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# Molecular Mechanisms of Nanoparticle Interaction with Bio Membranes

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**Abstract:** This review delves into the molecular mechanisms of nanoparticle interactions with biological membranes, highlighting their pivotal role in nanobiotechnology. Nanoparticles, sized between 1 and 100 nanometres, exhibit unique properties that allow them to interface at the cellular and molecular levels, significantly impacting their biodistribution, cellular uptake, and therapeutic efficacy. The review discusses various interaction mechanisms, including adsorption, penetration, and fusion, and their implications for nanoparticle design in drug delivery, diagnostics, and tissue engineering. By synthesizing current knowledge and identifying future research directions, this review aims to comprehensively understand nanoparticle-membrane interactions, their applications, and the associated safety and ethical considerations. It underscores the need for thorough investigations to responsibly harness nanoparticles' potential to advance medicine, diagnostics, and environmental applications, ensuring their safe and effective use in nanobiotechnology.

**Keywords:** nanoparticles; biological membranes; nanobiotechnology.



## 1. Introduction

Nanoparticles, typically 1 to 100 nanometres in size, have become pivotal in nanobiotechnology, a field that merges nanotechnology with biology and biotechnology [1,2]. These minuscule entities exhibit unique physical, chemical, and biological properties distinct from their bulk counterparts, primarily due to their high surface area-to-volume ratio and quantum effects. Their small size enables them to interact at the cellular and molecular levels, making them invaluable in various applications as shown in Table 1 [3,4].

In medicine, nanoparticles are revolutionizing drug delivery systems, enabling targeted therapy that delivers drugs directly to diseased cells while minimizing side effects on healthy tissues. They enhance the solubility and bioavailability of drugs, allowing for controlled release and improved therapeutic efficacy [5]. In diagnostics, nanoparticles improve the sensitivity and specificity of imaging and biosensing techniques, enabling early detection of diseases at the molecular level. Moreover, nanoparticles play a crucial role in tissue engineering, creating scaffolds that mimic the extracellular matrix to support cell growth and tissue regeneration [6,7]. Their surface modification capabilities enable the attachment of specific ligands, facilitating interactions with target cells or biomolecules and advancing personalized medicine [8,9].

In environmental and industrial applications, nanoparticles contribute to pollution remediation, catalysis, and the development of sustainable materials, showcasing their versatility [10,11]. However, given their widespread use, understanding their interactions with biological systems is imperative to ensure safety and efficacy, underscoring the significance of nanoparticles in advancing nanobiotechnology and their potential to address complex challenges across various sectors [12,13].

*1.1. Importance of nanoparticle interactions with biological membranes.*

Understanding how nanoparticles interact with biological membranes is crucial for their safe and effective application in nanobiotechnology. Biological membranes, primarily composed of lipid bilayers with embedded proteins, act as protective barriers for cells and organelles, regulating the entry and exit of substances. The interaction between nanoparticles and these membranes can significantly influence the nanoparticles' biodistribution, cellular uptake, and therapeutic efficacy [14-16].

When nanoparticles encounter biological membranes, they can adhere to, penetrate, or even disrupt these structures, impacting cellular functions. For instance, the ability of nanoparticles to penetrate cell membranes without causing significant damage is essential for drug delivery, allowing therapeutic agents to reach intracellular targets. Conversely, unintended membrane disruption can lead to cytotoxicity, underscoring the importance of understanding these interactions to mitigate potential risks [17-19].

The interaction between nanoparticles and membranes can trigger cellular signaling pathways, influencing cell behavior and fate. For drug delivery applications, it's crucial to understand how nanoparticles can be designed to modulate these pathways beneficially [20]. Similarly, in diagnostics, nanoparticles' interactions with membrane receptors can be harnessed to enhance the detection of disease markers [21]. The diversity of nanoparticles and biological membranes, and the interactions between them, are influenced by various factors, including nanoparticle size, shape, surface charge, and coating, as well as membrane composition and fluidity [22]. A deep understanding of these dynamics facilitates the rational design of nanoparticles for specific applications, ensuring they perform their intended functions while minimizing unintended consequences. Thus, studying nanoparticle-bio membrane interactions is fundamental for advancing nanobiotechnology and ensuring the ethical and responsible development of nanotechnologies.

The primary objective of this review is to elucidate the molecular mechanisms underlying interactions between nanoparticles and biological membranes, a critical aspect of nanobiotechnology with profound implications for medicine, diagnostics, and beyond. By synthesizing current knowledge and recent advances, the review aims to provide a comprehensive understanding of how nanoparticles interact with membranes, the factors that influence these interactions, and their beneficial and detrimental consequences [23,24].

And also to examine the diverse applications stemming from nanoparticle-membrane interactions, particularly in drug delivery, where understanding these interactions can lead to more effective and targeted therapies [25]. Similarly, the review intends to highlight how these interactions facilitate advancements in diagnostics, enabling more sensitive and specific detection of biomarkers. Additionally, the review seeks to identify gaps in the current understanding and propose directions for future research. This includes exploring how novel nanoparticle designs can enhance their interactions with biological membranes to improve therapeutic outcomes and diagnostic accuracy. Addressing safety and toxicity concerns is also

a crucial objective, aiming to provide insights into how nanoparticles can be engineered to minimize adverse effects while maximizing their beneficial properties [26,27].

Ultimately, this review aims to serve as a valuable resource for researchers, clinicians, and policymakers, offering a detailed and nuanced understanding of nanoparticle-membrane interactions [28]. By bridging gaps in knowledge and suggesting pathways for future inquiry, the review contributes to the responsible advancement of nanobiotechnology, ensuring that the potential of nanoparticles is fully harnessed in a manner that is safe, ethical, and impactful [29].

## 2. Overview of the Structure and Function of Biological Membranes

Biological membranes are dynamic structures that form the boundaries of cells and organelles, are crucial for maintaining homeostasis, and facilitate cellular functions [30]. Typically, these membranes are composed of a lipid bilayer, with phospholipids arranged so that their hydrophobic tails face inward and their hydrophilic heads face outward, creating a semipermeable barrier [31]. Embedded within this bilayer are various proteins, cholesterol, and carbohydrates, contributing to the membrane's functionality and fluidity [32,33].

The primary function of biological membranes is to regulate the passage of substances in and out of cells and organelles. They achieve this through selective permeability, allowing essential molecules like oxygen, glucose, and ions to enter or exit while keeping harmful substances out [34,35]. Membranes also play a pivotal role in cell communication and signaling, with membrane proteins acting as receptors and enzymes that respond to external signals, initiating intracellular reactions [36,37]. The biological membranes are integral to cellular compartmentalization, enabling distinct cellular processes to occur in specific organelles. This organization is vital for metabolic efficiency and cellular regulation. The dynamic nature of membranes enables endocytosis and exocytosis, processes that facilitate the intake and release of large molecules and particles, underscoring the membranes' active role in cellular interactions and homeostasis [38,39].

### *2.1. Mechanisms of nanoparticle interaction with biomembranes.*

Nanoparticles interact with biological membranes through several mechanisms, which are pivotal in determining their biological fate and efficacy in applications like drug delivery [40]. One primary mechanism is adsorption, in which nanoparticles bind to the membrane surface via various forces, including electrostatic and van der Waals interactions. This initial attachment can influence nanoparticle uptake and cellular response.

Penetration is another crucial mechanism where nanoparticles cross the membrane barrier, either passively or actively. Passive penetration often occurs through the lipid bilayer, depending on the nanoparticle's properties and the membrane's composition. Active penetration involves cellular processes like endocytosis, where the cell engulfs nanoparticles in a controlled manner [41,42].

Fusion is a less common but significant interaction where nanoparticles merge with the membrane, often delivering their payload directly into the cell or altering membrane properties. This mechanism is particularly relevant for lipid-based nanoparticles that can integrate into the lipid bilayer. The nanoparticles can induce membrane perturbations, leading to structural and functional alterations. This can lead to increased membrane permeability or, in extreme cases, cytotoxic effects due to membrane disruption [39,43-45].

**Table 1.** Types, sizes, and properties of nanoparticles.

| Nanoparticle type | Size range (nm) | Properties |
|---|---|---|
| Metallic nanoparticles | 1-100 | Conductive<br>Strong optical properties due to surface plasmon resonance<br>Catalytic activity |
| Oxide nanoparticles | 1-100 | Photocatalytic activity<br>Chemical stability<br>Used in coatings, sunscreens, and sensors |
| Carbon-based nanoparticles | 1-100 | High mechanical strength<br>Exceptional electrical and thermal conductivity<br>High surface area |
| Lipid nanoparticles | 10-100 | Biocompatible<br>Used for drug and gene delivery<br>Can merge with biological membranes |
| Quantum dots | 2-10 | Semiconductor properties<br>Size-tunable light emission<br>Used in imaging and electronics |
| Dendrimers | 1-10 | Highly branched, tree-like structure<br>Uniform size<br>Functionalize surface |
| Polymeric nanoparticles | 10-1000 | Versatile in drug delivery<br>Controlled release properties<br>Biodegradable options available |

## 3. Mechanism of Interaction

### *3.1. Adsorption.*

Nanoparticles adhere to membrane surfaces through a process known as adsorption, which is influenced by various physicochemical interactions. These interactions include electrostatic forces, hydrophobic interactions, van der Waals forces, and hydrogen bonding. The surface charge of nanoparticles plays a critical role in this process; for instance, positively charged nanoparticles are more likely to adhere to negatively charged cell membranes due to electrostatic attraction [46,47].

The composition and functionalization of the nanoparticle's surface also significantly impact adsorption. Nanoparticles can be engineered with specific ligands or coatings that recognize and bind to particular receptors or molecules on the membrane, enhancing specificity and efficiency in targeting cells. Furthermore, environmental conditions, such as pH and ionic strength, can modulate the interaction dynamics, influencing the adsorption strength and pattern.

Adsorption is not merely a preliminary step in nanoparticle internalization but can also trigger cellular responses, including alterations in signaling pathways, membrane reorganization, and even cytotoxic effects, depending on the extent and nature of the nanoparticle-membrane interaction. Understanding these adsorption mechanisms is crucial for designing nanoparticles with desired cellular interactions, particularly in drug delivery and diagnostic applications [48,49].

### *3.2. Penetration.*

Nanoparticle penetration through biological membranes can occur via passive or active mechanisms. Passive penetration involves the direct diffusion of nanoparticles across the lipid bilayer, a process influenced by the nanoparticles' size, lipophilicity, and the membrane's composition and fluidity. Smaller, more hydrophobic nanoparticles have an easier time traversing the lipid bilayer through passive diffusion.

On the other hand, active penetration involves energy-dependent processes, such as endocytosis, in which the cell transports nanoparticles across the membrane. This method allows for the internalization of larger or more polar nanoparticles that cannot easily diffuse through the membrane. Active transport mechanisms ensure that nanoparticles reach intracellular targets, which is crucial for therapeutic and diagnostic applications.

The choice of nanoparticle penetration pathway can significantly affect their biodistribution, efficacy, and potential toxicity. For instance, passive penetration may lead to unintended permeation and systemic exposure, whereas active transport enables more controlled, targeted delivery. Designing nanoparticles with the appropriate properties for the desired penetration mechanism is a key focus in nanomedicine and drug delivery research [50-52].

### *3.3. Fusion.*

Nanoparticle fusion with biological membranes is a process where nanoparticles integrate into the lipid bilayer, potentially delivering their payload directly into the cell or altering the membrane's properties. This fusion is particularly relevant for lipid-based nanoparticles, such as liposomes, which can fuse with cell membranes because of their lipid-like nature.

The conditions under which fusion occurs depend on the lipid composition and fluidity of both the nanoparticle and the membrane, the membrane's curvature and tension, and the presence of specific fusogenic proteins or peptides on the nanoparticle surface. Environmental factors like pH and temperature can also influence the fusion process.

Fusion can be a desirable mechanism for delivering molecular payloads directly into the cytoplasm, bypassing endosomal pathways that might degrade or inactivate therapeutic agents. However, uncontrolled fusion could disrupt membrane integrity and cellular homeostasis, underlining the importance of designing nanoparticles with controlled fusogenic properties for safe and effective applications in drug delivery and cellular engineering [18,53].

### *3.4. Endocytosis and exocytosis.*

Endocytosis is a cellular process in which cells engulf external materials, including nanoparticles, by invaginating their membranes to form vesicles that internalize the materials. There are several types of endocytosis, including phagocytosis, pinocytosis, and receptor-mediated endocytosis, each with distinct mechanisms and functions. Nanoparticles can be designed to exploit these pathways, enabling targeted delivery of therapeutic agents into cells.

Exocytosis is the reverse process, in which cells expel materials by fusing vesicles with the plasma membrane and releasing their contents into the extracellular space. This process is essential for eliminating waste, secreting signaling molecules, and presenting antigens on the cell surface.

The interplay between endocytosis and exocytosis is crucial for maintaining cellular homeostasis and enabling dynamic interactions with the extracellular environment. For nanoparticles, understanding and harnessing these processes can enhance targeted delivery, reduce toxicity, and improve therapeutic outcomes in nanomedicine applications. Designing nanoparticles that can effectively navigate these cellular processes is a key challenge in the field, requiring a deep understanding of cellular biology and materials science [44,51].

## 4. Factors Affecting Nanoparticle-Bio membrane Interactions

### *4.1. Size, shape, surface charge, and coating.*

The interaction between nanoparticles and biological membranes is profoundly influenced by the nanoparticles' intrinsic properties, such as size, shape, surface charge, and surface coating. The size of nanoparticles affects their cellular uptake, distribution, and clearance from the body. Smaller nanoparticles typically penetrate cells more easily and can circulate in the body longer, but they may also pose a greater risk of unintended systemic exposure and toxicity.

The shape is another critical factor; for instance, cells generally internalize spherical nanoparticles more efficiently than rod-shaped or irregularly shaped nanoparticles. This shape-dependent behavior influences how nanoparticles are distributed within the body and how they interact with different cellular components.

Surface charge impacts how nanoparticles interact with the charged components of cellular membranes. Positively charged nanoparticles tend to have a higher affinity for the negatively charged cell membranes, which can enhance cellular uptake but also potentially increase cytotoxicity. Conversely, negatively charged or neutral nanoparticles may exhibit reduced interaction with membranes and lower cytotoxicity.

Surface coating or functionalization can be designed to improve biocompatibility, reduce nonspecific interactions, and facilitate targeted delivery. Coatings can include polymers, antibodies, or ligands that bind to specific cell-surface receptors, enabling targeted interactions with specific cell types or tissues and thereby enhancing the therapeutic efficacy of nanoparticle-based delivery systems while minimizing off-target effects.

### *4.2. Membrane properties: composition, fluidity, and presence of specific receptors.*

The properties of biological membranes, such as their composition, fluidity, and the presence of specific receptors, play a crucial role in how they interact with nanoparticles. The lipid composition of a membrane affects its fluidity and lipid-molecular arrangement, which, in turn, influences how nanoparticles interact with and penetrate the membrane. Membranes with a higher cholesterol content, for example, tend to be less fluid and more ordered, which can affect nanoparticle uptake.

Membrane fluidity is a dynamic property that affects the mobility of embedded proteins and lipids, thereby impacting endocytosis, fusion, and other processes critical to nanoparticle interactions. The lipid bilayer's phase state (liquid-crystalline or gel) can influence the rate and mode of nanoparticle entry into cells.

Specific receptors and proteins on the membrane surface are another determinant of nanoparticle interaction. Nanoparticles can be engineered to recognize and bind to these specific molecules, facilitating receptor-mediated endocytosis, a selective and efficient route for cellular entry. This targeted approach can enhance the delivery of therapeutic agents to desired cells or tissues, thereby improving efficacy and reducing side effects of nanoparticle-based treatments.

### *4.3. Environmental factors: pH, temperature, and other biological molecules.*

Environmental factors, such as pH, temperature, and the presence of other biological molecules, significantly affect the interactions between nanoparticles and biological

membranes. pH can influence the ionization state of nanoparticle surfaces and membrane components, altering electrostatic interactions and potentially affecting nanoparticle stability, aggregation, and membrane penetration. For example, the acidic environment of tumor tissues or endosomes can alter nanoparticle properties or trigger the release of encapsulated drugs.

Temperature affects the fluidity of both nanoparticles and biological membranes, thereby influencing interaction dynamics. Higher temperatures can increase membrane fluidity and potentially enhance nanoparticle uptake, while lower temperatures might stabilize the membrane structure and impede nanoparticle entry.

The presence of other biological molecules, such as proteins and sugars, in the extracellular or intracellular milieu can also influence nanoparticle interactions. Proteins can adsorb onto nanoparticle surfaces, forming a "protein corona," which can alter nanoparticle recognition by cells and uptake mechanisms. Similarly, the interaction with extracellular matrix components can affect the mobility and localization of nanoparticles in tissue [54-57].

## 5. Consequences of Interactions

### *5.1. Cellular uptake.*

Cellular uptake of nanoparticles is a crucial process that determines their efficacy in applications like drug delivery and diagnostics. Nanoparticles can enter cells through various mechanisms, including endocytosis (phagocytosis, pinocytosis, and receptor-mediated endocytosis), direct penetration, or fusion with the cell membrane. The chosen pathway significantly influences their intracellular fate and potential effectiveness.

Once internalized, nanoparticles can be trafficked to different cellular compartments. For instance, nanoparticles entering via endocytosis are often encapsulated in endosomes and may be routed to lysosomes, where acidic conditions and enzymatic activity can lead to their degradation. This can affect the release and activity of the nanoparticle's payload. Some engineered nanoparticles are designed to escape the endosomal pathway, releasing their cargo directly into the cytoplasm, enhancing therapeutic effectiveness.

The intracellular fate of nanoparticles also depends on their size, composition, and surface modification. Smaller nanoparticles might more easily escape lysosomal degradation, while larger or specifically targeted nanoparticles can be directed to particular cellular locations. Understanding and controlling the cellular uptake and intracellular trafficking of nanoparticles is pivotal for optimizing their design for specific biomedical applications, ensuring they reach the desired target and exert the intended effect [58,59].

### *5.2. Membrane integrity.*

Nanoparticles can alter the integrity of biological membranes, thereby affecting their permeability and potentially inducing cytotoxic effects. When nanoparticles interact with cell membranes, they can induce structural and functional changes depending on their size, shape, charge, and concentration.

Alterations in membrane permeability can result in uncontrolled influx or efflux of ions and molecules, disrupting cellular homeostasis and potentially leading to cell death. For example, certain nanoparticles can create transient pores in the membrane, facilitating the delivery of therapeutic agents but also risking the unregulated exchange of substances that could harm the cell.

Furthermore, nanoparticles can induce oxidative stress, leading to lipid peroxidation and membrane damage. This can trigger a cascade of cellular responses, including apoptosis or necrosis. The extent of these effects often depends on the nanoparticles' material, size, surface properties, and exposure duration.

It is crucial to ensure nanoparticles maintain membrane integrity or control their interaction with membranes to prevent unintended cytotoxicity. This involves rigorous assessment of nanoparticle-membrane interactions in nanoparticle development's design and testing phases, ensuring that they achieve their intended purpose without compromising cell viability [60,61].

### *5.3. Signaling pathways.*

Nanoparticles can modulate cellular signaling pathways, influencing cell function and behavior. These interactions can be beneficial, as in the case of targeted therapies aiming to modulate specific pathways, or detrimental, leading to unintended cellular responses.

Upon interacting with or entering cells, nanoparticles can affect signaling pathways through various mechanisms. For instance, they can bind to cell surface receptors, triggering or inhibiting signal transduction pathways. Nanoparticles can also interact with intracellular signaling molecules, affecting downstream effects such as gene expression, cell proliferation, and apoptosis.

The influence of nanoparticles on signaling pathways can be tailored for therapeutic purposes. For example, nanoparticles can be designed to deliver molecules that specifically activate or inhibit particular signaling pathways, offering potential treatments for diseases like cancer, where certain pathways are dysregulated.

However, unintended interference with cellular signaling by nanoparticles can lead to adverse effects, including inflammation, toxicity, or uncontrolled cell proliferation. Therefore, understanding the modulation of signaling pathways by nanoparticles is crucial for developing safe and effective nanotherapeutics.

In designing nanoparticles for medical applications, it's essential to consider their potential impact on cellular signaling, ensuring that their interactions with cellular pathways are thoroughly understood and controlled to harness their benefits while minimizing risks [62-64].

## 6. Applications and Implications

### *6.1. Drug delivery: utilizing nanoparticle-bio membrane interactions for targeted drug delivery.*

Nanoparticles enhance drug delivery by exploiting their unique interactions with biological membranes, enabling targeted therapy. They can be engineered to recognize specific cell types, facilitating drug release at desired locations and thereby improving efficacy while reducing side effects. Nanoparticles can navigate biological barriers, deliver drugs to hard-to-reach sites, and provide controlled release, revolutionizing the delivery of chemotherapeutics and other medications, especially in oncology, where precision is crucial [65].

*6.2. Diagnostic tools: enhancing imaging and detection of diseases.*

Nanoparticles significantly improve medical diagnostics by serving as advanced contrast agents in imaging and sensitive detectors in assays. Their unique properties enhance the clarity and detail of medical images, aiding in accurate disease diagnosis. Additionally, nanoparticles enhance the sensitivity and specificity of biomarker detection, facilitating early disease identification and monitoring. By enabling precise localization and characterization of pathological changes, nanoparticles are pivotal in advancing diagnostic techniques, contributing to early intervention and personalized medicine strategies [66,67].

*6.3. Therapeutic applications: nanoparticles in gene therapy and immunotherapy.*

In gene therapy, nanoparticles efficiently deliver genetic material into cells, offering the potential to cure genetic disorders by correcting or silencing defective genes. Their protective and targeting capabilities ensure effective gene transfer and expression. In immunotherapy, nanoparticles enhance the immune response against diseases, notably cancer. They can deliver antigens or immunomodulatory compounds, focusing the immune system's attack on malignancies. This targeted approach minimizes side effects and improves therapeutic outcomes, showcasing nanoparticles' vital role in advancing gene-based and immune-mediated treatments, marking significant strides in personalized and precision medicine [68-70].

## 7. Challenges and Future Directions

*7.1. Overcoming biological barriers to improve nanoparticle efficiency.*

One major challenge in nanoparticle-based therapies is overcoming biological barriers, such as the blood-brain barrier and cellular membranes, to deliver therapeutics effectively. Innovations are needed in designing nanoparticles that can navigate these barriers without compromising their functionality or safety. Strategies include developing more effective targeting mechanisms, enhancing nanoparticle permeability, and ensuring stability across various biological environments. Overcoming these obstacles is crucial to maximizing the therapeutic potential of nanoparticles, particularly for treating elusive diseases such as brain tumors and neurodegenerative disorders [71,72].

*7.2. Addressing safety and toxicity concerns.*

Ensuring the safety and minimizing the toxicity of nanoparticles are paramount challenges. As nanoparticles interact intricately with biological systems, understanding and predicting their long-term effects remain complex. Research must focus on elucidating the biodistribution, clearance, and potential bioaccumulation of nanoparticles, along with their interactions at the cellular and molecular levels. Developing standardized protocols for toxicity assessment and focusing on biocompatible materials can aid in mitigating risks. Public and regulatory acceptance hinges on transparent and comprehensive safety evaluations, which are essential for advancing nanoparticle applications in healthcare [73,74].

*7.3. Future research areas and potential breakthroughs in nanoparticle design.*

Future research in nanoparticle design promises revolutionary breakthroughs, especially in personalized medicine and sustainable technologies. Key areas include creating multi-functional nanoparticles that can simultaneously diagnose, treat, and monitor disease, and designing environmentally friendly nanoparticles for industrial and environmental applications. Advances in nanorobotics and smart drug-delivery systems that respond to specific physiological triggers for targeted therapy are on the horizon. Integrating artificial intelligence for nanoparticle design and application could further enhance precision and efficiency, opening new frontiers in nanomedicine and pushing the boundaries of what's achievable with current technologies [75-77].

## 8. Conclusions

This comprehensive review elucidates the intricate molecular mechanisms by which nanoparticles interact with biological membranes, a cornerstone of nanobiotechnology with significant implications across medicine, diagnostics, and environmental applications. It systematically explores the interaction mechanisms of adsorption, penetration, and fusion and their consequences, emphasizing their critical role in determining nanoparticles' functionality and safety. The review highlights the applications of these interactions in drug delivery and diagnostics, where understanding membrane dynamics can lead to more effective and targeted interventions. Additionally, it addresses the challenges and future directions in nanoparticle research, focusing on overcoming biological barriers, addressing safety concerns, and exploring innovative designs for personalized medicine. By bridging knowledge gaps and suggesting new research avenues, the review fosters a deeper understanding of nanoparticle-membrane interactions, aiming to guide the responsible development and application of nanotechnologies to improve healthcare and environmental sustainability.

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## Conflicts of Interest

The authors have no conflicts of interest.

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