

# Advances in the use of cell-membrane encapsulated nanoparticles to target tumor drugs

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## ABSTRACT

Cancer treatment encounters numerous challenges, encompassing tumor heterogeneity, drug resistance, microenvironmental influences, treatment side effects, and cost considerations. The inherent diversity of tumors results in variable treatment responses among patients, underscoring the imperative for personalized therapeutic approaches. Moreover, the formidable resistance exhibited by tumor cells towards therapeutic agents necessitates innovative strategies to surmount this obstacle. In the vanguard of scientific and technological progress, nanotechnology has ushered in significant potential and opportunities for enhancing tumor treatments. Nanoparticle-based drug delivery systems offer a paradigm shift in augmenting drug efficacy while mitigating side effects through precise targeting and controlled release mechanisms. Particularly promising is the utilization of cell-membrane-coated nanoparticles in oncological therapy. By leveraging cell-membrane coatings, nanoparticles attain commendable biocompatibility, circumvent immune-mediated barriers, optimize cellular uptake, and amplify drug accumulation and retention within tumor tissues. These constructs exhibit an exceptional aptitude for drug delivery, maintaining drug stability, and orchestrating controlled release dynamics. This comprehensive review expounds upon the strides achieved in leveraging cell-membrane-coated nanoparticles for the targeted delivery of anticancer agents.

## KEYWORDS

Cell membrane; Nanoparticles; Oncology drug; Anticancer agents; Tumor

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## 1. Introduction

Tumor research stands as a pivotal focal point within the contemporary medical landscape. By delving deeply into the intricate mechanisms, biological attributes, and therapeutic stratagems of tumors, scientists strive to elevate the standards of early detection, precise intervention, and prognostic assessment in the realm of malignancies [1-3]. In recent years, nanotechnology has emerged as a focal point of interest in the domain of tumor treatment. Notably, nanoparticles encased within cell membranes have surfaced as an innovative approach for targeted tumor therapy. This genre of nanoparticles amalgamates the prowess of nanotechnology with the inherent biological activity of cell membranes, thus infusing fresh optimism into the arena of tumor treatment.

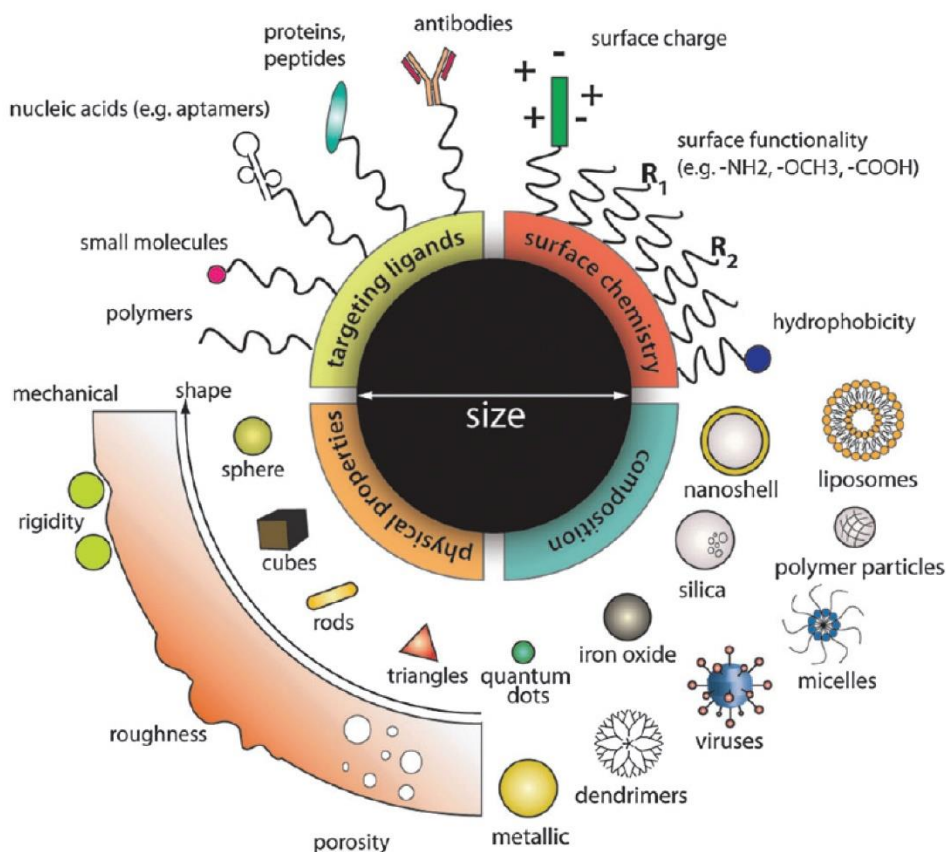
Employing cell membranes as enveloping agents endows nanoparticles with heightened biocompatibility and biological stability, concurrently mitigating immune responses and drug degradation during the course of drug delivery [4,5]. By encapsulating these nanoparticles with cell membranes derived from specifically targeted tumor cells, a heightened level of precision in targeting is achieved, allowing them to recognize and bind to surface receptors on tumor cells selectively. Furthermore, the surface of the cell membrane orchestrates interactions between nanoparticles and the tumor microenvironment, thereby amplifying mechanisms such as evading immune surveillance and augmenting tumor cell uptake. These dynamics collectively bolster drug delivery efficiency and therapeutic efficacy [6-8]. Noteworthy strides have already been accomplished in exploring nanoparticles enclosed in cell membranes. Researchers have effectively harnessed such nanoparticles to dispense chemotherapy agents, targeted antineoplastic drugs, and gene therapy payloads [9,10]. These nanoconstructs engender elevated local drug concentrations, thereby curtailing the noxious impact on normal cells while selectively homing in on tumor cells. This review delineates the advancement in utilizing cell membrane-enveloped nanoparticles for the targeted delivery of tumor therapeutics.

## 2. Application of Nanoparticle Drug Delivery Systems in Tumor Treatment

The utilization of nanoparticle drug delivery systems, rooted in nanotechnology, orchestrates the targeted conveyance and regulated release of medications through encapsulating drugs within nanoparticles. This innovation enhances drug bioavailability, extends drug retention within the body, and curtails harm to healthy tissues, thus augmenting therapeutic efficacy while mitigating adverse effects [11,12]. The blueprint for designing nanoparticle drug delivery systems comprises drug encapsulation and stability, precision targeting, and controlled release. Primarily, drugs must be adeptly ensconced within nanoparticles, maintaining stability to avert premature release or deactivation. Subsequently, nanoparticles can be meticulously tailored to recognize and adhere to tumor cells or pathological tissues through surface modifications or the integration of targeting ligands, thereby achieving pinpointed drug delivery. Finally, the nanoparticle drug delivery system can govern drug release kinetics by adjusting particle structure, size, and composition, culminating in sustained or gradual drug release profiles.

The hallmark of nanoparticle drug delivery systems is their aptitude for targeted drug delivery. Through surface modifications or the integration of targeting ligands, nanoparticles selectively engage with tumor cells or afflicted tissues, heightening drug accumulation within tumor domains while minimizing harm to healthy tissues. By adjusting particle size shape and leveraging the aberrant vascular and lymphatic systems within tumor tissue, nanoparticles also enhance tissue penetration and distribution of drugs [13,14]. A second advantage lies in the controlled release of drugs. The nanoparticle drug delivery system achieves sustained or gradual drug release by manipulating particle structure, composition, and incorporating materials or mechanisms for controlled release. This modality maintains therapeutic drug concentrations at the treatment site, diminishing drug metabolism and excretion, thus fostering enhanced therapeutic outcomes. Moreover, the nanoparticle drug delivery system embodies multifunctionality. Beyond drug delivery, nanoparticles can amalgamate diverse therapeutic modalities

by integrating or modifying functional molecules or materials. For instance, incorporating photosensitizers or thermosensitive agents can empower nanoparticles to facilitate photothermal therapy via photothermal effects. Similarly, the integration of genes or RNA can yield nanoparticles capable of gene therapy or RNA interference therapy. This adaptability broadens the purview of nanoparticle applications in tumor treatment. (Fig.1)



**Figure 1.** Structure of nanoparticle drug delivery system.

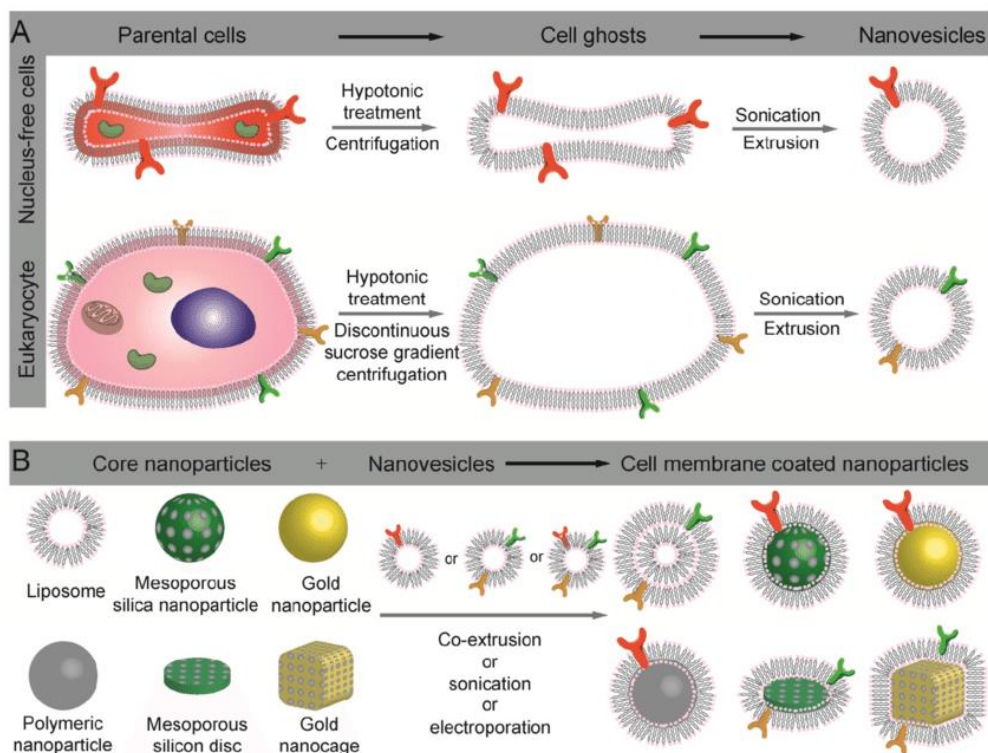
Note: Design of nanoparticle (NP)-based drug delivery platform, according to the size, shape, stiffness (composition), and surface properties of NPs. The figure is adapted from Reference with permission. (Polymers (Basel) 2016, 8(3):83.)

### 3. Cell Membrane-Encapsulated Nanoparticle Technology

The concept of cell membrane-encapsulated nanoparticles is an innovative nanotechnology that employs cellular membranes as the outer casings for nanoparticles, endowing them with attributes akin to natural cells. This strategy melds the physical, chemical, and biological properties of nanomaterials with the biocompatibility and bioactivity intrinsic to cell membranes, fostering a promising avenue of exploration [15,16]. The process of crafting nanoparticles enveloped by cell membranes typically involves two steps: first, core nanoparticles, such as metallic nanoparticles and drug carriers, are fabricated using nanotechnology; subsequently, these core nanoparticles are ensheathed or coated with cell membranes. Diverse methodologies, including blending, decellularization, and electrophoresis, can be employed to achieve cell membrane encapsulation. The encapsulation of nanoparticles within cell membranes yields manifold benefits. Primarily, the membrane encasement imparts nanoparticle surfaces with biomolecules akin to those found on cellular surfaces, such as membrane proteins and glycosylations, thus amplifying nanoparticles' compatibility and biological interaction within organisms. Moreover, cell membrane encapsulation imbues nanoparticles with targeted capabilities, enabling the identification and homing in on specific cell types through the selection of source cell membranes. Furthermore, nanoparticles encased within cell membranes demonstrate robust stability and prolonged lifespan.

Nanoparticles encased within cell membranes find extensive biomedical applications. Notably, their most prevalent application lies within drug delivery systems. Encasing drug carrier nanoparticles within cell membranes enhances drug stability, targeting precision, and therapeutic efficacy of drugs while undesirable effects are curbed [17,18]. Beyond drug delivery, cell membrane-encapsulated nanoparticles hold potential in tumor treatment, gene transference, and immunotherapy fields. Nevertheless, these nanoparticles face challenges. The preparation process is intricate, necessitating preserving the stability and congruence of the nanoparticles-cell membrane composite. Additionally, further scrutiny of the interaction mechanism between nanoparticles and cell membranes is requisite to optimize nanoparticles' performance and functionality. Moreover, the influence of nanoparticles' size, shape, and composition on their attributes and applications warrants deeper investigation.

Conclusively, cell membrane-encapsulated nanoparticles represent a burgeoning nanotechnology with considerable potential and prospects. Capitalizing on the attributes and functions of cell membranes, these nanoparticles hold promise for efficient drug delivery, precise targeted therapy, and diverse biomedical applications. As research advances and technology evolves, nanoparticles enveloped by cell membranes are poised to play a pivotal role in future tumor treatment paradigms. (Fig.2)



**Figure 2.** Method for preparing cell membrane encapsulated nanoparticles.

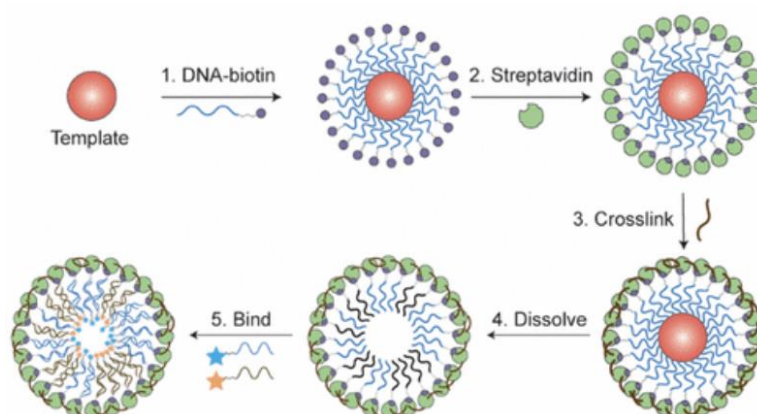
Note: Schematic illustration of the preparation of cell-membrane coated nanoparticles. (A) Extract of intact cell ghost from parent cells and further processing into nanovesicles. (B) Different types of nanoparticles that have been used as inner cores, and their fusion with nanovesicles to construct cell membrane coated nanoparticles. (Theranostics 2017, 7(10):2575-2592)

#### 4. Characteristics of Cell Membrane-Encapsulated Nanoparticles

Nanoparticles enveloped in cell membranes possess a spectrum of distinctive attributes that underscore their expansive potential in biomedicine. These unique characteristics amalgamate the tenets of nanotechnology with the intricacies of biological principles, rendering them a compelling application. Foremost, nanoparticles swathed in cell membranes exhibit remarkable biocompatibility due to the membrane's origin from autologous or allogenic



cells. This outer membrane layer attenuates the interaction and recognition between nanoparticles and the organism's immune system, thereby mitigating the prospects of immune rejection and associated side effects. Moreover, cell membrane-encapsulated nanoparticles manifest heightened biological selectivity. Leveraging membrane proteins and receptors on their surfaces, they match specific cell or tissue structures, enabling precision-targeted delivery. This precision empowers nanoparticles to homogenize onto tumor cells or diseased tissues, thereby enhancing drug efficacy while minimizing harm to healthy tissues. The encapsulated nanoparticles also demonstrate robust stability and endurance. The cell membrane furnishes an enveloping layer that shields against nanoparticle aggregation and degradation, thereby extending their circulation lifespan and duration of action within the body. This stability is conducive to sustained drug release, engendering prolonged therapeutic effects. Notably, nanoparticles encased by cell membranes exhibit remarkable biological affinity. The biomolecules, receptors, and signal transduction systems present on the cell membrane interact synergistically with corresponding components within the surrounding milieu and organisms, fostering enhanced histocompatibility and biocompatibility [19,20]. Collectively, these attributes position cell membrane-encapsulated nanoparticles to synergize nanotechnology and biological principles in the domain of tumor treatment. Their biocompatibility, biological selectivity, stability, and durability enable precise targeted delivery and controlled release, ushering in fresh possibilities and avenues for advancing tumor therapeutics. Nonetheless, while these attributes hold immense promise, further research and clinical validation are requisite to ensure their safety, efficacy, and applicability. (Fig.3)



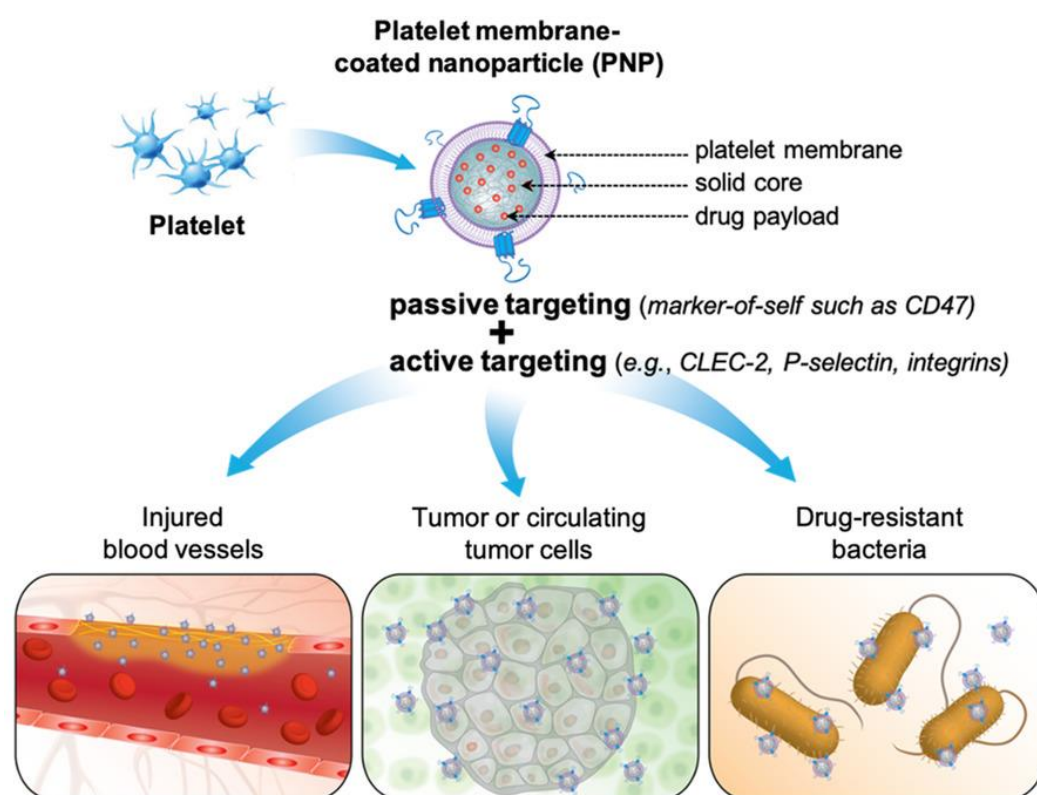
**Figure 3.** Characteristics of DNA-controlled encapsulation of small molecules in protein nanoparticles

Note: A nanoparticle can hold multiple types of therapeutic and imaging agents for disease treatment and diagnosis. However, controlling the storage of molecules in nanoparticles is challenging, because nonspecific intermolecular interactions are used for encapsulation. Here, we used specific DNA interactions to store molecules in nanoparticles. We made nanoparticles containing DNA anchors to capture DNA-conjugated small molecules. By changing the sequences and stoichiometry of DNA anchors, we can control the amount and ratio of molecules with different chemical properties in the nanoparticles. We modified the cytotoxicity of our nanoparticles to cancer cells by changing the ratio of encapsulated drugs (mertansine and doxorubicin). Specifically controlling the storage of multiple types of molecules allows us to optimize the properties of combination drug and imaging nanoparticles. (J Am Chem Soc 2020, 142(42):17938-17943.)

## 5. Targeting Strategies of Cell Membrane-Coated Nanoparticles

The targeting strategy constitutes a cardinal facet of cell membrane-coated nanoparticles in the landscape of tumor treatment. By homing in on specific receptors, proteins, or biomarkers on the tumor cell surface, these nanoparticles effectuate meticulous and directed delivery for therapeutic intervention. Various strategies encompass receptor-mediated targeting, cell membrane fusion targeting, environmental response targeting, and

tissue-specific targeting. Receptor-mediated targeting hinges on cell membrane receptors binding to ligands or antibodies on tumor cells, orchestrating precise molecular alignment. This tactic augments nanoparticle specificity within tumor tissues, diminishes damage to healthy tissues, and elevates local drug concentrations. Cell membrane fusion targeting involves the fusion of nanoparticles encased in cell membranes with tumor cells, facilitating direct drug release into tumor cells. This circumvents cellular barrier effects and augments therapeutic impact [21, 22]. Environmental response targeting exploits tumor microenvironment-specific conditions or biomolecules to trigger nanoparticle release or transformation. This strategy involves tailoring nanoparticles' physical or chemical properties, enabling alterations within the acidic tumor milieu or in response to specific enzymes, thereby realizing controlled drug release. Tissue-specific targeting, congruent with distinctive tumor tissue attributes, selects an appropriate cell membrane as the encapsulating material, thereby enhancing nanoparticle recognition and accumulation within tumor tissue. Collectively, these targeting strategies empower cell membrane-coated nanoparticles to achieve highly selective drug delivery and therapeutic impact, concomitantly reducing harm to healthy tissues and enhancing treatment safety and efficacy. The selection and design of these strategies hinge upon tumor types, therapeutic requisites, nanoparticle carriers, and cell membrane sources. Nonetheless, despite the theoretical allure of targeting strategies, practical application encounters challenges such as preparation intricacies, stability maintenance, and validation of targeting efficacy. These challenges necessitate ongoing research and optimization efforts. (Fig.4)



**Figure 4.** Schematic diagram of drug targeting mechanism of nanoparticles coated with platelet membrane  
 Note: Schematic summary of using PNPs for drug targeting. PNPs are made by wrapping membranes derived from natural platelets onto solid nanoparticle cores. PNPs leverage natural markers on the platelet membrane for drug targeting. The mechanism can be passive via markers-of-self such as CD47. It can also be active via surface antigens such as CLEC-2, P-selectin, integrin  $\alpha 6\beta 1$ , and integrin  $\alpha IIb\beta 3$ . PNPs have been used to target drug payload to injured vasculatures (bottom left), tumor or CTCs (bottom middle), and drug-resistant bacteria (bottom right). (Small Struct 2020, 1(1):2000018.)

## 6. Mechanisms of Drug Delivery by Cell Membrane-Coated Nanoparticles

Nanoparticles enclosed in cell membranes function as intricate drug delivery systems, exhibiting a spectrum of mechanisms for drug conveyance. These mechanisms encompass intracellular uptake, cell membrane fusion, permeation, and targeted delivery. Intracellular uptake occurs through binding with cell surface receptors or proteins, instigating cell membrane invagination, and forming endocytic vesicles that ferry nanoparticles into cells. Cell membrane fusion entails merging proteins on nanoparticle surfaces with the cell membrane, facilitating direct drug release into cells [23,24]. Osmotic mechanisms enable nanoparticles to traverse cell membranes and enter cells without endocytosis. Targeted delivery mechanisms involve nanoparticles binding with specific receptors on tumor cell surfaces, enabling accurate targeted drug delivery and intensifying local drug concentrations within tumor tissues. The selection of these mechanisms hinges upon nanoparticle attributes, the origin and characteristics of cell membrane encapsulation, and tailored therapeutic prerequisites. Varied drugs and treatment strategies may necessitate distinct delivery mechanisms to optimize outcomes. Consequently, investigating and refining these delivery mechanisms holds paramount importance to heighten drug delivery efficiency precision and to minimize adverse effects on healthy tissues, thereby maximizing the potential of nanoparticles in tumor treatment. Future research endeavors will further refine and innovate drug delivery mechanisms to meet the challenges within tumor treatment, offering more effective and personalized therapeutic protocols.

## 7. Preclinical Applications of Cell Membrane-Coated Nanoparticles

The preclinical application of cell membrane-encapsulated nanoparticles in tumor therapy encompasses pivotal facets, including the assessment of drug delivery efficacy, studies on biocompatibility and toxicity, investigations into in vivo distribution and metabolic kinetics, and evaluations of drug stability and release performance. Assessing drug delivery efficacy is a cornerstone of preclinical research involving cell membrane-coated nanoparticles. The efficiency and specificity of nanoparticle drug delivery can be appraised through in vitro cell experiments and animal model investigations. These evaluations encompass nanoparticle targeting, intracellular uptake efficiency, and drug release efficacy, ensuring nanoparticles effectively deliver drugs to designated cells or tissues, yielding the anticipated therapeutic outcomes [25,26]. Scrutiny of biocompatibility and toxicity is critical to ensure clinical safety. This entails evaluating nanoparticle toxicity and immune responses through in vitro cytotoxicity assays and animal model studies. Such assessments illuminate nanoparticles' toxic attributes like cytotoxicity, inflammatory reactions, and immunogenicity, thus securing their safety for clinical usage. Studies on in vivo distribution and metabolic kinetics evaluate nanoparticle behavior within living systems. The body's nanoparticle distribution, metabolic pathways, and clearance kinetics can be tracked and assessed by drug labeling or imaging techniques. This insight into in vivo nanoparticle behavior optimizes drug delivery efficacy and informs clinical application protocols. Evaluating drug stability and release performance is also pivotal for clinical reliability. This includes investigations into nanoparticles' physical and chemical stability under various conditions and drug stability to ensure the durability of nanoparticles during preparation, storage, and utilization. Additionally, assessing drug release performance, encompassing slow-release rates, controlled release, and targeted release, refines drug delivery system design and performance. Collectively, the preclinical application of cell membrane-coated nanoparticles in tumor treatment and beyond establishes a robust scientific foundation and technical support, validating their reliability and safety for clinical utilization. This encompasses evaluating drug delivery efficacy, biocompatibility and toxicity, in vivo distribution and metabolic kinetics, and assessing drug stability and release performance. These preclinical findings provide a sturdy bedrock for further development and the clinical translation of nanoparticles.

## 8. Clinical Applications of Cell Membrane-Coated Nanoparticles

The clinical exploration of nanoparticles enclosed in cell membranes spans diverse dimensions, including targeted tumor therapy, drug resistance reversal, and the augmentation of immunotherapy.

**Targeted Tumor Therapy:** Cell membrane-coated nanoparticles exhibit immense potential in targeted tumor therapy. By mimicking the membrane proteins present on tumor cell surfaces, these nanoparticles engage in specific interactions with tumor cells, enabling precise drug delivery. Clinical trials have already employed cell membrane-coated nanoparticles to transport anti-tumor drugs, including chemotherapy agents and targeted therapies, elevating therapeutic efficacy and curtailing side effects [27].

**Reversal of Drug Resistance:** Overcoming drug resistance poses a significant challenge in tumor treatment, which cell membrane-coated nanoparticles are poised to address. These nanoparticles, mirroring membrane proteins on tumor cell surfaces, interfere with drug resistance-associated pathways, such as the expression of multidrug resistance transporters. Clinical trials have demonstrated the potential of cell membrane-coated nanoparticles in reversing drug resistance, heightening drug sensitivity in tumor cells, and enhancing therapeutic efficacy.

**Immunotherapy Enhancement:** The role of cell membrane-coated nanoparticles extends to augmenting tumor immunotherapy. By enveloping immune cell membranes, these nanoparticles emulate surface markers of immune cells, like those present on antigen-presenting cells. This mimicry amplifies tumor antigen presentation and immune cell activation, bolstering the immune system's attack on tumors. Clinical trials have showcased the application of cell membrane-coated nanoparticles to enhance tumor immunotherapy, including tumor vaccines and CAR-T cell therapy.

While applying cell membrane-coated nanoparticles exhibits immense potential in clinical contexts, it confronts specific challenges. These encompass the refinement of nanoparticle preparation technologies for large-scale production, the imperative for drug stability and controlled release, and the evaluation of clinical safety and efficacy. Ongoing research endeavors and clinical trials will undoubtedly propel the utilization of cell membrane-encapsulated nanoparticles, fostering innovation and progress within the sphere of tumor treatment.

**Summary and Prospects:** Cell membrane-encapsulated nanoparticles present a promising avenue within tumor treatment. Their robust biocompatibility mitigates immune rejection and enhances drug accumulation and retention within tumor tissues. This property improves drug targeting precision, diminishes harm to normal cells, and bolsters therapeutic efficacy. Notably, the drug delivery capability of cell membrane-coated nanoparticles stands out. The cell membrane, as the nanoparticle's outer layer, confers tumor cell specificity. Tailoring the source of the cell membrane, whether tumor cells, immune cells, or stem cells, enables precise targeting across distinct tumor types, intensifying drug selectivity. Additionally, these nanoparticles offer excellent drug stability and controlled release. The cell membrane's protective function prevents drug degradation, extending drug effectiveness. Simultaneously, fine-tuning cell membrane characteristics enables gradual drug release, prolongs drug residence within tumor tissue, and heightens therapeutic impact.

Cell membrane-coated nanoparticles hold significant potential as an evolving strategy in targeted tumor therapy. Nevertheless, challenges persist, necessitating progress in preparation technology, biocompatibility, and clinical application. These challenges can be surmounted through rigorous research, innovation, and stringent clinical validation, propelling the broad application of cell membrane-encapsulated nanoparticles in tumor treatment. Future research shall focus on refining targeting strategies, developing multifunctional drug delivery systems, exploring controlled release methodologies, establishing quantitative evaluation and monitoring frameworks, and affirming clinical efficacy. Through steadfast research and innovation, cell membrane-encapsulated nanoparticles are poised to emerge as a pivotal strategy within tumor treatment, offering patients



more effective, precise, and personalized therapeutic avenues.

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## Conflict of interest

All the authors claim that the manuscript is completely original. The authors also declare no conflict of interest.

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