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Nanomaterials Staunchly Assisting Gene and Drug Delivery: Current Trends

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Abstract

Nanomedicine has revolutionised healthcare by providing precise, targeted and controlled approaches for drug and gene delivery. This paper reviews recent advancements in nanomaterial applications for gene and drug delivery, focusing on key technologies such as CRISPR/Cas9 and mRNA vaccines. It explores their use in smart drug delivery systems targeting cancer, neurological disorders, and regenerative medicine, including the innovative concept of nanorobots.

Keywords: Nanomedicine, Nanomaterials, Nanorobots, Drug Delivery, Gene delivery, CRISPR/Cas9, mRNA Vaccines

List of Abbreviations

PEG – Polyethylene Glycol
Doxil – Doxorubicin liposome
BBB – Blood Brain Barrier
NLC – Nanostructured lipid carriers
LNPs – Lipid nanoparticles
DCs – Dendritic cells
PEI – Polyethyleneimine
MNDP – Multistage drug delivery nano-shell
PBAEs - poly (β-amino esters)
PLGA - poly (lactic-co-glycolic acid)
Arg(NP) - Arginine-coated gold nanoparticles
GNPs - Gold nanoparticles
HDR - Homology directed repair
MSNs - Mesoporous silica nanoparticles
MRI – Magnetic resonance imaging
CNTs – Carbon nanotubes
CPP – Cell penetrating peptide
VLPs – Virus like particles
EVs – Extracellular vesicles
RBCs – Red blood cells
NGS – Next generation sequencing

1. Background

1.1. Gene and Drug Delivery: Importance and Challenges

Gene and drug delivery systems are pivotal in modern medicine, enabling the precise administration of therapeutic agents to target sites within the body. Effective delivery systems are essential to maximize therapeutic efficacy, minimize side effects, and address diseases at a molecular level. The importance of these systems is underscored by their potential to revolutionize treatments for a wide range of diseases, including cancer, genetic disorders, and infectious diseases. However, traditional delivery methods often

face significant challenges, such as poor bioavailability, limited targeting capabilities, and adverse reactions.

1.2. Nanomaterials: Revolutionizing Gene and Drug Delivery

Nanomaterials offer groundbreaking solutions to the limitations of conventional drug delivery systems. Due to their unique properties—such as high surface area to volume ratio, tunable surface chemistry, and the ability to encapsulate therapeutic agents—nanomaterials can enhance the delivery of poorly water-soluble drugs, target specific cells or tissues, and facilitate transcytosis across tight epithelial and endothelial barriers. Additionally, they can deliver macromolecule drugs to intracellular sites and enable the co-delivery of multiple drugs for combination therapies. Nanotechnology also integrates imaging modalities with therapeutic agents, allowing real-time assessment of therapeutic efficacy in vivo and paving the way for personalized medicine [1,2]. Major breakthroughs in the field of nanotechnology for gene and drug delivery has been represented in the figure 1, as shown below.

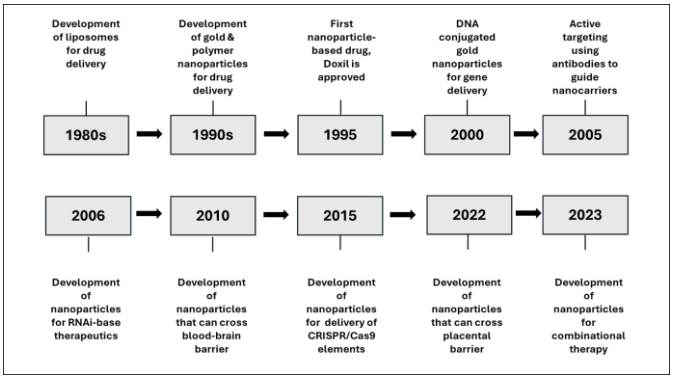

Figure 1: Major Milestones of Nanotechnology in Gene and Drug Delivery

Nanotechnology has transformed drug delivery systems significantly since the 1960s with the introduction of lipid vesicles, known as liposomes. In 1976, the first controlled-release polymer system for delivering macromolecules was described, followed by more sophisticated systems in 1980 capable of pH-responsive drug release and cell-specific targeting using liposomes. The concept of "stealth liposomes," designed for prolonged circulation, emerged in 1987 with the use of polyethylene glycol (PEG). This advancement paved the way for Doxil (doxorubicin liposome), approved in 1995 for AIDS-associated Kaposi's Sarcoma. Today, liposomal drugs and polymer-drug conjugates dominate, offering enhanced pharmaceutical efficiency, targeted release, and extended shelf life. Nanotechnology also revitalizes biologically active molecules previously considered challenging due to delivery issues, leveraging biomaterial combinations and precise targeting strategies. Important considerations include biocompatibility, ease of manufacturing, pharmacokinetic properties, and the presence of ligands for receptor-mediated endocytosis. Moving forward, controlled-release polymer technologies and liposomes are poised to continue making significant clinical impacts, while ongoing developments explore new biomarkers and optimize drug delivery systems for enhanced therapeutic outcomes [3].

1.3. CRISPR/Cas9: A Breakthrough in Genome Editing

CRISPR/Cas9 is a revolutionary genome editing tool that holds immense therapeutic potential for modifying genomes and advancing biomedical research. Despite its promise, the broader application of CRISPR/Cas9 is hindered by challenges in efficiently delivering the CRISPR elements in vivo. Nanotechnology provides a promising solution, enhancing the delivery of CRISPR components using lipid-based nanoparticles, polymeric nanoparticles, and viral vectors. These nanomaterials protect the CRISPR components, aid cellular uptake, enable endosomal escape, and can be customized with targeting ligands to improve specificity and minimize off-target effects [4].

1.4. mRNA Vaccines and Therapeutics

The recent success of mRNA vaccines, particularly in the context of the COVID-19 pandemic, has highlighted the potential of mRNA-based therapeutics. Nanotechnology plays a crucial role in stabilizing mRNA molecules, protecting them from degradation, and facilitating their delivery into target cells. This approach has opened new avenues for the treatment of various diseases, including cancer and genetic disorders.

1.5. Addressing Major Healthcare Challenges

1. **Cancer:** Targeted delivery of chemotherapeutic agents and gene therapies using nanomaterials can significantly improve treatment outcomes and reduce side effects.
2. **Neurological Disorders and the Blood-Brain Barrier (BBB):** Nanoparticles can facilitate the delivery of therapeutics across the BBB, addressing challenges in treating neurological conditions such as Alzheimer's and Parkinson's diseases.

1.6. Regenerative Medicine

Nanotechnology enhances the delivery of growth factors and genetic material to promote tissue regeneration and repair, offering promising solutions for injuries and degenerative diseases. Nanomaterials are at the forefront of addressing pressing healthcare issues through advanced gene and drug delivery systems. By

overcoming the limitations of traditional delivery methods, nanotechnology enables precise, efficient, and targeted therapeutic interventions. The integration of nanomaterials with cutting-edge techniques like CRISPR/Cas9 and mRNA therapeutics represents a significant leap forward in the field of medicine, promising improved patient outcomes and the realization of personalized medicine.

This review focuses on the application of an array of nanomaterials including nanorobots in gene and drug delivery, highlighting their confluence with breakthrough technologies such as CRISPR/Cas9 and mRNA therapeutics to address some of the most pressing healthcare issues like cancer and neurological disorders as well as to advance solutions in regenerative medicine.

2. Lipid-Based Nanomaterials

Lipid-based nanoparticles are highly efficient carriers for Cas9 delivery. Composed of cationic lipids or lipid-like materials, they encapsulate Cas9 and guide RNA, protecting them from degradation and ensuring efficient delivery into target cells. These nanoparticles can be optimized for size, surface charge, and functionalization, enhancing cellular uptake, and enabling precise, target-specific delivery, thereby improving the effectiveness of gene editing therapies [5].

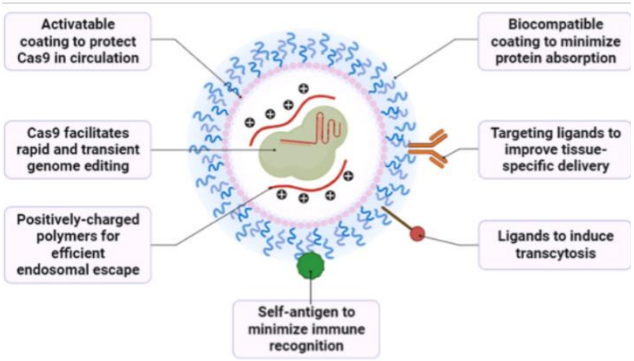

Figure 2: Versatility of CRISPR Within Polymeric Nanocarriers

The figure above illustrates the versatility of CRISPR encapsulated within polymeric nanocarriers. These customizable carriers feature biocompatible coatings and targeting moieties, enabling precise delivery to specific sites. They also possess an activatable coating to protect Cas9 during circulation and use positively charged polymers for efficient endosomal escape. Additionally, these carriers can be engineered with self-antigens to reduce immune recognition, enhancing the overall effectiveness and safety of the delivery system [5].

Research indicates that liposomes have been successfully used to encapsulate Cas9 mRNA for treating disorders such as tyrosinemia. One major advantage of liposome-based delivery over viral delivery is the reduction in off-target effects. Liposomes offer several benefits, including protecting the Cas9/sgRNA ribonucleoprotein complex from degradation during blood circulation due to their lipid bilayer [4]. Moreover, studies have shown that bio reducible LNPs with disulfide bonds exhibit high efficiency. A specific type of liposome, LNP-INT01, is used to deliver guide strand and the mRNA coding for SpCas9 effectively [4]. PEG-PEI-CHOL modified with an aptamer specific for osteosarcoma cells has been used to deliver CRISPR elements via plasmids as a treatment strategy for orthotopic osteosarcoma [6].

These advancements highlight the applicability of liposome-based systems for delivery in improving the efficiency and specificity of CRISPR therapies. Small interfering RNA drugs are employed to treat polyneuropathies such as Huntington's disease or Alzheimer's disease by targeting and inhibiting pathological proteins. They protect the cargo from degradation and facilitate its passage through the Blood Brain Barrier (BBB) [7]. Nanostructured lipid carriers (NLC) in nucleoside modified mRNA COVID-19 vaccines developed by BioNTech/Pfizer and Moderna provided excellent encapsulation and protection of the mRNA encoding the viral spike glycoprotein of SARS-CoV-2. The NLC was composed of cholesterol, neutral phospholipid, polyethylene glycol-lipid and an ionisable cationic lipid with a size of around 75nm [33].

mRNA-based cancer vaccines use advanced delivery systems such as liposomes and lipid nanoparticles (LNPs) as efficient carriers for mRNA including mRNA-4157 encoding neoantigens and V941 targeting mutated proteins, highlighting their ability to induce specific immune responses against the tumour antigens. Additionally, mannose-coated nanoparticles, known as Mann-capsules, enhance mRNA delivery efficiency by targeting dendritic cells (DCs) via mannose receptors. This approach promotes the mRNA encoded antigen presentation by DCs post uptake which is crucial for initiating robust immune responses against cancer cells by the T-cells [34-36].

Recent studies have explored the potential of lipid-based nanomaterials in regenerative medicine, yielding promising results [37]. These nanomaterials have shown effectiveness in various applications, including wound healing through the use of nano-emulsions and liposomes loaded with curcumin and hyaluronic acid. Additionally, PEG-modified liposomes have demonstrated

potential in skin repair, while tetrapeptide-modified liposomes and PEG-TAE-modified PLGA polymer liposomes have shown promise in treating spinal cord injuries [38]. Furthermore, PEG-modified liposomes and liposomes modified with serotonin and apolipoprotein E have exhibited potential in addressing neuron damage. These findings collectively highlight the potential of lipid-based nanomaterials in delivering therapeutic agents for regenerative medicine applications.

3. Polymer-Based Nanomaterials

The selection of polymers significantly influences critical factors, including payload release kinetics, cellular uptake efficiency, and biocompatibility. One of the standard polymers used for gene delivery is polyethyleneimine (PEI), which is effective for delivering large-sized plasmids. To reduce cytotoxicity, a complex of polyethyleneimine-β-cyclodextrin (PC) has been used for plasmid delivery. A DNA nanoclew coated with PEI has also been developed to efficiently deliver CRISPR elements, enhancing endosomal escape [4]. MDNP which is an acronym for multistage delivery nano-shell based nanoparticle has also been utilized to deliver CRISPR elements into tumour tissues. The MDNP core comprises a plasmid conjugated to PEI-phenyl boronic acid, and the outer shell consists of 2,3-dimethyl-maleic anhydride modified poly (ethylene glycol)-b-polylysine [4]. Additionally, modified nanosized CRISPR complexes (Cr-nanocomplexes) have been created for target-specific antimicrobial action. Another type of polymer, poly (β-amino esters) (PBAEs), demonstrated advantages in condensing negatively charged genetic material, enabling efficient gene delivery [4]. Chitosan nanoparticles are also being used for CRISPR mediated treatment of a genetically influenced disease named pulmonary arterial hypertension [8,9].

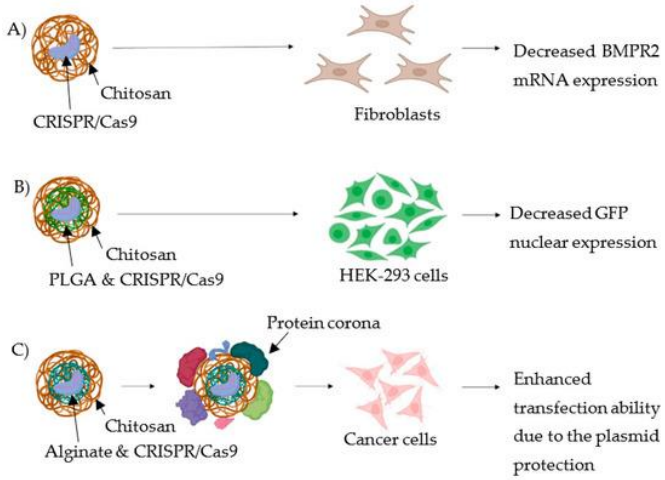

Figure 3: Overview of Approaches Involving pristine Chitosan Backbone Delivery of CRISPR/Cas9 System [8].

These versatile carriers can also be engineered to encapsulate drugs and deliver them to specific areas of the brain. Dendrimers are highly branched polymers that can encapsulate drugs and cross the BBB. They have been explored for delivering neuroprotective agents or targeting specific receptors involved in neurological disorders, such as dendrimers functionalized with peptides for Alzheimer's disease treatment [10,11]. Nanoparticles, nanofibers, and hydrogels made from polymers like chitosan, collagen, and poly (lactic-co-glycolic acid) (PLGA) have been designed for regenerative medicine purposes to release therapeutic agents, such as antibiotics and growth factors, in a controlled and sustained manner. These nanomaterials can also promote cellular proliferation and differentiation, enhance collagen synthesis, and improve tissue strength. Furthermore, polymer-based nanomaterials can create a protective barrier against bacterial invasion, reducing the risk of infection and promoting a conducive environment for wound healing [39].

4. Inorganic Nanomaterials

Gold nanoparticles are recognized for their unique structural properties and are highly effective as gene carriers. Nano assemblies have been engineered using cationic arginine-coated gold nanoparticles (ArgNP) to achieve direct and efficient delivery of Cas9/sgRNA RNP into the cytosol, achieving transfection efficiencies of up to 90% in HeLa cells [12]. Addressing gene mutation diseases, CRISPR-Gold integrates gold nanoparticles (GNPs) conjugated with Cas9 RNP, donor DNA, glutathione, and poly(N-(N-(2-aminoethyl)-2-aminoethyl) aspartamide) (PAsp (DET)). The gold core facilitates rapid release of Cas9 RNP and donor DNA, crucial for homology directed repair (HDR) to correct mutant genes into wild-type sequences [12,43]. Additionally, gold nanoparticles functionalized with single-stranded DNA enhance Cas9 binding to target sites, significantly improving DNA cleavage efficiency [12]. Research suggests gold nanoparticles as a promising new frontier in retinal disease treatment. Due to their small size, AuNPs can be designed to deliver drugs to specific parts of the retina. They can be linked to antibodies that target specific cells or engineered to release their cargo in response to a particular stimulus [13].

Mesoporous silica nanoparticles (MSNs), studied as carriers for CRISPR-Cas9 components, provide large surface areas and adjustable pore sizes that enable efficient incorporation of Cas9 protein and guide RNA. MSNs can be customized with targeting ligands, enabling accurate delivery of CRISPR elements to specific cell types, enhancing precision in genome editing applications [14,15]. Iron-based nanoparticles have been studied for use in drug delivery due to their unique properties. They can be used to deliver therapeutic drugs, siRNA, and DNA. Iron-based nanoparticles can be magnetically targeted to specific tissues or organs. They can also be used for photothermal therapy. Iron Oxide nanoparticles can be used for magnetic resonance imaging (MRI) and for delivering heat to kill cancer cells [16]. Iron oxide nanoparticles, such as magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3), are also used for magnetic targeting and imaging in neuro-oncology and neurodegenerative diseases. They can be guided to specific areas of the brain using external magnetic fields for precise drug delivery or imaging [17,18]. However, there are still challenges such as long-term toxicity and excretory mechanisms that need to be addressed before iron-based nanoparticles can be widely used in clinical applications. Gold nanoparticles conjugated with an antisense oligonucleotide against BCR-ABL mRNA, which translates into active tyrosine kinase, was used in mRNA silencing leading to increased K562 cell death [40].

5. Carbon-Based Nanomaterials

Graphene oxide nanocarrier functionalised with PEI and PEG has been developed for efficient transfer of Cas9/sgRNA complexes, ensuring high stability to protect RNA from enzymatic degradation in circulation. GO nanosheets, known for their expansive surface area and biocompatibility coupled with modifications for specific targeting are potential carriers too. GO nanosheets with a negative charge interact electrostatically with the net positively charged ribonucleoprotein complex of CRISPR, facilitating cell uptake [19,20]. Carbon nanotubes with a single wall, known for their high surface-volume ratio and natural permeability across the cell membrane, are increasingly studied as effective CRISPR transporters [21]. Carbon nanotubes find use in engineering neural tissues and delivery of drugs due to their unique electrical and mechanical properties. CNTs can also penetrate cells and deliver therapeutic cargo across the BBB, making them potential candidates for Parkinson's disease or brain tumors [16]. Carbon nanomaterials are being used in imaging as well as in detection of Alzheimer's [22]. Carbon nanotubes (CNTs) have been used as scaffolds for cardiac tissue engineering. Nanocs Inc., NanoTechLabs Inc., Brewer Science Inc. are a few companies marketing CNTs for biomedical applications [39].

6. Peptide-Based Nanomaterials

Combining peptide-modified gold nanoparticles (AuNPs) at the core with a lipid outer layer has enabled the release of CRISPR-containing plasmids into the cytosol upon laser irradiation. The addition of TAT peptide guides these plasmids into the nucleus for targeted gene knockout. The lipid encapsulation of nanoparticles improves their stability. Furthermore, CRISPR-Cas9 delivery is enhanced through the conjugation of a cell-penetrating peptide (CPP) to the Cas9 protein via a thioether bond, providing a positive charge that facilitates sgRNA condensation. Multiple studies across various cell lines, including human pluripotent embryonal carcinoma cells (NCCIT) and human embryonic stem cells, have validated the potential of CPP-mediated gene delivery. However, conventional CPPs have shown limitations in their ability to efficiently encapsulate large plasmids due to their limited cationic charge density [23]. Protamine, a polycationic peptide, stabilizes mRNA and prolongs its half-life, aiding in effective mRNA delivery. Combinations of protamine with liposomes, such as cationic liposome-protamine complexes, have demonstrated enhanced delivery efficacy in preclinical studies [41,42]. PuraMatrix™ developed by 3DM Inc. company is a self-assembling peptide-based hydrogel that forms nanogels and nanofibers for cell culture, stem cell biology and tissue engineering currently under preclinical studies [39].

7. Bio-Derived Nanomaterials

7.1. Virus vectors and Virus-Like Particles (VLPs)

AAV, which stands for Adeno Associated Virus has shown potential for the delivery of CRISPR-Cas9. These viruses without showcasing pathogenicity efficiently infect target cells and deliver the sg-RNA and CRISPR Associated 9 enzyme with high efficiency. Further research on AAV infection mechanisms and potential limitations like immunogenicity is crucial. Meanwhile, lentivirus as a vector offers a robust mechanism for delivery of the CRISPR elements, enabling stability in integration along with long-term gene edits. They can deliver large-sized DNA fragments and multiple genes. But, discussions should address lentiviral integration processes and associated risks like insertional mutagenesis, ensuring safe and effective use in gene therapy [5]. Researchers have developed a "core-shell" artificial virus (RRPHC) using a fluorinated polymer core (PF33) complexed with Cas9-hMTH1 plasmid (PF33/Cas9-hMTH1), surrounded by a multifunctional polymer shell (RGD-R8-PEG-HA, RRPH). This design enhances targeting abilities and facilitates escape from endosomes. The RRPHC/Cas9-hMTH1 showed high permeability in 3D tumor spheroids. In mice with SKOV3 tumors, treatment with RRPHC/Cas9-hMTH1 significantly inhibited tumor growth and proliferation of tumor cells [44,45].

7.2 Cell membrane Derived Nanoparticles

Exosomes have emerged as promising natural carriers for gene editing due to their non-immunogenic nature and high compatibility. Cancer-derived exosomes have been utilized to deliver CRISPR elements for therapeutic gene editing, and their functionalization has enhanced delivery efficiency. However, a limitation of exosomes lies in their efficacy in loading CRISPR elements or drugs directly into them, necessitating further research into loading strategies [46].

Hybrid exosome-liposome nanoparticles have been developed to improve delivery efficiency. Additionally, specialized extracellular vesicles (EVs), such as those derived from human red blood cells

(RBCs), offer potential as targeted delivery vehicles. A study demonstrated that RBC EVs loaded with Cas9 mRNA and gRNA targeting miR-125b via electroporation effectively delivered these components into leukemia cells. Treatment resulted in a significant decrease in miR-125b expression levels, highlighting the therapeutic potential of EV-based delivery systems [47,48].

CRISPR has the potential to revolutionize personalized medicine by targeting disease-causing genetic mutations. It combines with next-generation sequencing (NGS) in cancer treatment, where CRISPR/Cas9 is used to disable or correct genes linked to cancer. NGS identifies patient-specific genetic mutations, forming the basis for tailored treatment plans that precisely target these anomalies in cancer cells. Saturation genome editing is another promising approach, systematically editing every nucleotide in a gene to distinguish between benign and harmful mutations. CRISPR-based applications extend to engineering T cells for CAR-T cancer therapy and treating inherited blindness, highlighting its role in advancing precision medicine [5].

7.3. Nanorobots

Nanorobots offer distinct advantages for drug and gene delivery, able to navigate independently through the body, unlike traditional nanocarriers reliant on blood circulation. They are categorized into exogenously and endogenously powered types. Exogenously powered nanorobots are propelled by external sources such as magnetic fields, electric fields, acoustic fields, and light energy. For instance, worm-like nanorobots comprising G-quadruplex layer with CoFe2O4 nanoparticles coated on the body of mesoporous silica nanotubes (MSN) was used to deliver 6-carboxyfluoresceins to HeLa cells under the influence of an external magnetic field [24]. Xuan et al. developed a nanorobot that demonstrated directional motion under near infrared light, using Au half-nano shell to generate a heat gradient for self-thermophoretic propulsion, further enhanced by a macrophage cell membrane coating enabling active recognition and binding to cancer cells [25]. A rolling circle amplification DNA strand hybridized with siRNA wrapped around gold nanowire, propelled by ultrasonic waves was used for intracellular delivery of siRNA [26].

On the other hand, endogenously powered nanorobots are often propelled by chemical reaction energy. Anac et al. engineered a mesoporous silica-based nano shell robot functionalized with urease, a catalyst for the decomposition of urea into carbon dioxide and ammonia. The chemical reaction energy was used to self-propel the robot in ionic media for drug delivery [27]. Cell based and DNA Origami based nanorobots are recent advancements. Shao et al. designed a self-propelled hybrid micromotor containing neutrophils and mesoporous silica nanoparticles. E.coli was coated on MSNs loaded with Dox, facilitating movement along the chemoattractant gradients produced by it, targeting cancer cells [28]. Another approach was an RBC microrobot loaded with Dox as well as quantum dot imaging agents along with magnetic nanoparticles that could steer the movement of the robot under the control of an external magnetic field [29].

In DNA origami, a single-stranded DNA undergoes repeated folding, stabilized by short oligonucleotide staple strands based on the principle of complementary base pairing, thereby achieving the desired DNA nanostructures [30]. Li et al. designed a DNA origami nanorobot loaded with Adriamycin which effectively penetrated ovarian cancer cells [31]. These advancements in nanorobot technology hold promise for drug and gene delivery applications. However, further trials are essential to address long-term toxicity concerns in vivo before clinical implementation [32].

8. Conclusions

Nanomaterials have significantly advanced the fields of gene and drug delivery by providing precise, targeted, and controlled approaches. These materials, including lipid-based nanoparticles, polymer-based nanomaterials, inorganic nanomaterials, carbon-based nanomaterials, peptide-based nanomaterials, and bio-derived nanomaterials, offer unique properties that overcome the limitations of traditional delivery methods. Key technologies such as CRISPR/Cas9 and mRNA therapeutics, combined with nanotechnology, have revolutionized treatments for various diseases including cancer, neurological disorders, and regenerative medicine. Lipid-based nanomaterials have shown exceptional efficiency in delivering CRISPR/Cas9 components and mRNA, enhancing gene editing and therapeutic outcomes. Polymer-based nanomaterials offer versatility and biocompatibility, enabling controlled release and precise targeting. Inorganic nanomaterials like gold nanoparticles provide high efficiency and specificity in gene delivery. Carbon-based nanomaterials, with their unique structural properties, facilitate effective delivery across biological barriers. Additionally, peptide-based and bio-derived nanomaterials, such as virus vectors and exosomes, demonstrate potential in targeted and efficient delivery of therapeutic agents. Nanorobots, with their ability to navigate autonomously, represent a future direction for precise drug and gene delivery.

However, several challenges remain to be addressed to fully realize the potential of nanomaterials in gene and drug delivery:

Safety and Toxicity: Comprehensive studies on the long-term effects and potential toxicity of nanomaterials are necessary to ensure their safety for clinical use.

Excretory Mechanisms: Understanding and characterizing the excretory mechanisms of these nanomaterials in the body to ensure safe and effective clearance is essential.

Scalability and Manufacturing: Developing cost-effective and scalable manufacturing processes for high-quality nanomaterials is critical for widespread application.

Stability and Storage: Enhancing the stability and shelf-life of nanomaterials under various conditions is essential for their practical use.

Regulatory Hurdles: Establishing clear regulatory guidelines and standards for the approval of nanomaterial-based therapies is required to facilitate their clinical translation.

Thus, the integration of nanomaterials with advanced therapeutic technologies poses immense promise for improving patient outcomes, paving the way for personalized and precision

medicine. The continued development and optimization of these nanomaterials will further enhance their clinical applications and impact on healthcare.

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Conflict of Interest

The authors declare that no competing interest exists.

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