WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.453
Volume 14, Issue 21, 440-457. Review Article ISSN 2277–7105

ARTIFICIAL INTELLIGENCE-DRIVEN NANOPARTICLES STRATEGIES FOR EFFICIENT CRISPR- CAS9 DELIVERY: A COMPREHENSIVE REVIEW

Shaik Shireen*[a], B. Jayakeerthana[b], S. Akshaya[b], M. Shivani[c], A. Srujana[c], G. Ramya Sree[c]

[*a]Department of Pharmaceutics, St.Pauls College of Pharmacy, Turakayamjal, Hyderabad.
[b]Department of Pharm D, St.Pauls College of Pharmacy, Turakayamjal, Hyderabad.
[c]Department of Pharmacy, St.Pauls College of Pharmacy, Turakayamjal, Hyderabad.

Article Received on 04 Oct. 2025,
Article Revised on 24 Oct. 2025,
Article Published on 01 Nov. 2025,
https://doi.org/10.5281/zenodo.17473490

***Corresponding Author**
Shaik Shireen
Department of Pharmaceutics,
St.Pauls College of Pharmacy,
Turakayamjal, Hyderabad.

How to cite this Article: Shaik Shireen*, B. Jayakeerthana, S. Akshaya, M. Shivani, A. Srujana, G. Ramya Sree. (2025). Artificial Intelligence-Driven Nanoparticles Strategies For Efficient Crispr- Cas9 Delivery: A Comprehensive Review. World Journal of Pharmaceutical Research, 14(21), 440–457.

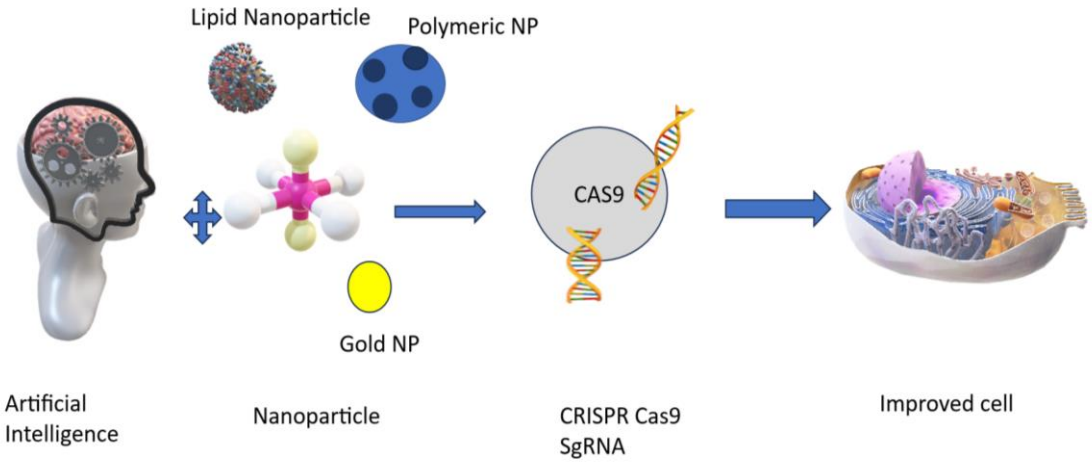
ABSTRACT

The CRISPR-Cas9 method has revolutionized genome editing due to its precision, applicability in a variety of organisms, and programmability. However, the safe and efficient delivery of the CRISPR-Cas9 components remains a major challenge in clinical translation. Delivery methods based on nanoparticles that offer controlled release, cellular targeting, and biocompatibility have been made feasible by recent advancements in nanotechnology. The use of artificial intelligence (AI) in this area presents a revolutionary opportunity to predict the efficacy of distribution, optimize the design of nanoparticles, and personalize gene editing. This review explores the potential for combining AI and nanotechnology to enhance CRISPR-Cas9 delivery methods. The accuracy and safety of editing are greatly increased by AI models, which also help predict off-target effects, optimize guide RNA design, and simulate cellular uptake and biodistribution patterns. A variety of nanoparticle types are examined in relation to their AI-optimized performance in CRISPR-Cas9 delivery, including lipid-based, polymeric, gold, and mesoporous silica nanoparticles. This review article also covers current in silico and experimental research that show improved genome editing results using AI-guided delivery methods. The combination of AI

with nanomedicine presents a viable path forward for next-generation gene therapies, despite persistent obstacles like immunogenicity, endosomal escape, and real-time tracking. Views on ethical ramifications, regulatory issues, and potential paths forward for incorporating AI-driven CRISPR delivery into precision medicine are included in the article's conclusion.

KEYWORDS: CRISPR, Nanoparticles, Gene Editing, AI, Modern technology, Drug delivery.

GRAPHICAL ABSTRACT



INTRODUCTION

The last ten years have seen a significant advancement in genome editing technologies, with CRISPR-Cas9 emerging as the most potent and adaptable tool for targeted genetic alterations.[1] Its uses range from fundamental biomedical research to possible treatments for infectious diseases, cancer, and genetic problems. Not with standing its revolutionary promise, a significant obstacle to the practical translation of CRISPR-Cas9 is the safe, effective, and tissue-specific delivery of its constituent parts—Cas9 nuclease and guide RNA—into target cells.[2] Despite their effectiveness, traditional viral vectors have drawbacks such immunogenicity, insertional mutagenesis, and scalability problems, underscoring the urgent need for biocompatible, non-viral delivery methods. Because of their customizable physicochemical characteristics, capacity to encapsulate and preserve proteins or nucleic acids, and potential for targeted administration, nanoparticles have become attractive delivery vehicles for CRISPR-Cas9.[3] For this, a broad range of nanoparticle systems have been investigated, such as lipid nanoparticles, polymeric carriers, inorganic

nanomaterials, and hybrid systems. It is still a difficult, multi-parameter task to optimize these delivery methods to optimize therapeutic efficacy while minimizing toxicity.

Pharmaceutical sciences are changing because of artificial intelligence (AI), especially machine learning and deep learning techniques, which make data-driven decision-making and predictive modeling possible. By anticipating important formulation characteristics, biological interactions, and off-target consequences, artificial intelligence (AI) can speed up the design and optimization of nanoparticle systems in the context of CRISPR-Cas9 delivery.[4] AI also makes it easier to construct guide RNAs, choose target sites, and profile toxicity, all of which lead to safer and more efficient genome editing techniques. This review highlights the potential synergy between nanotechnology and computational intelligence in pharmaceutical development by concentrating on the latest developments in AI-assisted CRISPR-Cas9 delivery using nanoparticles. It seeks to give a thorough review of delivery systems based on nanoparticles, the contribution of AI to better performance and design, and the most recent developments in this burgeoning multidisciplinary subject. The review also identifies issues that need to be resolved for clinical translation, including endosomal escape, immunological response, and transport efficiency. Pharmaceutical researchers can open new avenues for personalized medicine and precision gene therapies by combining AI with nano-formulation techniques.

Current Status of CRISPR-cas9 Delivery Challenges

Derived from the prokaryotic adaptive immune system, the CRISPR-Cas9 genome editing system has emerged as a vital tool in molecular biology and the development of therapeutics.[5] The effective and targeted transport of its components into host cells is a significant barrier preventing its widespread clinical application, despite its unmatched accuracy, usability, and programmability. The Cas9 endonuclease protein and single-guide RNA (sgRNA), which together cause site-specific DNA double-strand breaks, are usually needed for the CRISPR-Cas9 system to successfully alter genomes.[6] Achieving great editing efficiency with few off-target impacts requires efficiently delivering these components to the target cells' nucleus while preserving their functional integrity. Now, delivery systems can be broadly divided into two categories: viral and non-viral. Because of their high transfection efficiency and persistent expression, viral vectors like lentiviruses, adenoviruses, and adeno-associated viruses (AAV) have been employed extensively.[7] These methods do have some serious disadvantages, though, including as immunogenicity, insertional mutagenesis, limited

packaging capacity, and regulatory issues, especially in therapeutic settings. Interest in safer and more versatile non-viral vectors for clinical translation has increased due to these restrictions.

Physical techniques including electroporation, microinjection, and hydrodynamic injection are among the non-viral procedures that have the highest efficacy in vitro but are not scalable and frequently cause considerable damage in vivo.[8] Chemical delivery methods, particularly nanoparticles, are gaining traction as they offer adjustable features like as surface charge, size, biodegradability, and ligand-mediated targeting. Preclinical and early clinical research is presently being conducted to investigate the delivery of CRISPR via lipid nanoparticles (LNPs), polymer-based carriers, and inorganic nanomaterials.[9]

However, several significant obstacles still exist despite these developments. These include

- Endosomal entrapment, which results in decreased nuclear delivery; fast clearance and short circulation half-life; poor cellular absorption in particular tissue types;[10]
- Off-target gene editing, which raises questions about safety;[11]
- Low effectiveness of editing in stem cells or primary cells;
- Reactions of the immune system to foreign proteins such as Cas9.[12]

A comparison table for CRISPR-Cas9 delivery systems was listed down below.

Table 1: A Comparison between different CRISPR-Cas9 delivery systems.

Delivery systems	Viral vectors (AAV, Lentivirus, Adenovirus)	Non- Viral vectors (Nanoparticles, physical methods)[13]
Advantages	High transfection efficiency	Safer and reduced immunogenicity
	Stable and longterm expression[14]	Adjustable physico-chemical properties[15]
Limitations	Immunogenicity and insertional mutagenesis	Lower efficiency in-vivo
	Limited packaging capacity	Endosomal escape problems
	Regulatory hurdles[16]	Rapid clearance[17]

Balancing stability, biocompatibility, and functional performance makes designing nanoparticle formulations for gene editing applications even more difficult.[18] Traditional trial-and-error techniques are insufficient in this situation, which calls for a multi-parameter optimization strategy. Artificial intelligence presents a viable answer in this regard by facilitating the logical design and predictive modeling of CRISPR-Cas9 delivery systems.

Nanoparticle- Based CRISPR- Cas9 Delivery System

One of the most promising non-viral options for the effective, precise, and secure delivery of CRISPR-Cas9 components into mammalian cells is the use of nanoparticle-based delivery systems.[19] They are especially well-suited for therapeutic genome editing because of their capacity to encapsulate and shield proteins or nucleic acids, as well as their adjustable physicochemical characteristics and surface modification potential.[20] Nanoparticles are appealing candidates for clinical translation because, in contrast to viral vectors, they reduce the hazards related to immunogenicity, insertional mutagenesis, and regulatory constraints.[21] Lipid-based nanoparticles (LNPs) are the most extensively researched type of nanoparticle among the different types for CRISPR delivery. By facilitating their cellular uptake by endocytosis, LNPs can encapsulate plasmid DNA, Cas9-sgRNA ribonucleoproteins (RNPs), or mRNA expressing Cas9.[22] It is possible to adjust their composition to improve tissue-specific targeting, endosomal escape, and biocompatibility. Notably, interest in LNP platforms for gene editing applications has increased due to the development of mRNA COVID-19 vaccines.

Polymeric nanoparticles, including those derived from poly(lactic-co-glycolic acid) (PLGA), polyethyleneimine (PEI), and chitosan, offer biodegradability and a range of surface functionalization options.[23] These devices can be made to release CRISPR components over an extended period and co-deliver different proteins. However, their cytotoxicity and transfection efficacy remain uncertain and often depend on the polymer's molecular weight and composition. Magnetic targeting, photothermal activation, and imaging-guided transport can all benefit from the unique optical and magnetic properties of inorganic nanoparticles, such as gold nanoparticles (AuNPs), mesoporous silica nanoparticles (MSNs), and magnetic nanoparticles.[24] AuNPs are suitable carriers of the Cas9-sgRNA complex because of their exceptional cellular absorption and modifiable surface chemistry.[25] However, evaluations of long-term toxicity and in vivo clearance are currently ongoing. For clear understanding, a comparative overview of different Nanoparticle classes for CRISPR delivery are listed in the below table.

Table 2: Nanoparticle classes for CRISPR Delivery.

Type of the Nanoparticles (NPs)	Advantages	Challenges
Lipid- based NPs	Bio-compatible, Efficient encapsulation,	Endosomal escape inefficiencies,

	Success with mRNA /LNP Vaccines.	Stability problems.[26]
Polymeric NPs(PLGA, PEI, Chitosan)	Biodegradable, Adjustable release, Versatile surface function.	Cytotoxicity, Varied efficiency based on composition.[27]
Gold NPs	High cellular uptake, Modifiable surface, Optical/magnetic imaging potential.	Potential long-term toxicity, Slow clearance in-vivo.[28]
Mesoporous silica NPs	Large surface area, Controlled release, Versatile modification.	Poor bio-degradability, Limited in-vivo validation.[29]
Hybrid NPs (lipid-polymer combination)	Has both advantages of lipid and polymeric particles, Improved stability and targeting.	Complex design, Scale-up challenges.[30]

By combining properties from multiple classes (lipid-polymer hybrids, for instance), hybrid nanoparticles aim to optimize advantages including stability, biocompatibility, and targeted specificity. Some research have demonstrated the effectiveness of these techniques as in vivo genome editing tools, particularly when combined with ligands like as aptamers, peptides, or antibodies for cell-specific delivery.[31]

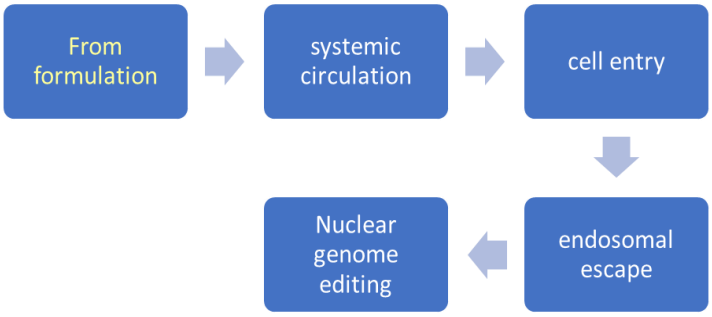


Fig: CRISPR -cas9 delivery pathway.

Despite promising advancements, there are still significant challenges in the delivery of CRISPR via nanoparticles. These include limited transfection efficacy in primary cells, uncontrolled breakdown or premature release, ineffective endosomal escape, and obstacles to target tissue penetration.[32] To overcome these challenges, recent research has focused on intelligent nanoparticle design, where machine learning approaches3 aid in the prediction and optimization of formulation parameters.[33] An AI-driven technique for creating nanoparticles will be discussed in the next section.

The function of artificial Intelligence in genome editing

Genome editing is one biomedical field where artificial intelligence (AI) has become a game-changing method. Because it can evaluate large amounts of data, find hidden patterns, and

forecast biological outcomes, it has been very useful for refining CRISPR-Cas9 technology.[34] By enhancing the precision, security, and effectiveness of CRISPR-Cas9 applications at several phases—from guide RNA synthesis to delivery system optimization—AI-driven models may hasten the development of genome editing techniques. One of the most significant applications of AI in genome editing is the creation of sgRNA (single-guide RNA).[35] The ability of sgRNA to precisely bind to the target region without producing off-target effects is a crucial component of CRISPR-Cas9's efficacy and specificity.[36] AI methods, particularly machine learning and deep learning models, evaluate large genomic datasets to identify the most effective and least error-prone guide sequences.[37] Tools like DeepCRISPR, CRISPR-Net, and CROP-IT use convolutional neural networks (CNNs) and support vector machines (SVMs) to precisely quantify on-target efficiency and decrease off-target activity.[38] AI applications and their roles in genome editing are described in the below table.

Table 3: AI applications in genome editing.

AI Application	Role
SgRNA Design	Uses deep learning to predict high-efficiency guides to minimize oof-targets.[39]
Nanoparticle optimization	Predicts optimal particle size, charge, shape, and ligand choice for enhanced delivery.[40]
Target site prediction	Identifies efficient and safe location for genome editing by adding genomic context.[41]
Safety and toxicity profiling	Predicts immunogenicity, and toxicity before in-vivo studies[42]

AI significantly helps with target site prediction by integrating genomic context, epigenetic modifications, chromatin accessibility, and other regulatory factors to identify a safe and efficient locus for gene editing. This is particularly crucial in therapeutic contexts when unintentional alterations could result in genotoxicity or oncogenesis. Beyond genome targeting, artificial intelligence (AI), especially in conjunction with nanotechnology, is revolutionizing delivery system design. AI models can predict the optimal nanoparticle properties, such as size, shape, surface charge, and ligand selection, for the efficient dispersion of CRISPR components.[43] By analyzing high-dimensional formulation data, AI can identify correlations between nanoparticle properties and biological outcomes such as cellular uptake, endosomal escape, and gene editing efficiency.[44] This predictive power reduces the need for laborious experimental screening and expedites the formulation optimization process.

AI also aids with safety evaluation, which includes immunogenicity prediction and the toxicity profile of delivery systems and CRISPR components.[45] AI-based screening techniques can detect potential side effects and replicate host immune responses before to in vivo testing.[46]

Over all, adding AI to genome editing procedures increases precision, speeds up development, and reduces experimental costs. AI creates the foundation for personalized genome editing therapies that are appropriate for each patient's particular traits and medical issues, in addition to making it easier to rationally design nanoparticles for CRISPR-Cas9 delivery.

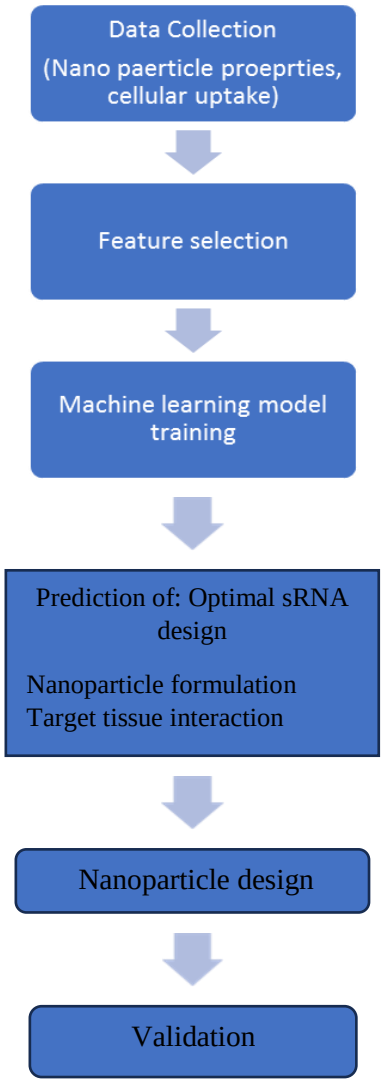


Fig: AI-driven optimization pipeline.

Recent advancements and experimental findings

The combination of nanotechnology and artificial intelligence (AI) has led to significant improvements in CRISPR-Cas9 delivery systems, particularly in improving the precision, safety, and efficacy of genome editing applications. AI-guided nanoparticle design has the potential to overcome some of the primary limitations of traditional delivery systems, as demonstrated by recent in silico calculations and real-world studies.[47] A significant development in the field was the development of delivery methods that were mediated by lipid nanoparticles (LNP) and enhanced by machine learning techniques.[48] For example, researchers have successfully assessed thousands of lipid compositions using AI techniques and predicted combinations that maximize encapsulation efficiency and transfection rates. In a groundbreaking study, Wei et al. (2021) demonstrated an AI-optimized LNP formulation that delivered CRISPR-Cas9 RNPs with >70% gene knockdown effectiveness in hepatocytes, with few off-target effects and no detectable immunotoxicity in vivo. The following picture depicts a more clear description of AI-assisted CRISPR-Ca9 using nanoparticles.

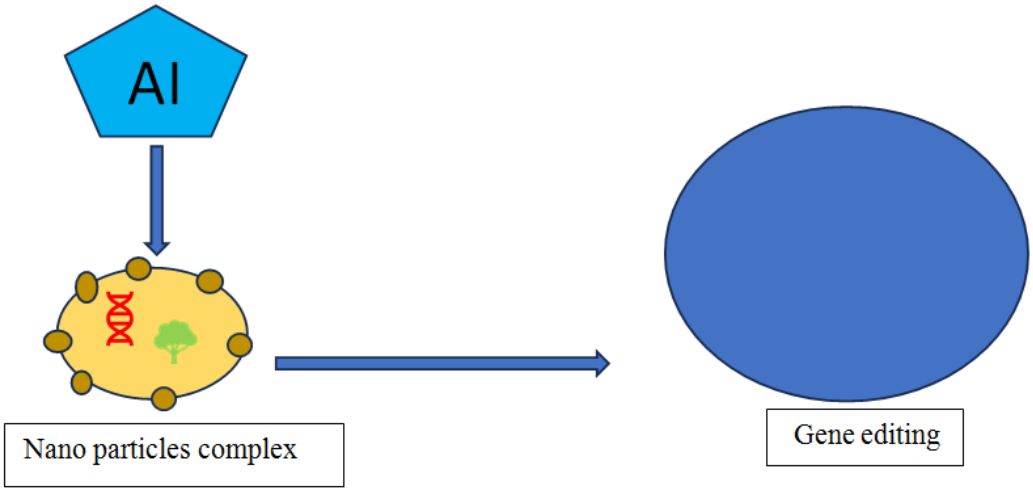


Fig. 1: AI- assisted CRISPR-Cas9 using Nanoparticles.

PEI-based polymers with enhanced endosomal escape characteristics and decreased cytotoxicity have been produced in the field of polymeric nanoparticles using deep learning methods. Experimental validations of these AI-predicted polymers showed superior editing efficiency in human embryonic kidney (HEK293T) cells and primary T-cells.[49] Such technologies are now being used to study ex vivo genome editing in CAR-T cell therapy. The significance of integrating AI into CRISPR-nanoparticle platforms is reinforced by all these computational and experimental advancements. They demonstrate how AI accelerates

development and improves the translational viability of genome editing technologies, bringing them closer to safe and effective clinical applications.[50]

Challenges and prospects for the future

Despite the rapid advancement of CRISPR-Cas9 delivery systems and the potential of artificial intelligence (AI) in formulation design, several major barriers still stand in the way of these technologies' clinical translation. Solving these issues is essential to developing safe, efficient, and personalized genome editing therapies.

1. Biological and Physiological Barriers

The primary biological challenge is distributing CRISPR-Cas9 components in a tissue-specific and efficient manner without triggering immune responses. Inadequate penetration across biological membranes, rapid clearance by the reticuloendothelial system (RES), and difficulty accessing difficult-to-reach areas like the brain and bone marrow are problems with many nanoparticle systems.[51] Additionally, endosomal entrapment remains a significant barrier, preventing ingested nanoparticles from releasing their cargo into the cytoplasm or nucleus, leading to inadequate editing efficiency.[52]

2. Off-Target effects and Genotoxicity

Off-target gene changes remain a major safety concern even if AI improves the design of sgRNA as in vivo systems are complicated, existing prediction methods may not fully account for dynamic interactions, chromatin structure, and patient-specific genetic variation.[53] Inadvertent changes can result in long-term consequences such as loss-of-function mutations or oncogenic changes, more accurate and predictive AI models that are linked to real genomic data are required.[54]

3. Nanoparticle toxicity and Biodegradability

Certain nanoparticles, especially inorganic systems like gold or magnetic nanoparticles, have problems with toxicity and biodegradation. Reactive oxygen species generation, inflammatory responses, and accumulation in non-target tissues limit their clinical value.[55]

Even though surface modifications like PEGylation increase circulation time, repeated dosing may result in anti-PEG immune reactions.[56]

4. Data limitations and Algorithm Transparency

AI models used for genome editing and nanoparticle optimization sometimes rely on sparse or skewed datasets, especially in human in vivo contexts. Most models are trained on data from in vitro research or animals, which may not be accurate predictors of human outcomes. Additionally, many machine learning models function as "black boxes," which limits their interpretability and appeal to regulators.[57] The need for explainable AI (XAI) methods that provide transparent decision-making is growing to ensure reproducibility and compliance.[58]

5. Ethical, Regulatory, and Manufacturing Barriers

Genome editing is subject to intense ethical and legal examination, especially when it comes to humans. AI-generated formulations require rigorous quality control and validation in accordance with Good Manufacturing Practice (GMP). The fact that the large-scale and cost-effective production of AI-optimized nanoparticles is still in its infancy adds to worries about accessibility and scalability.[59] Future safe, highly customized, and targeted genome editing treatments could be made possible by the development of multimodal platforms that integrate genomics, proteomics, AI, and nanotechnology.[60] Collaboration between biologists, data scientists, pharmaceutical formulators, and regulators will be crucial. Future AI systems must also be adaptive, continuously learning from real-world data, to enhance both design and treatment outcomes.

CONCLUSION

Combining artificial intelligence (AI) with nanoparticle-based delivery methods is a significant advancement in the development of CRISPR-Cas9 genome editing technology. Even though CRISPR-Cas9's precision and programmability have transformed genetic alteration, the lack of a safe, efficient, and targeted delivery mechanism continues to be a major barrier to clinical translation. Nanoparticles, which can encapsulate CRISPR components and deliver them to specific tissues, offer a promising non-viral platform. However, controlling a complex range of biological and physicochemical variables is necessary to optimize these carriers.AI has developed into a powerful tool for handling this complexity. By simulating cellular interactions, refining sgRNA sequences, and employing predictive modeling to sArtitreamline the development of nanoparticle formulations, machine learning approaches can lessen the need for trial-and-error methods. utilized historically in the creation of pharmaceuticals. This synergistic approach not only enhances the safety and

precision of CRISPR-Cas9 systems, but it also expedites development and expands scalability for clinical use.

Despite tremendous progress, problems with off-target effects, endosomal escape, nanoparticle toxicity, and regulatory acceptability persist. Future developments must focus on ensuring translational conformity with GMP standards, expanding validated datasets, and developing explainable AI models. Furthermore, long-term safety data and ethical concerns will be crucial in determining if AI-optimized gene editing treatments are used in human applications. In conclusion, the combination of AI and nanotechnology offers a novel and very promising approach for accurately, individually, and clinically administering CRISPR-Cas9 components. Ongoing multidisciplinary research in this area is expected to fuel the next generation of genome-editing medicines.

Key Takeaway from this article

1. CRISPR-Cas9 holds immense therapeutic promise, but safe and efficient delivery remains the main obstacle.
2. Nanoparticles are promising non-viral carriers, with lipid, polymeric, gold, silica and hybrid systems offering adjustable properties but challenges in stability, toxicity and scalability.
3. Artificial Intelligence enhances delivery optimization by predicting sgRNA efficiency, nanoparticles properties, biodistribution and safety profiles.
4. AI -guided nanocarriers have shown superior performance in recent studies improving editing efficiency while minimizing off-targets effects and toxicity.
5. Future progress requires explainable AI, improved biocompatibility and multidisciplinary collaboration.

ACKNOWLEDGEMENTS

1. We are grateful to the administration of St. Pauls College Of Pharmacy for providing the facilities needed to complete.
2. This work does not include any clinical trials included in this.
3. Ethics, Consent to Participate, and Consent to Publish declarations: not applicable.
4. Author contributions: All authors made contributions to the conception and design of the investigation. Shaik Shireen, B. Jaya Keerthana, S. Akshaya, M. Shivani, A. Srujana, G. Ramya Sree for material preparation, data collection, and analysis. Shaik Shireen authored the initial draft of the manuscript, and all authors provided feedback on interim

versions of the document. The final manuscript was reviewed and endorsed by all authors.

5. Funding: No funding was provided by a company, funding agency, or non-profit research body.
6. Data availability: The corresponding author can be reached for a reasonable request for the datasets used and/or analyzed in the current study.
7. Code availability Not applicable.
8. Declarations: Not Applicable
9. Consent to participation: Not applicable.
10. Competing interests: The authors have no relevant financial or non-financial interests to disclose.

REFERENCES

1. Selvakumar SC, Preethi KA, Ross K, Tusubira D, Khan MW, Mani P, Rao TN, Sekar D. CRISPR/Cas9 and next generation sequencing in the personalized treatment of Cancer. Molecular Cancer, Mar. 24, 2022; 21(1): 83.
2. Zhuo C, Zhang J, Lee JH, Jiao J, Cheng D, Liu L, Kim HW, Tao Y, Li M. Spatiotemporal control of CRISPR/Cas9 gene editing. Signal Transduction and Targeted Therapy, Jun 20, 2021; 6(1): 238.
3. Rauf MA, Rao A, Sivasoorian SS, Iyer AK. Nanotechnology-Based Delivery of CRISPR/Cas9 for Cancer Treatment: A Comprehensive Review. Cells, Jul. 23, 2025; 14(15): 1136.
4. Gowda A. AI-Driven Optimization of Nanoparticle-Based Gene Delivery Systems.
5. Allemailem KS, Alsahli MA, Almatroudi A, Alrumaihi F, Al Abdulmonem W, Moawad AA, Alwanian WM, Almansour NM, Rahmani AH, Khan AA. Innovative strategies of reprogramming immune system cells by targeting CRISPR/Cas9-based genome-editing tools: a new era of cancer management. International Journal of Nanomedicine, Dec. 31, 2023; 5531-59.
6. Liu SC, Feng YL, Sun XN, Chen RD, Liu Q, Xiao JJ, Zhang JN, Huang ZC, Xiang JF, Chen GQ, Yang Y. Target residence of Cas9-sgRNA influences DNA double-strand break repair pathway choices in CRISPR/Cas9 genome editing. Genome Biology, Aug. 1, 2022; 23(1): 165.

7. Asmamaw Mengstie M. Viral vectors for the in vivo delivery of CRISPR components: advances and challenges. Frontiers in bioengineering and biotechnology, May 12, 2022; 10: 895713.
8. Demirci S, Essawi K, Germino-Watnick P, Liu X, Hakami W, Tisdale JF. Advances in CRISPR delivery methods: perspectives and challenges. The CRISPR Journal, Oct. 1, 2022; 5(5): 660-76.
9. Park S, Lu GL, Zheng YC, Davison EK, Li Y. Nanoparticle-Based Delivery Strategies for Combating Drug Resistance in Cancer Therapeutics. Cancers, Aug. 11, 2025; 17(16): 2628.
10. Ma X, Tian Y, Yang R, Wang H, Allahou LW, Chang J, Williams G, Knowles JC, Poma A. Nanotechnology in healthcare, and its safety and environmental risks. Journal of nanobiotechnology, Nov. 15, 2024; 22(1): 715.
11. Guo C, Ma X, Gao F, Guo Y. Off-target effects in CRISPR/Cas9 gene editing. Frontiers in bioengineering and biotechnology, Mar. 9, 2023; 11: 1143157.
12. Brezgin S, Kostyusheva A, Bayurova E, Volchkova E, Gegechkori V, Gordeychuk I, Glebe D, Kostyushev D, Chulanov V. Immunity and viral infections: modulating antiviral response via CRISPR–Cas systems. Viruses, Jul. 15, 2021; 13(7): 1373.
13. Dogbey DM, Torres VE, Fajemisin E, Mpondo L, Ngwenya T, Akinrinmade OA, Perriman AW, Barth S. Technological advances in the use of viral and non-viral vectors for delivering genetic and non-genetic cargos for cancer therapy. Drug delivery and translational research, Nov. 2023; 13(11): 2719-38.
14. Arsenijevic Y, Berger A, Udry F, Kostic C. Lentiviral vectors for ocular gene therapy. Pharmaceutics, Jul. 31, 2022; 14(8): 1605.
15. Mavi AK, Kumar M, Singh A, Prajapati MK, Khabiya R, Maru S, Kumar D. Progress in Non-Viral Delivery of Nucleic Acid: Advancement in Biomedical Technology. Integration of Biomaterials for Gene Therapy, Oct. 26, 2023: 281-322.
16. Huang J, Li J, Xu X, Li K. Adeno-Associated Virus Vectors in Retinal Gene Therapy: Challenges, Innovations, and Future Directions. Biomolecules, Jun. 28, 2025; 15(7): 940.
17. Tasset A, Bellamkonda A, Wang W, Pyatnitskiy I, Ward D, Peppas N, Wang H. Overcoming barriers in non-viral gene delivery for neurological applications. Nanoscale, 2022; 14(10): 3698-719.
18. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. Nature reviews drug discovery, Feb. 2021; 20(2): 101-24.

19. Sinclair F, Begum AA, Dai CC, Toth I, Moyle PM. Recent advances in the delivery and applications of nonviral CRISPR/Cas9 gene editing. Drug delivery and translational research, May 2023; 13(5): 1500-19.
20. Wu QX, De Isla N, Zhang L. Biomaterial-Based Nucleic Acid Delivery Systems for In Situ Tissue Engineering and Regenerative Medicine. International Journal of Molecular Sciences, Jul. 30, 2025; 26(15): 7384.
21. Li X, Qi J, Wang J, Hu W, Zhou W, Wang Y, Li T. Nanoparticle technology for mRNA: Delivery strategy, clinical application and developmental landscape. Theranostics, Jan. 1, 2024; 14(2): 738.
22. Lin Y, Wagner E, Lächelt U. Non-viral delivery of the CRISPR/Cas system: DNA versus RNA versus RNP. Biomaterials Science, 2022; 10(5): 1166-92.
23. Geszke-Moritz M, Moritz M. Biodegradable polymeric nanoparticle-based drug delivery systems: comprehensive overview, perspectives and challenges. Polymers, Sep. 7, 2024; 16(17): 2536.
24. Farjadian F, Ghasemi S, Akbarian M, Hoseini-Ghahfarokhi M, Moghoofei M, Doroudian M. Physically stimulus-responsive nanoparticles for therapy and diagnosis. Frontiers in Chemistry, Sep. 14, 2022; 10: 952675.
25. Duan L, Ouyang K, Xu X, Xu L, Wen C, Zhou X, Qin Z, Xu Z, Sun W, Liang Y. Nanoparticle delivery of CRISPR/Cas9 for genome editing. Frontiers in Genetics, May 12, 2021; 12: 673286.
26. Nalla LV, Gajula SN, Chavda VP. Nanoparticle-Based mRNA Vaccines: Are We One Step Closer to Targeted Cancer Therapy?. Nanocarrier Vaccines: Biopharmaceutics-Based Fast Track Development, Dec. 2, 2024; 275-303.
27. Khan T, Vadivel G, Ramasamy B, Murugesan G, Sebaey TA. Biodegradable conducting polymer-based composites for biomedical applications—a review. Polymers, May 29, 2024; 16(11): 1533.
28. Singh P, Pandit S, Balusamy SR, Madhusudanan M, Singh H, Amsath Haseef HM, Mijakovic I. Advanced nanomaterials for cancer therapy: gold, silver, and iron oxide nanoparticles in oncological applications. Advanced Healthcare Materials, Feb. 2025; 14(4): 2403059.
29. Song Y, You Q, Chen X. Transition metal-based therapies for inflammatory diseases. Advanced Materials, Sep. 2023; 35(39): 2212102.

30. Sivadasan D, Sultan MH, Madkhali O, Almoshari Y, Thangavel N. Polymeric lipid hybrid nanoparticles (plns) as emerging drug delivery platform—A comprehensive review of their properties, preparation methods, and therapeutic applications. Pharmaceutics, Aug. 18, 2021; 13(8): 1291.
31. Iqbal Z, Rehman K, Xia J, Shabbir M, Zaman M, Liang Y, Duan L. Biomaterial-assisted targeted and controlled delivery of CRISPR/Cas9 for precise gene editing. Biomaterials science, 2023; 11(11): 3762-83.
32. Kaupbayeva B, Tsoy A, Safarova Y, Nurmagambetova A, Murata H, Matyjaszewski K, Askarova S. Unlocking genome editing: Advances and obstacles in CRISPR/Cas delivery technologies. Journal of Functional Biomaterials, Oct. 31, 2024; 15(11): 324.
33. Jain N, Kaul S, Triveni KA, Sinha A, Mathur T, Pandey M, Nagaich U. 8 QbD and artificial intelligence in nanoparticulate drug delivery systems: recent advances. Volume 2 computational drug delivery, Oct. 7, 2024: 163-82.
34. Konstantakos V, Nentidis A, Krithara A, Paliouras G. CRISPR–Cas9 gRNA efficiency prediction: an overview of predictive tools and the role of deep learning. Nucleic Acids Research, Apr. 22, 2022; 50(7): 3616-37.
35. Li Z, Khan WU, Bai G, Dong C, Wang J, Zhang Y, Wang C, Zhang H, Wang W, Luo M, Ch en F. From Code to Life: The AI-Driven Revolution in Genome Editing. Advanced Science, 2025; e17029.
36. Allemailem KS, Almatroudi A, Rahmani AH, Alrumaihi F, Alradhi AE, Alsubaiyel AM, Algahtani M, Almousa RM, Mahzari A, Sindi AA, Dobie G. Recent updates of the CRISPR/Cas9 genome editing system: Novel approaches to regulate its spatiotemporal control by genetic and physicochemical strategies. International Journal of Nanomedicine, Dec. 31, 2024; 5335-63.
37. Chafai N, Bonizzi L, Botti S, Badaoui B. Emerging applications of machine learning in genomic medicine and healthcare. Critical Reviews in Clinical Laboratory Sciences, Feb. 17, 2024; 61(2): 140-63.
38. Saini H, Semwal A, Nanda D, Juyal T, Kumar N, Srivastava H. Role of Artificial Intelligence Tools in CRISPR-Cas9 Genomic Editing Technique for Precision Agriculture. Industrial Biotechnology, 2025 Jul 28.
39. Karlson CK, Mohd-Noor SN, Nolte N, Tan BC. CRISPR/dCas9-based systems: mechanisms and applications in plant sciences. Plants, Sep. 29, 2021; 10(10): 2055.

40. Kim B, Hosn RR, Remba T, Yun D, Li N, Abraham W, Melo MB, Cortes M, Li B, Zhang Y, Dong Y. Optimization of storage conditions for lipid nanoparticle-formulated self-replicating RNA vaccines. Journal of Controlled Release, Jan. 1, 2023; 353: 241-53.
41. Li C, Chu W, Gill RA, Sang S, Shi Y, Hu X, Yang Y, Zaman QU, Zhang B. Computational tools and resources for CRISPR/Cas genome editing. Genomics, proteomics & bioinformatics, Feb., 2023; 21(1): 108-26.
42. Kissner T, Blaich G, Baumann A, Kronenberg S, Hey A, Kiessling A, Schmitt PM, Driessen W, Carrez C, Kramer D, Fretland J. Challenges of non-clinical safety testing for biologics: A Report of the 9th BioSafe European Annual General Membership Meeting. InMAbs, Jan. 1, 2021; 13(1): 1938796. Taylor & Francis.
43. Gao XJ, Ciura K, Ma Y, Mikolajczyk A, Jagiello K, Wan Y, Gao Y, Zheng J, Zhong S, Puzyn T, Gao X. Toward the integration of machine learning and molecular modeling for designing drug delivery nanocarriers. Advanced Materials, Nov. 2024; 36(45): 2407793.
44. Amoako K, Mokhammad A, Malik A, Yesudasan S, Wheba A, Olagunju O, Gu SX, Yarovinsky T, Faustino EV, Nguyen J, Hwa J. Enhancing nucleic acid delivery by the integration of artificial intelligence into lipid nanoparticle formulation. Frontiers in Medical Technology, Jun. 16, 2025; 7: 1591119.
45. Vora LK, Gholap AD, Jetha K, Thakur RR, Solanki HK, Chavda VP. Artificial intelligence in pharmaceutical technology and drug delivery design. Pharmaceutics, Jul. 10, 2023; 15(7): 1916.
46. Daneshvar A, Lukianov SN. Artificial Intelligence-Mediated Computer-Aided Design of Viral Gene Therapies. GEN Biotechnology, Dec. 1, 2023; 2(6): 482-9.
47. Irfan M, Habiba U, Maryam A. Next-generation cancer therapeutics: unveiling the potential of liposome-based nanoparticles through bioinformatics. Microchimica Acta., Jul. 2025; 192(7): 428.
48. Agrahari V, Choonara YE, Mosharraf M, Patel SK, Zhang F. The Role of Artificial Intelligence and Machine Learning in Accelerating the Discovery and Development of Nanomedicine. Pharmaceutical Research, Dec. 2024; 41(12): 2289-97.
49. Boretti A. The transformative potential of AI-driven CRISPR-Cas9 genome editing to enhance CAR T-cell therapy. Computers in biology and medicine, Nov. 1, 2024; 182: 109137.
50. Abughalia A, Flynn M, Clarke PF, Fayne D, Gobbo OL. The Use of Computational Approaches to Design Nanodelivery Systems. Nanomaterials, Sep. 3, 2025; 15(17): 1354.

51. Mateus RF. Nanodelivery Strategies for Bone Targeting: Bone Pathologies and Nanoparticle Treatment Approaches (Master's thesis, Universidade de Lisboa (Portugal)).
52. Tashima T. Non-Invasive Delivery of CRISPR/Cas9 Ribonucleoproteins (Cas9 RNPs) into Cells via Nanoparticles for Membrane Transport. Pharmaceutics, Feb. 6, 2025; 17(2): 201.
53. Kalter N, Fuster-García C, Silva A, Ronco-Díaz V, Roncelli S, Turchiano G, Gorodkin J, Cathomen T, Benabdellah K, Lee C, Hendel A. Off-target effects in CRISPR-Cas genome editing for human therapeutics: progress and challenges. Molecular Therapy Nucleic Acids, 2025 Jul 17.
54. Srivastav AK, Mishra MK, Lillard Jr JW, Singh R. Transforming pharmacogenomics and CRISPR gene editing with the power of artificial intelligence for precision medicine. Pharmaceutics, Apr. 24, 2025; 17(5): 555.
55. Thakur A, Kumar A. Strategies for enhancing biocompatibility of nanoparticles. Nanopart Toxic Compat, Mar. 15, 2024; 161: 182-224.
56. Fu S, Zhu X, Huang F, Chen X. Anti-PEG Antibodies and Their Biological Impact on PEGylated Drugs: Challenges and Strategies for Optimization. Pharmaceutics, Aug. 20, 2025; 17(8): 1074.
57. Hassija V, Chamola V, Mahapatra A, Singal A, Goel D, Huang K, Scardapane S, Spinelli I, Mahmud M, Hussain A. Interpreting black-box models: a review on explainable artificial intelligence. Cognitive Computation, Jan. 2024; 16(1): 45-74.
58. Rane N, Choudhary S, Rane J. Explainable Artificial Intelligence (XAI) approaches for transparency and accountability in financial decision-making. Available at SSRN 4640316. 2023 Nov 17.
59. Sah MK, Ettarhouni ZO, Pathak R, Gawad J, Bonde C, Arya SP, Bhattarai A. Green Chemistry: Strategies and Sustainable Approaches for Bridging UN SDGS. ChemistrySelect, Jul. 2025; 10(25): e00847.
60. Manik MM, Hossain S, Ahmed MK, Rozario E, Miah MA, Moniruzzaman M, Islam MS, Saimon AS. Integrating genomic data and machine learning to advance precision oncology and targeted cancer therapies. Nanotechnology Perceptions, 2022; 18(2): 219-43.