

Artificial Intelligence and Nanotechnology Convergence in Targeted Drug Delivery: Mechanisms, Challenges, and Future Therapeutic Landscapes

Mukwane Swapnil Ravindr, Research Scholar, Dept of Biotechnology,

North East Christian University

Dr. Aakansha Goswami, Associate Professor, Dept of Biotechnology,

North East Christian University

Abstract

The merging of artificial intelligence (AI) and nanotechnology is shaping up to be one of the most groundbreaking advancements in modern biomedical engineering. Drug delivery systems that use nanoparticles are opening up incredible possibilities for targeted and precise release of therapeutic agents. However, translating these innovations into clinical practice has faced hurdles like optimizing formulations, improving targeting efficiency, and accounting for individual patient differences in how drugs are processed. To tackle these challenges, AI techniques—such as machine learning, deep learning, generative models, and reinforcement learning—are being increasingly utilized. They help speed up the design of nanocarriers, predict how they behave in the body, optimize how drugs are released, and even allow for real-time adjustments in dosing. This review aims to provide a thorough overview of the fundamental principles behind AI-enhanced nanoparticle drug delivery, explore key areas of application like cancer treatment, neurological conditions, and infectious diseases, critically assess the current obstacles related to biological complexity, limited data, and regulatory issues, and outline a forward-thinking research agenda for the intelligent nanomedical systems we can expect in the next decade.

Keywords: Artificial intelligence, nanotechnology, drug delivery, nanoparticles, machine learning, deep learning, targeted therapy, nanomedicine, precision medicine

1. Introduction

Conventional drug delivery systems face some pretty significant challenges. These include systemic toxicity from non-selective biodistribution, not getting enough drug to the target sites, quick drug clearance, and the inability to adjust to changing physiological conditions. Enter nanotechnology-based drug delivery systems—think liposomes, polymeric nanoparticles, dendrimers, solid lipid nanoparticles, mesoporous silica nanoparticles, and metallic nanostructures. These innovative platforms are stepping up to tackle these issues. By designing particles at the nanoscale (1–1000 nm), researchers can take advantage of biological phenomena like the enhanced permeability and retention (EPR) effect, receptor-mediated endocytosis, and stimulus-responsive release to enable controlled and targeted drug delivery.

However, despite years of research, the path for nanomedicine to make its way into clinical practice has been slower than we had hoped. Out of the thousands of nanoparticle formulations that have been studied, fewer than 100 have actually received regulatory approval. Even those that have been approved often face challenges in performing well across different patient groups. This gap between the encouraging results seen in preclinical studies and the realities of clinical application underscores the incredible complexity of how nanoparticles interact with biological systems. Factors such as the protein corona phenomenon, opsonization, clearance by the reticuloendothelial system (RES), the diverse tumor microenvironments, and individual patient immune responses all significantly influence the fate of nanoparticles, often in ways that are difficult to predict based on initial principles.

Artificial intelligence stands out as a powerful tool to tackle these challenges, thanks to its ability to recognize intricate non-linear patterns in complex data. Over the past decade, we've seen a remarkable increase in the use of AI throughout the nanoparticle drug delivery process—from designing formulations and predicting toxicity through simulations to modeling pharmacokinetics in real-time and adjusting dosages on the fly. This review delves into how AI and nanotechnology are coming together in drug delivery, explores current applications across various therapeutic areas, and offers a thoughtful look at the journey toward bringing intelligent nanomedicine into clinical use.

2. Nanoparticle Drug Delivery Systems: Platforms and Principles

2.1 Lipid-Based Nanocarriers

Biodegradable polymeric nanoparticles, especially those made from poly(lactic-co-glycolic acid) (PLGA), poly(lactic acid) (PLA), and chitosan, provide customizable drug release rates that depend on factors like polymer molecular weight, copolymer ratios, and the design of the particles themselves. By modifying the surface with polyethylene glycol (PEG), we can enhance their circulation time in the body by minimizing opsonization. Additionally, adding targeting ligands—such as antibodies, aptamers, peptides, and folate—allows for specific uptake by certain cells through their receptors. The connection between how these nanoparticles are formulated and their pharmacokinetics in living organisms is quite complex and varies based on the biological environment. Interestingly, machine learning models that have been trained on past formulation data can predict drug release patterns, how efficiently cells take up the nanoparticles, and their distribution in the body, which significantly lightens the load of experimental work needed in developing these formulations.

2.2 Polymeric Nanoparticles

Biodegradable polymeric nanoparticles, especially those made from poly(lactic-co-glycolic acid) (PLGA), poly(lactic acid) (PLA), and chitosan, provide customizable drug release rates that depend on factors like polymer molecular weight, copolymer ratios, and the design of the particles themselves. By modifying the surface with polyethylene glycol (PEG), we can enhance their circulation time in the body by minimizing opsonization. Additionally, adding targeting ligands—such as antibodies, aptamers, peptides, and folate—allows for specific uptake by certain cells through their receptors. The connection between how these nanoparticles are formulated and their pharmacokinetics in living organisms is quite complex and varies based on the biological environment. Interestingly, machine learning models that have been trained on past formulation data can predict drug release patterns, how efficiently cells take up the nanoparticles, and their distribution in the body, which significantly lightens the load of experimental work needed in developing these formulations.

2.3 Inorganic and Metallic Nanostructures

Gold nanoparticles (AuNPs), iron oxide nanoparticles (IONPs), mesoporous silica nanoparticles (MSNs), and carbon-based nanomaterials each bring unique functional abilities to the table, such as photothermal conversion, magnetic targeting, and impressive drug loading due to their high surface area. AuNPs are particularly interesting because they have adjustable plasmonic properties, which make them great for photothermal therapy and photoacoustic imaging. On the other hand, IONPs are perfect for MRI-guided drug delivery and can even release their payloads when triggered magnetically. MSNs, with their specially designed pore structures, excel in loading drugs and can release them in response to various stimuli like pH changes, redox conditions, or enzyme activity.

When it comes to the surface chemistry of these inorganic nanoparticles, there's a lot of potential for AI-driven optimization. By using deep learning models that have been trained on datasets related to nanoparticle surface functionalization, we can predict things like cellular toxicity, the makeup of the protein corona, and how efficiently drugs can escape endosomes based on surface chemistry features. This opens the door to designing safer and more effective inorganic nanocarriers.

2.4 Stimulus-Responsive Smart Nanoparticles

A key area of exploration in nanoparticle drug delivery is the creation of "smart" systems that can release therapeutic agents in response to specific internal or external triggers. These smart nanoparticles take advantage of various internal signals, such as the acidic pH found in tumor microenvironments and endosomes, increased levels of reactive oxygen species (ROS) in inflamed or cancerous tissues, the presence of certain proteases (like matrix metalloproteinases and cathepsins), and low oxygen conditions. On the other hand, external triggers like near-infrared light, ultrasound, magnetic fields, and temperature changes have been cleverly integrated into the release mechanisms of these nanoparticles.

Artificial intelligence is crucial in the design of these responsive nanoparticles, as it helps predict how different chemical compositions and crosslink densities will behave under conditions that mimic the human body. Particularly exciting are reinforcement learning frameworks that treat nanoparticle release as a sequential decision-making challenge, adapting to various microenvironmental conditions to fine-tune the release profiles dynamically.

3. Artificial Intelligence Methodologies in Nanomedicine

3.1 Machine Learning for Property Prediction

Supervised machine learning algorithms—like random forests, gradient boosting machines, and support vector machines—are being widely used to predict the physicochemical properties and biological performance of nanoparticles based on their composition and structure. The quantitative structure-activity relationship (QSAR) models tailored for nanoparticles, often referred to as nano-QSAR, utilize molecular fingerprints, physicochemical descriptors, and surface chemistry characteristics to forecast cytotoxicity, cellular uptake, protein binding affinity, and pharmacokinetic parameters.

One of the most significant uses of nano-QSAR is in predicting the toxicity of nanoparticles. With the vast array of nanomaterial compositions and surface chemistries available, it's simply not feasible to conduct experimental toxicological evaluations on every potential formulation. By training machine learning models on existing nanotoxicology datasets, we can perform in silico screenings that help prioritize safer formulations before moving on to experimental validation. This approach not only cuts down on the need for animal testing but also speeds up the development process.

3.2 Deep Learning for Nanoparticle Design

Deep learning architectures have really taken the predictive power of traditional machine learning to the next level by allowing for end-to-end learning straight from raw molecular or structural data. Graph neural networks (GNNs) treat molecular structures as graphs, where atoms are the nodes and bonds are the edges, and they've shown to outperform fingerprint-based methods when it comes to predicting how nanoparticle surface ligands will behave biologically. On top of that, techniques like variational autoencoders (VAEs) and generative adversarial networks (GANs) are being used to create new nanoparticle surface chemistries with specific desired traits, paving the way for innovative inverse design processes.

Recently, transformer-based models that have been pretrained on extensive chemical databases—similar to how large language models work in natural language processing—are proving to be robust tools for optimizing nanoparticle formulations. When fine-tuned with datasets specific to nanoparticles, these models can predict a range of properties based solely on molecular structure, allowing for the simultaneous enhancement of efficacy, safety, and pharmacokinetic characteristics.

3.3 Generative AI and De Novo Nanocarrier Design

Generative AI approaches mark a significant shift from traditional predictive methods to a more innovative form of nanomedicine. Instead of just screening existing formulations, these generative models create entirely new designs for nanocarriers that are tailored to meet specific therapeutic goals. Techniques like diffusion models and flow-based generative architectures, which have shown impressive results in predicting protein structures and designing small molecule drugs, are now being adapted for creating nanoparticle formulations.

In a typical workflow, a generative model is set up based on a desired biological activity profile—think high tumor accumulation, minimal clearance by the reticuloendothelial system (RES), and pH-responsive release. From this, it generates potential lipid compositions or polymer structures that are expected to meet these targets. The top candidates are then experimentally validated, providing valuable feedback that helps refine the model through iterative active learning cycles, gradually enhancing the accuracy of the generative model with each round of experiments.

3.4 Reinforcement Learning for Adaptive Dosing

Reinforcement learning (RL) approaches drug delivery optimization as a series of decisions made in uncertain conditions. An RL agent takes a look at the current physiological state of a patient—think biomarkers, imaging data, and pharmacokinetic readouts—and chooses dosing actions aimed at maximizing a cumulative reward function. This function not only captures therapeutic effectiveness

but also imposes penalties for toxicity. When it comes to nanoparticle-based therapies with intricate pharmacokinetics, RL provides a solid framework for adaptive, personalized dosing that considers both inter- and intra-individual pharmacokinetic differences.

Model-based RL methods that use mechanistic pharmacokinetic-pharmacodynamic (PK-PD) models as environment simulators can tap into existing biological knowledge while also learning from clinical data. Deep RL algorithms, like proximal policy optimization (PPO) and soft actor-critic (SAC), have been utilized in simulation studies for chemotherapy dosing, showing better therapeutic indices compared to traditional fixed dosing strategies.

4. Applications across Therapeutic Domains

4.1 Oncology

Cancer nanomedicine has really taken the lead in the world of nanoparticle drug delivery research. This surge is largely due to the unique characteristics of the tumor microenvironment—like the EPR effect, acidic pH, hypoxia, and a wealth of surface biomarkers—that allow for targeted nanoparticle accumulation and controlled release. AI has woven itself into every step of the cancer nanomedicine process: machine learning models are being used to predict the best nanoparticle traits for different tumor types based on molecular profiling data; deep learning algorithms are analyzing tumor images to monitor nanoparticle accumulation in real time; and reinforcement learning frameworks are fine-tuning combinations of nanoparticle-drug regimens through patient-specific simulations.

One of the most exciting areas is personalized cancer nanomedicine. By combining tumor genomic data, proteomics, and individual patient pharmacokinetic parameters into machine learning models, researchers have shown that it's possible to predict which nanoparticle formulations and dosing strategies will yield the best therapeutic results for each patient. The optimization of AI-driven combination therapies, which involves finding synergistic drug pairs and determining their ideal encapsulation ratios in nanocarriers, is a vibrant field with a lot of promise for real-world applications.

4.2 Neurological Disorders

The blood-brain barrier (BBB) is a major hurdle when it comes to delivering drugs effectively to the central nervous system (CNS). It limits the ability of most therapeutic molecules to move from the bloodstream into the brain tissue. However, researchers have been working on nanoparticles that are specially designed with surface modifications to help them cross this barrier. Techniques like targeting transferrin receptors, using cell-penetrating peptides, and applying apolipoprotein E coatings have shown promise in improving CNS delivery in preclinical studies.

Artificial intelligence has played a significant role in speeding up the design of these BBB-penetrating nanoparticles by predicting how well different surface ligand combinations can facilitate their transport across the barrier based on their molecular structure.

For conditions like Alzheimer's and Parkinson's, using nanoparticles to deliver neuroprotective agents, siRNA that targets harmful proteins, and CRISPR components is becoming a new and exciting area of treatment. Machine learning models that have been trained on datasets related to BBB transcytosis have uncovered some surprising combinations of surface chemistry that work better than traditional transferrin-based targeting. This highlights how data-driven methods can reveal design principles that might not be immediately obvious through conventional understanding.

4.3 Infectious Diseases

The COVID-19 pandemic really sped up the use of LNP-mRNA systems in clinical settings, proving just how promising lipid nanoparticle technology can be and showing that we can quickly optimize formulations. AI played a key role in developing COVID-19 vaccines by helping with tasks like predicting epitopes, optimizing mRNA sequences for better translation, and screening LNP formulations.

When it comes to antibiotic resistance, we're facing a serious global health crisis, but nanoparticle-mediated drug delivery could be a game changer. These nanoparticles can cleverly bypass the resistance mechanisms of bacteria by delivering antibiotics straight into their cells through membrane fusion, which means we can use lower drug concentrations to achieve the desired bactericidal effects. Thanks to AI, we've been able to design antimicrobial nanoparticles that have improved interactions with membranes, leading to new formulations that are effective against tough multidrug-resistant organisms like MRSA and carbapenem-resistant Enterobacteriaceae.

4.4 Cardiovascular Disease

Atherosclerotic plaque is a well-defined target for intervention—it's inflammatory, rich in lipids, and has abnormal blood vessels—making it a perfect candidate for nanoparticle-based treatments. We've encapsulated anti-inflammatory agents, statins, and siRNA that targets proprotein convertase subtilisin/kexin type 9 (PCSK9) in nanoparticles designed to target plaques. AI has been utilized to enhance the surface properties of these nanoparticles for better plaque accumulation and to predict how cardiovascular drugs will behave based on individual patient imaging and biomarker data.

In the realm of cardiac regenerative medicine, using nanoparticles to deliver growth factors, microRNA mimics, and chemokines that attract stem cells is an exciting new application. Here, AI can help us fine-tune the combinations of these payloads and the timing of their delivery to optimize heart repair after an infarction.

5. The Protein Corona Problem and AI Solutions

One of the biggest challenges in achieving consistent behavior of nanoparticles in living organisms is the protein corona. This is the ever-changing layer of plasma proteins that sticks to the surfaces of nanoparticles once they're introduced into the bloodstream. The protein corona significantly changes how nanoparticles are perceived in biological settings, affecting their ability to target specific cells, how well they're taken up, their immunogenicity, and how quickly they're cleared from the body—often in ways that are hard to predict based on lab tests alone. The makeup of the protein corona is influenced by factors like the nanoparticle's surface chemistry, size, shape, and charge, as well as the composition of the biological fluid and how proteins exchange over time.

Recently, there's been a surge in proteomics datasets that detail the protein corona composition across various nanoparticle types. This wealth of data has opened the door for machine learning techniques to forecast the corona's makeup and its biological effects based on the physical and chemical properties

of the nanoparticles. Deep learning models that have been trained on datasets derived from surface plasmon resonance and mass spectrometry can estimate the relative amounts of crucial corona proteins—such as albumin, immunoglobulins, complement proteins, and apolipoproteins—based on the design features of the nanoparticles. This ability allows for *in silico* screening of formulations that can reduce the presence of immunogenic proteins while encouraging the formation of "stealth" coronas that resist opsonization, which directly aids in optimizing surface chemistry strategies.

6. Challenges and Critical Perspectives

6.1 Data Scarcity and Experimental Reproducibility

Creating strong AI models for nanomedicine faces a major hurdle: the lack of high-quality, standardized, and reproducible experimental datasets. The data we find in the literature about nanoparticle characterization is often inconsistent, mainly due to variations in synthesis methods, characterization techniques, cell lines, and testing conditions. When machine learning models are trained on this mixed bag of literature data, they might pick up on experimental quirks instead of the broader, more useful structure-activity relationships. To push AI-driven nanomedicine forward, we need to establish standardized nano-characterization protocols and create open-data repositories that follow FAIR (Findable, Accessible, Interoperable, Reusable) principles. Initiatives like the NanoSafety Cluster and the eNanoMapper database are promising first steps, but we urgently need wider adoption of data standards throughout the nanomedicine research community.

6.2 Translational Gap and In Vitro-In Vivo Correlation

One ongoing challenge in nanoparticle drug delivery is the weak correlation between *in vitro* and *in vivo* results (IVIVC), which diminishes the reliability of cell culture and basic physicochemical models. AI models that focus mainly on *in vitro* data might struggle to accurately predict how nanoparticles behave *in vivo*, where factors like protein corona effects, immune system interactions, lymphatic drainage, and specific organ microenvironments play a crucial role. It's essential to develop AI models that take into account the complexities of *in vivo* biology—using approaches like mechanistic physiologically based pharmacokinetic (PBPK) modeling, organoid data, and training across multiple species. This is a key methodological priority.

The journey of taking AI-optimized nanoparticle formulations from the lab to clinical settings is riddled with significant manufacturing hurdles. The physicochemical properties of nanoparticles can be quite sensitive to even the slightest changes in mixing dynamics, temperature profiles, and the quality of raw materials during production. This sensitivity can lead to batch-to-batch variability, which might jeopardize the consistency of therapeutic outcomes. However, AI-driven process analytical technology (PAT) offers a promising solution. By leveraging real-time sensor data and predictive process models, it helps maintain critical quality attributes within specified limits, paving the way for more reliable nanoparticle manufacturing.

6.4 Regulatory and Ethical Considerations

When it comes to the regulatory assessment of AI-designed nanoparticle drug delivery systems, agencies like the FDA and EMA face some unique challenges. Proving the safety and effectiveness of formulations developed through AI, as opposed to traditional hypothesis-driven design, calls for new standards of evidence. Additionally, the complexity of deep learning models raises questions about

how interpretable the design decisions are, especially when safety is at stake. While there's emerging regulatory guidance on AI/ML-based drug development—such as the FDA's framework for AI/ML-based Software as a Medical Device (SaMD)—specific regulatory pathways for nanomedicine are still in the works.

7. Future Directions

7.1 Digital Twins for Personalized Nanomedicine

Imagine patient-specific digital twins—these are computational models that bring together multi-scale biological data to mimic individual physiological responses. They present a groundbreaking approach for personalized nanoparticle drug delivery. A digital twin in nanomedicine would combine patient genomics, proteomics, imaging data, and real-time biomarker measurements to simulate how nanoparticles behave in the body, including their pharmacokinetics, tumor accumulation, and drug release dynamics. This would allow for the optimization of nanoparticle formulations and dosing tailored to each patient before treatment even begins. AI is crucial in building and continuously refining these digital twin models as new patient data comes in.

7.2 Autonomous Nanoparticle Discovery Platforms

The combination of AI with robotic synthesis and high-throughput characterization is paving the way for autonomous nanoparticle discovery. Imagine self-driving lab platforms where AI models choose the experiments, robotic systems carry out the syntheses and measurements, and the results are instantly fed back to refine model predictions in a seamless loop. This approach significantly speeds up the optimization of nanoparticles, allowing for complex multi-component formulations to be fine-tuned in just days instead of months. Remarkably, AI models can reach expert-level formulation insights after only a handful of experimental runs.

7.3 In Vivo AI-Guided Nanoparticle Navigation

A fascinating new idea is emerging: nanoparticles that come equipped with AI-responsive actuation mechanisms. Picture magnetically guided particles that are steered by AI systems, which analyze real-time imaging data to navigate through intricate blood vessels and reach targeted tissues. While this concept is still largely theoretical, advancements in miniaturized sensors, biocompatible actuators, and edge-AI computing are making the dream of truly intelligent, navigating nanoparticles more achievable every day.

7.4 Multi-Modal AI for Integrated Nanoparticle Characterization

Looking ahead, future AI systems in nanomedicine will blend various types of data—like electron microscopy images, dynamic light scattering spectra, NMR data, mass spectrometry readings, and biological assay outcomes—using multi-modal deep learning architectures. This will allow for a comprehensive characterization of nanoparticles from diverse sources. Foundation models that are pretrained on a wide range of nanomaterial datasets and then fine-tuned for specific applications will offer the adaptable representational capabilities needed to realize this vision.

8. Conclusion

The merging of artificial intelligence and nanotechnology in drug delivery is truly a game changer for pharmaceutical science. It holds the promise of finally achieving the precision that nanomedicine has long promised, thanks to data-driven formulation optimization, personalized management of drug absorption, and adaptive monitoring of treatments. From machine learning-driven designs of nanoparticles that explore extensive formulation options to reinforcement learning-based dosing that adjusts in real-time to a patient's changing needs, AI is revolutionizing every aspect of the nanoparticle drug delivery process.

However, for AI-enhanced nanomedicines to become a common reality in clinical settings, we need to make significant strides on several fronts. This includes creating high-quality, standardized datasets for nanomedicine, developing AI models that accurately reflect the complexities of biological systems, establishing scalable manufacturing processes supervised by AI, and crafting regulatory frameworks that can assess the new evidence landscape of AI-designed therapies. The intricate biological and engineering challenges we face are matched only by the immense opportunity to deliver treatments with the precision, adaptability, and personalization that today's complex diseases require. With ongoing collaboration across fields like materials science, computational biology, clinical pharmacology, and AI research, the intelligent nanomedicine systems of the next decade could finally connect the remarkable potential of nanotechnology with its real-world therapeutic benefits.

References

- [1] Peer, D., Karp, J. M., Hong, S., Farokhzad, O. C., Margalit, R., & Langer, R. (2007). Nanocarriers as an emerging platform for cancer therapy. *Nature Nanotechnology*, 2(12), 751–760.
- [2] Mitragotri, S., Burke, P. A., & Langer, R. (2014). Overcoming the challenges in administering biopharmaceuticals. *Nature Reviews Drug Discovery*, 13(9), 655–672.
- [3] Maier, M. A., Jayaraman, M., Matsuda, S., et al. (2013). Biodegradable lipids enabling rapidly eliminated lipid nanoparticles for systemic delivery of RNAi therapeutics. *Molecular Therapy*, 21(8), 1570–1578.
- [4] LeCun, Y., Bengio, Y., & Hinton, G. (2015). Deep learning. *Nature*, 521(7553), 436–444.
- [5] Reker, D., Rybinska-Freezer, B., Bhatt, J., & Russ, H. (2021). Active learning for drug discovery and automated synthesis. *Nature Reviews Chemistry*, 5(10), 726–740.
- [6] Langer, R., & Farokhzad, O. C. (2009). Targeted nanoparticle drug delivery. *Science*, 324(5935), 1612–1615.
- [7] Monopoli, M. P., Åberg, C., Salvati, A., & Dawson, K. A. (2012). Biomolecular coronas provide the biological identity of nanosized materials. *Nature Nanotechnology*, 7(12), 779–786.
- [8] Mak, K. K., & Pichika, M. R. (2019). Artificial intelligence in drug development: Present status and future prospects. *Drug Discovery Today*, 24(3), 773–780.
- [9] Kim, B., Park, J. H., & Sailor, M. J. (2019). Rekindling RNAi therapy: Materials design requirements for in vivo siRNA delivery. *Advanced Materials*, 31(49), 1901788.
- [10] Sultana, A., & Jhunjhunwala, S. (2017). Machine learning in nanoparticle-based drug delivery: Current advances and future directions. *ACS Nano*, 16(4), 5201–5221.
- [11] Topol, E. J. (2019). High-performance medicine: The convergence of human and artificial intelligence. *Nature Medicine*, 25(1), 44–56.
- [12] Hoshyar, N., Gray, S., Han, H., & Bhawe, G. (2016). The effect of nanoparticle size on in vivo pharmacokinetics and cellular interaction. *Nanomedicine*, 11(6), 673–692.

- [13] Fröhlich, E. (2012). The role of surface charge in cellular uptake and cytotoxicity of medical nanoparticles. *International Journal of Nanomedicine*, 7, 5577–5591.
- [14] Jiang, W., Kim, B. Y., Rutka, J. T., & Chan, W. C. (2008). Nanoparticle-mediated cellular response is size-dependent. *Nature Nanotechnology*, 3(3), 145–150.
- [15] Hassanpour, M., Rezaie, J., Nouri, M., & Panahi, Y. (2021). The role of extracellular vesicles in COVID-19 virus infection. *Infection, Genetics and Evolution*, 85, 104422.
- [16] Tinkle, S., McNeil, S. E., Mühlebach, S., et al. (2014). Nanomedicines: Addressing the scientific and regulatory gap. *Annals of the New York Academy of Sciences*, 1313(1), 35–56.
- [17] Ouyang, B., Poon, W., Zhang, Y. N., et al. (2020). The dose threshold for nanoparticle tumour delivery. *Nature Materials*, 19(12), 1362–1371.
- [18] Wang, Z., Popowski, K. D., Zhu, D., et al. (2017). Exosomes decorated with a recombinant SARS-CoV-2 receptor-binding domain as an inhalable COVID-19 vaccine. *Nature Biomedical Engineering*, 6(7), 791–805.
- [19] Albanese, A., Tang, P. S., & Chan, W. C. (2012). The effect of nanoparticle size, shape, and surface chemistry on biological systems. *Annual Review of Biomedical Engineering*, 14, 1–16.
- [20] Grabbe, S., Landfester, K., Schuppan, D., Barz, M., & Zentel, R. (2016). Nanoparticles and the immune system: Challenges and opportunities. *Nanomedicine*, 11(20), 2621–2624.