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HYBRID RED BLOOD CELL-TUMOR CELL MEMBRANE-COATED NANOPARTICLES FOR CANCER THERAPY: BIOLOGICAL PRINCIPLES, THERAPEUTIC APPLICATIONS, AND TRANSLATIONAL CHALLENGES

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ABSTRACT

With 9.7 million deaths reported in 2022 and approximately 20 million new cancer cases diagnosed annually, cancer-related mortality and disease burden remain major global health concerns. The development of targeted nanomedicines is driven by the limited specificity and systemic toxicity of conventional cancer therapies. Nanoparticles can enhance therapeutic efficacy by improving permeability, retention, and active cellular uptake. Among emerging biomimetic drug delivery strategies, coating nanoparticles with natural cell membranes, particularly those derived from red blood cells (RBCs) and cancer cells, has shown considerable promise. RBC membranes prolong circulation time, enhance biocompatibility, and facilitate immune evasion through their native membrane proteins and lipid composition. In contrast, tumor-specific antigens and adhesion molecules present on cancer cell membranes enable homologous targeting of tumor cells and may stimulate antitumor immune responses. Importantly, these biological functions can be preserved when cancer cell membranes are used as nanoparticle coatings. Hybrid membrane-coated nanoparticles, generated by combining RBC and tumor cell membranes, integrate the complementary advantages of both membrane types into a single delivery platform. Such systems have been investigated for a range of applications, including tumor targeting, drug delivery, and photodynamic therapy. In this review, we examine the characteristics of RBC and tumor cell membranes, their functional roles in nanoparticle coatings, and recent advances in hybrid membrane engineering. We discuss how hybrid membrane coatings enhance circulation time, targeting efficiency, and therapeutic outcomes while addressing key challenges related to manufacturing, membrane sourcing, scalability, and clinical translation. Collectively, the available evidence highlights the potential of hybrid membrane-coated nanoparticles as multifunctional platforms for cancer nanomedicine and underscores the need for further optimization to facilitate their large-scale production and clinical implementation.

Keywords: Cancer Nanomedicine; Red Blood Cell Membrane; Cancer Cell Membrane; Hybrid Membrane-Coated Nanoparticles; Targeted Drug Delivery; Biomimetic Nanoparticles.

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INTRODUCTION

Despite decades of advances in diagnostic technologies, surgical interventions, radiotherapy, and systemic therapies, cancer remains one of the leading causes of morbidity and mortality worldwide. In 2022 alone, the disease was responsible for approximately 9.7 million deaths, with nearly 20 million new cases diagnosed annually [1]. Although conventional therapeutic approaches have improved survival outcomes for several malignancies, many cancers remain difficult to treat effectively because of systemic toxicity,

poor drug selectivity, multidrug resistance, and inadequate penetration into tumor tissues. These limitations are particularly evident in aggressive and metastatic tumors, where treatment failure often results not from a lack of potent therapeutic agents but from the inability to deliver them precisely and safely to diseased tissues. Nanomedicine emerged, in part, as a response to these challenges [2]. By engineering drug delivery systems at the nanoscale, researchers sought to improve pharmacokinetic profiles, prolong circulation time, and enhance intratumoral drug accumulation while minimizing off-target toxicity [3]. Early nanoparticle-based systems demonstrated promising results in controlled drug release and passive tumor targeting through the enhanced permeability and retention (EPR) effect [4].

however, the clinical performance of many synthetic nanocarriers ultimately proved less transformative than initially anticipated. Following systemic administration, nanoparticles encounter numerous biological barriers, including opsonization, rapid clearance by the mononuclear phagocyte system, heterogeneous tumor vasculature, dense extracellular matrices, and inefficient cellular uptake. Collectively, these obstacles continue to limit therapeutic delivery efficiency in clinical oncology. Recognition of these limitations has gradually shifted research attention toward biomimetic nanotechnology [5].

Rather than attempting to evade biological systems through purely synthetic surface modifications, biomimetic approaches exploit naturally evolved cellular structures and functions to improve nanoparticle performance. Cell membrane-coated nanoparticles represent one of the most prominent examples of this strategy. By cloaking synthetic nanoparticle cores with natural cellular membranes, these systems inherit membrane-associated proteins, antigens, and signaling molecules capable of mediating immune interactions and tissue recognition in ways that conventional nanoparticles cannot easily replicate [6–8].

Among the various membrane sources investigated, red blood cell (RBC) membranes and tumor cell membranes have attracted considerable interest because they provide highly complementary biological functions. Erythrocyte membranes exhibit prolonged circulation and exceptional immune compatibility, largely mediated by membrane proteins such as CD47, which suppress macrophage-mediated phagocytosis [6,9]. In contrast, tumor cell membranes preserve tumor-associated antigens and adhesion molecules that facilitate homotypic targeting and selective interactions with homologous tumor tissues [10]. Individually, each membrane type offers significant advantages; however, neither alone fully addresses the complex challenges associated with effective cancer drug delivery.

This limitation has driven the development of hybrid membrane-coated nanoparticles. By integrating erythrocyte membranes with tumor-derived membranes, hybrid biomimetic nanoparticles seek to combine prolonged systemic circulation with active tumor targeting within a single multifunctional platform [11]. The rationale is compelling: immune camouflage may enhance nanoparticle persistence in circulation, while tumor membrane-mediated recognition may improve selective accumulation and intracellular delivery within malignant tissues. In principle, such systems could overcome several limitations that continue to restrict the clinical effectiveness of conventional nanomedicine (Figure 1) [12].

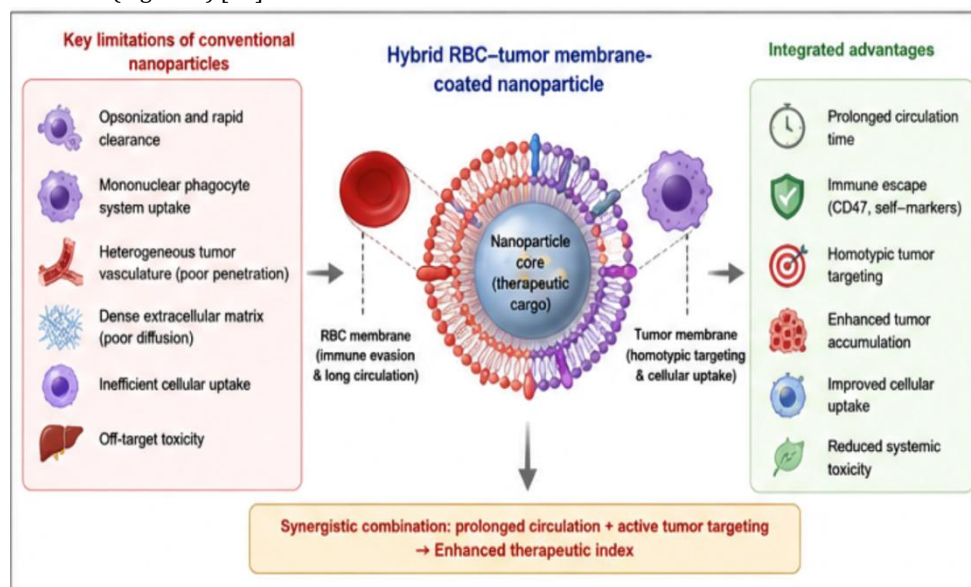


Figure 01: Rational and advantages of hybrid RBC-tumor membrane-coated nanoparticles.

The field has expanded rapidly in recent years. Hybrid membrane-coated nanoparticles have been investigated in a wide range of applications, including chemotherapy, photothermal therapy, photodynamic therapy, immunotherapy, gene delivery, and theranostics [13,14]. Numerous preclinical studies have reported improved pharmacokinetic behavior, enhanced tumor accumulation, and reduced systemic toxicity compared with uncoated nanoparticles or single-membrane systems. At the same time, the increasing complexity of these biomimetic platforms has introduced new translational challenges related to manufacturing scalability, membrane reproducibility, biosafety, immunogenicity, and regulatory classification (Figure 01).

Importantly, the field remains in an early stage of development. Many experimental findings continue to rely heavily on simplified animal models that may not fully recapitulate the vascular heterogeneity, stromal architecture, and immune complexity of human tumors. Consequently, enthusiasm surrounding hybrid biomimetic nanoparticles must be balanced against the substantial challenges that remain before their widespread clinical implementation becomes feasible [15].

This review examines the biological principles, fabrication strategies, therapeutic applications, and translational challenges associated with hybrid red blood cell-tumor membrane-coated nanoparticles in cancer nanomedicine. Particular emphasis is placed on the mechanisms underlying immune evasion and homotypic targeting, current therapeutic applications, manufacturing limitations, biosafety considerations, and future directions for clinical translation. Collectively, these systems illustrate how modern nanomedicine

is increasingly moving toward biologically integrated therapeutic platforms designed not merely to carry therapeutic agents but to interact dynamically with complex disease environments.

BIOMIMETIC NANOPARTICLES IN CANCER NANOMEDICINE

Nanomedicine was initially envisioned as a solution to one of oncology's most persistent challenges: delivering highly potent therapeutics to tumors while minimizing systemic toxicity. The concept appeared straightforward. Nanoparticles could theoretically protect therapeutic cargo during circulation, improve drug solubility, prolong systemic retention, and preferentially accumulate within tumors through the enhanced permeability and retention (EPR) effect. In practice, however, biological systems proved far less accommodating than early theoretical models suggested [16,17].

Upon entering the bloodstream, synthetic nanoparticles encounter a highly complex physiological environment. Plasma proteins rapidly adsorb onto nanoparticle surfaces, forming protein coronas that alter biodistribution and accelerate immune recognition. Macrophages in the liver and spleen efficiently remove many circulating particles before meaningful tumor accumulation can occur. Even nanoparticles that successfully reach tumors face additional obstacles, including abnormal vasculature, elevated interstitial pressure, dense extracellular matrices, and heterogeneous cellular uptake. Consequently, despite encouraging experimental findings, the clinical benefits of many conventional nanocarriers have remained relatively modest [18,19].

These limitations prompted a broader reassessment of nanoparticle design strategies. Rather than relying exclusively on synthetic surface modifications such as polyethylene glycol (PEG)ylation or ligand conjugation, researchers increasingly turned to biological mimicry as a more adaptive means of overcoming physiological barriers. Biomimetic nanoparticles emerged from this conceptual shift. Instead of attempting to disguise nanoparticles artificially, biomimetic systems exploit naturally evolved cellular structures that already possess sophisticated immune and tissue-interaction capabilities [20].

Cell membrane-coated nanoparticles represent one of the most significant developments within this field. In these systems, synthetic nanoparticle cores are cloaked with membranes derived from natural cells, enabling them to inherit membrane-associated proteins, receptors, antigens, and signaling molecules from their source cells [6]. This biological interface fundamentally alters how nanoparticles interact with the immune system and surrounding tissues. In many respects, membrane coating transforms nanoparticles from passive delivery vehicles into biologically interactive platforms [21].

Different membrane sources confer distinct functional advantages. Red blood cell membranes, for example, are particularly effective in promoting immune evasion because erythrocytes naturally circulate for extended periods without triggering significant immune clearance. This behavior is mediated in part by CD47 signaling, which suppresses macrophage phagocytosis through interaction with signal regulatory protein alpha (SIRP α) receptors. Consequently, nanoparticles coated with RBC membranes exhibit prolonged circulation times and reduced uptake by the mononuclear phagocyte system [6,22].

Other membrane sources offer entirely different benefits. Cancer cell membranes preserve tumor-associated antigens and adhesion molecules involved in homotypic cellular recognition, thereby enabling selective interactions with tumors of similar cellular origin [10]. Platelet membranes contribute vascular adhesion properties and facilitate interactions with circulating tumor cells, whereas macrophage membranes may promote inflammatory homing and enhanced penetration into the tumor microenvironment [23]. Each membrane source provides a unique biological functionality that can be therapeutically exploited.

Importantly, biomimetic nanotechnology represents more than a technical modification of nanoparticle engineering. It reflects a broader conceptual transition within nanomedicine. Conventional nanoparticle systems often rely on simplified engineering assumptions, such as the belief that longer circulation automatically improves delivery or that smaller particle size necessarily enhances tissue penetration. Biological systems are rarely so predictable. Biomimetic approaches acknowledge this complexity by incorporating naturally evolved biological mechanisms directly into therapeutic design (Figure 02) [24].

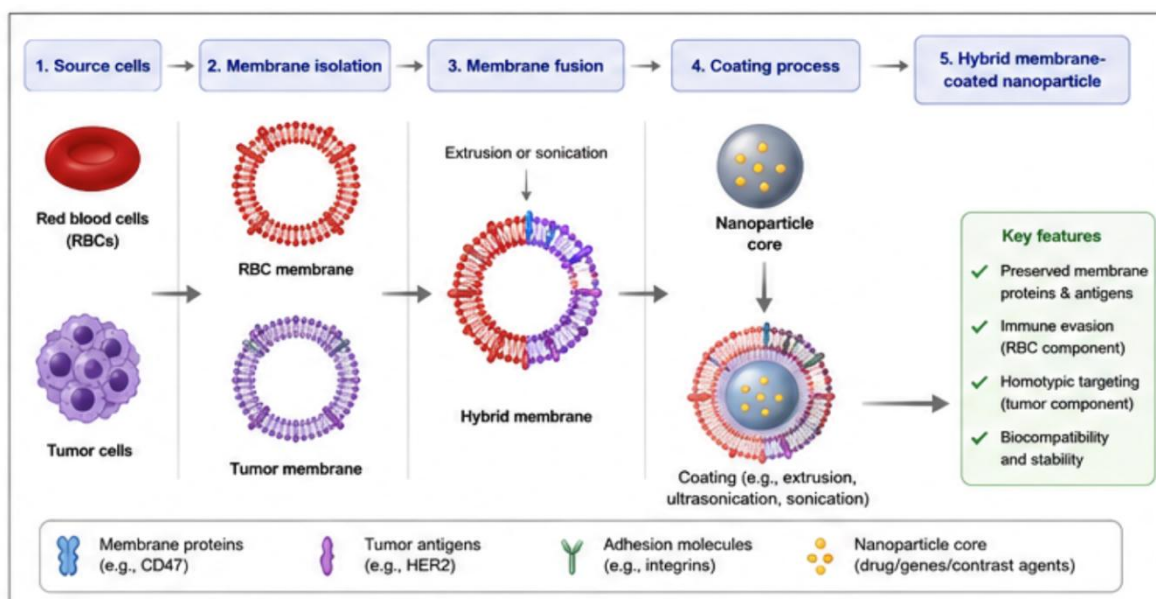


Figure 02: Fabrication strategies for hybrid RBC-tumor membrane-coated nanoparticles

Despite their promise, significant challenges remain. Membrane-coated nanoparticles are biologically more sophisticated than traditional synthetic systems, but this sophistication introduces additional sources of variability. Membrane composition can differ among cell populations, membrane extraction procedures may compromise protein orientation and integrity, and large-scale manufacturing remains technically demanding [25]. Furthermore, many proposed targeting mechanisms have been validated primarily in murine tumor models that may not accurately reproduce the heterogeneity and immunological complexity of human cancers.

Another important consideration is that biomimicry alone does not guarantee therapeutic success. Prolonged circulation may increase tumor exposure, but it does not necessarily overcome poor vascular penetration or inefficient intracellular drug release. Likewise, homotypic targeting may enhance tumor interactions under controlled experimental conditions while remaining less predictable in clinically heterogeneous tumors. Such nuances are becoming increasingly important as the field advances toward translational and clinical applications [26].

Nevertheless, momentum in biomimetic nanomedicine continues to grow rapidly. Advances in membrane engineering, microfluidic fabrication, immunotherapy, and precision oncology are steadily expanding the capabilities of membrane-coated nanoparticle systems. What was once considered a niche biomaterials strategy is gradually emerging as a central focus of contemporary cancer nanotechnology research (Figure 03) [27].

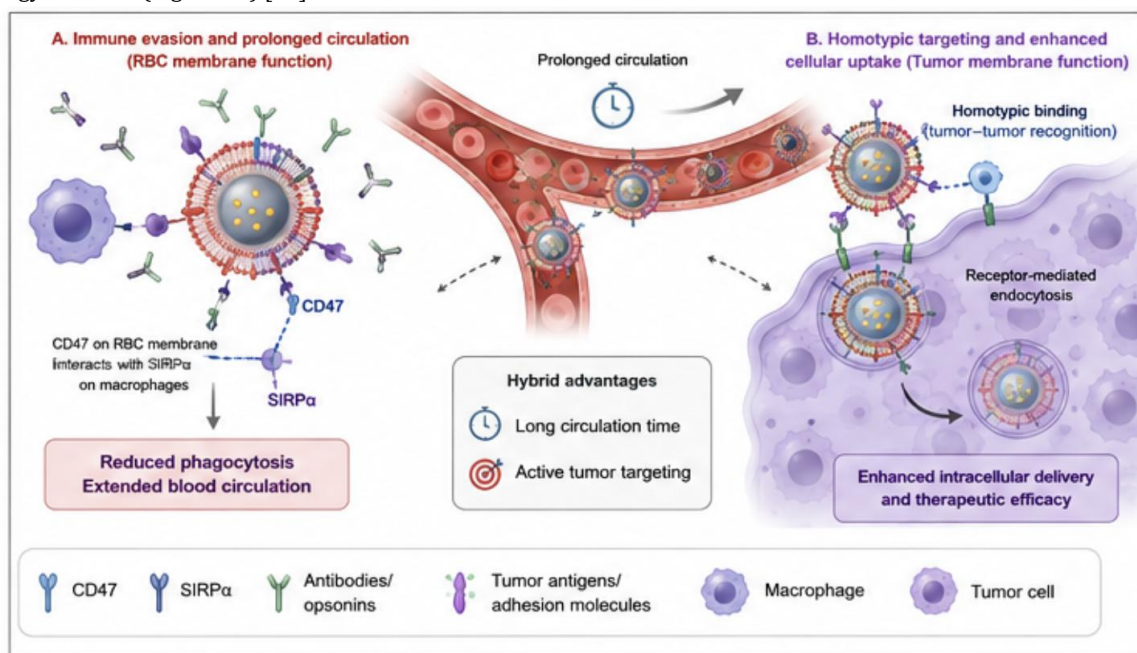


Figure 03: Biological mechanisms of hybrid RBC-tumor membrane-coated nanoparticles.

Within this evolving landscape, hybrid membrane-coated nanoparticles have emerged as particularly attractive platforms because they seek to integrate multiple biological functions simultaneously. By combining the complementary properties of different membrane sources, these systems aim to address several delivery barriers concurrently rather than individually. Among these approaches, nanoparticles coated with both red blood cell membranes and tumor cell membranes represent one of the most extensively investigated and biologically rational designs in contemporary biomimetic nanomedicine [8].

The complementary strengths and limitations of individual membrane sources have motivated the development of increasingly sophisticated biomimetic platforms. Among these, RBC membrane-coated nanoparticles and tumor membrane-coated nanoparticles represent two foundational strategies that ultimately converged in the design of hybrid membrane systems.

RED BLOOD CELL MEMBRANE-COATED NANOPARTICLES

Red blood cells (RBCs) are remarkably efficient biological carriers. They circulate continuously for approximately 120 days while largely avoiding immune recognition, mechanical destruction, and rapid clearance by macrophages. From a nanomedicine perspective, such biological stability is highly attractive. Consequently, erythrocyte membranes became one of the earliest and most extensively investigated membrane sources in biomimetic nanoparticle engineering [6,9].

The appeal of RBC membranes extends beyond their inherent biocompatibility. Erythrocyte membranes possess a highly specialized surface architecture composed of phospholipids, glycoproteins, membrane-associated proteins, and carbohydrate structures that collectively maintain cellular flexibility and immune tolerance throughout circulation. Among these components, CD47 has received particular attention because of its critical role in immune evasion. By interacting with signal regulatory protein alpha (SIRPα) receptors on macrophages, CD47 transmits a “don’t eat me” signal that suppresses phagocytosis and reduces immune-mediated clearance (Figure 4) [6].

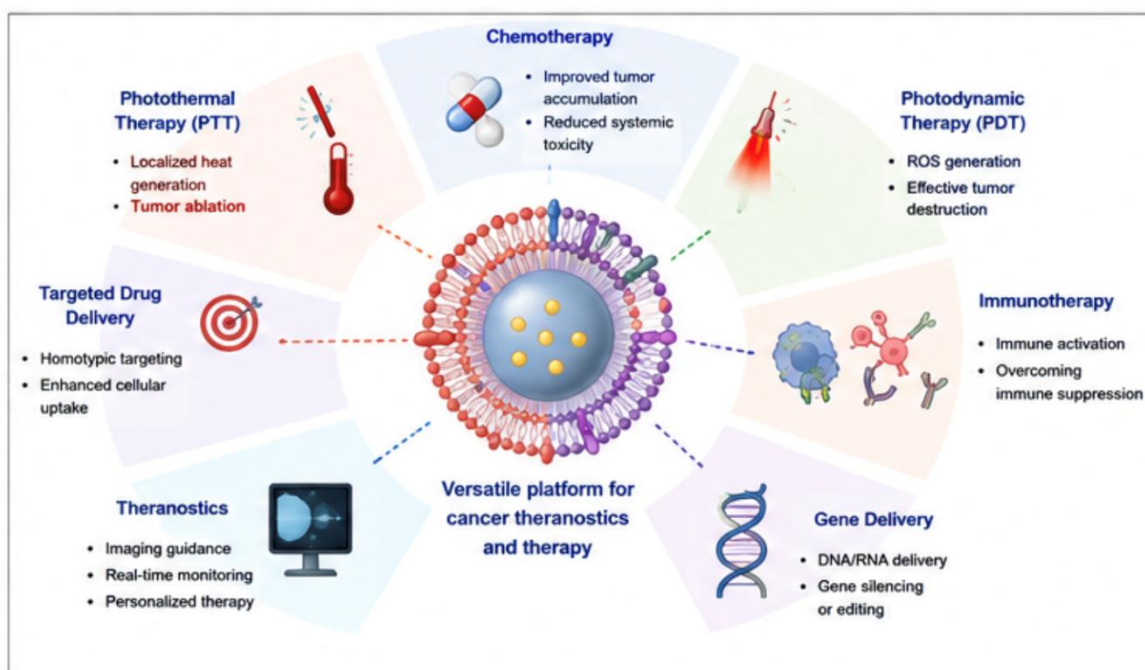


Figure 04: Therapeutic applications of hybrid RBC-tumor membrane-coated nanoparticles.

This mechanism forms the foundation of RBC membrane-coated nanotechnology. When erythrocyte membranes are transferred onto nanoparticle surfaces, they partially retain these endogenous immune-regulatory properties. As a result, synthetic nanoparticles acquire a biological camouflage that enables prolonged circulation and reduced recognition by the mononuclear phagocyte system. Compared with many conventional nanocarriers, RBC membrane-coated nanoparticles consistently demonstrate lower macrophage uptake and extended systemic retention in vivo [9].

This advantage is particularly important because one of the major limitations of conventional nanomedicine is the inefficient delivery of nanoparticles to tumor tissues. A substantial proportion of administered nanoparticles is rapidly sequestered by the liver and spleen within hours of systemic administration. Therefore, extending circulation time increases the likelihood that nanoparticles will encounter and accumulate within tumor tissues, particularly in highly vascularized malignancies where the enhanced permeability and retention (EPR) effect remains partially operative [28].

Beyond immune evasion, RBC membranes offer several practical advantages for biomedical applications. Mature erythrocytes are abundant, relatively easy to isolate, and lack nuclei and intracellular organelles, thereby reducing concerns regarding genetic material transfer and intracellular contamination. Furthermore, their membranes exhibit considerable mechanical flexibility, enabling efficient coating of a wide range of nanoparticle cores, including polymeric, metallic, and mesoporous nanomaterials [29].

Despite these advantages, RBC membrane-coated nanoparticles are not without limitations. Prolonged circulation alone does not guarantee effective tumor targeting. One of the primary criticisms of RBC-based systems is their heavy reliance on passive accumulation mechanisms. Tumor delivery depends largely on vascular permeability and circulation time rather than active biological recognition. This

limitation becomes particularly significant in poorly vascularized tumors or highly heterogeneous tumor microenvironments, where passive accumulation may be insufficient to achieve therapeutic efficacy [9,30].

To address these shortcomings, researchers have explored various strategies, including ligand conjugation, receptor-mediated targeting, and hybrid membrane engineering. While these approaches may improve tumor specificity, they also increase structural complexity and can partially compromise the simplicity and biocompatibility that originally made RBC membranes attractive [6].

Another challenge that deserves greater attention is the preservation of membrane integrity during nanoparticle fabrication. The biological functionality of RBC-coated nanoparticles depends heavily on maintaining membrane protein orientation and structural stability throughout membrane extraction, purification, and coating procedures. Improper processing may disrupt membrane asymmetry, denature membrane proteins, or diminish CD47 activity, thereby weakening immune-evasion capabilities and reducing therapeutic performance. Although membrane functionality is frequently discussed in the literature, relatively few studies have comprehensively characterized how fabrication conditions influence biological behavior at the molecular level [9,31,32].

Nevertheless, RBC membrane-coated nanoparticles remain among the most influential innovations in biomimetic nanomedicine. Their success demonstrated that improving nanoparticle performance does not necessarily require increasingly sophisticated synthetic modifications. Instead, leveraging naturally evolved cellular systems may provide a more effective strategy for overcoming biological barriers than attempting to engineer entirely artificial solutions from the ground up [9,33].

This realization has significantly influenced the evolution of biomimetic nanotechnology and paved the way for more

advanced membrane-engineering strategies, including hybrid membrane systems designed to integrate prolonged circulation with active tumor targeting within a single multifunctional platform.

CANCER CELL MEMBRANE-COATED NANOPARTICLES

If red blood cell membranes provide immune camouflage, cancer cell membranes provide biological recognition. This distinction fundamentally transformed the way researchers approached biomimetic targeting strategies. Conventional targeted nanoparticles typically rely on individual ligands, antibodies, or receptor-specific modifications to recognize tumor tissues. Although such approaches offer selectivity in theory, tumor biology is rarely simple enough for a single receptor or signaling pathway to determine therapeutic success. Tumors are highly heterogeneous, dynamic, and continuously evolve under selective pressures. Consequently, a targeting strategy that is effective in one cellular population may prove ineffective in another.

Cancer cell membranes introduced an alternative strategy [34]. Rather than engineering isolated targeting ligands onto nanoparticle surfaces, researchers began utilizing entire tumor-derived membranes that naturally preserve complex arrays of membrane proteins, adhesion molecules, glycans, and tumor-associated antigens. This approach creates a biologically representative interface that more closely resembles native tumor cells than most synthetic targeting systems can achieve [10,35].

One of the most important properties retained within tumor cell membranes is homotypic targeting. Tumor cells originating from the same tissue source frequently exhibit preferential self-recognition mediated by adhesion molecules such as cadherins, integrins, epithelial cell adhesion molecule (EpCAM), galectins, and Thomsen–Friedenreich antigens [31]. When these membrane components remain intact following membrane extraction and nanoparticle coating, they can facilitate selective interactions between membrane-coated nanoparticles and homologous tumor tissues.

In essence, tumors can help nanoparticles locate tumors [32,36]. This concept attracted considerable attention because it provided a biologically intuitive targeting mechanism without requiring extensive synthetic surface engineering. Numerous preclinical studies have demonstrated that cancer cell membrane-coated nanoparticles exhibit enhanced uptake by source tumor cells compared with uncoated nanoparticles or nanoparticles coated with unrelated membranes [10]. Increased intratumoral retention and improved intracellular delivery have also been reported across multiple experimental models.

Despite these promising findings, homotypic targeting is likely more complex than initially assumed. Many experimental investigations employ highly controlled murine tumor models in which identical source and target cell lines are used. Under such conditions, selective recognition can appear remarkably efficient. Human tumors, however, are substantially more heterogeneous. Membrane protein expression may vary not only among patients but also among different regions of the same tumor. Furthermore, metastatic lesions often diverge biologically from primary tumors during disease progression.

As a result, the consistency and reliability of homotypic targeting in clinically relevant cancers remain uncertain [37, 38].

This uncertainty is particularly important because reproducible targeting performance ultimately determines translational value.

Another significant advantage of cancer cell membranes is their potential role in immune modulation. Tumor-derived membranes retain tumor-associated antigens capable of interacting with antigen-presenting cells and stimulating adaptive immune responses [39]. Consequently, cancer membrane-coated nanoparticles may function not only as drug delivery vehicles but also as immunologically active therapeutic platforms. This dual functionality has become increasingly relevant as immunotherapy continues to reshape modern oncology.

Several research groups have explored cancer membrane-coated nanoparticles as nanovaccines capable of enhancing dendritic cell activation and cytotoxic T-cell responses. Others have combined tumor membrane coatings with immune checkpoint inhibitors, photothermal therapy, or immunostimulatory adjuvants to amplify systemic antitumor immunity [40]. These combination approaches reflect a broader trend in oncology, where therapeutic strategies are becoming increasingly integrated rather than operating as isolated treatment modalities [41].

At the same time, tumor-derived membranes introduce biosafety concerns that are largely absent in RBC membrane-based systems.

Unlike erythrocytes, tumor cells possess highly abnormal molecular signatures. Residual oncogenic proteins, mutated antigens, inflammatory mediators, or intracellular contaminants may persist following membrane isolation if purification procedures are incomplete [25]. Although most preclinical studies report acceptable short-term safety profiles, the long-term biological and immunological consequences of exposure to tumor-derived membrane components remain insufficiently understood.

A further challenge arises from the intrinsic variability of tumor membranes.

Even well-characterized tumor cell lines can undergo phenotypic drift during prolonged culture, altering membrane composition and potentially affecting targeting performance. Patient-derived membranes introduce an even greater degree of variability. Although personalized membrane systems may improve targeting specificity, they simultaneously complicate manufacturing standardization, quality control, scalability, and regulatory evaluation. This balance between personalization and reproducibility may ultimately become one of the defining translational challenges in biomimetic nanomedicine [42].

Despite these limitations, cancer cell membrane-coated nanoparticles have significantly expanded the conceptual boundaries of targeted drug delivery. They demonstrated that biological targeting does not necessarily require single-receptor precision. Instead, preserving the complexity of natural cellular interfaces may, in some cases, prove more effective than reducing targeting to isolated molecular interactions [43].

This realization ultimately inspired the development of hybrid membrane engineering strategies aimed at combining the prolonged circulation and immune compatibility of erythrocyte membranes with the targeting capabilities of tumor-derived membranes within a single multifunctional nanosystem.

HYBRID RED BLOOD CELL-TUMOR MEMBRANE-COATED NANOPARTICLES

By the time researchers began combining red blood cell membranes with tumor cell membranes, a broader realization had emerged within nanomedicine: no single membrane source could effectively address every biological barrier associated with drug delivery.

RBC membranes excel at immune evasion and prolonged circulation, whereas tumor cell membranes provide selective recognition and homotypic targeting. Individually, each membrane type addresses only part of the therapeutic challenge. Hybrid membrane engineering emerged as an effort to integrate these complementary biological functions into a single nanoscale platform [11].

Conceptually, the strategy is highly attractive.

If erythrocyte membranes can reduce immune clearance while tumor membranes enhance selective tumor interactions, then combining the two should theoretically produce nanoparticles capable of prolonged circulation, improved tumor accumulation, and more efficient delivery of therapeutic cargo than either system alone. This rationale rapidly propelled hybrid membrane-coated nanoparticles to the forefront of biomimetic nanotechnology research [8].

Importantly, these systems are not merely physical mixtures of membranes. Their biological behavior depends heavily on the interactions that occur following membrane fusion. Factors such as membrane ratios, protein orientation, membrane integrity, and nanoparticle core composition can significantly influence biological performance in ways that remain only partially understood [25]. In many respects, hybrid biomimetic nanoparticles function less like conventional drug carriers and more like engineered biological interfaces.

Fabrication generally involves three principal stages: membrane isolation, membrane fusion, and nanoparticle coating. Erythrocyte and tumor cell membranes are first collected separately through centrifugation, hypotonic lysis, washing, and purification procedures designed to preserve membrane-associated proteins and structural integrity. The isolated membranes are subsequently fused using techniques such as extrusion, sonication, electroporation, or, increasingly, microfluidic assembly methods [44].

Each fabrication strategy offers distinct advantages and limitations.

Extrusion remains one of the most widely employed methods because of its simplicity and ability to produce relatively uniform membrane coatings. However, repeated mechanical extrusion may disrupt membrane protein orientation or damage delicate membrane structures. Sonication-based approaches simplify membrane coating but may expose proteins to thermal and mechanical stress. Microfluidic technologies have attracted increasing attention because they provide greater control over membrane fusion and

nanoparticle uniformity, although large-scale implementation remains technically challenging [45].

An often-overlooked aspect of these systems is their biological fragility.

The functionality of hybrid nanoparticles depends not only on successful membrane fusion but also on preserving the biological activity of membrane-associated proteins throughout fabrication. A nanoparticle may appear structurally intact under transmission electron microscopy while simultaneously losing critical immune-evasion or targeting functions at the molecular level. This discrepancy between physical characterization and biological functionality remains an underappreciated challenge within the field.

Nevertheless, preclinical findings have been highly encouraging [8,46].

Numerous studies have reported that hybrid membrane-coated nanoparticles outperform both uncoated nanoparticles and single-membrane systems with respect to circulation stability, tumor accumulation, and therapeutic retention [11,47]. In photothermal therapy models, for example, hybrid-coated nanoparticles demonstrated prolonged circulation combined with enhanced tumor localization following near-infrared irradiation. Similar benefits have been observed in chemotherapy, photodynamic therapy, immunotherapy, and gene delivery applications.

A major advantage of these systems lies in their multifunctionality. Hybrid nanoparticles do not rely on a single biological mechanism. Instead, they simultaneously integrate immune camouflage, homotypic targeting, antigen presentation, and controlled therapeutic delivery within a single platform. In principle, this multifunctional behavior may enable more effective management of the complex and multifactorial nature of tumor biology than narrowly targeted systems. However, increased complexity introduces new challenges [48, 49].

As these nanoparticles become more biologically sophisticated, they also become more difficult to standardize, manufacture, and regulate. Hybrid membrane systems introduce additional sources of variability, including membrane source selection, fusion efficiency, membrane composition, and preservation of functional proteins. Even minor fabrication differences may significantly alter biodistribution, targeting efficiency, and therapeutic performance. Such variability becomes particularly problematic when attempting to scale production beyond controlled laboratory environments [35].

A broader translational question also remains unresolved: how much biological complexity is clinically practical?

Highly personalized and multifunctional systems may demonstrate impressive experimental performance, but successful clinical implementation depends equally on reproducibility, manufacturability, cost-effectiveness, and regulatory feasibility. A nanoparticle platform may be biologically sophisticated yet still fail clinically if it cannot be produced consistently and safely at scale [50].

Despite these challenges, hybrid membrane-coated nanoparticles remain among the most promising developments in contemporary cancer nanomedicine. More importantly, they reflect a broader shift in therapeutic design philosophy. Rather than viewing biological systems solely as obstacles to

overcome, these platforms seek to cooperate with endogenous cellular mechanisms to enhance therapeutic performance. This conceptual transition may ultimately influence the future direction of biomimetic therapeutics not only in oncology but across a wide range of biomedical applications [25,32,39].

TRANSLATIONAL CHALLENGES AND CLINICAL CONSIDERATIONS

Although hybrid membrane-coated nanoparticles demonstrate encouraging preclinical performance, the field remains dominated by proof-of-concept studies conducted in relatively simplified animal models. Many investigations rely on rapidly growing subcutaneous tumors that do not accurately reproduce the stromal complexity, vascular heterogeneity, and immune landscape of human malignancies. Consequently, the extent to which current findings will translate into meaningful clinical benefit remains uncertain and requires further validation in more clinically relevant models.

Despite the remarkable progress achieved in the development of hybrid red blood cell-tumor membrane-coated nanoparticles, substantial barriers continue to hinder their translation from laboratory research to clinical practice. While many preclinical studies report encouraging therapeutic outcomes, the pathway from proof-of-concept experiments to approved clinical products remains complex and uncertain.

One of the most significant challenges is manufacturing reproducibility. Unlike conventional synthetic nanoparticles, hybrid membrane-coated systems are composed of biological materials whose composition may vary according to cell source, isolation procedures, culture conditions, and processing techniques. Such variability can affect membrane protein content, membrane integrity, fusion efficiency, and biological functionality. Consequently, achieving consistent batch-to-batch production remains considerably more difficult than for traditional nanomedicine formulations [25,51].

This issue becomes increasingly important during scale-up.

Laboratory-scale production often relies on methods such as membrane extrusion, sonication, and centrifugation, which may be suitable for small experimental batches but are difficult to standardize for large-scale manufacturing. Commercial translation will require robust, reproducible, and scalable production processes capable of maintaining membrane integrity and biological functionality while complying with regulatory quality standards. Although advances in microfluidic technologies and automated manufacturing systems offer promising solutions, these approaches remain under active development [45,52].

Another critical challenge concerns quality control and characterization. Conventional nanoparticle formulations can typically be characterized through measurements of particle size, surface charge, morphology, and drug-loading efficiency. Hybrid membrane-coated nanoparticles, however, possess an additional layer of biological complexity. Comprehensive characterization requires not only physical analysis but also confirmation of membrane composition, protein orientation, membrane fusion efficiency, and preservation of biological activity. At present, universally accepted standards for evaluating these parameters remain limited, creating challenges for both researchers and regulatory agencies [53].

Biosafety considerations represent another important translational concern. Although erythrocyte membranes are generally regarded as highly biocompatible, tumor-derived membranes introduce additional uncertainties. Residual intracellular components, oncogenic proteins, inflammatory mediators, or other biologically active molecules may persist if purification procedures are incomplete. While current preclinical studies have not demonstrated significant safety concerns, long-term investigations remain limited, and the potential consequences of repeated administration have not yet been fully elucidated [54].

Immunogenicity presents a similarly complex issue. Biomimetic nanoparticles are often described as immune-compatible because they utilize endogenous cellular materials. However, biological compatibility should not be assumed universally. Variations in membrane source, donor characteristics, tumor heterogeneity, and manufacturing procedures may influence immune recognition and immunological responses. Furthermore, repeated administration could potentially induce adaptive immune responses that alter therapeutic efficacy over time. These considerations highlight the need for comprehensive immunological evaluation during preclinical and clinical development [55].

Regulatory classification represents another unresolved challenge. Hybrid membrane-coated nanoparticles occupy a unique position at the intersection of biologics, medical devices, and pharmaceutical products. Their complex composition complicates regulatory evaluation because existing frameworks were not designed specifically for multifunctional biomimetic systems. Questions regarding source material standardization, quality assurance, safety testing, and product classification remain under active discussion. Regulatory uncertainty may therefore become a significant factor influencing the pace of clinical translation [56].

Patient-specific applications introduce additional opportunities and challenges. Personalized membrane-coated nanoparticles derived from patient tumors may enhance targeting specificity and therapeutic effectiveness. However, individualized manufacturing substantially increases production complexity, cost, quality-control requirements, and regulatory burden. Determining whether the therapeutic advantages of personalized systems justify these practical challenges remains an important question for future clinical development [57].

Importantly, translational success depends not only on technological innovation but also on realistic clinical applicability. Nanoparticle systems that demonstrate exceptional performance in controlled experimental settings may still encounter obstacles related to manufacturing feasibility, economic sustainability, clinical workflow integration, and regulatory approval. Consequently, future research must balance biological sophistication with practical considerations to ensure successful implementation in clinical oncology [58].

FUTURE PERSPECTIVES

Emerging technologies such as CRISPR-based genome engineering, synthetic membrane biology, and machine-

learning-assisted nanoparticle design may further expand the capabilities of hybrid biomimetic systems. These approaches could enable the rational development of next-generation membrane-coated nanoparticles with programmable biological functions tailored to specific tumor types and therapeutic objectives.

The rapid evolution of hybrid membrane-coated nanoparticles reflects a broader transformation occurring throughout nanomedicine. Rather than relying exclusively on synthetic engineering approaches, researchers are increasingly integrating biological principles into therapeutic design. This convergence of nanotechnology, cell biology, immunology, and materials science is expected to shape the next generation of cancer therapeutics.

One promising direction involves the refinement of membrane engineering technologies. Current hybrid membrane systems largely depend on naturally occurring membrane compositions. Future approaches may incorporate selective membrane modification strategies designed to enhance specific biological functions while preserving overall biocompatibility. Advances in genetic engineering, synthetic biology, and membrane functionalization may enable the creation of customized membrane interfaces optimized for particular therapeutic applications [59].

Microfluidic manufacturing platforms are also expected to play an increasingly important role. Precise control over membrane fusion, nanoparticle assembly, and formulation consistency may improve reproducibility while facilitating large-scale production. Such technologies could help address one of the most persistent obstacles facing biomimetic nanomedicine: the transition from laboratory-scale fabrication to clinically relevant manufacturing processes [45].

The integration of hybrid nanoparticles with immunotherapy represents another highly promising area of investigation. Modern oncology increasingly recognizes that effective cancer treatment requires not only direct tumor destruction but also modulation of the immune system. Hybrid membrane-coated nanoparticles are uniquely positioned to contribute to this objective because they combine targeted delivery capabilities with the potential for antigen presentation and immune activation. Future strategies may incorporate immune checkpoint inhibitors, cytokines, nucleic acid therapeutics, or personalized cancer vaccines within multifunctional biomimetic platforms [60].

Artificial intelligence and computational modeling may further accelerate development. Predictive algorithms capable of analyzing membrane composition, nanoparticle behavior, pharmacokinetics, and tumor interactions could improve formulation design while reducing reliance on empirical trial-and-error approaches. Such computational tools may facilitate the optimization of membrane combinations, therapeutic cargo selection, and patient-specific treatment strategies [61].

Personalized biomimetic nanomedicine also remains an attractive long-term objective. Advances in tumor profiling, genomic sequencing, and precision oncology may eventually enable the routine production of patient-specific membrane-coated nanoparticles tailored to the molecular characteristics of individual tumors. While significant manufacturing and

regulatory challenges remain, the concept aligns closely with broader trends toward individualized cancer treatment [62].

At the same time, future progress will require a deeper understanding of the biological mechanisms underlying nanoparticle behavior in vivo. Although hybrid membrane systems demonstrate promising therapeutic performance, many aspects of their interactions with immune cells, vascular systems, extracellular matrices, and tumor microenvironments remain incompletely understood. Addressing these knowledge gaps will be essential for improving predictability, safety, and clinical efficacy [63].

Ultimately, the future success of hybrid membrane-coated nanoparticles will depend on achieving a balance between biological complexity and translational practicality. The most effective systems may not necessarily be those with the greatest number of functionalities but rather those that provide meaningful clinical benefit while remaining manufacturable, reproducible, safe, and economically viable.

CONCLUSION

Hybrid red blood cell-tumor membrane-coated nanoparticles represent one of the most innovative developments in contemporary cancer nanomedicine. By integrating the prolonged circulation and immune-evasion properties of erythrocyte membranes with the homotypic targeting and antigenic characteristics of tumor cell membranes, these biomimetic platforms seek to address several major limitations that continue to restrict the effectiveness of conventional nanoparticle-based therapies.

The development of these systems reflects a broader conceptual shift in nanomedicine. Rather than viewing biological processes solely as barriers to therapeutic delivery, hybrid membrane-coated nanoparticles exploit naturally evolved cellular mechanisms to improve circulation stability, tumor recognition, and therapeutic performance. This strategy has generated considerable interest because it combines engineering precision with biological functionality in a manner that conventional synthetic systems often struggle to achieve.

Preclinical studies have demonstrated encouraging results across a wide range of therapeutic applications, including chemotherapy, photothermal therapy, photodynamic therapy, immunotherapy, gene delivery, and theranostics. Enhanced circulation time, improved tumor accumulation, reduced systemic toxicity, and multifunctional therapeutic capabilities have consistently been reported. These findings suggest that hybrid membrane engineering may provide meaningful advantages over both traditional nanocarriers and single-membrane biomimetic systems.

Nevertheless, important challenges remain before widespread clinical implementation can be realized. Manufacturing scalability, quality control, biosafety evaluation, immunogenicity assessment, regulatory classification, and long-term reproducibility continue to represent significant obstacles. Furthermore, many current findings are derived from experimental models that may not fully capture the biological complexity and heterogeneity of human cancers.

Future progress will depend on interdisciplinary collaboration among researchers in nanotechnology, oncology, immunology, materials science, bioengineering, and regulatory science.

Advances in membrane engineering, microfluidic manufacturing, precision medicine, and computational modeling are expected to further improve the design and translational potential of these systems. Equally important will be the establishment of standardized characterization methods and clinically relevant evaluation frameworks capable of supporting regulatory approval and commercial development. In conclusion, hybrid red blood cell–tumor membrane-coated nanoparticles represent a promising and rapidly evolving platform at the intersection of nanotechnology and biology. Although significant scientific and translational challenges remain, hybrid red blood cell–tumor membrane-coated nanoparticles represent a compelling paradigm in biomimetic nanomedicine and may contribute to the development of safer, more selective, and more effective cancer therapies in the coming decades.

ABBREVIATIONS

RBC, Red blood cell; EPR, Enhanced permeability and retention; SIRPα, Signal regulatory protein α; MPS, Mononuclear phagocyte system; PTT, Photothermal therapy; PDT, Photodynamic therapy; ECM, Extracellular matrix; EpCAM, Epithelial cell adhesion molecule.

DECLARATIONS AND STATEMENTS

This study did not involve human or animal subjects; therefore, institutional review board (IRB) approval and informed consent were not required.

ETHICS

A review article does not require ethics committee approval.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

MMHA and IMHA collected the articles and drafted the manuscript, while NÖ reviewed, revised, and finalized the manuscript.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DECLARATIONS

Authors hereby declare that generative AI technologies such as Large Language Models and text-to-image generators have not been used during the writing. Chat GPT is used only for grammar checking and graphical abstract generation.

CONCENT FOR PUBLICATION

Not applicable

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