nanoparticles can serve as versatile scaffolds for conjugating thiol-modified oligonucleotides, peptides, or Cas9 proteins [47]. They also support external control strategies such as photothermal activation for spatiotemporal release of gene-editing complexes. Mesoporous silica nanoparticles have a high cargo loading capacity and can be engineered for pH- or enzyme-responsive release, while calcium phosphate nanoparticles exhibit excellent biocompatibility and degradation under acidic intracellular conditions [48]. Despite these merits, concerns about possible cytotoxicity, aggregation, and long-term tissue accumulation hinder their wide clinical applications.

4.4 Hydrogel- and Scaffold-Based Local Delivery Systems

Hydrogel-based and scaffold-supported platforms enable localized and sustained release of CRISPR elements, making them well-suited for tissue-targeted therapies. Hydrogels derived from natural (e.g., alginate, gelatin) or synthetic (e.g., PEG) polymers can encapsulate RNPs, mRNA, or DNA and release them in response to physiological stimuli, such as pH or enzymatic activity [49]. These systems are particularly beneficial for *ex vivo* gene editing or regenerative medicine, where the edited cells can be delivered within biocompatible matrices. Scaffold-based constructs, including electrospun fibers and

3D-printed architectures, further offer mechanical and spatial control, thus promoting efficient gene modulation [50].

4.5 Bioinspired and Hybrid Systems (Exosomes, Membrane-Coated Nanoparticles)

Bioinspired systems bridge the gap between synthetic precision and biologic compatibility. Using exosomes-naturally derived extracellular vesicles innate delivery vehicles, researchers engineer them to be capable of transferring CRISPR cargos across biological barriers with minimal immune activation [51]. Surface modification with targeting ligands or the fusion of synthetic lipids can enhance delivery specificity and efficiency. Likewise, cell membrane-coated nanoparticles employing erythrocyte, platelet, or cancer cell membranes use natural surface proteins to effect immune evasion and homotypic targeting [52,53]. As recently described by Dara *et al.* (2024). The most recently developed hybrid platforms combine polymers, lipids, and biological membranes to synergize stability, targeting accuracy, and intracellular trafficking, constituting a promising frontier for next-generation CRISPR therapeutics [54].

Recent advances discussed by Baig *et al.* (2025) have diversified biomaterial platforms for CRISPR-Cas delivery, each with unique structural and functional advantages. The nature of composition, physicochemical behavior, and cellular interaction mechanisms thus varies among these systems; therefore, each system can uniquely be optimized for its specific CRISPR cargos, plasmid DNA, mRNA, or RNP complexes [55]. The major classes of biomaterials explored to date are summarized in Table 1, along with respective representative compositions, mechanistic features, and comparative advantages that overcome biological barriers toward efficient genome editing.

Table 1. Classes of Biomaterials for CRISPR–Cas Delivery: Composition, Mechanistic Features, and Key Advantages

Biomaterial Class	Representative Materials	Mechanistic Highlights	Key Advantages for CRISPR Delivery	Ref.
Polymeric nanocarriers	PLGA, PEI, chitosan, PEGylated polymers	Electrostatic complexation with CRISPR cargo; tunable degradation; endosomal escape via "proton sponge" effect	High encapsulation efficiency, adjustable release kinetics, suitable for pDNA/mRNA/RNP	**[56]**
Lipid-based systems	Cationic liposomes, lipid nanoparticles (LNPs), ionizable lipids	Formation of lipid–nucleic acid complexes; pH-triggered release in endosomes	Clinically validated platform (e.g., mRNA vaccines); efficient mRNA and RNP delivery	**[57]**
Inorganic nanocarriers	Gold, silica, calcium phosphate nanoparticles	Surface functionalization enables electrostatic and covalent cargo attachment; photothermal or magnetic responsiveness	Structural rigidity, easy surface modification, multimodal imaging potential	**[58]**
Hydrogel and scaffold systems	PEG hydrogels, alginate scaffolds, fibrin gels	Localized, sustained release via diffusion or degradation-controlled mechanisms	Enables spatial control of editing, tissue regeneration compatibility	**[59]**
Bioinspired and hybrid carriers	Exosomes, cell membrane-coated nanoparticles, virus-mimetic vesicles	Natural membrane proteins confer immune evasion and cell targeting; hybridization with synthetic materials for stability	Enhanced biocompatibility, low immunogenicity, improved tissue specificity	**[60]**

5. Strategies for CRISPR Component Delivery

The therapeutic success of CRISPR-based genome engineering intrinsically depends on the efficient and safe delivery of its molecular components, Cas nuclease, guide RNA, and sometimes donor templates to target cells and tissues [61]. Depending on the physical form in which CRISPR constituents are introduced, such as plasmid DNA (pDNA), messenger RNA (mRNA), and RNP complexes, various delivery strategies have been established. Each of these methods possesses certain advantages and disadvantages concerning delivery efficiency, temporal control, and immunogenicity, critically dependent on the design and physicochemical properties of the carrier systems [62]. The key differences in intracellular processing and temporal dynamics of CRISPR delivery formats are illustrated in Figure 3.

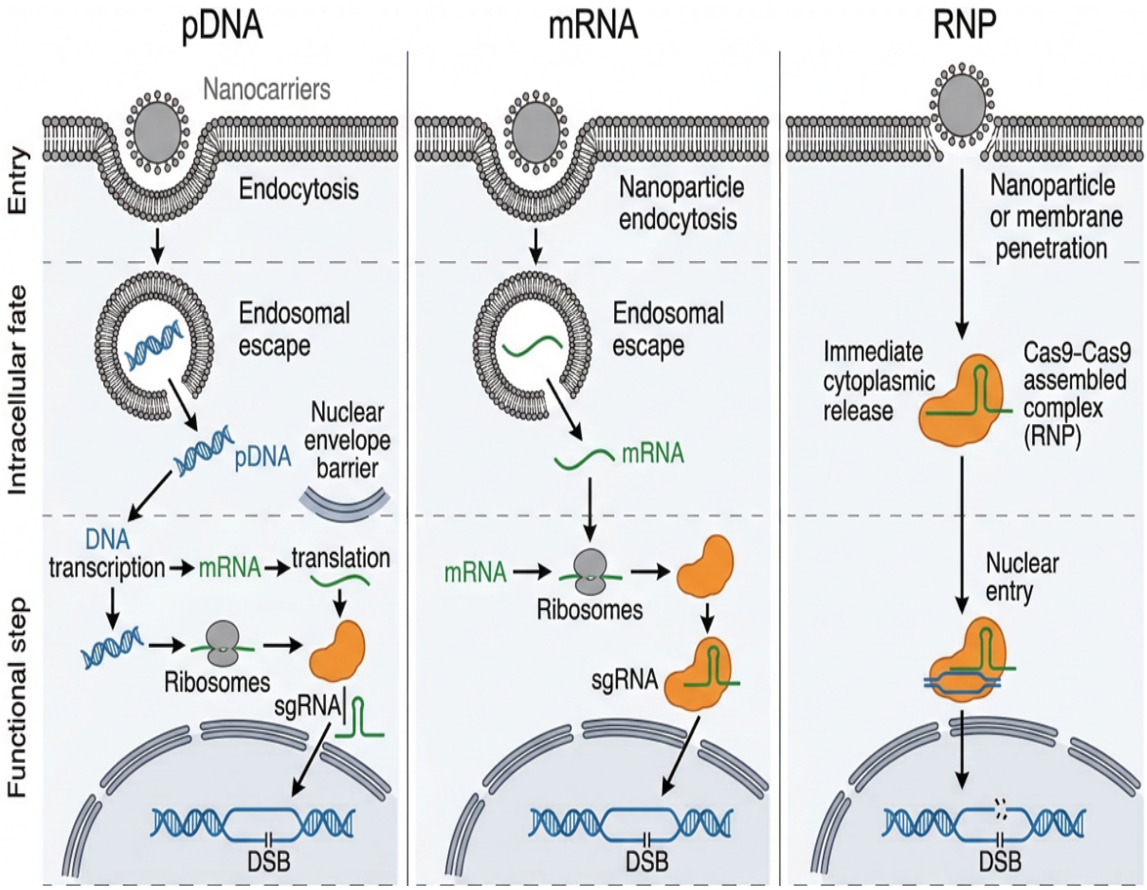

Figure 3. Comparative intracellular fate and temporal dynamics of CRISPR delivery formats.

5.1. Delivery of Plasmid DNA Encoding Cas and sgRNA

Plasmid DNA-based delivery represents one of the earlier and more straightforward methods for CRISPR-mediated gene editing. In this approach, either a single plasmid or dual-vector system encodes both the Cas endonuclease and the single-guide RNA, thus allowing transient or semi-stable expression within the host cell. The method benefits from the relative ease of large-scale production of plasmids and structural stability at physiological conditions [63]. However, delivery efficiencies are typically limited by the large size of CRISPR plasmids, poor nuclear uptake, and potential risks of random genomic integration. A number of polymeric nanocarriers, including PEI, PLGA, and chitosan derivatives, have been engineered to enable improved endosomal escape and high-efficiency transfection with reduced cytotoxicity. [64]. While pDNA systems continue to be highly useful *in vitro* and *ex vivo*, translation *in vivo* will require further refinements in vector design to limit potentially prolonged Cas expression and off-target risks.

5.2. mRNA-Based CRISPR Delivery

mRNA delivery provides a transient and non-integrative route for the expression of CRISPR components, with improved biosafety compared to plasmid-based methods. By co-delivering Cas nuclease mRNA and sgRNA into target cells, both rapid translation and genome editing can occur before the eventual degradation of these RNA species [65]. To date, LNPs have emerged as one of the leading platforms for CRISPR mRNA delivery, benefiting from their use in clinically successful mRNA vaccine technologies. The addition of ionizable lipids and PEGylation enhances endosomal release and can protect against the nuclease degradation of cargo. Additionally, chemical modifications of mRNA and sgRNA, which include pseudouridine or 5-methylcytidine incorporation, significantly reduce innate immune recognition and further enhance intracellular stability [66]. Despite these advances, mRNA delivery remains challenged by limited tissue specificity and potential inflammatory responses upon systemic administration.

5.3. Ribonucleoprotein (RNP) Complex Delivery

Various efforts have been directed toward the direct delivery of pre-assembled Cas-sgRNA ribonucleoprotein complexes as a precise and transient editing modality. RNPs can exert immediate genome-editing activity upon cellular entry with minimized risk of off-target cleavage and no possibility of vector integration [67]. However, large size and negative charge, characteristics of RNPs, require sophisticated carrier systems that enable cellular uptake. So far, RNPs have been encapsulated into and optimally released from cationic polymers, cell-penetrating peptides, gold nanoparticles, and lipid-based nanocarriers [68]. As per Volodina & Smirnikhina (2024), biodegradable polymeric systems and bioinspired carriers, including exosome-like vesicles, have demonstrated improved

cytoplasmic delivery with nuclease activity preserved. The RNP approach is of particular interest in the context of *ex vivo* gene editing applications, such as hematopoietic stem cell or T-cell engineering, where precise temporal control is often required [69].

5.4. Co-Delivery of CRISPR with Regulatory RNAs or Proteins

Emerging evidence suggests that co-delivery of CRISPR components with regulatory RNAs or accessory proteins can significantly enhance editing precision and therapeutic efficacy. Small RNAs such as microRNAs or siRNAs can be co-packaged to modulate endogenous repair pathways or suppress immune responses to Cas proteins [70]. Similarly, co-delivery of donor DNA templates or recombination-enhancing factors can promote homology-directed repair (HDR) efficiency in targeted gene correction applications. Thus, hybrid biomaterial systems integrating lipids, polymers, and inorganic nanoparticles have been employed to achieve spatiotemporal coordination of multiple biomolecules and enable the synchronization of delivery with controlled release kinetics [71]. Approaches like this represent part of a trend toward multiplexed, systems-level control in CRISPR therapies.

5.5 Spatiotemporal Control and Targeted Tissue-Specific Release

The spatiotemporal precision in CRISPR delivery is critical to maximize therapeutic efficacy while minimizing off-target or systemic effects. Biomaterials have been designed to permit controlled release of CRISPR cargos through physiological or external stimuli, including pH, temperature, enzymatic activity, magnetic fields, or light [72]. Specific cell types or tissues, including hepatocytes, neurons, or tumor cells, are selectively targeted with ligand-mediated targeting using antibodies, aptamers, or peptide motifs. Hydrogel scaffolds and implantable matrices enable localized and sustained release, especially in applications within the realm of regenerative medicine or oncology. This type of spatial and temporal control can be combined with computational modeling and real-time imaging to accelerate the development of next-generation precision gene editing platforms [73].

6. Emerging Applications

CRISPR-Cas technologies combined with engineered biomaterials pave new frontiers in precision medicine. These permit local, effective, and biocompatible gene modulation and overcome many pharmacokinetic and immunological limitations of conventional delivery systems. Biomaterials are providing structural and functional versatility that is extending the reach of CRISPR into oncology, genetic disorders, neurodegenerative diseases, and regenerative medicine, thereby bridging the gap between preclinical innovation and clinical translation [74].

6.1 Oncogene silencing and cancer immunotherapy

CRISPR-based gene editing reshapes cancer therapy through the precise disruption of oncogenic drivers and the modulation of immune pathways. Biomaterial-mediated delivery systems, especially lipid nanoparticles, polymeric nanocarriers, and hybrid vesicles, have silenced critical oncogenes including KRAS, MYC, and PD-L1, which sensitize tumors to immune checkpoint inhibitors [75]. Besides, biomaterial-assisted *ex vivo* platforms have improved editing precision, viability, and expansion in CRISPR editing of immune effector cells such as CAR-Ts and NK cells. The use of biodegradable carriers allows localized delivery within tumor microenvironments, reducing systemic exposure and improving therapeutic selectivity [76].

6.2. Correction of Hereditary and Other Rare Genetic Disorders

CRISPR-Cas systems combined with non-viral biomaterial carriers represent safer and more transient methods of correcting pathogenic mutations in monogenic diseases. According to Kaur *et al.* (2024) lipid nanoparticles and polymeric systems have achieved the correction of mutations in CFTR (cystic fibrosis), HBB (β-thalassemia, sickle cell disease), and DMD (Duchenne muscular dystrophy) in several preclinical models [77]. Recent development of tissue-specific biomaterials enables targeted delivery to the liver, muscle, and lung in particular, while avoiding systemic delivery barriers. RNP delivery minimizes prolonged nuclease exposure, reducing risks of genomic instability and off-target editing-key considerations for clinical translation [78].

6.3. Neurodegenerative and Metabolic Disease Models

Genome editing in the central nervous system and metabolic tissues is, however, challenging because of biological barriers like the blood-brain barrier (BBB) [79]. Several biomaterial systems, including PEGylated nanoparticles, exosome-inspired carriers, and receptor-targeted liposomes, are now allowing for CRISPR delivery across these barriers. In models of neurodegenerative diseases, such as Alzheimer's and Parkinson's, these platforms have enabled modulation of pathogenic genes including APP, SNCA, and LRRK2. Biomaterial-facilitated CRISPR has also been applied to modulate insulin signaling and lipid homeostasis in models of metabolic disorders. Temporal control in gene editing, with timing of intervention matched with disease pathophysiology, is further possible in stimuli-responsive delivery systems [80–82].

6.4 Regenerative Medicine and Stem Cell Gene Modulation

Biomaterial scaffolds that truly mimic the extracellular matrix provide specific gene-editing environments and are revolutionizing CRISPR-mediated modulation of the fate and differentiation of stem cells [83]. Hydrogels, nanofibrous matrices, and 3D-printed scaffolds can now be engineered to support localized CRISPR activation or repression of genes involved in osteogenesis, myogenesis, and angiogenesis [84]. *Ex vivo* gene editing of stem cells before implantation further improves graft integration and reduces immunogenicity. This synergy between gene-editing precision and biomaterial architecture marks a pivotal advance for patient-specific regenerative therapies [85].

6.5 CRISPR Editing *Ex Vivo*

Ex vivo genome editing has gained a central role in the field of personalized medicine, where biomaterial interfaces have significantly contributed to the improvement of efficiency and functionality of cells [86]. Reconstituted microenvironments-from hydrogel matrices to bioinspired scaffolds-can decrease cellular stress upon editing and maintain the phenotypic stability of cells. Non-viral nanocarriers, including polymeric and lipid-based systems, will be used to deliver CRISPR-Cas RNP complexes at high efficiency into hematopoietic stem cells and immune cells. Activities at this scale will support regulatory-compliant manufacturing of gene-edited cell therapeutics for oncological, hematologic, and regenerative applications [87].

7: Future Directions and Technological Convergence

7.1 AI and Computational Modeling for Biomaterial Design

Artificial intelligence and computational modeling have been increasingly important in biomaterial design for CRISPR delivery. Machine learning algorithms on large, multivariate data sets can predict how physicochemical properties such as molecular weight, charge density, and hydrophobicity affect delivery efficiency and cellular uptake [88–90]. Deep neural networks and generative models now allow *in silico* design of nanocarriers with tailored surface chemistry and biodegradation profiles [91,92]. More importantly, molecular dynamics simulations yield deep atomic-level insight into the conformational behavior of Cas proteins and inform RNA folding stability under physiological conditions. Integration of this AI-driven predictive modeling with iterative *in vitro* validation might accelerate the finding of disease-specific, patient-adapted delivery systems and would reduce time and cost compared with traditional empirical screening [93].

7.2. Integration with Microfluidics and Organ-on-Chip Systems

Microfluidics and organ-on-chip represent the next generation in delivering game-changing solutions for preclinical evaluation of CRISPR-based therapeutics. These systems can simulate a tissue-specific microenvironment that is capable of dynamically mimicking biomaterial transport and biodistribution, and assessing genome-editing efficiency. Microfluidic devices can control the synthesis and encapsulation of CRISPR components that will enable reproducibility and scalable manufacturing of nanoparticles [94]. Meanwhile, other organ-on-chip systems, such as liver-, BBB-, and tumor-on-chip models, each provide physiologically relevant insight into editing performance and toxicity profiles. Embedding biosensors and live-cell imaging within such systems provides real-time cellular response feedback, hence allowing for rapid optimization of delivery strategies prior to animal or clinical studies. Such is a concept that bridges the gap between laboratory research and translational development [95].

7.3. CRISPR Optimization Using Quantum and Synthetic Biology

The intersection of quantum-inspired computation with synthetic biology has opened new avenues of CRISPR optimization. Quantum computing methods are now being explored to model the energetics and reaction dynamics of the CRISPR-Cas systems with unprecedented accuracy, with promises of improved understanding of off-target interactions and DNA repair kinetics. Synthetic biology offers a toolkit toward programming CRISPR activity via engineered regulatory circuits, inducible promoters, and RNA scaffolds that respond in a direct fashion to environmental or metabolic cues. These provide ways to design context-sensitive, tunable genome-editing platforms with enhanced precision and minimal collateral activity. Such hybrid frameworks, though in their infancy, could set the stage for intelligent gene-editing modalities of the next generation [96].

7.4 Translational and Clinical Challenges in Scalable Manufacturing

Despite rapid advances in technology, numerous significant challenges will be overcome before clinically approved therapies are realized with the translation of CRISPR-biomaterial systems. One fundamental bottleneck for this involves scalable, reproducible, and GMP-compliant manufacturing. Variability in nanoparticle size, encapsulation efficiency, and surface modification may affect therapeutic outcome and thus require robust PAT and continuous manufacturing approaches [97]. Notwithstanding the scientific hurdles, regulatory agencies are also still developing comprehensive guidelines for assessing the safety, immunogenicity, and long-term stability of gene-editing material. Equitable access and oversight of heritable edits are some of the ethical and social considerations that must also be thoughtfully embedded into such translational frameworks. Meeting these multidisciplinary challenges will necessitate coordinated advances in materials science, regulatory policy, and computational engineering to realize the full therapeutic potential of CRISPR-enabled biomaterial systems [98].

Advances increasingly drive interdisciplinary innovations in the design and application of CRISPR-biomaterials at the interfaces between materials science, computational biology, and synthetic systems engineering. AI, microfluidic modeling, and synthetic or quantum biology are empowering predictive, scalable, and precision-driven design of delivery vectors.

An overview of major technological domains currently driving next-generation CRISPR platforms-including mechanistic contributions, existing challenges, and representative studies supporting these emerging strategies-is given in Table 2 below

Table 2. Emerging Technological Strategies for Next-Generation CRISPR Delivery Platforms

Technological Domain	Strategic Approach	Mechanistic Contribution to CRISPR Efficacy	Current Limitations / Translational Challenges	Ref.
AI-driven biomaterial design	Machine learning for predicting material–cargo interactions; generative design of polymers and lipids	Rational optimization of carrier composition, size, and charge for specific CRISPR cargos	Requires large, curated datasets; limited interpretability of deep models	[99]
Microfluidic synthesis and organ-on-chip screening	Controlled nanoparticle assembly and organotypic CRISPR testing	Improves batch consistency, mimics physiological barriers for validation	Scalability and integration with GMP manufacturing remain limited	[100]
Synthetic biology-assisted control	Use of inducible promoters, RNA switches, and feedback circuits	Enables spatiotemporal control of editing activity and minimizes off-target events	Circuit stability and biocontainment challenges in vivo	[101]
Quantum and computational modeling	Quantum mechanics-based modeling of Cas protein energetics and DNA repair dynamics	Predicts off-target binding and informs Cas variant design	Computational cost; limited experimental validation	[102]
Translational and regulatory engineering	Development of GMP-compatible continuous manufacturing and safety frameworks	Ensures reproducibility, scalability, and clinical compliance	Regulatory heterogeneity; complex classification of combination products	[103]

8. Conclusion

This review emphasizes that the main challenge for the clinical translation of CRISPR therapies is the development of safe, efficient, and precisely controlled delivery systems that can overcome complex biological interfaces. The strategy is now shifting from conventional encapsulation to a rational biomaterial design based on a range of polymers, lipids, hydrogels, and hybrids of bioinspired materials with engineered physicochemical properties to improve cellular uptake, endosomal escape, and nuclear localization. Selection of materials increasingly depends on the nature of the CRISPR cargo-plasmid DNA, mRNA, or ribonucleoprotein complexes-and allows temporal and dosage control over gene-editing events. Advanced biomaterials have therefore emerged from passive carriers to active functionalities of precision medicine, extending the therapeutic scope of genome editing. Still, scalable and GMP-compliant manufacturing, as well as clear regulatory and ethical environments, are important prerequisites for clinical translation. Integration of materials science with AI-driven modeling and organ-on-chip validation platforms is among promising strategies for accelerating the clinical translation of CRISPR-enabled biomaterial systems into safe, effective, and patient-specific therapies

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