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REVIEW

Membrane-derived biomimetic nanovesicles in anti-tumor immunotherapy: Advances and outlook

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Abstract Membrane-derived biomimetic nanovesicles have emerged as a promising platform in cancer immunotherapy due to their intrinsic biocompatibility, functional plasticity, and capability to modulate immune responses. By integrating various immunotherapeutic agents, including immune checkpoint inhibitors, tumor antigens, and immunostimulatory adjuvants, these vesicles can be engineered to mimic natural immune communication and overcome key barriers in the tumor immune microenvironment. This review summarizes recent advances in the design, functionalization, and application of biomimetic

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Nanovaccine;
Immune checkpoint inhibitor;
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nanovesicles for anti-tumor immunity. We particularly highlight strategies that harness these vesicles to enhance innate and adaptive immune responses, reverse immune suppression, and synergize with existing immunotherapy modalities. Furthermore, we discuss the challenges associated with biosafety, large-scale manufacturing, and clinical translation. Continued innovation in vesicle engineering and immunological modulation will be crucial for transforming biomimetic nanovesicles into viable next-generation cancer immunotherapeutics.

1. Introduction

As researchers continue to reveal the complex mechanisms by which the immune system, including both innate and adaptive immunity, the tumor microenvironment (TME), recognize and eliminate cancer cells. Significant progress has been made in the development immunotherapeutic strategies aimed at manipulating the immune system and overcoming tumor evasion. Tumor cells have evolved various complex mechanisms to escape immune surveillance and suppression, such as recruiting immunosuppressive cell populations, and upregulating inhibitory immune checkpoints. All of these can weaken the effective anti-tumor immune responses[1-3]. To counteract their mechanisms, a series of immune system manipulation methods targeting the immunological characteristics of different tumor types have been proposed. These methods include targeted cytokine therapies that the activity of immune cells, immune checkpoint inhibitors (ICIs), cancer vaccines, oncolytic viruses, etc[4-6]. Over the past decade, significant progress has been made in both preclinical research and clinical applications of cancer immunotherapy. It is worth noting that various types of tumors, especially hematological malignancies, have demonstrated significant clinical responses to immunotherapeutic interventions[7-10]. However, despite these encouraging achievements, the wide application of immunotherapy still faces several limitations[11]. Response rates vary greatly, and the exact mechanisms underlying treatment efficacy and resistance are not yet fully understood.

In the clinical application of cancer immunotherapy, current challenges include unpredictable potential toxicities, inconsistent therapeutic efficacy, and limited treatment response rates. Among the most concerning adverse events are a series of immune-related adverse effects (irAEs) and cytokine release syndrome. Both of these will significantly affect patient safety and treatment outcomes[12,13]. The occurrence and development of irAEs are mainly associated with ICI therapies and are believed to arise from autoreactive T cell infiltration and the subsequent release of pro-inflammatory cytokines[14]. These toxicities can affect almost any organ system, including the skin, gastrointestinal tract, endocrine glands, and nervous system, with skin reactions being the most commonly reported[15-19]. Addressing these adverse effects is a major focus of current research, aiming to optimize treatment plans, establish comprehensive prevention strategies, and develop predictive models for patient-specific toxicity risk. Furthermore, a thorough understanding of the pathophysiological mechanisms behind these toxic reactions is critical for improving toxicity management and guiding future treatment design[4,20]. In addition to toxicity, the efficacy of immunotherapy also varies and often difficult to predict[21]. This variability is evident in several aspects: the same immunotherapeutic agent may exhibit dramatically different response rates across distinct tumor types; even within the same tumor type, patients at different disease stages may respond differently; and in many cases, patients initially responsive to therapy eventually relapse after partial immunotherapy is effective due to acquired resistance[22-25]. To overcome these limitations, researchers are actively investigating biomarkers and predictive strategies to identify patients who are most likely to benefit from immunotherapy[26,27].

The unfavorable and heterogeneous responses observed in cancer immunotherapy are closely associated with the presence of immunosuppressive cytokines and regulatory cell populations within the TME[28,29]. One of the major unresolved challenges in the field is the function plasticity of anti-tumor T cells, particularly the mechanisms underlying T cell dysfunction and exhaustion, as well as their interplay with cytokine networks[30]. Exhausted T cells progressively lose their effector functions and upregulate multiple inhibitory receptors, such as PD1, CTLA4, TIM3 and LAG3[31-33]. During the process of tumorigenesis and tumor metastasis, the increased expression of these inhibitory molecules, the expansion of immunosuppressive immune subsets, and the downregulation of effector cytokines collectively contribute to immune evasion and therapeutic resistance[34,35]. Key immunosuppressive cell populations, represented by neutrophils, regulatory T cells, and especially tumor-associated macrophages (TAMs) play pivotal roles in facilitating tumor growth, invasion and metastasis[36-38]. TAMs, in particular, can polarize toward an M2-like phenotype, secreting anti-inflammatory cytokines and promoting angiogenesis and stromal remodeling. Therefore, ongoing research is increasingly focused on revealing the complex immune−tumor interaction network[39,40]. Identifying the specific cellular components, signaling pathways, and soluble mediators that drive immunosuppression within the TME is critical for the rational design of next-generation immunotherapies aimed at revitalizing anti-tumor immunity.

Immunoglobulins, or antibodies, are soluble glycoproteins characterized by their high specificities and affinity for corresponding antigens[41]. The introduction of mAb technology in 1975 marked a turning point in oncology, enabling targeted therapies that significantly improved both diagnostic accuracy and therapeutic efficacy. This breakthrough has laid the foundation for several transformative cancer immunotherapy models, including ICIs, tumor vaccines, and adoptive cell transfer therapies[42]. Despite these advances, the clinical efficacy of antibody-based therapies still faces limitations such as rapid clearance, suboptimal tumor accumulation, and off-target toxicity. To overcome these hurdles, the integration of nanotechnology with antibody therapeutics has emerged as a powerful strategy[43]. There are many advantages for nanoparticles in the application of cancer treatments. Nanoparticles can improve pharmacokinetics by

prolonging circulation half-life, enhancing tumor accumulation *via* the enhanced permeability and retention (EPR) effect, and allowing for co-delivery of multiple agents[44-47]. Our team once developed an exosome-like sequential-bioactivating prodrug nanoplatform, showed satisfied efficacy in amplifying prodrug bioactivation, prolonging blood circulation, selectively targeting of homotypic tumor cells, and enhancing tumor penetration[48]. In addition to this passive accumulation, nanoparticles can be tailored for active targeting by decorating their surfaces with affinity ligands, such as monoclonal antibodies, peptides, aptamers or small molecules, that bind to specific tumor-associated receptors[41,49,50]. However, for nanocarrier drugs more suitable for circulation and concentration in the complex internal environment of the human body, researchers have begun to make nanoparticles interact more effectively with biological systems by making nanomaterials simulate cellular functions, especially in the field of immune recognition and systemic clearance. This has led to the development of biomimetic nanocarriers, particularly those cloaked in natural or engineered cell membranes[51-54]. We once constructed an extracellular vesicles-mediated self-propelled liposome containing monensin and photosensitizer pyropheophorbide-a, leading to deep tumor penetration and enhanced phototherapeutic efficacy[55]. By leveraging cell membrane-coating techniques, researchers have created nanoparticles that retain surface proteins and functional characteristics from source cells, enabling immune evasion, enhanced biocompatibility, and homotypic targeting capabilities[56-59]. Our team also designed a nanovaccine based on dendritic cell (DC) cytomembrane, enabled spatiotemporally synchronous cytokine delivery[60]. These membrane-derived nanovesicles, encompassing red blood cell (RBC) membranes, leukocyte membranes, cancer cell membranes, bacterial outer membrane vesicles, and even hybrid membranes, are collectively referred to as membrane-derived biomimetic nanovesicles[61-64].

Compared with other nanoscale delivery systems, biomimetic nanovesicles exhibit distinctive advantages. Exosomes, for example, are naturally secreted extracellular vesicles with endogenous biological relevance and intrinsic communication functions, but they are limited by heterogeneity, low yield, and challenges in large-scale production[65,66]. Unlike exosomes, biomimetic nanovesicles reconstructed from source cell membranes preserve native membrane proteins while offering greater flexibility in design, enhanced scalability, and broader opportunities for surface functionalization. Similarly, traditional lipid-based nanocarriers such as liposomes and lipid nanoparticles (LNPs) represent important synthetic benchmarks, while liposomes act as classical bilayer systems and LNPs optimized for nucleic acid delivery[67]. However, both of them lack the complexity of biological membranes and cannot inherently reproduce immune evasion or ligand−receptor interactions. Biomimetic nanovesicles bridge this gap by combing the structural stability of lipid bilayers with biocoding functions, enabling unique properties such as prolonged circulation, homologous targeting, and regulation of the tumor immune microenvironment. Membrane-derived biomimetic nanovesicles represent a promising new platform that differs from exosomes and traditional artificial nanocarriers, providing unique opportunities for functional customization and therapeutic development.

These platforms have multiple therapeutic advantages: low immunogenicity, prolonged systemic retention, selective tumor targeting, and the ability to interact with the immune system in a more appropriate manner. These properties have catalyzed their application in personalized cancer immunotherapy, particularly when combined with tumor-specific antibodies or ligands[68]. With the advancement of biotechnology, researchers can now bind antibodies or other recognition components to the surface of biomimetic nanovesicle, thereby creating a hybrid drugs that can be concluded as membrane-derived biomimetic nanovesicles. These constructs not only retain the inherent advantages of both components but also offer the flexibility for multi-target design, immune activation, and modulation of the TME, potentially enhancing therapeutic efficacy while minimizing systemic toxicity[69-71].

In recent years, the engineered membrane-derived biomimetic nanovesicles showed great potential in both preclinical models and early clinical trials, extending their ability from hematological malignancies to a various solid tumors[72]. In this review, we will summarize the basic design principles and biological advantages of these engineered platforms. We will also discuss the current strategies used for surface antibody expression and vesicle preparation, and explore their roles in overcoming tumor immune escape and enhancing anti-tumor immunity, as illustrated in Fig. 1.

2. Optimal parameters of engineered membrane-derived biomimetic nanovesicle and their advantages

The therapeutic effects of membrane-derived biomimetic nanovesicles are closely influenced by a series of biochemical parameters, including vesicle size, shape, surface charge, hydrophobicity, membrane roughness, and compositional complexity[73-75]. These characteristics collectively determine the behavior of nanovesicles *in vivo*, affecting their circulation time, biodistribution, cellular uptake, and immunomodulatory capacity[76,77]. In this section, we systematically discuss these critical design parameters and explore how to optimize each factor to significantly enhance the effectiveness of cancer immunotherapy. Understanding and fine-tuning these variables not only improves delivery efficiency and tumor targeting but also contributes to minimizing systemic toxicity and promoting precise immune activation.

2.1. *Impact of particle size*

The particle size of nanoparticles plays a critical role in determining their cellular uptake pathways, *in vivo* clearance rates, and overall biodistribution characteristics within biological systems[78]. Generally speaking, nanoparticles within the 20−200 nm size range are considered optimal for exploiting the EPR effect, allowing them to penetrate into tumor tissue while avoiding rapid renal clearance (<20 nm) or isolation by the reticuloendothelial system (>200 nm)[79,80]. Moreover, nanoparticles with more than 500 nm diameter are more likely to be swallowed, and an increased risk of adverse events such as pulmonary capillaries blockage[81,82]. Studies on synthetic nanocarriers, including liposomes and polymeric nanoparticles, have consistently shown that smaller vesicles (<100 nm) can penetrate tissues more effectively, whereas larger vesicles (>200 nm) exhibit prolonged circulation but reduced tumor penetration[83]. The range above strikes a balance between avoiding renal filtration, minimizing phagocyte uptake, and enhancing passive targeting through the EPR effect in tumor tissues[84,85]. The ideal size distribution for nanoparticles is illustrated in Fig. 2.

Beyond these general principles, membrane-derived biomimetic nanovesicles exhibit unique size-related characteristics,

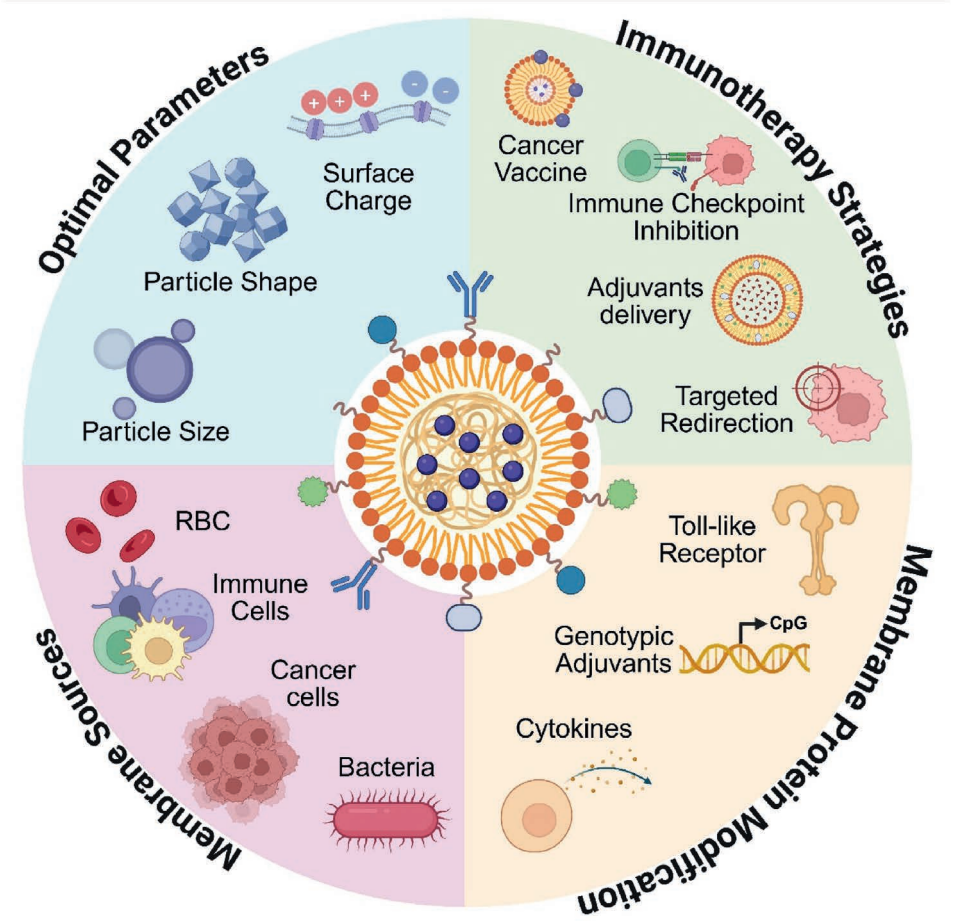


Figure 1 Schematic illustration of the main sections of this review. Created with BioRender.com.

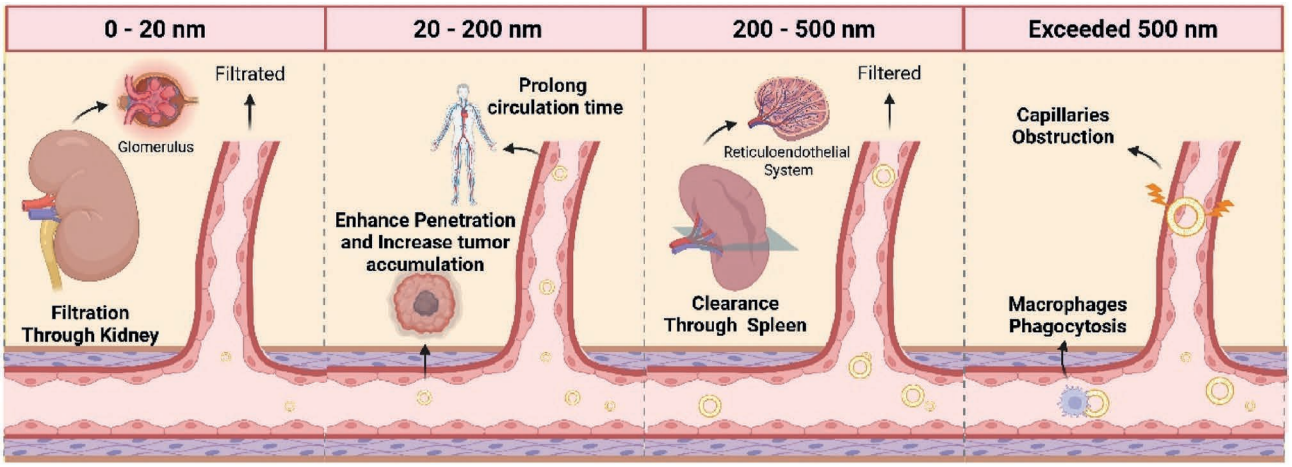


Figure 2 Schematic illustration of the preferred size range (20−200 nm) for biomimetic nanoparticles to optimize circulation time and tumor accumulation while minimizing renal and splenic clearance. Created with BioRender.com.

which are formed by their parental cell sources and preparation method, rather than artificial design[79]. For instance, RBC-derived nanovesicles typically exhibit relatively uniform sizes around 100−150 nm, reflecting their stable membrane structure, which helps to prolong circulation and immune evasion[86]. Another study designed and compared RBC membrane-derived nanoparticles in four distinct sizes; they indicated that different-sized RBC membrane nanovesicles did not cause significant immunogenic response differences, but smaller particles exhibited longer systemic retention[87]. Cancer cell-derived nanovesicles are often relatively larger and more heterogeneous, which enhances their homotypic adhesion and tumor accumulation[88]. In contrast, DC-

derived vesicles are usually less than 150 nm, show enhanced lymph node transport and strong antigen-presenting capability, thereby more efficiently promoting T-cell activation.

In conclusion, these findings indicate that although membrane-derived nanovesicles generally follow size-principles rules established in nanoparticles, their functional significance is closely related to their membrane origin. Rather than acting as a purely adjustable parameter, size in biomimetic nanovesicles reflects inherited biological properties that determine circulation behavior, targeting specificity, and immune activation potential. This emphasizes the need to consider size not in isolation but in combination with the unique molecular features conferred by the source membrane.

2.2. *Impact of particle shape*

The morphology of nanoparticles plays a special role in mediating their cellular internalization, biodistribution, and therapeutic efficacy[89]. Various nanoparticle shapes, including spheres, rods, cubes, and stars, have been systematically studied to evaluate their influence on cellular uptake and *in vivo* behavior. Fig. 3A and B shows some typical sphere and cube nanoparticles[89,90]. Among these, spherical nanoparticles are the most commonly used due to their thermodynamic stability, as they require the lowest free energy for self-assembly. This stable structure helps to prolonged circulation and uniform organ biodistribution[90]. However, deviations from the spherical form may offer unique advantages in certain contexts. For example, high aspect ratio rods can increase contact area with cell membranes, thus significantly enhanced internalization efficiency into HeLa cells compared to cylindrical or disc-shaped particles[90]. In contrast, other investigations have reported that spherical particles internalize more efficiently, underscoring cell-type and context-dependence[76].

Beyond simple spheres and rods, cubes, discs, stars, tetrahedral DNA-framework hybrids, and even hexagonal nanosheets such as layered double hydroxides have revealed that the critical parameters such as local curvature and edge density are essential for modulating ligand accessibility, receptor clustering, and intracellular transportation, such as tetrahedral DNA-framework hybrids shown in Fig. 3C and hexagonal nanosheets Fig. 3D[91-93]. In response to the increasing demand for smart, responsive drug delivery systems, deformable or shape-adaptive constructs further add a temporal dimension. Stimuli-responsive hydrogels or hybrid architectures that swell, soften, or reconfigure in response to matrix metalloproteinase-2, pH, or redox cues can accelerate release or switch uptake pathways in the TME[94-96], an enzymatically controlled microswimmer has shown in Fig. 3E. These findings show that shape is not a passive feature but a determinant of how nanomedicine engages with cellular function.

For membrane-derived biomimetic nanovesicles, shape considerations should be integrated with membrane-derived features. Because they preserve native proteins from their source cells, the same change in curvature can also reorganize CD47, integrins, cadherins, or major histocompatibility complex (MHC) complexes on the surface, thereby regulating biological recognition. For example, cancer membrane coated rods may present homotypic adhesion molecules such as CD44 and E-cadherin, over an enlarged contact interface, promoting tumor-specific binding and retention. As demonstrated in cancer cell membrane-coated nanoparticles that exhibit enhanced homotypic targeting and tumor suppression[88]. Meanwhile, spherical RBC membrane vesicles can maintain CD47 clustering on low-curvature surfaces to reduce opsonization and phagocytic uptake, consistent with findings that shape and rigidity affect CD47-mediated 'self' signaling, and that CD47 clustering in lipid rafts enhances binding to SIRPA, amplifying the 'don't-eat-me' signal[97,98]. DC derived nanovesicles with mildly anisotropic shapes may facilitate immune synapse-like interfaces to interact T cells more effectively[99]. Similarly, biomimetic nanovesicles with elongated shape may marginate toward the inflamed endothelium and exploit ICAM1/VCAM1 interactions[100]. These bio-structural combinations differentiate membrane-derived biomimetic nanovesicles from synthetic carriers, suggesting that the particle shape is tightly consistent with membrane resource and receptor topology.

While these innovations are promising, the impact of nanoparticle shape on biological performance remains an emerging field of study[101]. Although the morphology is linked to transportation and uptake, the presence of native membrane proteins and glycans enables the shape to become a biologically active design variable in membrane-derived biomimetic nanovesicles. Future optimization should therefore combine morphology and membrane composition together to the intended mechanism, such as circulatory stealth, homotypic targeting, or immune synapse formation, to elevate immunotherapeutic outcomes[102-104].

2.3. *Impact of particle surface charge*

Surface charge is a critical parameter that influences several key properties of nanoparticles, including cellular internalization, colloidal stability, and *in vivo* biodistribution. Generally, nanoparticles with a positive surface charge tend to have higher internalization efficiency due to the electrostatic attraction between the positively charged particles and the negatively charged cell membrane. This property helps the cell absorb therapeutic agents, especially in cancer cells with high content of surfaces anions. However, despite their improved uptake, positively charged nanoparticles also bring significant challenges. Studies have demonstrated that a strong positive surface charge is associated with increased both cytotoxicity and systemic toxicity, as it can disrupt cell membranes and induce nonspecific interactions with serum proteins and non-target tissues[105,106]. Moreover, the positively charged nanoparticles often result in rapid conditioning and clearance by the mononuclear phagocyte system (MPS), thereby significantly shortening the circulation time of the particles *in vivo*[107].

For membrane-derived biomimetic nanovesicles, surface charge is not simply an artificial design choice but also reflects the biochemical properties of the parental cell membranes. For example, RBC membranes are enriched in sialic acid-bearing glycophorins, which impart a natural negative charge and hydrophilic glycocalyx, thereby reducing nonspecific protein adsorption and prolonging circulation[108]. Cancer cell membranes, by contrast, often display heterogeneous charge distributions shaped by adhesion molecules and altered lipid compositions, which can enhance homotypic binding and tumor accumulation[109]. Immune cell membranes, such as those from DCs and T cells, exhibit charge features linked to receptor clustering and immune synapse formation, directly influencing T-cell activation and antigen presentation[110,111]. These inherited electro properties show that the functional outcomes of biomimetic nanovesicles depend not only on size or surface chemistry but also on the unique charge signatures encoded by their membrane origin.

These natural characteristics are matched with engineered charge-modulation strategies. Many biomimetic strategies now

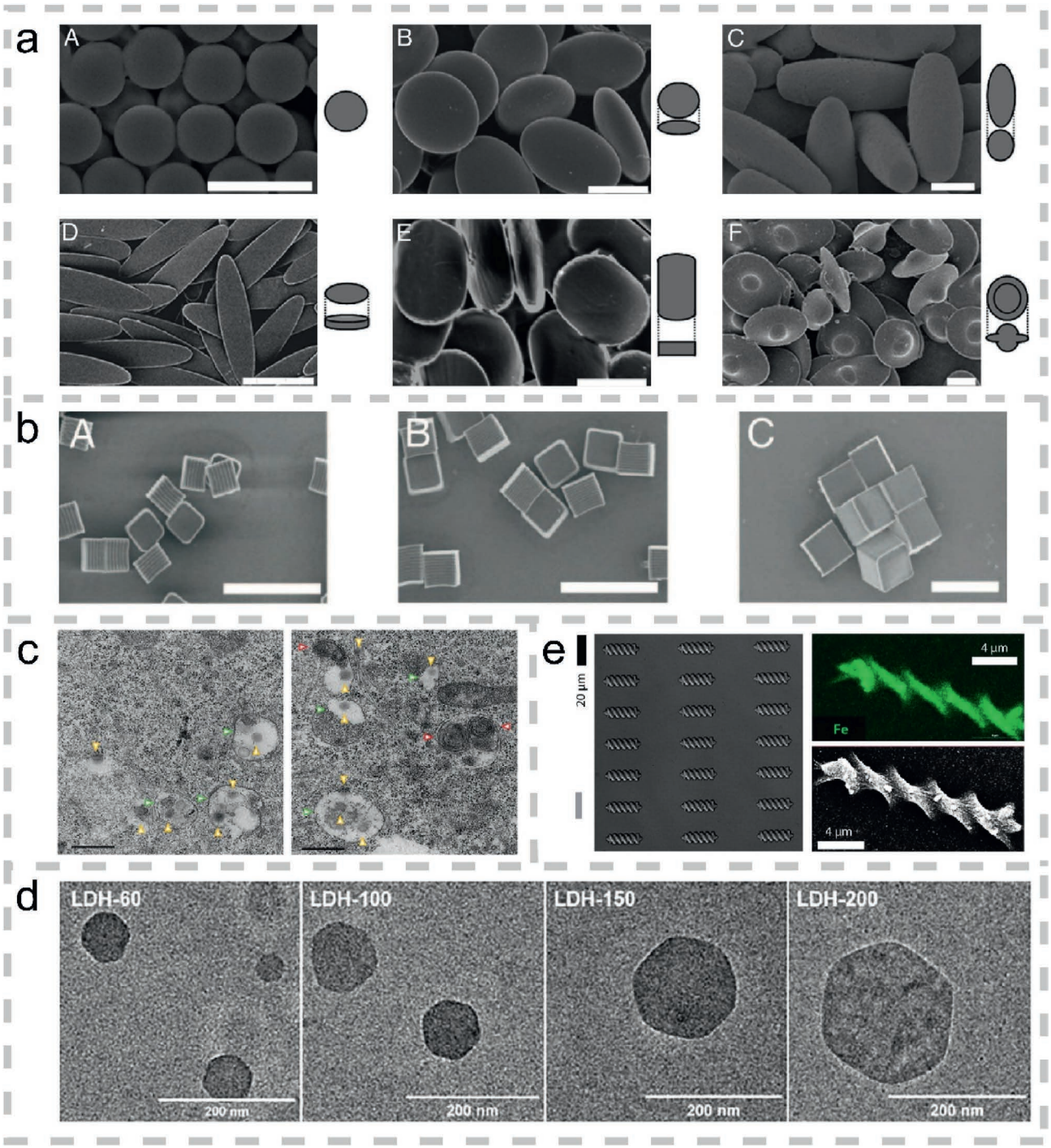


Figure 3 (a) Scanning electron micrographs for some typical nanoparticles with different shapes: A. Spheres; B. Oblate ellipsoids; C. Prolate ellipsoids; D. Elliptical disks; E. Rectangular disks; F. UFOs[89]. Reproduced with permission from Ref. 89. Copyright © 2025, National Academy of Sciences. (b) Scanning electron micrographs for some cubic particles with diameters equal to A: 2 μm, B: 3 μm, C: 5 μm[90]. Reproduced with permission from Ref. 90. Copyright © 2025, National Academy of Sciences. (c) TEM images showing the cell ultrastructure with TDN@GNP treatment. Yellow arrows represent TDN@GNP[91]. Reproduced with permission from Ref. 91. Copyright © 2025, John Wiley and Sons. (d) Transmission electron microscopy (TEM) images of layered double hydroxide nanoparticles with different size distributions[93]. Reproduced with permission from Ref. 93. Copyright © 2025, John Wiley and Sons. (e) Optical microscope differential interference contrast image of microswimmer and the enzymatically controlled drug release from the hydrogel microswimmers[96]. Reproduced with permission from Ref. 96. Copyright © 2025, American Chemical Society.

favor neutral or slightly negative surface charges to improve biocompatibility, as their reduced protein adsorption allows for extended circulation and more effective exploitation of the EPR effect[107,112]. One study fabricated a series of lipid nanovesicles with varying surface charges and reported that those bearing a negative surface potential demonstrated modestly superior performance in both blood circulation and tumor accumulation[113]. Because most plasma proteins carry a net negative charge, the strong electrostatic attraction between these proteins and positively charged nanovesicles is a major factor contributing to the rapid clearance of cationic nanocarriers. In contrast, nanovesicles with a slightly negative surface charge are less prone to nonspecific protein adsorption, thereby maintaining prolonged circulation *in vivo*[114,115]. This extended circulation time allows negatively charged nanovesicles to exploit the EPR effect more effectively[116]. These mechanisms together maintain higher bioavailability and improve the likelihood of therapeutic delivery to the TME.

On this basis, surface charge properties have been further utilized in the design of stimuli-responsive nanocarriers. One promising strategy involves design nanovesicles with reversible surface charges, enabling them to respond to environmental stimuli such as pH[117-120]. Such responsive strategies allow nanovesicles to in a relatively neutral or weakly negative during circulation, thereby avoiding nonspecific clearance, and only convert to a positively charged state within the acidic TME, thereby enhancing tumor uptake. When combined with the intrinsic charge features of a specific membrane source, this dynamic regulation provides a refined approach for precise cancer treatment[121].

In summary, the biophysical and biochemical parameters of engineered membrane-derived biomimetic nanovesicles, such as particle size, shape, and surface charge, play vital roles in determining their pharmacokinetics, tumor-targeting efficiency, and immunotherapeutic performance. Although these vesicles inherit complex biological features of their source membranes, the *in vivo* behavior still broadly follows the general physicochemical principles of nanoparticles, such as size-dependent distribution and charge-mediated clearance. A comprehensive understanding and reasonable design of these parameters are essential to optimize their clinical translation and efficacy in cancer immunotherapy. While engineering strategies lay the foundation for constructing functional biomimetic nanovesicles, their therapeutic efficacy ultimately depends on how they interact with the immune system. Therefore, we will focus on clarifying the immune mechanisms activated by these nanovesicles and pay particular attention to their ability to regulate both innate and adaptive immune responses.

3. Engineered membrane-derived biomimetic nanovesicle anti-tumor immunotherapy strategies

Owing to their ability to inherit the properties of natural cell membrane, and achieves membrane-related cellular and molecular signaling, engineered membrane-derived biomimetic nanovesicles exhibit excellent biocompatibility, immune evasion capabilities, and the potential for precise immunological targeting[122,123]. These vesicles can actively engage in membrane-mediated cellular communication and molecular signaling, enabling them to circulate *in vivo* with prolonged half-life and target tumor tissues more effectively.

In recent years, a growing body of research has explored the potential of membrane-derived biomimetic nanovesicles in cancer immunotherapy[72,124]. In this section, we will review recent advances in this field, focusing on the classification and therapeutic mechanisms of these nanovesicles based on their surface antigen profiles and functional modifications. We broadly categorized current strategies into four major approaches: therapeutic cancer vaccine (TCV), ICIs, immune adjuvant delivery systems, and targeted redirection of immune responses. Table 1[60,88,125-143] summarizes the representative studies of each strategy. It is worth noting that these immunotherapy strategies are not mutually exclusive—many innovative biomimetic nanoplatforms integrate multiple modalities to synergistically enhance anti-tumor efficacy and overcome the limitations of single-agent immunotherapies.

Table 1 Studies and strategies on the anti-tumor immunotherapy of engineered membrane-derived biomimetic nanovesicle antibodies.

Author	Tumor	Anti-tumor strategy		Antibody	Membrane source	Ref.
		Strategy	Target			
Reuven EM	$Neu5Gc^+$ tumors	TCV	–	–	RBC	125
Alexander S Cheung	–	TCV	–	–	Cancer cell	126
Lukasz J Ochyl	–	TCV	–	–	DC	127
Wen-long Liu	Breast cancer	TCV	–	–	Hybrid cell membrane	128
Chao Liu	Melanoma	TCV/ICI	PDL1	PD1	DC	129
Christopher D Pack	Breast cancer	TCV/ICI	CTLA4	aCTLA4 mAb	Cancer cell	130
Yuanwei pan	Breast cancer	TCV/ICI	PDL1	CD40L/PD1	Cancer cell	131
Qian-Fang Meng	Melanoma/breast cancer	ICI	CD47/PDL1	SIRPA × PD-1 BiAn	Hybrid cell membrane	132
Luyao Zhang	Breast cancer	ICI	CD47/PDL1	SIRPA × PD-1 BiAn	HEK293 cell	133
Lang Rao	Melanoma	ICI	CD47	SIRPA	Hybrid cell membrane	134
C Wang	Melanoma/breast cancer	ICI	PDL1	PD-1	Platelets	135
Liyan Li	Melanoma	ICI	PDL1	PD1/CD64	HEK293T cell	136
M Jung	Melanoma	ICI	αCTLA4	aCTLA-4 mAb	DC	137
Chenchen Zhao	Breast cancer	ICI	PDL1	PD1	Hybrid cell membrane	138
Lei Ding	Breast cancer	ICI	PDL1	PD1	CHO cell	139
Rui Chen	$PDL1^+$ tumor	ICI/targeted redirection	PDL1/CD3	PD1 × aCD3 BiAn	HEK293T cell	140
Fang Xu	$PDL1^+$ tumor	ICI/targeted redirection	PDL1/CD19	PD1 × aCD19 BiAn	DC	141
Y Li	HCC	ICI/targeted redirection	CD47/GPC3	SIRPA × aGPC3 BiAn	OMV	142
X Sun	–	Adjuvant delivery/TCV	–	–	RBC	143
Kaiyuan Wang	Breast cancer	Adjuvants delivery/TCV	–	–	DC	60
Ronnie H Fang	–	Adjuvants delivery/TCV	–	–	Cancer cell	88

3.1. Therapeutic cancer vaccine (TCV)

Over the past few decades, cancer vaccines have been extensively explored in both basic research and clinical research, reflecting their potential as a promising approach in cancer immunotherapy[144]. The immune system is capable of monitoring tumorigenesis through a process known as immune surveillance, during which it recognizes tumor-associated antigens (TAAs) presented within the TME[145]. A critical function of cancer vaccines is to properly mimic the presentation state of professional antigen-presenting cells (APCs), transmitting key immunological signals to properly activate and direct immune effector cells towards tumor elimination[146].

Cancer vaccines can be broadly categorized into prophylactic cancer vaccines (PCVs) and TCVs[147]. PCVs are primarily designed based on tumor-specific or TAAs and are designed to improve immune surveillance and prevent tumor initiation. Several PCVs have already entered preclinical studies and early-phase clinical trials for specific cancer types[148,149]. In contrast, TCVs aim to enhance ongoing anti-tumor immune responses by activating and expanding tumor-specific immune cells. TCVs have been widely tested in patients with advanced-stage cancers. However, their clinical efficacy remains limited and inconsistent[145,150,151]. Several challenges may lead to poor clinical efficacy of TCVs. These include: poor antigenic targets, immunosuppressive properties of the TME, the absence of potent immunostimulatory adjuvants, and an insufficient number of activated immune cells entering the tumor core[152,153]. In response to these challenges, recent research has focused on optimizing vaccine formulations, delivery platforms, and antigen selection to enhance therapeutic outcomes[154,155]. Among the various delivery platforms, lipid-based nanoparticles have become common carriers for cancer vaccines due to their biocompatibility and efficient delivery capabilities. More recently, membrane-derived biomimetic nanovesicles have attracted much attention because they can utilize endogenous cell membrane components, enabling them to simulate natural cellular communication and recognition pathways[156,157]. These vesicles exhibit reduced immunogenicity and toxicity, prolonged circulation times, and enhanced tumor targeting. Leveraging their biomimetic properties, these nanovesicles are expected to become the next-generation cancer vaccine carriers, offering a flexible and effective strategy for therapeutic cancer immunity[158].

Generally speaking, the role of TCVs can be classified into two main categories: those targeting specific TAAs and those aiming to elicit responses against a broad spectrum of tumor antigens[159,160]. The latter strategy has received increasing attention due to the high heterogeneity and antigenic diversity in cancer cells. To address this complexity and preserve the full antigenic profile of tumor cells, Cheung et al.[126] developed a novel immunogenic subcellular vesicular particle derived from the membranes of cancer cells. This novel vesicular particle preserved multiple tumor antigens inherited from the parental cancer cells, thereby maintaining the original antigenic diversity and stimulating a powerful antigen-specific immune response. This approach takes advantage of the inherent advantage of biomimetic vesicles and can present a naturally complex antigen map to the immune system. Based on this strategy, Ochyl et al.[127] further enhanced the immunostimulatory capacity of such biomimetic nanovaccines incorporating the Toll-like receptor 4 (TLR4) agonist monophosphoryl lipid A (MPLA). As illustrated in Fig. 4A by pretreating membrane-derived immune cells MPLA, they successfully amplified T cell activation, indicating that rational adjuvant integration can further potentiate the immunogenicity of these vesicles. Except for protein antigens, the altered glycosylation patterns on tumor cells provide another source of tumor-specific epitopes[161]. Sialic acid (Sia), particularly *N*-glycolylneuraminic acid (Neu5Gc), is often abnormally expressed in malignant tissues, giving rise to tumor-specific glycan neoantigens[162]. Reuven et al.[125] exploited this abnormal glycosylation pattern as a target for cancer vaccines and synthesized biomimetic glyconanoparticles expressing Neu5Gc-glycoconjugates that successfully induced robust and durable anti-Neu5Gc immune responses, as shown in Fig. 4B, highlighting the potential of tumor-associated glycans as promising vaccine targets.

In addition to targeting tumor antigens, some cancer vaccine strategies have focused on simultaneously promoting antigen presentation and immune cell activation through innovative membrane engineering approaches. For instance, Liu and colleagues[128] developed a unique vaccine platform using reprogrammed cytomembranes derived from fusing cells created by the hybridization of DCs and tumor cells, as shown in Fig. 4C. This fusion process enabled the co-expression of both tumor antigen complexes and essential immunological co-stimulatory molecules on their surfaces. The dual-functional presentation effectively mimicked the APC phenotype and elicited potent T cell activation, thereby enhancing antitumor immune responses. Expanding on this concept, Liu et al.[129] integrated a genetically engineered cell membrane nanovesicle that combined antigen self-presentation with a strategy to reverse tumor-induced immunosuppression, as shown in Fig. 4D. Their nanovesicle construct not only presented tumor antigens but also incorporated functional elements capable of reactivating exhausted T cells, in addition to priming naïve T cells. This dual-activation strategy provids a promising approach for reinvigorating antitumor immunity in immunologically "cold" tumors where T cell exhaustion is a major barrier to effective therapy.

These innovative strategies demonstrate how to rationally design membrane-derived biomimetic nanovesicles to simultaneously address multiple limitations of traditional cancer vaccines, enhance antigen delivery, provide immunostimulatory cues, and overcome the immunosuppressive TME.

3.2. Immune checkpoint inhibitors (ICIs)

Cancer cells often evade immune system by exploiting immune checkpoint pathways and regulatory mechanisms that normally serve to maintain self-tolerance and prevent autoimmune responses[163]. These immune checkpoint proteins act as co-inhibitory molecules that suppress the activation, proliferation, and cytokine production of immune cells, thereby inhibiting antitumor immunity and allowing tumor progression out of control[164,165]. ICIs are antibodies designed to block certain signals, thereby reviving exhausted T cells and restoring effective antitumor immune responses. To date, ICIs such as CTLA4 inhibitors and PD1/PDL1 pathways have achieved remarkable breakthroughs in clinical oncology and have been approved for the treatment of various malignancies, such as melanoma, non-small cell lung cancer, and urothelial carcinoma[166,167]. Despite their clinical success, ICIs are also accompanied by limitations. A significant number of patients experience irAEs, which are believed to originate from systemic immune activation. These irAEs are often difficult to predict and specific, and in some cases may result in permanent organ damage or life-threatening

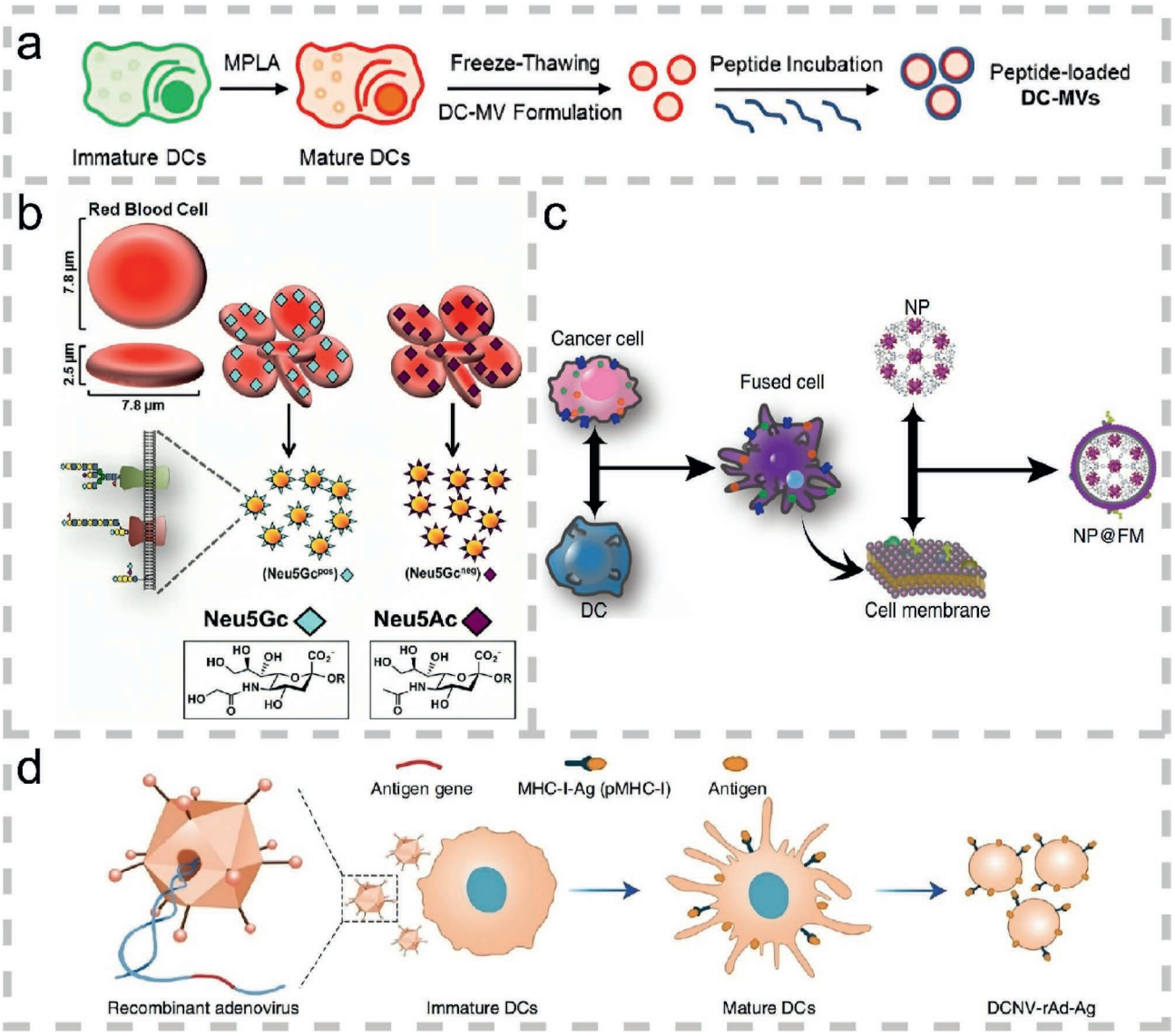


Figure 4 (a) Immunostimulatory nanovesicles derived from MPLA-activated DCs, carrying MHC-peptide complexes, costimulatory signals, and cytokines to enhance T cell activation[127]. Reproduced with permission from Ref. 127. Copyright © 2025, John Wiley and Sons (b) Nanovesicles (NGs) prepared from RBCs of two porcine strains expressing different Sia-containing glycoproteins ($Neu5Gc^{+}$ and $Neu5Ac^{-}$). Reprinted with permission[125]. Reproduced with permission from Ref. 125. Copyright © 2025, American Chemical Society. (c) Formation of fused cells (FCs) by PEG-induced fusion of DCs and ethanol-pretreated cancer cells displaying enhanced 'eat-me' signals[128]. Reproduced with permission from Ref. 128. Copyright © 2025, Springer Nature. (d) Generation of DC-derived nanovesicles (DC-NVs) from adenovirus-infected DC2.4 cells expressing tumor-specific antigens for enhanced immunotherapy[129]. Reproduced with permission from Ref. 129. Copyright © 2025, Springer Nature.

conditions[168,169]. In this context, biomimetic nanovesicles have emerged as a promising platform to optimize ICI-based immunotherapy. These vesicles can be modified to display immune checkpoint antibodies on their surfaces, thereby being able to target and block inhibitory pathways within the TME[170]. Moreover, thanks to their high drug-loading capacity and biocompatibility, biomimetic nanovesicles can be used as carriers for co-delivering ICIs alongside other immunomodulatory agents or chemotherapeutics[171].

A deeper understanding of the immune regulatory mechanisms within the TME, especially the roles of immune checkpoints on both adaptive and innate immune cells, is essential for improving the efficacy of ICI therapies[172]. These insights not only contribute to the application of current ICIs therapies but are also critical for developing combination therapies targeting multiple checkpoint pathways. Fig. 5 illustrates the representative strategies that utilize membrane-derived biomimetic nanovesicle platforms for ICI delivery and functional enhancement.

Among immune checkpoints, PDL1 has emerged as a critical target in a wide range of cancers, and multiple PD-L1-targeted therapies have already been approved by the US FDA and European EMA for cancer diagnosis and treatment[173,174]. Integrating PDL1-targeted strategies into biomimetic nanovesicle systems has shown satisfactory efficacy. For example, Wang et al.[135] engineered platelets to display a monoclonal antibody (mAb) against PDL1 on their surfaces. When administered postoperatively in

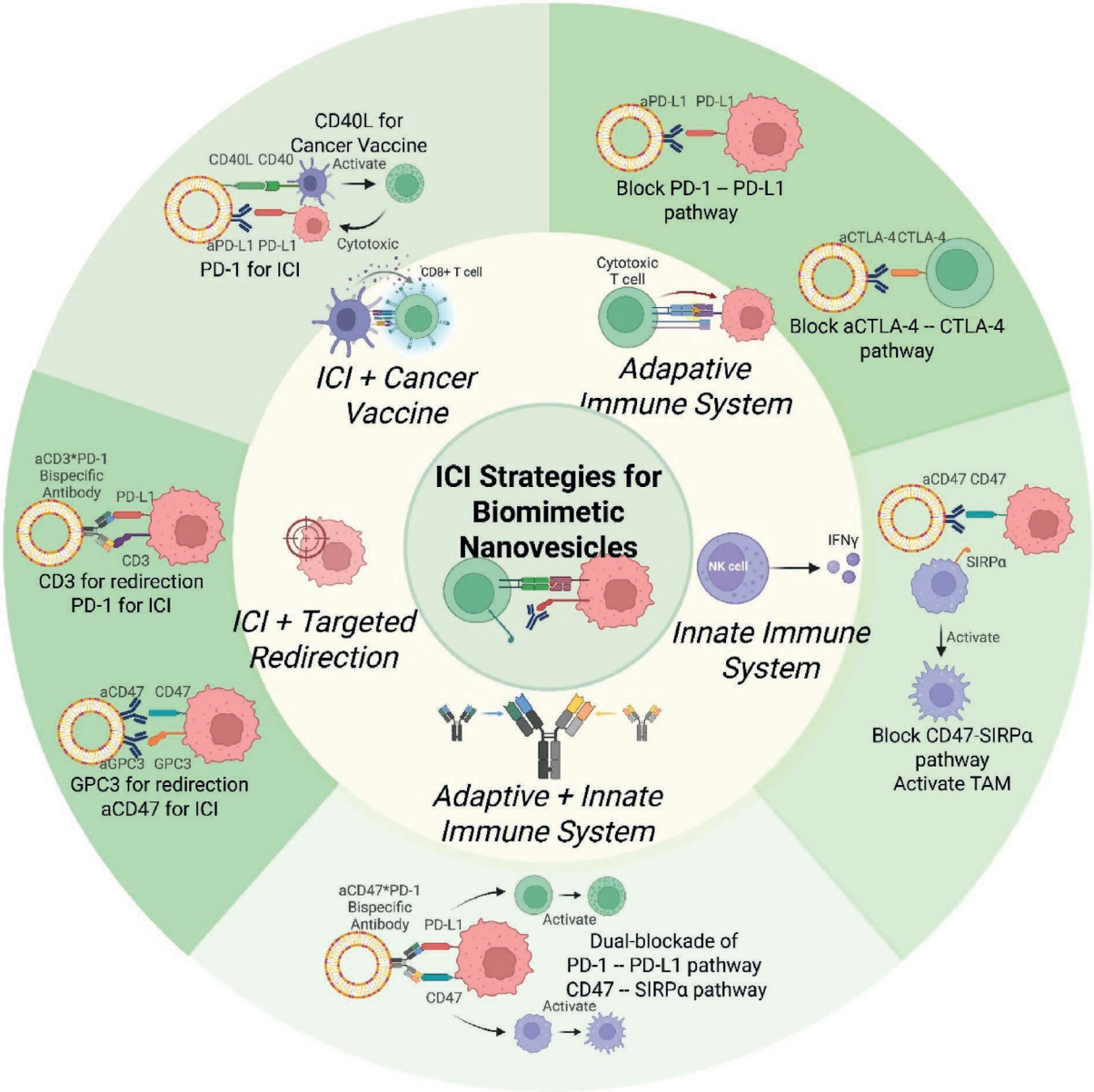


Figure 5 Strategies utilizing biomimetic nanovesicle platforms for the delivery and functional enhancement of immune checkpoint inhibitors (ICIs). Created with BioRender.com.

mice with partially resected primary melanoma or triple-negative breast cancer, this system effectively suppressed tumor recurrence and metastasis. Building on this approach, Li et al.[136] further overexpressed CD64 on top of the PDL1 antibody nanovesicles, enabling high-affinity capture of anti-PDL1 antibodies and facilitating the precise delivery of the nanocarriers to PDL1-overexpressing tumor cells. To overcome resistance to ICI therapy, combinatorial strategies have also been investigated. For instance, as shown in Fig. 6A, to enhance the immune response, co-delivery of *ADAR1*-siRNA alongside PDL1-targeting nanovesicles has demonstrated potential in sensitizing tumors to ICI therapy[139]. CTLA4 is another important immune checkpoint involved in early T cell activation, has been widely explored. Several CTLA4-blocking antibodies have entered phase III clinical trials and received FDA approval for various cancer treatments[175-177]. Jung et al.[137] reported a DC-derived nanovesicle functionalized with anti-CTLA4 mAbs, which selectively activated tumor-specific cytotoxic T lymphocytes (CTLs) while minimizing systemic immune activation, thereby reducing the incidence of irAEs.

Beyond single-target inhibition, biomimetic nanovesicle systems have also been engineered to perform dual functionalities, such as immune checkpoint blockade combined with T cell redirection. Chen et al.[140] reported a bispecific T cell conjugated exosome system expressing both anti-PDL1 and anti-CD3, enabling the recruitment and activation of T cells directly at the tumor site. This platform, shown in Fig. 6B successfully enhanced tumor infiltration of T cells while maintaining PDL1 blockade. Similarly, Xu et al.[141] employed a dual-targeting strategy in CD19-positive tumors by concurrently blocking PDL1 and directing T cells to the tumor site, resulting in enhanced antitumor efficacy.

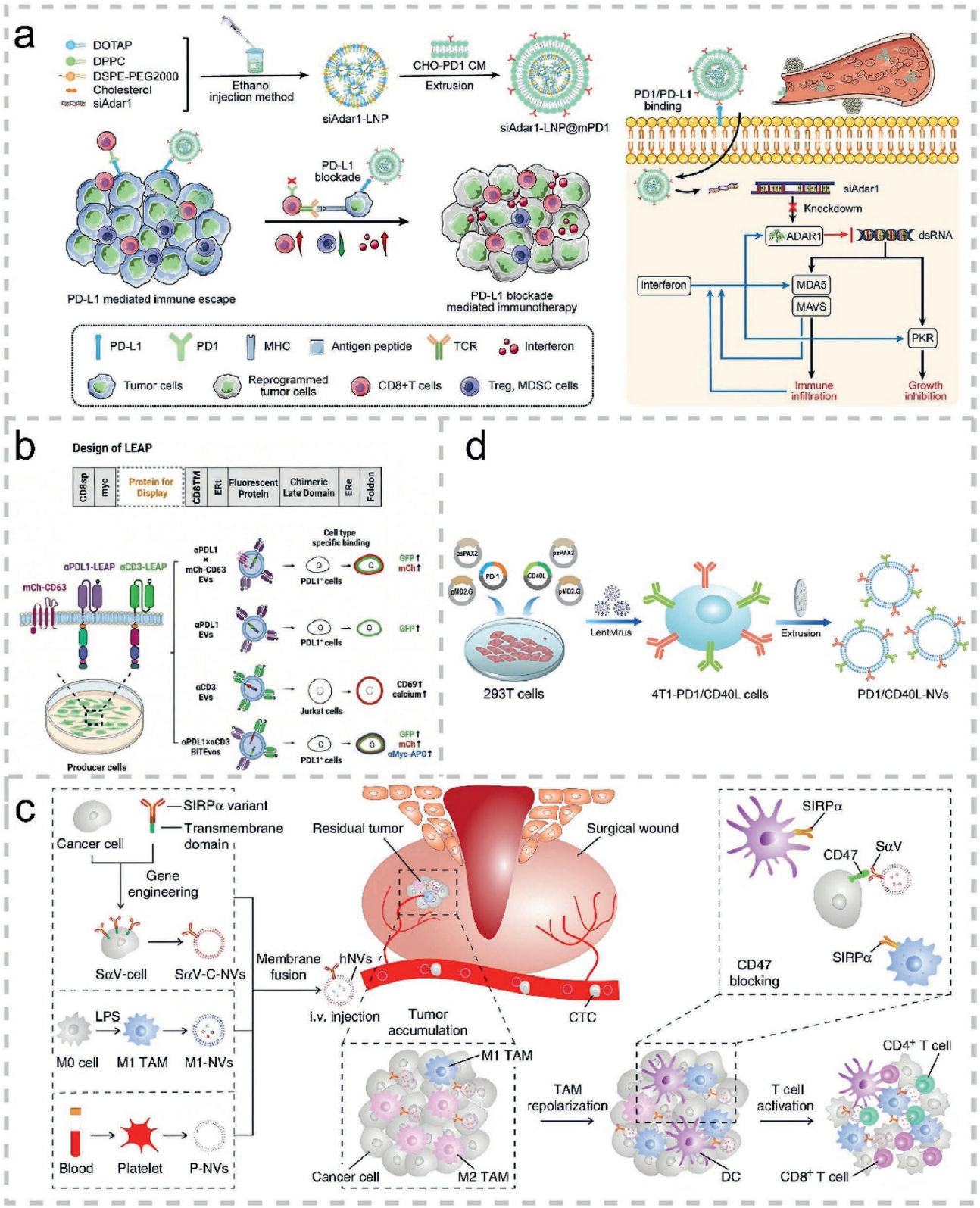


Figure 6 (a) GECM-cloaked lipid nanoparticles (LNPs) loaded with synthetic ADAR1 siRNA for *in vivo* silencing of ADAR1, blocking the PD-1/PD-L1 pathway, and enhancing immune checkpoint blockade (ICB) therapy[139]. Reproduced with permission from Ref. 139. Copyright © 2025, with permission from Elsevier. (b) Design of the LEAP scaffold: aPD-L1 scFv and aCD3 scFv were fused to generate aPDL1-EVs, aCD3-EVs, and bispecific aPDL1 × aCD3 BiTExos for targeted immune modulation[140]. Reproduced with permission from Ref. 140. Copyright © 2025, John Wiley and Sons. (c) Schematic showing hybrid nanovesicles (hNVs) composed of SaV-C-NVs, M1-NVs, and P-NVs, promoting CTC targeting, TAM repolarization, CD47−SIRPa pathway blockade, and enhanced antitumor T cell immunity[134]. Reproduced with permission from

In addition to adaptive immunity mediated by T cells, ICIs targeting innate immune cells represented by macrophages have also been investigated and applied in cancer immunotherapy[178]. Among these targets, CD47 which is overexpressed on various tumor cells, plays a critical role in immune evasion by delivering 'don't eat me' signals through interaction with SIRPα on myeloid cells[179,180]. This CD47−SIRPα axis suppresses macrophage-mediated phagocytosis and contributes to immune tolerance of tumors. Therefore, blocking the CD47−SIRPα pathway has emerged as a potential immunotherapeutic strategy, and its ability to stimulate the tumor cell phagocytosis and enhance anti-tumor immune response *in vivo* has been validated in multiple preclinical studies[181,182]. Rao et al.[134] developed a hybrid nanovesicle (hNV) constructed from platelets, M1 macrophages, and tumor cells, functionalized with high-affinity SIRPα variants, like Fig. 6C. These nanovesicles not only blocked the CD47−SIRPα interaction to promote phagocytosis of tumor cells, but also reprogrammed TAMs toward the M1-like pro-inflammatory phenotype. In addition, they enhanced antigen presentation by macrophages and DCs, further amplifying immune activation. Incorporating immune cell redirection strategies, Li et al.[142] designed dual-targeted bacterial outer membrane vesicles (OMVs) that simultaneously displayed anti-CD47 antibodies and anti-GPC3 single-chain variable fragments (scFv). This approach enabled the vesicles to actively target and accumulate at the orthotopic hepatocellular carcinoma (HCC) site, thereby potentiating local immune responses.

Furthermore, combining innate and adaptive immune checkpoint blockade has been proposed to synergistically improve immunotherapeutic outcomes. Meng et al.[132] and Zhang et al.[133] separately developed biomimetic nanovesicle systems capable of simultaneous blockade of CD47 and PDL1. These dual-targeting nanovesicles significantly enhanced macrophage phagocytic and antigen-presenting capabilities, while simultaneously activating cytotoxic T cell responses, thereby providing stable and comprehensive anti-tumor immune effect.

The combination of cancer vaccine and immune checkpoint blockade on the surface of a single nanovesicle represents a novel and promising strategy. Pan et al.[131] developed a genetically engineered cancer cytomembrane nanovesicle that simultaneously displayed the co-stimulatory molecule CD40L and the ICI PD1. This dual-functional platform synergistically enhances anti-tumor immunity by promoting DC-mediated cytotoxic T cell activation *via* tumor antigen presentation and simultaneously blocking the PD1/PDL1 axis to relieve T cell exhaustion, as shown in Fig. 6D. The resulting nanovesicles exhibited potent therapeutic efficacy and biosafety, highlighting their potential as a multifunctional platform for combinatorial immunotherapy.

In summary, by utilizing membrane-derived biomimetic nanovesicles to deliver or display ICIs, either alone or in combination with other immunomodulatory strategies, researchers have enhanced the specificity, efficacy, and safety of ICI-based tumor immunotherapy.

3.3. Immune adjuvants delivery

Immune adjuvants are a class of substances that can stimulate, enhance, or regulate the immune response against antigens. They are commonly used in vaccines preparations to improve the immunogenicity and therapeutic efficacy of antigens[183-185]. Through the activation of innate immune pathways, adjuvants can enhance antigen presentation and promote the development of a strong and long-lasting adaptive immune responses. When combined with engineered membrane-derived biomimetic nanovesicles, immune adjuvants can be precisely delivered to target tissues, particularly the TME, thereby improving local immune activation while minimizing systemic toxicity[186,187]. Currently, various types of adjuvants have been integrated into nanovesicle platforms, including TLR agonists, genotypic adjuvants such as CpG oligodeoxynucleotides, and immunostimulatory cytokines, as summarized in Fig. 7.

TLRs are important pattern recognition receptors (PRRs) in the immune system, responsible for identifying pathogen-associated molecular patterns (PAMPs) from microorganisms or danger-associated molecular patterns released from damaged tissues, thereby initiating innate and adaptive immune responses[188]. Among genotypic adjuvants, CpG oligodeoxynucleotides can mimic bacterial DNA and activate immune pathways *via* TLR9, effectively improving the function of professional APCs, and boosting the generation of innate and adaptive immune responses[189]. Co-activation of TLRs and CpG has been shown to synergistically induce a strong anti-tumor immune response. For instance, Wen et al.[190] developed a tannic acid-based nanovaccine that co-delivers Mn^{2+} and CpG as a bi-adjuvant, as illustrated in Fig. 8A, significantly enhancing local immune activation and delaying tumor progression.

Cytokines, primarily secreted by immune cells, plays essential roles in regulating cellular functions and mediating intercellular communication during both homeostasis and pathological conditions[191,192]. They can be broadly categorized into interleukins, interferons, chemokines, members of the tumor necrosis factor superfamily, and growth factors[193]. Both the immunostimulatory properties of cytokines and the therapeutic potential of antagonizing dysregulated cytokine signaling have been explored in immunotherapy[194]. Several cytokines and their inhibitors, such as IL2, IL12, IL15, IFNG, and various antagonists, have entered clinical trials or been approved for therapeutic use[195-200]. However, existing evidence suggests that targeting a single is unlikely to maintain a sustained clinical response in advanced cancers unless in a limited subset of patients[193]. Consequently, cytokine-based therapies are often combined with TCAs or ICIs in drug design to achieve optimal therapeutic efficacy. To overcome the challenges associated with the poor pharmacokinetic profiles and systemic toxicity of cytokines, membrane-derived biomimetic nanovesicles have emerged as promising platforms for efficient and targeted cytokine delivery[201,202].

To integrate the immunostimulatory effects of cytokines with the antigen-presenting function of cancer vaccines, as shown in Fig. 8B, Wang et al.[60] employed cell membrane vesicles derived from genetically engineered DCs to achieve spatiotemporal synchronization of IL-15 and MHC, successfully eliciting a broad spectrum of antigen-specific T cell responses. Similarly, Sun et al.[143] developed a unique RBC-based artificial APCs, functionalized with MHC1 loaded with antigenic peptides, CD28 co-stimulatory antibodies, and surface-tethered IL-2 on the surface of the RBC membrane. Both strategies aim to mimic DC antigen

Ref. 134. Copyright © 2025, Springer Nature. (d) Preparation of PD1/CD40L nanovesicles (PD1/CD40L-NVs) derived from 4T1 cells co-expressing PD1 and CD40L[131]. Reproduced with permission from Ref. 131. Copyright © 2025, John Wiley and Sons.

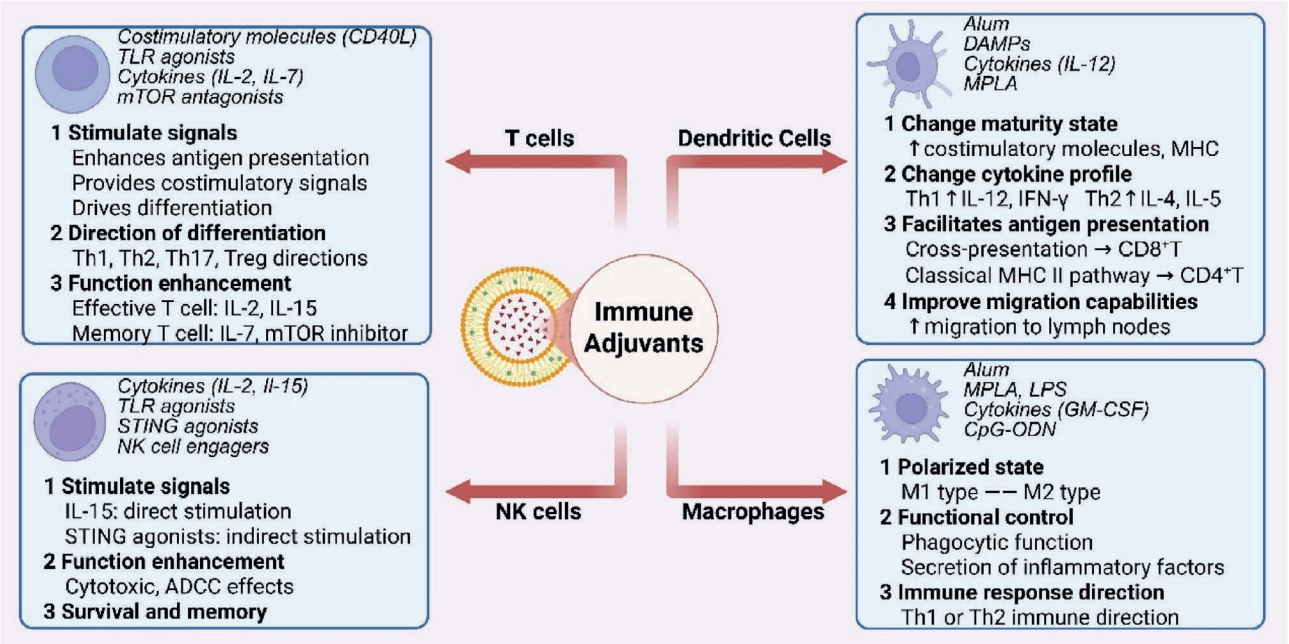


Figure 7 Common strategies for incorporating immune adjuvants into membrane-derived biomimetic nanovesicles to enhance local immune activation. Created with BioRender.com.

presentation while delivering cytokines to strongly activate T cell-mediated anti-tumor immunity. Building upon this approach, the combination of immune checkpoint blockade therapy can further enhance therapeutic efficacy. For instance, Pack et al.[130] designed tumor membrane vesicles displaying immunostimulatory B71 (CD80) and IL12 molecules; they demonstrated synergistic anti-tumor effects when combined with anti-CTLA4 mAb therapy.

Other immune adjuvants can also be engineered and delivered *via* biomimetic nanovesicles. Unlike the strategy by Ochyl et al.[127], who pretreated membrane-derived cells with MPLA adjuvants, Fang et al.[88] functionalized biodegradable polymeric nanoparticles with the cancer cell membrane to co-expressed the membrane-bound TAAs along with MPLA. This design enabled the co-delivery of antigen-presenting nanoplatform and immune adjuvants to APCs, as shown in Fig. 8C, thereby enhancing anti-tumor immunotherapy.

In addition to immunotherapy-focused applications, membrane-derived biomimetic nanovesicles have also been explored as versatile carriers for small molecules and nucleic acid drugs. By retaining functional membrane proteins and structural stability, these vesicles can prolong systemic circulation, reduce nonspecific clearance, and enhance tumor accumulation, thereby improving the therapeutic index of conventional chemotherapeutics such as doxorubicin and paclitaxel. For instance, cancer cell membrane-cloaked platforms have demonstrated enhanced homotypic targeting and significant tumor suppression when delivering doxorubicin in HCC models and co-delivery of doxorubicin and PD-L1 siRNA[203,204]. Beyond small molecules, biomimetic nanovesicles also show strong potential for gene delivery. For example, genetically engineered vesicles with ligand−receptor mediated and enzyme-controlled fusion functions enabled highly efficient cytosolic siRNA delivery, achieving potent gene silencing and tumor inhibition[205]. The membrane-associated ligands and receptors facilitate efficient cellular uptake and endosomal escape, while protecting fragile payloads such as siRNA or mRNA from enzymatic degradation. Unlike synthetic LNPs, which largely rely on chemical functionalization, biomimetic vesicles lead to natural biological interactions, thereby achieving receptor-mediated targeting and immune modulation[206,207]. These characteristics have broadened the therapeutic scope of biomimetic nanovesicles, enabling them to go beyond immunomodulators, and become promising delivery carriers for both conventional and genetic medicines in oncology.

In conclusion, the integration of immune adjuvants with membrane-derived biomimetic nanovesicles enables precise spatiotemporal delivery to the TME, effectively enhancing innate and adaptive immune activation. This strategy not only amplifies antigen-specific responses but also synergizes with TCVs and ICIs to potentiate anti-tumor immunotherapy.

3.4. *Targeted redirection*

Biomimetic nanovesicles can precisely deliver therapeutic agents, including drugs, antibodies, or bioactive molecules, to specific target sites. This targeted redirection can be achieved through various strategies. One common approach is to surface-modify nanovesicles using specific ligands, such as antibodies, peptides, or other small molecules, that selectively bind to overexpressed receptors on target cells, thereby enhancing cellular uptake and site-specific delivery[65]. Alternatively, biomimetic nanovesicles can utilize the inherent recognition properties of native cell membranes, such as the homotypic targeting ability of cancer cell-derived membranes, to achieve selective tumor localization[208]. Furthermore, membrane-derived biomimetic nanovesicles can be engineered to respond to pathological stimuli, such as pH value or enzyme activity within the TME, thereby achieving spatiotemporal controlled drug release and improving therapeutic efficacy[209,210].

Bispecific antibodies are a class of antibodies that can recognize and bind to two different antigens or epitopes simultaneously,

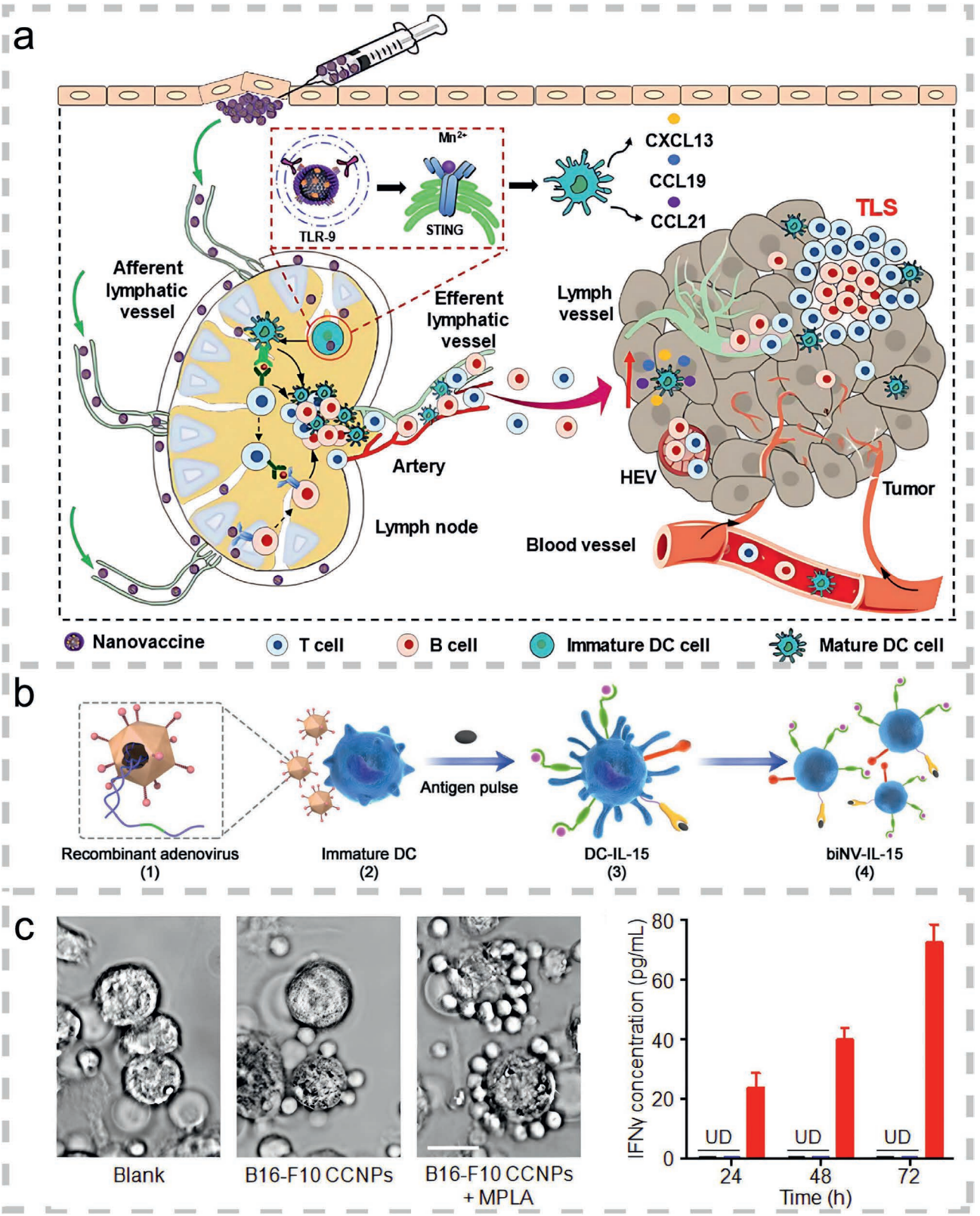


Figure 8 (a) Schematic of a pECM-based nanovaccine designed for nasopharyngeal carcinoma (NPC) therapy *via* tertiary lymphoid structure (TLS) formation[190]. Reproduced with permission from Ref. 190. Copyright © 2025, American Chemical Society (b) Stepwise fabrication of biNV-IL15. BMDCs were transduced with IL15/IL15RA-encoding adenoviral vectors, leading to surface expression of membrane-bound IL15. Tumor antigen priming and dendritic cell maturation were followed by nanovesicle isolation[60]. Reproduced with permission from Ref. 60. Copyright © 2025, Springer Nature (c) Dendritic cells treated with blank, CCNPs, or MPLA-loaded CCNPs were cocultured with splenocytes from pmel-1 mice. Left: microscopy image showing T cell clustering around DCs after 72 h. Right: IFNG secretion, indicating antigen-specific T cell activation, measured by ELISA at 24, 48, and 72 h[88]. Reproduced with permission from Ref. 88. Copyright © 2025, American Chemical Society.

offered enhanced targeting precision and functional versatility compared to conventional monoclonal antibodies[211,212]. For instance, a bispecific DC-T cell engager has been developed to strengthen the interaction between conventional type I DCs and T cells, thereby promoting immune activation[213]. Clinically, the anti-CD19/CD3 bispecific T cell engager blinatumomab has demonstrated significant therapeutic efficacy in the treatment of B-cell acute lymphoid leukemia[214]. Given their ability to physically bridge immune and tumor cells, multi-specific antibodies are particularly well-suited for conferring biomimetic nanovesicles with targeted redirection capabilities.

Targeted retargeting strategies are frequently integrated with other immunotherapeutic approaches, including immune checkpoint blockade and cytokine delivery, to achieve synergistic antitumor effects[140,141]. In some recent studies, nanovesicles engineered for targeted redirection can modulate the intercellular communication between immune cells and cancer cells, or between immune cells. This approach holds promise for regulating the TME of cancer and transforming immunologically 'cold' tumors into 'hot' tumors, representing a prospective direction for future cancer immunotherapy research[215].

Targeted redirection strategies enhanced the specificity and efficacy of cancer immunotherapy by promoting precise intercellular interactions, facilitating immune cell recruitment, and enabling combined treatment model, thereby bringing great hope for reshaping the TME and improving treatment outcomes.

In conclusion, current immunotherapeutic strategies based on engineered biomimetic nanovesicles, including TCVs, ICIs, immune adjuvant delivery, and targeted redirection, have demonstrated synergistic and complementary effects in enhancing antitumor immunity. These approaches not only promote antigen presentation and T cell activation but also overcome immune suppression and improve immune cell infiltration in the TME. By rationally combining these strategies, it is possible to achieve more precise, potent, and long-lasting anti-tumor immune responses.

Understanding the immune mechanisms triggered by biomimetic nanovesicles provides crucial insights into their therapeutic action. However, immune activation must be carefully controlled in both space and time to ensure efficacy while minimizing off-target effects. We further introduce strategies for achieving spatiotemporal control over nanovesicle-induced immune responses, which is key to enhancing treatment precision.

4. Membrane protein modification strategies

To fully utilize the anti-tumor immunotherapy potential of biomimetic nanovesicles, it is generally necessary to functionalize their surface with engineered functional proteins[216,217]. With the development of vesicle engineering technologies, current antibody modification strategies can be broadly divided into two main categories: direct modification of the nanovesicles themselves, and indirect modification through the modification of vesicles-derived cells. These strategies are summarized in Fig. 9. Among them, direct surface modification typically involves chemical conjugation methods, allowing functional groups to be precisely attached to the vesicle membrane after vesicle formation. In contrast, source cell-derived strategies, such as genetic engineering and membrane hybridization, can express or integrate functional membrane proteins before vesicle formation, thereby preserving membrane integrity and biological activity in a more native-like form.

Different engineering strategies were used to expand the functional variability of biomimetic nanovesicles for cancer immunotherapy. Click chemistry, with its high selectivity and mild reaction conditions, is frequently applied to couple antibodies, ligands, or small peptides, making it particularly suitable for checkpoint blockade and retargeting. Genetic engineering of source cells allows stable expression of membrane proteins or fusion receptors with specific structure, thereby supporting applications in adjuvant delivery and engineered checkpoint inhibition. Meanwhile, membrane hybridization integrates functional proteins from multiple cell types, enabling combined advantages such as immune evasion and immune activation, which are especially valuable for adjuvant delivery and targeted redirection. Together, these strategies explained how engineering choices can be combined with therapeutic aims, thereby advancing biomimetic nanovesicles as flexible platforms for precision immune modulation.

4.1. Direct modification of the membrane surface

In order to fully utilize the potential of the membrane vesicle platform, a variety of chemical modification techniques have been developed to enable the overexpression of target proteins directly on the surface of biological membranes[218,219]. These methods can be categorized into two main types: noncovalent modification and covalent modification.

Non-covalent modification strategies are relatively mild and do not significantly disrupt membrane integrity[220]. Several approaches have been explored for non-covalent modification. For instance, targeting the negatively charged biofilms by coating the surface of nanovesicles with positively charged molecules relies on multivalent electrostatic interactions. Cationic liposomes have been widely employed to introduce immunomodulators, such as antibodies and adjuvants, thereby enhancing immune responses[221]. For example, Szachniewicz et al.[222] utilized cationic pH-sensitive liposomes as a delivery system for subunit tuberculosis, demonstrating efficient antigen delivery and immune activation. In addition, peptides, including cell-penetrating peptides, cell-targeting peptides and coiled-coil peptides, have also been applied to lipid-based nanoparticles to modify their properties. Sugimoto et al.[223] successfully engineered extracellular vesicles using KK-(EK)4-lipid, a novel cell-penetrating peptide-modified lipid, to enhance intracellular nanoparticle translocation. Furthermore, hydrophobic interactions provide another strategy for membrane engineering, which enables the incorporation of functional groups into nanovesicle membrane through fusion with fusogenic liposomes[224].

Covalent modification represents a primary chemical approach for surface modification of membrane-derived nanovesicles[68]. Compared with non-covalent modification, covalent conjugation provides a more stable anchoring of functional groups. For instance, Musicò et al.[225] systematically compared covalent *versus* non-covalent conjugation of the antibody cetuximab to extracellular vesicles, demonstrating that covalently modified vesicles *via* click chemistry exhibited superior binding affinity and cellular uptake efficiency toward target cells.

Click chemistry technology is a powerful bioconjugation tool due to its high selectivity, fast kinetics, excellent biocompatibility, and ability to proceed under mild conditions. Unlike conventional chemical reactions that often require harsh conditions, such as extreme pH, temperature, or osmolarity, which may compromise membrane integrity. Click chemistry preserves vesicle structure,

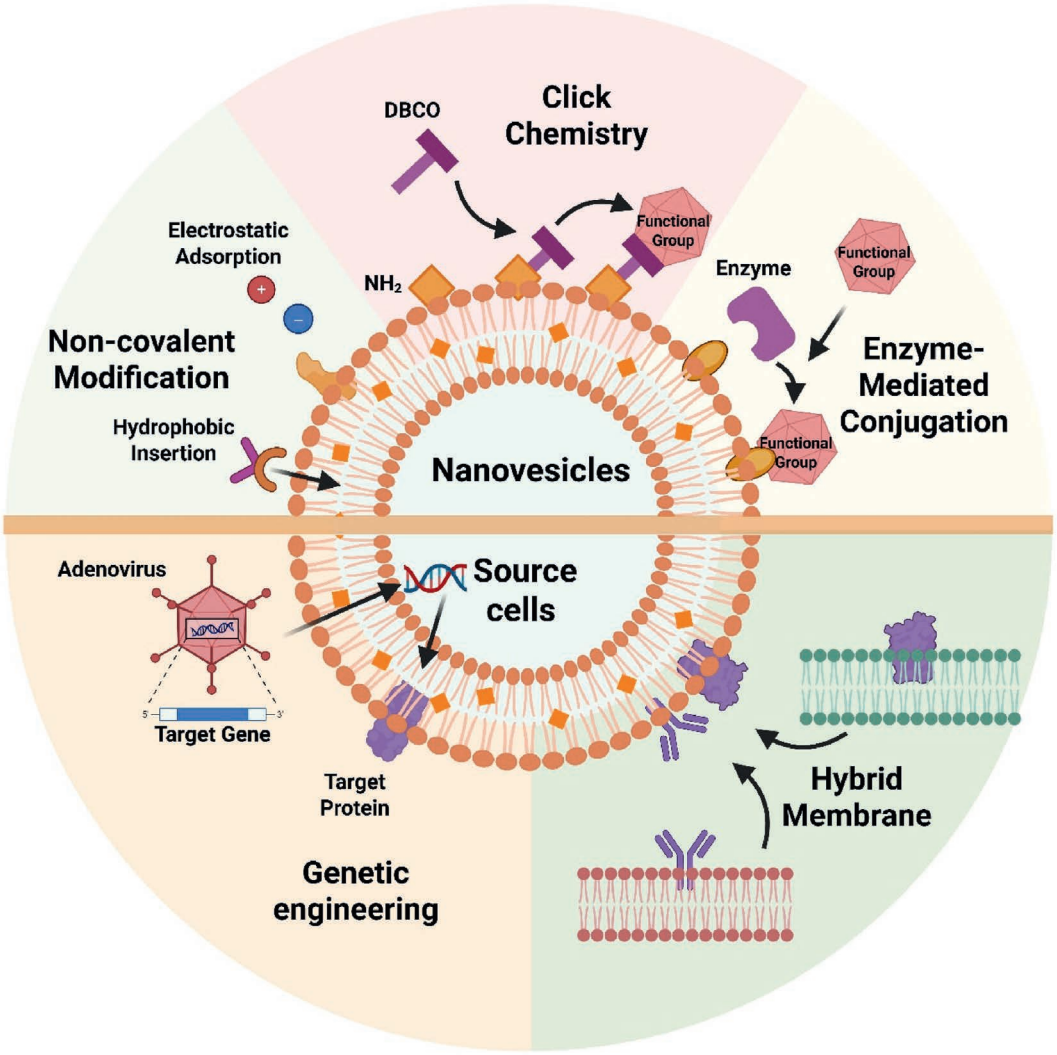


Figure 9 Schematic summary of antibody modification strategies for biomimetic nanovesicles, including direct vesicle surface engineering and indirect engineering *via* modified source cells. Created with BioRender.com.

making it particularly suitable for extracellular vesicle modification. For example, Ruan et al.[226] applied copper-free click chemistry to simultaneously decorate M2 microglia-derived extracellular vesicles with a vascular injury-targeting peptide and a stem cell recruitment factor, successfully improving the differentiation of neural stem cells at the site of injury. In the application of antitumor immunotherapy, Bhatta et al.[227] developed a cancer nanovaccine by introducing unique chemical tags onto the surface of nanovesicle membrane *via* click chemistry, which can effectively target and activate immune cells. Similarly, Lee et al.[224] also used copper-free click chemistry to bind tumor-targeting antigens to extracellular vesicles, significantly improving their tumor homing and therapeutic potential. Despite its advantages, the application of click chemistry in vesicle surface engineering still faces challenges, mainly due to the non-specific interactions. Activated functional groups may unpredictably bind to membrane surface proteins, which may disrupt the natural functions of the membrane and limit the therapeutic precision.

Another approach for covalent surface modification of nanovesicles is enzyme-mediated reaction, in which functional proteins are covalently bind to the membrane surface through specific enzymatic processes. For example, Zhou et al.[228] integrated microfluidics with enzymatic glycoengineering to achieve efficient and controlled surface functionalization of nanovesicles, significantly improved the efficiency and uniformity of extracellular glycosylation modifications. Although enzymatic strategies have advantages such as high substrate specificity and mild reaction conditions, their application in nanovesicle engineering still faces technical challenges. Limited enzyme substrate compatibility, strict reaction conditions, and the fine structure of membrane vesicles all restrict the wide use of enzymatic methods for vesicle surface functionalization[220]. Consequently, while promising, enzymatic modification strategies require further optimization to realize their full potential in clinical and translational settings.

4.2. Inheritance from membrane-derived cells

Compared with post-vesicle surface modification, source-cell engineering offers the critical advantage of preserving correct membrane protein topology during vesicle formation, thereby maintaining their native orientation and biological functionality. Since the direct anchoring of functional groups onto vesicle

surfaces is often time-consuming and may cause damage to the structure integrity of nanovesicles, currently there are increasing investigators chose to equip the membrane-derived source cells with functional proteins when preparing nanovesicles for antitumor immunotherapies. By modifying the functional protein on the cell surface, nanovesicles carrying these proteins can be subsequently harvested through a variety of engineering approaches. Additionally, in order to combine the advantages of multiple types of membrane proteins, membrane hybridization techniques have been developed to enable nanovesicles to inherit functional proteins from different parent cells. Notably, recent studies have pointed out that direct decoration of nanovesicles may lead to incorrect membrane orientation thus influencing their pharmacokinetics and biological behavior. By contrast, engineering membrane-derived cells promotes the correct membrane topology during vesicle formation[229]. Therefore, strategies based on inheritance from membrane-derived cells are increasingly becoming the mainstream for preparing and functionalizing biomimetic nanovesicles. Representative applications of these functional membrane protein engineering methods are summarized in Table 2[60,128,129,131-134,136,138,140-142,230-233].

Genetic engineering technology has been widely applied in the preparation of functionalized nanovesicles[65]. This strategy primarily involves introducing the gene fragment encoding target membrane proteins into the genome of source cells *via* plasmid vectors or lentiviral transport vectors, thereby enabling stable expression of the desired proteins on the surface of the target cell membrane. Subsequently, nanovesicles were further harvested from the relevant cells through various techniques such as multistep density gradient centrifugation, membrane co-extrusion, or sonication[234]. Compared with direct modification of nanovesicle surfaces, genetic engineering technology offers several advantages: it preserves the biological activity of native membrane proteins, allows for precise control over the expression levels and localization of target proteins, and enables the establishment of stable cell lines, which facilitates large-scale production and long-term storage of functionalized nanovesicles[235].

The most widely adopted transfection strategy in genetic engineering is the use of lentiviral vectors to integrate exogenous genes into the host cell genome, thereby enabling stable and long-term expression of target proteins[236]. For example, Fang et al.[231] use lentiviral infection to engineer NIH3T3 cells with IL15/IL15RA expression, and achieved nanovesicles presenting IL15/IL15RA through massively cultured engineered NIH3T3-overexpressed stable cells lines. Plasmid transfection is also frequently employed for the transient or stable expression of recombinant proteins, and further collects vesicles. Li et al.[136] successfully expressed CD64 on the surface of HEK293T cells *via* plasmid transfection, and collected cell membrane-derived nanovesicles with an average size of approximately 100 nm. Genetic engineering strategies offer several advantages, including high specificity, precise controllability of protein expression, and the preservation of the native biological activity and structural stability of membrane proteins. Moreover, they avoid the adverse effects that are often associated with chemical modifications. However, certain challenges still exist, such as the technical complexity of genetic manipulation, variability in expression efficiency among different cell types, and the potential risk of immunogenicity. With the continuous advancement of genetic engineering technologies, these limitations are expected to be progressively addressed, further enhancing the potential applications of biomimetic nanovesicles[237].

In addition, membrane hybridization has also been widely used for enhancing the function of biomimetic nanovesicles. By fusing two or more different types of cell membranes or nanoparticles, hNVs can integrate multiple biological properties into a single platform. This method can inherit and synergistically combine the functional characteristics of different cell sources, such as immune evasion, prolonged circulation time, and enhanced targeting capability, to optimize the performance of nanovesicles in the application of antitumor immunotherapy[69,238]. Typically, hybrid membrane design follows a modular strategy, where one membrane type provides basic cellular identity, while the other contributes specific functional enhancements, such as immunomodulation or target specificity[239]. Wang et al.[230] developed a hybrid nanoparticle by hybridizing ginseng-derived extracellular vesicle-like particles with membranes derived from resected autologous tumor tissues. This personalized hybrid vaccine effectively induced tumor-specific cell-mediated immune responses and demonstrated potent therapeutic efficacy against cancer.

These membrane protein modification strategies have enabled precise functionalization of biomimetic nanovesicles, significantly enhancing their targeting capability and immunotherapeutic efficacy against tumors. So that compared with other nanocarrier systems, membrane-derived biomimetic nanovesicles offer unique advantages. Exosomes which naturally enriched with bioactive proteins, they especially suitable for delivering small molecules or nucleic acid drugs, their surface engineering attempts to reducing toxicity and side effects and maximizing therapeutic efficacy. A study developed an exosome-based platform for doxorubicin delivery, in which exosome membrane protein Lamp2b was fused with the αv integrin-specific iRGD peptide (CRGDKGPDC) to enhance tumor targeting, thereby reducing immunogenicity and systemic toxicity[240]. The major challenge of exosome-based delivery lies in developing scalable production and isolation methods to improve preparation efficiency. In contrast, biomimetic nanovesicles are relatively easier to manufacture, and their surface engineering strategies are more accessible, thereby offering greater advantages for large-scale production and clinical translation.

Synthetic liposomes and LNPs, which are also widely used as nanocarriers through surface functionalization, rely on artificial lipid formulations and primarily depend on chemical ligand conjugation. For example, a liposome functionalized with aCD3 scFv-aCD19 scFv fragments on its surface was developed, which facilitated the simultaneous binding of T cells and tumor cells and achieved similar potent as traditional T cell-dependent bispecific antibodies[241]. They can also be used as simultaneously delivering TLR9 and CpG, which elicited strong tumor-specific T-cell responses[242]. However, compared with biomimetic nanovesicles, which inherit a broad repertoire of native membrane proteins from their source cells, they lack natural functional components that thoroughly adapt to the intrinsic environment. These natural features endow biomimetic nanovesicles with superior biological fidelity, receptor-mediated targeting, and immune-interactive functions, which can be further enhanced by engineering strategies.

The ability to spatiotemporally regulate immune responses is closely tied to the intrinsic properties of the nanovesicles themselves, which are largely determined by their membrane origins. In the next part, we will examine how different cell membranes confer distinct biological functionalities to biomimetic nanovesicles and discuss their implications in anti-tumor immunotherapy.

Table 2 Engineering strategy and modification of membrane surface proteins.

Modification strategy	Methods	Functional protein	Biofunction	Ref.
Membrane hybridization	Fusion of ginseng-derived vesicles and cancer membrane	Ginseng membrane and cancer membrane surface proteins	Enhance dendritic cell function and maturation	230
Membrane hybridization	Fusion of M1 macrophage-derived nanovesicles and PD1-overexpressed cancer cell-derived nanovesicles	M1 macrophage and cancer cell membrane surface proteins	Promote TAMs; block the PD-1/PD-L1 pathway	138
Membrane hybridization	Fusion of dendritic cells and cancer cells	DCs and cancer cell membrane surface proteins	Activate tumor-infiltrated T cells, induce T cell immunoactivation	128
Genetic engineering	IL-15 or IL-15Rα plasmids were transfected into HEK 293T	IL-15 or IL-15Rα	Activate tumor-infiltrated T cells	231
Genetic engineering	CD64 plasmids were transfected into HEK 293T	CD64	Block the PD-1/PD-L1 pathway	136
Genetic engineering	PD-1 was transfected into cancer cells	PD-1	Block the PD-1/PD-L1 pathway	232
Genetic engineering	PD-1 and CD40L were transfected into cancer cells	PD-1 and CD40L	Induce DC-mediated T cell immunoactivation, block the PD-1/PD-L1 pathway	131
Genetic engineering	aCD19 and PD-1 were transfected by lentivirus synchronously into DCs	aCD19 and PD-1	Accumulate in huCD19-expressing solid tumors, block PD-1/PD-L1 pathway	141
Genetic engineering	GPC3-scFv-CD47-nanobody DNA fragment and three C-terminal hemagglutinin tags was fused to the bacterial outer membrane protein ClyA	aGPC3 and aCD47	Actively targeting at HCC tumor site, block tumor CD47 and promote TAM	142
Genetic engineering	Plasmids that co-expressing the PD-1 and SIRPα Ig domain were transfected into HEK293 cells	PD-1 and SIRPα	Block the CD47/SIRPα and PD-1/PD-L1 pathway	133
Genetic engineering	SIRPα was transfected into cancer cells by lentivirus	SIRPα	Block CD47−SIRPα pathway, promote M2-to-M1 repolarization	233
Genetic engineering	CD64 cDNA was transfected into HEK 293T	CD64	Block the PD-1/PD-L1 pathway	136
Genetic engineering	aPD-L1 and aCD3 were transfected into HEK 293T	aPD-L1 and aCD3	Block the PD-1/PD-L1 pathway	140
Genetic engineering	IL-15/IL-15Rα gene transfected into BMDCs *via* adenovirus vectors	IL-15/IL-15Rα	Targets IL-15 to antigen-specific CTL	60
Genetic engineering	pMHC-I, aPD-1 and B7 co-stimulatory molecules were simultaneously transfected into DCs	pMHC-I, aPD-1 and B7 co-stimulatory molecules	Improve antigen delivery to lymphoid organs	129
Genetic engineering and membrane hybridization	PD-1 was transfected into cancer cells, fusing M1-NVs and PD1-overexpressed cancer cell-derived nanovesicles	PD-1 and macrophage cell membrane proteins	Block the PD-1/PD-L1 pathway	138
Genetic engineering and membrane hybridization	SIRPα, PD-1 were separately transfected into cancer cell; fusion of two cancer cell membranes	SIRPα and PD-1	Block the CD47/SIRPα and PD-1/PD-L1 pathway	132
Genetic engineering and membrane hybridization	SIRPα was transfected into cancer cells by lentivirus; SαV-C-NVs, M1-NVs, and P-NVs were mixed, sonicated and extruded through nanopores repeatedly to form hNVs	SIRPα, M1 macrohpage membrane proteins	Block CD47−SIRPα pathway, promote M2-to-M1 repolarization	134

5. Cell membrane origins and functional implications

The surface of the cell membrane exhibits specific proteins, enabling different cell types to be regarded as naturally functionalized liposomes[72]. Biomimetic nanovesicles derived from these membranes inherit the intrinsic biological characteristics of their source cells. In a variety of biomimetic nanovesicles derived from different cell origins, they play different roles in anti-tumor immunotherapy. The selection of membrane sources is primarily based on three key functional considerations: targeting capability,

immune evasion, and therapeutic needs. Targeting refers to the ability of membrane-derived vesicles to home to specific tissues or cells, exemplified by the homologous targeting of cancer cell membranes to tumors of the same origin[243]. Immune evasion strategies, such as utilizing RBC membranes, allow nanovesicles to evade clearance by the host immune system and functional requirements such as the hemostatic function of platelet membranes[244,245]. Through the rational selection of the membrane sources, biomimetic nanovesicles can achieve enhanced precision in drug delivery and improved therapeutic outcomes. Commonly used cell membranes include those derived from RBCs, cancer cells, immune cells, platelets and bacteria, each offering distinct advantages and limitations, as summarized in Fig. 10. In this section, we focus on discussing the characteristics and applications of several representative membrane sources.

5.1. Red blood cell membranes

Pharmacokinetics and biodistribution are key parameters that affect the therapeutic index of nanomedicines. Traditional nanoparticles are easily and rapidly cleared *in vivo*, which significantly limits their clinical application potential. In contrast, due to RBCs' inherent biochemical properties, a unique platform was provided for constructing drug delivery systems that can extend circulation time and continuously release therapeutic agents[246,247]. Proteomic analyses of human RBC membranes has identified over 300 distinct proteins, with CD47 and glycoproteins are the most abundant, highlighting their critical roles in immune evasion and circulation stability[248]. On the one hand, RBC membranes express CD47 which interacts with SIRPα on phagocytes to transmit a 'don't eat me' signal. Retaining CD47 expression in RBC-membrane-coated nanoparticles markedly reduces clearance by the MPS, thereby prolonging circulation time and improving bioavailability[87]. On the other hand, glycophorins (*e.g.*, Glycophorin A) are highly glycosylated and enriched in Sias, endowing RBC membranes and their derived nanovesicles with pronounced hydrophilicity and a net negative surface charge[249]. This negatively charged glycocalyx minimizes nonspecific adsorption of plasma proteins, further extending systemic retention and facilitating tumor accumulation through the EPR effect.

Harnessing these advantages, attempts have been made to exploit this functional feature to develop erythrocyte membrane-derived nanovesicles to enhance systemic drug delivery[250]. For example, Ding et al.[251] fabricated an RBC membrane-coated theranostic nanovesicles, where the RBC membrane coating notably prolonged circulation time and improved pharmacokinetic behavior. Pan et al.[252] further engineered RBC membrane-coated nanovesicles loaded with salidroside and indocyanine green, achieving hypoxia-targeted phototherapy for triple-negative breast cancer. The RBC membrane not only extended its circulation time but also facilitated escape from immune surveillance. Recent studies have also highlighted that the physiological status of RBCs significantly influences the functional performance of their derived nanovesicles. Fresh RBC membranes maintain CD47 expression and a well-preserved glycocalyx, so that ensuring efficient immune evasion and prolonged circulation. By contrast, senescent RBCs undergo membrane remodeling, including loss or modification of surface Sias, oxidation of membrane proteins, which collectively increase their recognition and clearance by macrophages in the liver and spleen[93,253].

Although it can provide excellent biocompatibility, long-term circulation, and immune evasion ability, RBC membrane-derived

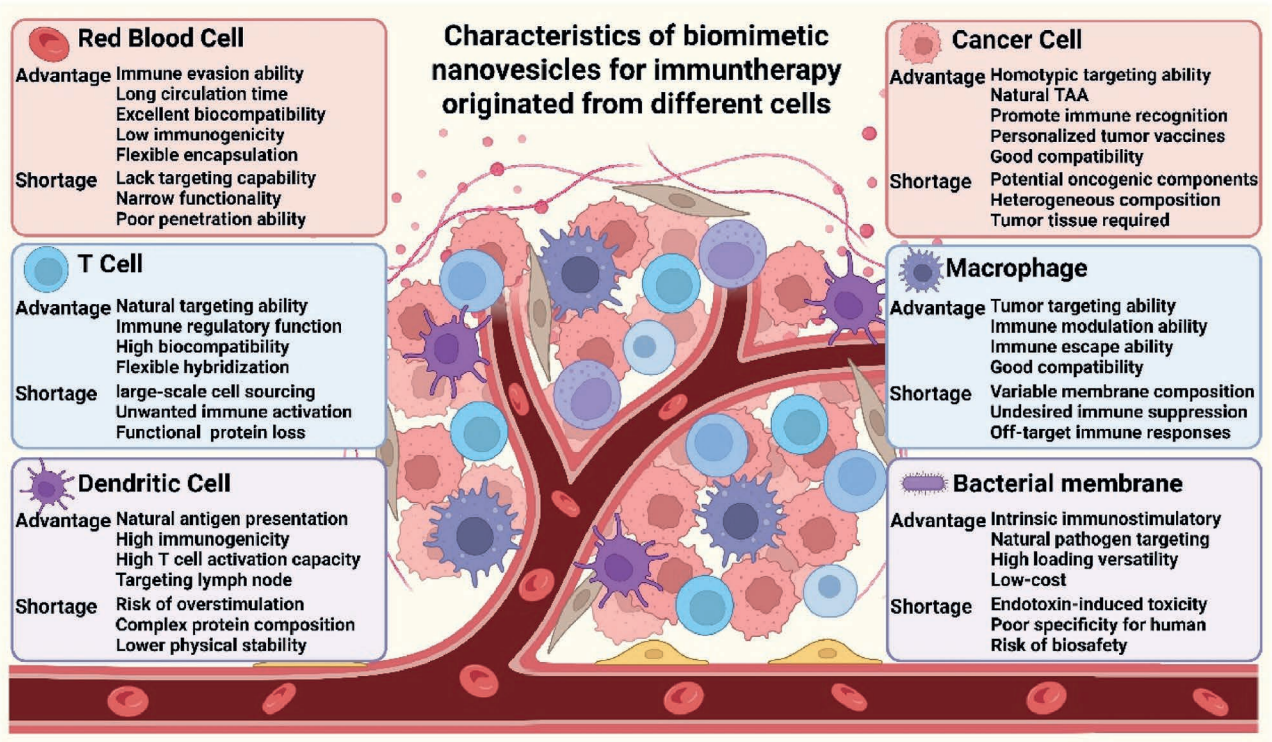


Figure 10 Key characteristics of immunotherapeutic biomimetic nanovesicles derived from distinct cellular origins. Created with BioRender.com.

nanovesicles still face certain limitations. Due to the absence of nuclei and organelles, RBC membranes contain relatively rare functional and targeting proteins, restricting their broader applicability in targeted therapies. Moreover, if there is a blood type mismatch between the source of erythrocyte membrane and the recipient, there may be a risk of xenogeneic immune response. To overcome these shortcomings, advanced strategies such as membrane hybridization and functional surface modifications are being actively explored, offering promising solutions to enhance the targeting capabilities and functional versatility of RBC-derived nanovesicles[254].

5.2. *Cancer cell membranes*

Cancer cell membranes have also been emerged as a widely utilized source in the designing of biomimetic nanovesicles[255]. Proteomic profiling of cancer cell plasmalemma, such as Ziegler et al.'[256]s study, identified a rich set of surface proteins, including tyrosine kinases, adhesion molecules, and structural proteins, across different breast cancer subtypes, demonstrating the molecular basis for homologous targeting and functional customization of nanovesicles. Owing to the presence of cell adhesion molecules, such as E-cadherin, N-cadherin, CD44, and EpCAM on their surface, cancer cell membranes endow nanovesicles with homologous targeting capabilities, thereby achieving more efficient tropism toward homologous tumor cells *in vivo* and enhancing tumor accumulation and intratumoral bioavailability[257,258]. For instance, Go et al.[259] prepared a nanovaccine based on a cancer cell membrane nanoparticle, which effectively activated tumor-specific $CD8^+$ T cells in both the presence and absence of DCs, thus induces more potent responses of tumor-specific $CD8^+$ T cells. To further enhance functionality, Xiong et al.[260] engineered a hybrid membrane system by fusing cancer cell membranes with RBC membranes, simultaneously improving both homologous targeting efficacy and systemic circulation longevity of the nanovesicles.

In addition, a variety of functional proteins and signaling molecules inherited from the parental cancer cell membranes are conducive to binding and penetrating into tumor tissues. For example, in HCC, the Cloaked nanocarrier platform retains membrane-specific proteins, enabling vesicles to strongly recognize HepG2 tumor cells and significantly inhibit tumor growth[261]. Moreover, CD47 is commonly observed on cancer cell membranes, which is a mechanism to evade clearance by host immune cells[262].

However, despite their promising advantages, cancer cell membrane-derived nanovesicles also face notable limitations. These include that cancer cell membranes may have residual cancer promoting factors, the high costs associated with large-scale membrane preparation, and substantial variability in membrane protein and lipid composition among different cancer cell lines, which collectively pose significant challenges to industrialization and standardization. Future efforts focusing on refining the preparation and purification processes are essential to fully harness the therapeutic potential of cancer cell membrane-based nanovesicles.

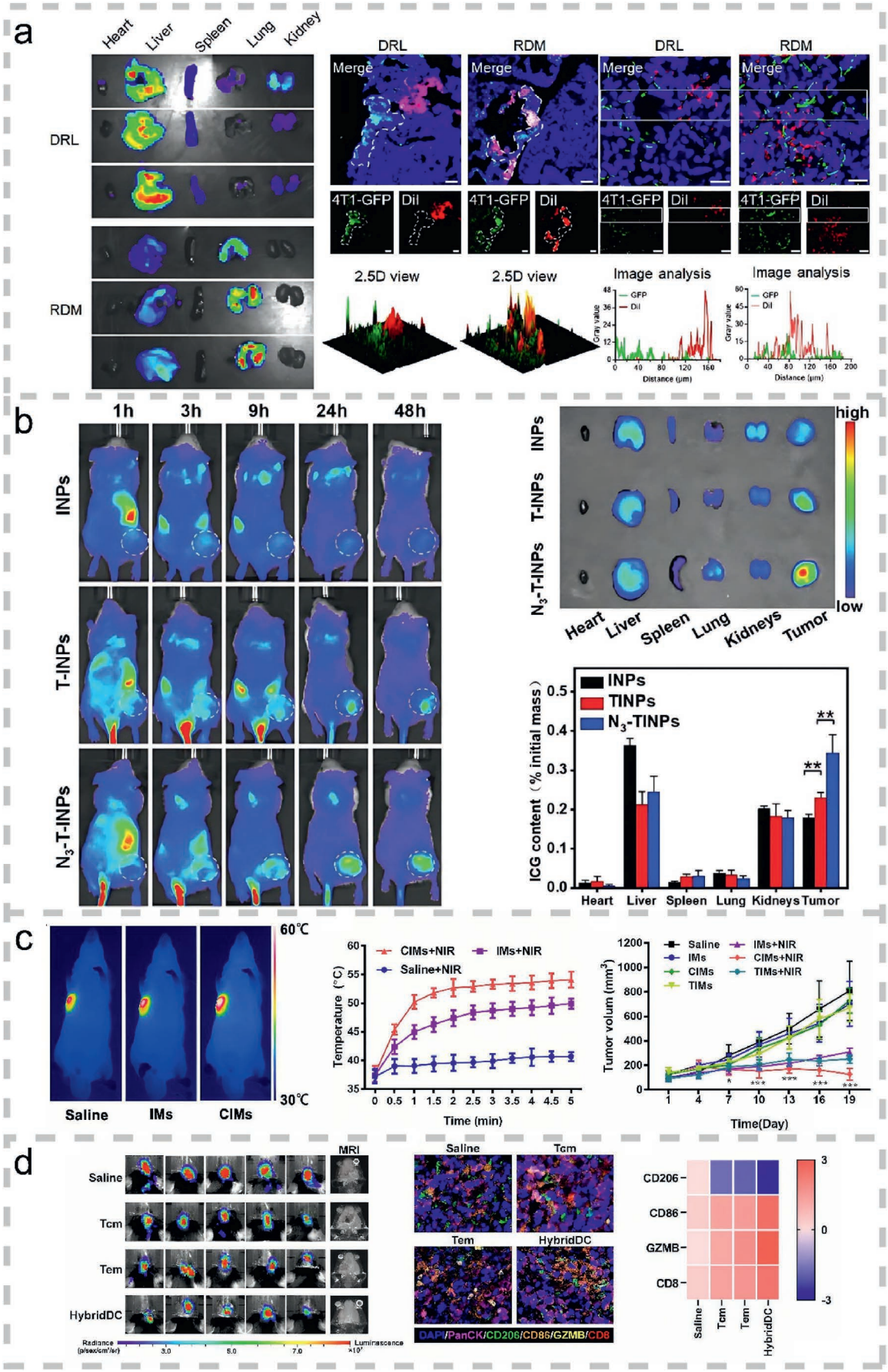
5.3. *Immune cell membranes*

Immune cells are an important component of the TME, and manipulating and regulating the interactions among different immune cell population is a key factor in the success of antitumor immunotherapy. Biomimetic nanovesicles covering immune cell membranes can inherit surface proteins, thereby enhancing their targeting capability and ability to regulate cellular interactions within the immune system[239,263]. Recent proteomic analyses of immune cell membranes have revealed highly specialized repertoires of receptors, adhesion molecules, and costimulatory ligands that underpin their functional diversity[264,265]. Given that distinct immune cells possess unique membrane protein profiles and functional attributes, a variety of immune cell types, including macrophages, T cells, and DCs, have been explored as membrane sources for the engineering of biomimetic nanovesicles. These designs aim at using the immunomodulatory properties of immune cells to optimize anti-tumor immunotherapeutic outcomes.

Macrophages are important participants in the innate immune response, with membrane surfaces enriched in diverse receptor proteins, showing natural tropism toward sites of inflammation and tumor tissues[266]. Firstly, macrophage membranes contain multiple integrins such as Mac-1, also known as CD11b/CD18, and adhesion receptors like VCAM1/ICAM1, which mediate recognition and binding with tumor or inflamed cells. Nanovesicles retaining these integrins and adhesion molecules can therefore enhance targeting and accumulation at tumor sites[267]. Secondly, macrophage membranes naturally express SIRPα, high-affinity SIRPα variants can molecularly bind tumor cells to disrupt the 'don't eat me' signal. This mechanism not only enhances the targeting of nanovesicles to CD47-overexpressing tumor cells, but also promotes macrophage polarization toward the M1 phenotype, thereby strengthening phagocytosis and antitumor responses[134]. In addition, the macrophage membranes are rich in PRRs recognition receptors, such as TLRs and chemokine receptors, which endow them with endocytosis capacity and immune stimulation potential[268]. These membrane proteins enable vesicle-coated carriers to simulate the behavior of macrophage, penetrate the tumor matrix more effectively, and simultaneously activate local immune responses.

Biomimetic nanovesicles derived from macrophages membranes aim to take advantages of this membrane protein-mediated tumor-targeting capability. In preclinical applications, macrophage-derived biomimetic nanovesicles have demonstrated potent antitumor immune effects, particularly against metastatic lesions, such as lung metastases, highlighting their potential as a promising platform for targeted cancer immunotherapy, as shown in Fig. 11A[269,270].

T cells, as central players in adaptive immunity, are unique in that they have T cell receptor (TCR) complex, which recognizes MHC-peptide complexes and determines antigen specificity. When preserved in biomimetic nanovesicles, TCRs confer tumor antigen-specific binding capacity, thereby enhancing targeting precision and immunoregulatory function. This property has been used to develop T cell membrane-derived nanoparticles, which have demonstrated effective tumor-targeting capabilities mediated by membrane-associated proteins[271]. However, due to the substantial heterogeneity both between different tumors and within individual tumors, this single targeting strategy may compromise the therapeutic efficacy of tumor targeting. Compared with a single targeting strategy, a dual-targeting strategy may provide a better efficiency of tumor accumulation, as shown in Fig. 11B[272]. In addition, T cell membranes are naturally enriched with the CD3 complex and the co-stimulatory molecule CD28, which are critical for signal transduction and T cell activation. Retaining these molecules within vesicles enables them to mimic the first and second signals provided by APCs, thereby activating exogenous T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DAPI/PanCK/CD206/CD86/GZMB/CD8
CD206
CD86
GZMB
CD8

cells and promoting anti-tumor immunity[273]. Besides, chimeric antigen receptor T cell (CAR-T) technology offers a more defined and enhanced antigen specificity for T cell populations. Incorporating membranes from engineered CAR-T cells into biomimetic nanovesicles has been shown to further improve targeting precision, often outperforming vesicles derived from homologous cancer cell membranes in preclinical studies, as shown in Fig. 11C[274,275]. These findings highlight the potential of leveraging engineered T cell membranes to overcome tumor heterogeneity and enhance the therapeutic outcomes of nanovesicle-based immunotherapies.

DCs serve as a critical bridge between innate and adaptive immunity, playing a central role in initiating and modulating pathogen-specific adaptive immune responses[276].

Their membranes are characterized by the abundant expression of MHC1 and MHC2 molecules, as well as co-stimulatory molecules such as CD80 and CD86, these molecules can mimic the antigen presenting function of DCs, providing the first signal (MHC−antigen complex) and the second signal (CD80/CD86) to T cells, thereby activating both $CD4^+$ and $CD8^+$ T cells and enhancing antitumor immune responses[277]. For example, Ochyl et al.[127] developed a DC membrane-based vesicle platform capable of efficiently activating T cells, thereby enhancing immune responses against tumors. In addition, DC membranes contain chemokine receptors such as CCR7 and adhesion molecules such as ICAM1, which facilitate nanovesicle trafficking to lymph nodes and strengthen interactions with T cells, promoting antigen presentation and immunogenicity[278]. However, traditional DC vaccines are subject to various limitations, such as low antigen delivery efficiency, poor lymph node targeting, and the potential risks of live-cell transfusion. Recent progress has addressed these challenges by modifying DC membranes with additional functional components. Modified hybrid DC membranes-derived nanovesicles have demonstrated the ability to reprogram the TME, as showed in Fig. 11D, significantly enhancing the effectiveness of tumor immunotherapy[279]. These strategies suggest a promising direction for overcoming the inherent shortcomings of traditional DC-based therapies.

Recent studies have shown that the phenotypic state of immune cells strongly influences the biological properties of their derived nanovesicles. For instance, macrophage polarization toward the M1 or M2 phenotype results in different membrane proteomic profiles: M1-derived vesicles are rich in pro-inflammatory mediators and can promote immune activation; M2-derived vesicles carry anti-inflammatory markers and may contribute to tumor immune evasion[280]. Similarly, T cells in different activated states exhibit different expression of co-stimulatory molecules such as CD28 and immune checkpoints like PD1, which can be inherited by their vesicles and directly affect the results of immune regulatory outcomes[281]. DCs also show maturation-dependent differences. Vesicles from mature DCs exhibit higher levels of MHC and co-stimulatory molecules, enhancing T cell priming compared with vesicles from immature DCs[282]. These phenotype-dependent variations emphasize the importance of carefully selecting and characterizing the source of immune cells when designing biomimetic nanovesicles, as they directly impact target specificity, immune modulation, and overall therapeutic efficacy.

In conclusion, immune cell-derived biomimetic nanovesicles utilize the biological functions conferred by their native membrane surface proteins to actively reshape the TME. Similar to other sources of membrane vesicles, immune cell membranes can be further engineered through techniques such as genetic transfection, membrane hybridization, and chemical modification, thereby endowing nanovesicles with enhanced or multifunctional properties. Importantly, the functional performance of these vesicles is also influenced by the physiological state of the donor cells, as factors such as RBC aging or immune cell activation phenotypes can significantly alter membrane stability, receptor profiles, and targeting efficiency. These strategies significantly broaden the application potential of immune cell membrane-derived vesicles in anti-tumor immunotherapy.

5.4. Bacterial outer membranes

OMVs are spherical nanostructures naturally secreted by Gram-negative bacteria and encapsulated by lipid bilayers, typically ranging from 20 to 250 nm in diameter[283]. More than a century ago, a cancer patient accidently contracted bacterial, which triggered the initial exploration of using bacteria to stimulate anti-tumor immune responses[284]. In recent years, an increasing amount of evidence has shown that OMV possesses unique biological properties, including inherent immunogenicity, adjuvant properties, and the ability to naturally deliver bioactive molecules, making them promising platforms for anti-tumor immunotherapy.

One of the most notable advantages of OMVs is that they are naturally rich in innate immunostimulating molecules, such as lipopolysaccharides (LPS), outer membrane proteins, and lipoproteins, which are recognized as PAMPs by PRRs such as TLR4 and TLR2[187]. These molecules endow OMVs with strong immunogenicity, enabling activation of DCs and macrophages, thereby promoting antigen presentation and innate immune responses and ultimately enhancing adaptive immunity. Particularly, OMVs from physiochemical or genetically engineered bacteria show enhanced potential for the development of anti-tumor vaccine[285]. For instance, Li et al.[142] designed a genetically programmed nanovesicle based on OMVs, displaying anti-CD47 nanobodies and anti-GPC3 scFv on its surface, significantly reshaping the TME by taking advantages of the immunogenicity of OMVs. Lu et al.[286] further utilized the strong immunostimulatory properties of OMVs to activate the expression of co-stimulatory signals in APCs, enhancing the overall immune activation. Moreover, Yang et al.[287] developed a covalent organic framework based on the membrane of *Fusobacterium nucleatum (F.n.)*, a common intratumoral bacterium. This bacterial membrane-based system effectively

Figure 11 (a) *Ex vivo* imaging of Dil-labeled liposome (named as DRL) and a spatial drug-laden M1 macrophages system (named as RDM) in the major organs and metastatic lungs at 4 h postinjection[269]. Reproduced with permission from Ref. 269. Copyright © 2025, American Chemical Society. (b) *In vivo* targeting and biodistribution of dual-targeting indocyanine green nanoparticles coated with N3-labeled T cell membrane[272]. Reproduced with permission from Ref. 272. Copyright © 2025, John Wiley and Sons. (c) *In vivo* anti-tumor effects of IR780-loaded mesoporous silica nanoparticles and CAR-T Cell membrane-coated nanoparticles[275]. Reproduced with permission from Ref. 275. Copyright © 2025, Ivyspring International Publisher. (d) Luminescence images and multiplex immunofluorescence analysis shows the personalized DC-mimicking nanovaccine boosts memory T cells for long-lasting immunity[276]. Reproduced with permission from Ref. 276. Copyright © 2025, American Chemical Society.

'warmed' the immunologically 'cold' tumor by remodeling the TME and inducing the formation of tertiary lymphoid structures, offering a new strategy for overcoming tumor immune resistance.

In addition to their immunogenicity, OMVs also has an inherent targeting capabilities, enabling them to penetrate biological barriers such as the blood−brain barrier, which endows the application of nanodrug delivery with unique applications[288]. Moreover, OMVs exhibit strong tolerance to a variety of bioengineering manipulations, including ultrasonication, filtration compression, and electroporation, thus facilitating their functionalization for diverse therapeutic strategies[289]. However, there are still several challenges remain to be addressed before clinical translation. OMVs derived from bacteria itself contain components with endotoxin activity, posing the risk of toxic reactions such as fever and septic shock. Furthermore, although the PAMPs on the surface of OMV are valuable for immune activation, overstimulation may induce excessive inflammatory responses or systemic toxicity. Therefore, ensuring biosafety remains a critical consideration in the clinical development and application of OMV-based biomimetic nanovesicles.

5.5. Synthetic membrane-based nanocarriers

Although we focus on nanovesicles derived from natural cell membranes, it is also important to consider the artificially originated nanovesicles. Liposomes and LNPs are the most widely used artificial membrane-based nanocarriers and have long been the benchmarks for drug delivery, particularly in oncology and vaccine fields[67,290]. Unlike biomimetic nanovesicles, which inherit functional proteins and receptors directly from their parental cells, liposomes and LNPs rely on artificial lipid formulations and chemical modifications to achieve targeting or immunomodulatory functions. Therefore, they provide valuable backgrounds for evaluating the advantages and limitations of membrane-derived vesicles.

Structurally, liposomes and LNPs are composed of lipid bilayers or lipid−polymer assemblies that can encapsulate small molecules, nucleic acids, or proteins. For example, Anthiya et al.[291] designed an LNP loaded with *KRAS* siRNA, which demonstrated strong tumor accumulation and antitumor efficacy. Clinically, they form the basis of some FDA-approved preparations, including doxorubicin liposomes for cancer chemotherapy and LNP-based mRNA vaccines, highlighting their translational feasibility[292,293].

However, these systems lack the endogenous surface proteins in biomimetic nanovesicles, which limit their ability to participate in natural biological interactions. In contrast, biomimetic nanovesicles can inherit functional complexity from their parental cells. This endows them with enhanced immune compatibility, reduced clearance rates, and programmable functions through surface engineering, thereby providing a unique balance between natural bioactivity and design versatility. Therefore, biomimetic vesicles offer greater flexibility in immune modulation. Together, these differences highlight why biomimetic nanovesicles are increasingly regarded as a promising next-generation alternative to traditional artificial nanocarriers.

Beyond synthetic systems, membrane-derived nanovesicles from different cell types remain the most widely used sources for therapeutic design. In addition, other membrane sources, such as those derived from platelets and stem cells, have also been explored. Each possesses unique biological properties, including targeting, immune modulation, and tissue repair capabilities. Furthermore, as naturally secreted extracellular vesicles, exosomes originate from the endosomal biogenesis pathway and carry a wide range of cargos, including proteins, lipids, and nucleic acids, which reflect the heterogeneous composition of their donor cells[294]. This endogenous membrane structure provides them with inherent biocompatibility and natural communication functions, making them attractive as drug delivery platforms. However, biomimetic nanovesicles directly inherit membrane proteins and receptors from defined parental cells, preserving specific biological functions such as immune evasion (from RBCs), homotypic targeting (from cancer cells), or immune activation (from DCs). This origin-aware design provides greater predictability and consistency, underscoring its advantage over exosomes in functional optimization.

Each membrane type presents unique advantages and limitations. In Table 3, we summarized different membrane sources and synthetic nanocarriers, highlighting how their characteristic surface proteins contribute to specific advantages and limitations in cancer immunotherapy. Therefore, the selection of appropriate membrane sources should be based on a comprehensive evaluation of TME characteristics, therapeutic objectives, and the specific requirements of antitumor immunotherapy strategies.

6. Conclusions and perspectives

Membrane-derived biomimetic nanovesicles keep the functional proteins, receptor molecules, and structural features of their source cell membranes. They also keep their natural lipid bilayer structure, thereby exhibiting inherent biological activities, excellent biocompatibility and reduced immunogenicity. Recent advances in antibody design, including bispecific and trispecific antibodies, have further enriched the functional diversity of biomimetic nanovesicle platforms, thereby achieving precise immune modulation[295,296]. Meanwhile, bioengineering techniques such as genetic engineering, click chemistry, and membrane hybridization offer powerful tools to change the biological functions of nanovesicles[297]. Together, these innovations highlight the great potential of membrane-derived biomimetic nanovesicles in cancer immunotherapy, such as cancer vaccine delivery, immune checkpoint blockade, and cytokine transport.

Due to the flexible of their surface molecules, biomimetic nanovesicles can regulate many aspects of anti-tumor immunity. They can block immune escape pathways, activate various immune effector cells, remodel the immunosuppressive TME, and enhance antigen-specific immune responses. By participating in these key immune processes, nanovesicles contribute to achieving more robust, precise, and personalized cancer immunotherapies. Although nanovesicles have diverse functions, a comprehensive understanding of the biological mechanisms underlying their interaction with the immune system remains incomplete[213,298]. Clarifying these mechanisms is crucial for optimizing the design of nanovesicles and maximizing therapeutic effects.

When placing biomimetic nanovesicles within the broader nanomedicine fields, it is important to compare them with other major delivery systems, including exosomes and synthetic nanocarriers. Exosome-based therapeutics have also attracted much attention in recent years as a novel class of biologics with promising applications in drug delivery, intercellular communication, and immunomodulation. Several exosome-based therapies have already entered clinical trials. Especially in the field of oncology and regenerative medicine, showing their translational

Table 3 Comparative features of different membrane sources and synthetic nanocarriers.

Membrane source	Key surface proteins	Advantages	Limitations	Protein−function relationship
RBC membranes	CD47, sialic acid rich glycoproteins	Excellent immune evasion, prolonged circulation, reduced clearance by mononuclear phagocyte system (MPS)	Lack of targeting ligands; risk of alloimmunity if donor −recipient mismatch	CD47 binds SIRPA to deliver 'don't eat me' signals; glycophorin sialic acid confers negative charge reducing opsonization and protein adsorption
Cancer cell membranes	CAMs (E-cadherin, N-cadherin, EpCAM, CD44), CD47	Homotypic targeting to parental tumor, preservation of diverse tumor-associated antigens	Risk of carrying oncogenic factors; variability in membrane composition; scalability issues	CAMs mediate homotypic adhesion to tumor cells; CD47 reduces immune clearance
Macrophage membranes	Integrins, ICAM1/ VCAM1, SIRPA, TLRs	Natural tropism toward inflamed/tumor sites, immune activation potential, MPS mimicry	Possible unintended immune stimulation; phenotypic variability	Integrins/ICAM1 enable tumor adhesion; SIRPα variants block CD47 'don't eat me' signals; TLRs provide innate immune activation
T cell membranes	TCR complex, CD3, CD28	Antigen-specific targeting; potential to provide activation signals to T cells	Limited by tumor antigen heterogeneity; may require CAR-T modification	TCR recognizes MHC −peptide complexes; CD3/ CD28 provide activation signals mimicking APC function
Dendritic cell membranes	MHC1, MHC2, CD80/CD86, CD40, ICAM1, CCR7	Strong antigen presentation capacity, promotion of $CD4^+$ and $CD8^+$ T cell activation, LN homing	Limited large-scale production; short lifespan *in vivo*	MHC + CD80/CD86 mimic antigen-presenting cells; CCR7 supports LN targeting; CD40/CD83 promote immune activation
OMVs	LPS, OmpA, porins, adhesins, lipoproteins	Strong innate immune activation, natural adjuvanticity, ability to cross biological barriers	Risk of endotoxin toxicity; variability in composition	LPS/TLR4 activate DCs and macrophages; adhesins promote host-cell binding and uptake
Synthetic liposomes/ LNPs	Artificial lipid bilayer (no native proteins)	High stability, scalable production, regulatory familiarity, proven success (*e.g.*, mRNA vaccines, doxorubicin liposomes)	Lack of intrinsic biological signals; depending on chemical conjugation for targeting; limited immune interaction	Surface ligands must be artificially conjugated; absence of native proteins limits immune evasion and natural targeting

potential. However, exosomes still face challenges related to low yield, mixed cargo, and limited engineering flexibility due to their endogenous biogenesis *via* endosomal pathways. Membrane-derived biomimetic nanovesicles, by contrast, offer higher scalability, repeatable, and wider range of opportunities for surface engineering, while retaining essential membrane proteins and lipids from source cells. These features allow for the adoption of modular strategies such as hybridization, ligand coupling, and genetic modification, giving them outstanding design flexibility and production efficiency for immune modulation and targeted cancer therapy. Similarly, artificial nanocarriers such as liposomes and LNPs remain the most established delivery platforms, with well-developed manufacturing protocols, regulatory familiarity, and formulation versatility. Their limitations, however, lie in the absence of intrinsic biological signals, as they rely on artificial lipid compositions and chemical conjugation for functionalization. In contrast, membrane-derived biomimetic nanovesicles naturally integrate complex membrane proteins and receptors, combining endogenous bioactivity with flexible engineering strategies. This unique balance positions them as a compelling alternative to both exosomes and artificial nanocarriers in cancer immunotherapy.

Although membrane-derived biomimetic nanovesicles have attracted extensive research interest, considerable challenges must be addressed to facilitate their clinical translation[299]. On the one hand, immunotherapy strategies are evolving rapidly, with the emergence of multi-specific antibody technologies offering possibilities for orchestrating complex immune cell interactions and achieving spatiotemporally controlled therapeutic delivery. On the other hand, the discovery and validation of novel TAAs may provide opportunities to enhance the specificity and durability of nanovesicle-based immunotherapies[300,301]. Despite these exciting prospects, most research on biomimetic nanovesicles remains confined to preclinical studies, with only a few advancing into early-phase clinical trials, as summarized in Table 4[302-307].

To successfully transform membrane-derived biomimetic nanovesicles into clinical applications, it is crucial to establish a standardized and reproducible manufacturing process. Current preparation methods include membrane extrusion, sonication, microfluidics, and freeze−thaw cycling. Each method has unique advantages in terms of vesicle uniformity, scalability, and preservation of membrane proteins[308,309]. Among these, microfluidic-based platforms are promising, as they can achieve continuous, controllable, and high-throughput vesicle fabrication with minimizing structural damage to the greatest extent[310]. Beyond the manufacturing steps, purification methods such as density-gradient centrifugation, tangential flow filtration, and size-exclusion chromatography are also required to ensure high purity and remove contaminants, such as cellular debris and endotoxins[309]. It is also necessary to define and monitor key Critical quality attributes (CQAs) to ensure both safety and efficacy. Key parameters include

Table 4 Biomimetic nanovesicles entered clinical trials.

Country	Membrane source	Tumor	Biofunction	Phase	Enrollment	NCT number	Current status	Last update posted	Ref.
China	UCMSC	AML	Promoting recovery of myelosuppression	I	9	NCT06245746	Not yet recruiting	01/2025	302
U.S.	MSC	PDAC	Deliver KrasG12D siRNA	I	15	NCT03608631	Active, not recruiting	10/2024	303
U.S.	Not applicable	HCC	Macrophage reprogramme	I	9	NCT05375604	Terminated	06/2023	304
China	Hybrid cell membrane	Bladder cancer	Activate the immune response and improve the TME of cancer lesions	I	9	NCT05559177	Recruiting	09/2022	305
France	Cancer cell	DLBCL	Analyze the function of CD20 and PDL1 expression on DLBCL subtypes and patient outcomes	−	90	NCT03985696	Recruiting	07/2022	306
France	DC	NSCLC	Activate the innate and adaptive immunity	II	47	NCT01159288	Completed	03/2018	307

vesicle size distribution and polydispersity index, surface charge (zeta potential), membrane protein composition and orientation, lipid-to-protein ratio, sterility, and endotoxin levels[311,312]. Stability and batch-to-batch consistency are equally important, and standardized storage conditions and validated release testing. In fact, reproducibility in surface protein profiles has been demonstrated by Korchak et al.[313] using a multiplex bead-based assay across 37 markers for MSC-derived EVs. For immunotherapy applications, the functional retention of membrane proteins represents a unique CQA that directly influences immune evasion, targeting specificity, and immunomodulatory efficacy. Regulatory agencies are increasingly emphasizing the need for strong characterization, including proteomic profiling and potency assays, to establish a reliable correlation between manufacturing quality and therapeutic performance[314]. Future clinical trials should also be designed to validate these standardized vesicle platforms, with early-phase studies focusing on combination strategies with checkpoint inhibitors or stratified designs to highlight source-specific advantages.

Establishing standard manufacturing steps and defining CQAs are essential. However, even with these strategies in place, there are still many barriers to clinical translation. The main concern includes biosafety risks, such as residual toxicity, the oncogenic potential of certain source membranes, and the possibility of eliciting excessive immune activation due to the intrinsic immunogenicity of materials like bacterial membranes or cancer cell membranes. Moreover, the complexities involved in large-scale production because of the cell source, the complex preparation processes, and ethical considerations. These problems create major technical and regulatory challenges that must be carefully overcome.

In conclusion, membrane-derived biomimetic nanovesicles offer a novel and highly versatile platform for the development of next-generation cancer immunotherapies. They have significantly expanded our understanding of the immune landscape in oncology, illuminating key processes such as immune activation, tumor immune microenvironment remodeling, and immune evasion mechanisms. Leveraging their plasticity, functional tunability, and excellent biocompatibility, engineered biomimetic nanovesicles hold great promise for personalized and precision immunotherapy.

Looking forward, integrating good manufacturing practice-compatible platforms with automated production and advanced analytics will be critical to accelerate their clinical deployment. By defining standardized workflows and critical quality benchmarks, this emerging class of therapeutics can be translated more efficiently and safely into clinical practice, thereby strengthening their potential as next-generation cancer immunotherapy platforms.

Future research directions should therefore focus on rationally integrating biomimetic nanovesicles with emerging therapeutic modalities, optimizing their biological performance, addressing safety and production challenges, and accelerating clinical translation. In addition, early-phase clinical trials should explore rational combinations of biomimetic nanovesicles with existing immunotherapies, as well as stratified trial designs that utilize membrane-specific advantages. By overcoming these obstacles, biomimetic nanovesicles are poised to make substantial contributions to the advancement of cancer treatment and improve outcomes for patients worldwide.

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Conflicts of interest

The authors declare no conflicts of interest.

Declaration of generative AI

During the preparation of this work, the authors used ChatGPT (OpenAI) and Grammarly in order to polish the scientific language and check grammatical accuracy. After using these tools, the authors carefully reviewed and edited the content as needed and take full responsibility for the content of the published article.

References

1. Andrews LP, Yano H, Vignali DAA. Inhibitory receptors and ligands beyond PD-1, PD-L1 and CTLA-4: breakthroughs or backups. *Nat Immunol* 2019;**20**:1425−34.
2. Lu C, Yang D, Klement JD, Colson YL, Oberlies NH, Pearce CJ, et al. G6PD functions as a metabolic checkpoint to regulate granzyme B expression in tumor-specific cytotoxic T lymphocytes. *J Immunother Cancer* 2022;**10**:e003543.
3. Wildes TJ, Dyson KA, Francis C, Wummer B, Yang C, Yegorov O, et al. Immune escape after adoptive T-cell therapy for malignant gliomas. *Clin Cancer Res* 2020;**26**:5689−700.
4. Kennedy LB, Salama AKS. A review of cancer immunotherapy toxicity. *CA Cancer J Clin* 2020;**70**:86−104.
5. Shen KY, Zhu Y, Xie SZ, Qin LX. Immunosuppressive tumor microenvironment and immunotherapy of hepatocellular carcinoma: current status and prospectives. *J Hematol Oncol* 2024;**17**:25.
6. Brandenburg A, Heine A, Brossart P. Next-generation cancer vaccines and emerging immunotherapy combinations. *Trends Cancer* 2024;**10**:749−69.
7. Wellhausen N, O'Connell RP, Lesch S, Engel NW, Rennels AK, Gonzales D, et al. Epitope base editing CD45 in hematopoietic cells enables universal blood cancer immune therapy. *Sci Transl Med* 2023;**15**:eadi1145.
8. Rohaan MW, Borch TH, van den Berg JH, Met O, Kessels R, Geukes Foppen MH, et al. Tumor-infiltrating lymphocyte therapy or ipilimumab in advanced melanoma. *N Engl J Med* 2022;**387**:2113−25.
9. Garassino MC, Gadgeel S, Speranza G, Felip E, Esteban E, Domine M, et al. Pembrolizumab plus pemetrexed and platinum in nonsquamous non-small-cell lung cancer: 5-year outcomes from the phase 3 KEYNOTE-189 study. *J Clin Oncol* 2023;**41**:1992−8.
10. Chan ATC, Lee VHF, Hong RL, Ahn MJ, Chong WQ, Kim SB, et al. Pembrolizumab monotherapy *versus* chemotherapy in platinum-pretreated, recurrent or metastatic nasopharyngeal cancer (KEYNOTE-122): an open-label, randomized, phase III trial. *Ann Oncol* 2023;**34**:251−61.
11. Wang DR, Wu XL, Sun YL. Therapeutic targets and biomarkers of tumor immunotherapy: response *versus* non-response. *Signal Transduct Targeted Ther* 2022;**7**:331.
12. Keam S, Turner N, Kugeratski FG, Rico R, Colunga-Minutti J, Poojary R, et al. Toxicity in the era of immune checkpoint inhibitor therapy. *Front Immunol* 2024;**15**:1447021.
13. Liu LL, Skribek M, Harmenberg U, Gerling M. Systemic inflammatory syndromes as life-threatening side effects of immune checkpoint inhibitors: case report and systematic review of the literature. *J Immunother Cancer* 2023;**11**:e005841.
14. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med* 2018;**378**:158−68.
15. Belum VR, Benhuri B, Postow MA, Hellmann MD, Lesokhin AM, Segal NH, et al. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. *Eur J Cancer* 2016;**60**:12−25.
16. De Martin E, Michot JM, Papouin B, Champiat S, Mateus C, Lambotte O, et al. Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors. *J Hepatol* 2018;**68**:1181−90.
17. O'Hare M, Guidon AC. Peripheral nervous system immune-related adverse events due to checkpoint inhibition. *Nat Rev Neurol* 2024;**20**:509−25.
18. Ding M, Zhang X, Wang J, Gao F, Zheng X, Yuan J, et al. Treatment and outcomes of immune checkpoint inhibitors-associated colitis/diarrhea: a systematic review and meta-analysis. *Dig Liver Dis* 2023;**55**:1621−31.
19. Johnson J, Goldner W, Abdallah D, Qiu F, Ganti AK, Kotwal A. Hypophysitis and secondary adrenal insufficiency from immune checkpoint inhibitors: diagnostic challenges and link with survival. *J Natl Compr Cancer Netw* 2023;**21**:281−7.
20. Johnson DB, Nebhan CA, Moslehi JJ, Balko JM. Immune-checkpoint inhibitors: long-term implications of toxicity. *Nat Rev Clin Oncol* 2022;**19**:254−67.
21. Deshpande RP, Sharma S, Watabe K. The confounders of cancer immunotherapy: roles of lifestyle, metabolic disorders and sociological factors. *Cancers (Basel)* 2020;**12**:2983.
22. Jansen YJL, Rozeman EA, Mason R, Goldinger SM, Geukes Foppen MH, Hoejberg L, et al. Discontinuation of anti-PD-1 antibody therapy in the absence of disease progression or treatment limiting toxicity: clinical outcomes in advanced melanoma. *Ann Oncol* 2019;**30**:1154−61.
23. Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. *J Clin Oncol* 2010;**28**:3167−75.
24. Shen X, Zhao B. Efficacy of PD-1 or PD-L1 inhibitors and PD-L1 expression status in cancer: meta-analysis. *BMJ* 2018;**362**:k3529.
25. Akamatsu H, Teraoka S, Takamori S, Miura S, Hayashi H, Hata A, et al. Nivolumab retreatment in non-small cell lung cancer patients who responded to prior immune checkpoint inhibitors and had ICI-free intervals (WJOG9616L). *Clin Cancer Res* 2022;**28**:OF1−7.
26. Kong J, Zhao X, Singhal A, Park S, Bachelder R, Shen J, et al. Prediction of immunotherapy response using mutations to cancer protein assemblies. *Sci Adv* 2024;**10**:eado9746.
27. Ding L, Chen F. Predicting tumor response to PD-1 blockade. *N Engl J Med* 2019;**381**:477−9.
28. Abizanda-Campo S, Virumbrales-Munoz M, Humayun M, Marmol I, Beebe DJ, Ochoa I, et al. Microphysiological systems for solid tumor immunotherapy: opportunities and challenges. *Microsyst Nanoeng* 2023;**9**:154.
29. Zhang B, Liu J, Mo Y, Zhang K, Huang B, Shang D. $CD8^+$ T cell exhaustion and its regulatory mechanisms in the tumor microenvironment: key to the success of immunotherapy. *Front Immunol* 2024;**15**:1476904.
30. Franco F, Jaccard A, Romero P, Yu YR, Ho PC. Metabolic and epigenetic regulation of T-cell exhaustion. *Nat Metab* 2020;**2**:1001−12.
31. Pauken KE, Sammons MA, Odorizzi PM, Manne S, Godec J, Khan O, et al. Epigenetic stability of exhausted T cells limits durability of reinvigoration by PD-1 blockade. *Science* 2016;**354**:1160−5.
32. Ma S, Tian Y, Peng J, Chen C, Peng X, Zhao F, et al. Identification of a small-molecule Tim-3 inhibitor to potentiate T cell-mediated antitumor immunotherapy in preclinical mouse models. *Sci Transl Med* 2023;**15**:eadg6752.
33. Aggarwal V, Workman CJ, Vignali DAA. LAG-3 as the third checkpoint inhibitor. *Nat Immunol* 2023;**24**:1415−22.

34. Zebley CC, Zehn D, Gottschalk S, Chi H. T cell dysfunction and therapeutic intervention in cancer. *Nat Immunol* 2024;**25**:1344−54.
35. Schietinger A, Philip M, Krisnawan VE, Chiu EY, Delrow JJ, Basom RS, et al. Tumor-specific T cell dysfunction is a dynamic antigen-driven differentiation program initiated early during tumorigenesis. *Immunity* 2016;**45**:389−401.
36. Dikiy S, Rudensky AY. Principles of regulatory T cell function. *Immunity* 2023;**56**:240−55.
37. Kim R, Hashimoto A, Markosyan N, Tyurin VA, Tyurina YY, Kar G, et al. Ferroptosis of tumour neutrophils causes immune suppression in cancer. *Nature* 2022;**612**:338−46.
38. Chen D, Zhang X, Li Z, Zhu B. Metabolic regulatory crosstalk between tumor microenvironment and tumor-associated macrophages. *Theranostics* 2021;**11**:1016−30.
39. Oliver AJ, Keam SP, von Scheidt B, Zanker DJ, Harrison AJ, Tantalo DG, et al. Primary and metastatic breast tumors cross-talk to influence immunotherapy responses. *OncoImmunology* 2020;**9**: 1802979.
40. Zhou Y, Mo S, Cui H, Sun R, Zhang W, Zhuang X, et al. Immune−tumor interaction dictates spatially directed evolution of esophageal squamous cell carcinoma. *Natl Sci Rev* 2024;**11**:nwae150.
41. Jovcevska I, Muyldermans S. The therapeutic potential of nanobodies. *BioDrugs* 2020;**34**:11−26.
42. Sun S, Ding Z, Yang X, Zhao X, Zhao M, Gao L, et al. Nanobody: a small antibody with big implications for tumor therapeutic strategy. *Int J Nanomed* 2021;**16**:2337−56.
43. Fang RH, Zhang L. Nanoparticle-based modulation of the immune system. *Annu Rev Chem Biomol Eng* 2016;**7**:305−26.
44. Sun R, Xiang J, Zhou Q, Piao Y, Tang J, Shao S, et al. The tumor EPR effect for cancer drug delivery: current status, limitations, and alternatives. *Adv Drug Deliv Rev* 2022;**191**:114614.
45. Takakura Y, Takahashi Y. Strategies for persistent retention of macromolecules and nanoparticles in the blood circulation. *J Control Release* 2022;**350**:486−93.
46. Wang X, Ning S, Tao W, Wang K, Li J, Huang L, et al. Cytomembrane-targeted photodynamic priming triggers extracellular vesicle storm for deep penetration and complete destruction of bladder cancer. *Nano Today* 2024;**56**:102311.
47. Yang Y, Liu Y, Yang Q, Liu T. The application of selenium nanoparticles in immunotherapy. *Nano Biomedicine and Engineering* 2024;**16**:345−56.
48. Wang K, Ye H, Zhang X, Wang X, Yang B, Luo C, et al. An exosome-like programmable-bioactivating paclitaxel prodrug nanoplatform for enhanced breast cancer metastasis inhibition. *Biomaterials* 2020;**257**:120224.
49. Deng S, Gu J, Jiang Z, Cao Y, Mao F, Xue Y, et al. Application of nanotechnology in the early diagnosis and comprehensive treatment of gastrointestinal cancer. *J Nanobiotechnol* 2022;**20**:415.
50. Azizi M, Dianat-Moghadam H, Salehi R, Farshbaf M, Iyengar D, Sau S, et al. Interactions between tumor biology and targeted nanoplatforms for imaging applications. *Adv Funct Mater* 2020;**30**: 1910402.
51. Sun F, Ning S, Fan X, Wang X, Lin Z, Zhao J, et al. Engineered cytomembrane nanovesicles trigger *in situ* storm of engineered extracellular vesicles for cascade tumor penetration and immune microenvironment remodeling. *Nano Today* 2025;**61**:102604.
52. Fan Z, Jiang C, Wang Y, Wang K, Marsh J, Zhang D, et al. Engineered extracellular vesicles as intelligent nanosystems for next-generation nanomedicine. *Nanoscale Horiz* 2022;**7**:682−714.
53. Fan X, Wang K, Lu Q, Lu Y, Sun J. Cell-based drug delivery systems participate in the cancer immunity cycle for improved cancer immunotherapy. *Small* 2023;**19**:e2205166.
54. Espiau-Romera P, Gordo-Ortiz A, Ortiz-de-Solórzano I, Sancho P. Metabolic features of tumor-derived extracellular vesicles: challenges and opportunities. *Extracell Vesicles Circ Nucleic Acids* 2024; **5**:455−70.
55. He Y, Wang K, Lu Y, Sun B, Sun J, Liang W. Monensin enhanced generation of extracellular vesicles as transfersomes for promoting tumor penetration of pyropheophorbide-a from fusogenic liposome. *Nano Lett* 2022;**22**:1415−24.
56. Wang S, Wang D, Duan Y, Zhou Z, Gao W, Zhang L. Cellular nanosponges for biological neutralization. *Adv Mater* 2022;**34**: e2107719.
57. Miao Y, Yang Y, Guo L, Chen M, Zhou X, Zhao Y, et al. Cell membrane-camouflaged nanocarriers with biomimetic deformability of erythrocytes for ultralong circulation and enhanced cancer therapy. *ACS Nano* 2022;**16**:6527−40.
58. Jha A, Nikam AN, Kulkarni S, Mutalik SP, Pandey A, Hegde M, et al. Biomimetic nanoarchitecturing: a disguised attack on cancer cells. *J Control Release* 2021;**329**:413−33.
59. Hu CM, Fang RH, Luk BT, Chen KN, Carpenter C, Gao W, et al. 'Marker-of-self' functionalization of nanoscale particles through a top-down cellular membrane coating approach. *Nanoscale* 2013;**5**: 2664−8.
60. Wang K, Zhang X, Ye H, Wang X, Fan Z, Lu Q, et al. Biomimetic nanovaccine-mediated multivalent IL-15 self-transpresentation (MIST) for potent and safe cancer immunotherapy. *Nat Commun* 2023;**14**:6748.
61. Yang J, Wang F, Lu Y, Qi J, Deng L, Sousa F, et al. Recent advance of erythrocyte-mimicking nanovehicles: from bench to bedside. *J Control Release* 2019;**314**:81−91.
62. Zhu JY, Zheng DW, Zhang MK, Yu WY, Qiu WX, Hu JJ, et al. Preferential cancer cell self-recognition and tumor self-targeting by coating nanoparticles with homotypic cancer cell membranes. *Nano Lett* 2016;**16**:5895−901.
63. Bai X, Li C, Qiu J, Wu L, Liu X, Yin T, et al. A "plug-and-display" nanoparticle based on attenuated outer membrane vesicles enhances the immunogenicity of protein antigens. *J Control Release* 2025;**378**: 687−700.
64. Go YK, Leal C. Polymer−lipid hybrid materials. *Chem Rev* 2021; **121**:13996−4030.
65. Liang Y, Duan L, Lu J, Xia J. Engineering exosomes for targeted drug delivery. *Theranostics* 2021;**11**:3183−95.
66. Kimiz-Gebologlu I, Oncel SS. Exosomes: large-scale production, isolation, drug loading efficiency, and biodistribution and uptake. *J Control Release* 2022;**347**:533−43.
67. El Moukhtari SH, Garbayo E, Amundarain A, Pascual-Gil S, Carrasco-León A, Prosper F, et al. Lipid nanoparticles for siRNA delivery in cancer treatment. *J Control Release* 2023;**361**: 130−46.
68. Chen Z, Wang Z, Gu Z. Bioinspired and biomimetic nanomedicines. *Acc Chem Res* 2019;**52**:1255−64.
69. Chen HY, Deng J, Wang Y, Wu CQ, Li X, Dai HW. Hybrid cell membrane-coated nanoparticles: a multifunctional biomimetic platform for cancer diagnosis and therapy. *Acta Biomater* 2020;**112**:1−13.
70. Khosravi N, Pishavar E, Baradaran B, Oroojalian F, Mokhtarzadeh A. Stem cell membrane, stem cell-derived exosomes and hybrid stem cell camouflaged nanoparticles: a promising biomimetic nanoplatforms for cancer theranostics. *J Control Release* 2022;**348**: 706−22.
71. Zhao Q, Feng J, Liu F, Liang Q, Xie M, Dong J, et al. Rhizoma Drynariae-derived nanovesicles reverse osteoporosis by potentiating osteogenic differentiation of human bone marrow mesenchymal stem cells *via* targeting ERα signaling. *Acta Pharm Sin B* 2024;**14**: 2210−27.
72. Ding Y, Wang L, Li H, Miao F, Zhang Z, Hu C, et al. Application of lipid nanovesicle drug delivery system in cancer immunotherapy. *J Nanobiotechnol* 2022;**20**:214.
73. Abesekara MS, Chau Y. Recent advances in surface modification of micro- and nano-scale biomaterials with biological membranes and biomolecules. *Front Bioeng Biotechnol* 2022;**10**:972790.
74. Zhang P, Chen D, Li L, Sun K. Charge reversal nano-systems for tumor therapy. *J Nanobiotechnol* 2022;**20**:31.
75. Albanese A, Tang PS, Chan WC. The effect of nanoparticle size, shape, and surface chemistry on biological systems. *Annu Rev Biomed Eng* 2012;**14**:1−16.

76. Verma A, Stellacci F. Effect of surface properties on nanoparticle−cell interactions. *Small* 2010;**6**:12−21.
77. Hickey JW, Santos JL, Williford JM, Mao HQ. Control of polymeric nanoparticle size to improve therapeutic delivery. *J Control Release* 2015;**219**:536−47.
78. Zhao F, Zhao Y, Liu Y, Chang X, Chen C, Zhao Y. Cellular uptake, intracellular trafficking, and cytotoxicity of nanomaterials. *Small* 2011;**7**:1322−37.
79. Petros RA, DeSimone JM. Strategies in the design of nanoparticles for therapeutic applications. *Nat Rev Drug Discov* 2010;**9**:615−27.
80. Wang J, Byrne JD, Napier ME, DeSimone JM. More effective nanomedicines through particle design. *Small* 2011;**7**:1919−31.
81. May RC, Machesky LM. Phagocytosis and the actin cytoskeleton. *J Cell Sci* 2001;**114**:1061−77.
82. Decuzzi P, Godin B, Tanaka T, Lee S-Y, Chiappini C, Liu X, et al. Size and shape effects in the biodistribution of intravascularly injected particles. *J Controlled Release* 2010;**141**:320−7.
83. Moreira JN, Gaspar R, Allen TM. Targeting stealth liposomes in a murine model of human small cell lung cancer. *Biochim Biophys Acta* 2001;**1515**:167−76.
84. Xu M, Qi Y, Liu G, Song Y, Jiang X, Du B. Size-dependent *in vivo* transport of nanoparticles: implications for delivery, targeting, and clearance. *ACS Nano* 2023;**17**:20825−49.
85. Hoshyar N, Gray S, Han H, Bao G. The effect of nanoparticle size on *in vivo* pharmacokinetics and cellular interaction. *Nanomedicine* 2016;**11**:673−92.
86. Hu CM, Zhang L, Aryal S, Cheung C, Fang RH, Zhang L. Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform. *Proc Natl Acad Sci U S A* 2011;**108**:10980−5.
87. Li H, Jin K, Luo M, Wang X, Zhu X, Liu X, et al. Size dependency of circulation and biodistribution of biomimetic nanoparticles: red blood cell membrane-coated nanoparticles. *Cells* 2019;**8**:881.
88. Fang RH, Hu CM, Luk BT, Gao W, Copp JA, Tai Y, et al. Cancer cell membrane-coated nanoparticles for anticancer vaccination and drug delivery. *Nano Lett* 2014;**14**:2181−8.
89. Champion JA, Mitragotri S. Role of target geometry in phagocytosis. *Proc Natl Acad Sci U S A* 2006;**103**:4930−4.
90. Gratton SE, Ropp PA, Pohlhaus PD, Luft JC, Madden VJ, Napier ME, et al. The effect of particle design on cellular internalization pathways. *Proc Natl Acad Sci U S A* 2008;**105**:11613−8.
91. Xu K, Du Y, Xu B, Huang Y, Feng W, Yu D, et al. Gelatin-encapsulated tetrahedral DNA nanostructure enhances cellular internalization for treating noise-induced hearing loss. *Small* 2024;**20**:e2310604.
92. Zhang LX, Jia YB, Huang YR, Liu HN, Sun XM, Cai T, et al. Efficient delivery of clay-based nanovaccines to the mouse spleen promotes potent anti-tumor immunity for both prevention and treatment of lymphoma. *Nano Res* 2021;**14**:1326−34.
93. Shao J, Wang M, Huang J, Wang Y, Zhao J, Wang R, et al. Biomimetic nanomedicines deliver naringin for enhanced acute liver failure therapy *via* balanced regulation of hepatocyte oxidative stress and kupffer cell inflammation. *Adv Funct Mater* 2025;**35**:2502801.
94. Tanjeem N, Minnis MB, Hayward RC, Shields CWt. Shape-changing particles: from materials design and mechanisms to implementation. *Adv Mater* 2022;**34**:e2105758.
95. Pisani S, Genta I, Modena T, Dorati R, Benazzo M, Conti B. Shape-memory polymers hallmarks and their biomedical applications in the form of nanofibers. *Int J Mol Sci* 2022;**23**:1290.
96. Ceylan H, Yasa IC, Yasa O, Tabak AF, Giltinan J, Sitti M. 3D-printed biodegradable microswimmer for theranostic cargo delivery and release. *ACS Nano* 2019;**13**:3353−62.
97. Sosale NG, Rouhiparkouhi T, Bradshaw AM, Dimova R, Lipowsky R, Discher DE. Cell rigidity and shape override CD47's "self"-signaling in phagocytosis by hyperactivating myosin-II. *Blood* 2015;**125**:542−52.
98. Lv Z, Bian Z, Shi L, Niu S, Ha B, Tremblay A, et al. Loss of cell surface CD47 clustering formation and binding avidity to SIRPα facilitate apoptotic cell clearance by macrophages. *J Immunol* 2015;**195**:661−71.
99. Tkach M, Kowal J, Zucchetti AE, Enserink L, Jouve M, Lankar D, et al. Qualitative differences in T-cell activation by dendritic cell-derived extracellular vesicle subtypes. *Embo j* 2017;**36**:3012−28.
100. Shuvaev VV, Muro S, Arguiri E, Khoshnejad M, Tliba S, Christofidou-Solomidou M, et al. Size and targeting to PECAM *vs* ICAM control endothelial delivery, internalization and protective effect of multimolecular SOD conjugates. *J Controlled Release* 2016;**234**:115−23.
101. Zhang W, Lopez H, Boselli L, Bigini P, Perez-Potti A, Xie Z, et al. A nanoscale shape-discovery framework supporting systematic investigations of shape-dependent biological effects and immunomodulation. *ACS Nano* 2022;**16**:1547−59.
102. Yang L, Zhou Z, Song J, Chen X. Anisotropic nanomaterials for shape-dependent physicochemical and biomedical applications. *Chem Soc Rev* 2019;**48**:5140−76.
103. Klinger D, Wang CX, Connal LA, Audus DJ, Jang SG, Kraemer S, et al. A facile synthesis of dynamic, shape-changing polymer particles. *Angew Chem Int Ed Engl* 2014;**53**:7018−22.
104. Matsumoto NM, Buchman GW, Rome LH, Maynard HD. Dual pH- and temperature-responsive protein nanoparticles. *Eur Polym J* 2015;**69**:532−9.
105. Vales G, Suhonen S, Siivola KM, Savolainen KM, Catalan J, Norppa H. Size, surface functionalization, and genotoxicity of gold nanoparticles *in vitro. Nanomaterials (Basel)* 2020;**10**:271.
106. Weiss M, Fan J, Claudel M, Sonntag T, Didier P, Ronzani C, et al. Density of surface charge is a more predictive factor of the toxicity of cationic carbon nanoparticles than zeta potential. *J Nanobiotechnol* 2021;**19**:5.
107. Alexis F, Pridgen E, Molnar LK, Farokhzad OC. Factors affecting the clearance and biodistribution of polymeric nanoparticles. *Mol Pharm* 2008;**5**:505−15.
108. Zhu W, Zhou Y, Guo L, Feng S. Biological function of sialic acid and sialylation in human health and disease. *Cell Death Discov* 2024;**10**:415.
109. Szlasa W, Zendran I, Zalesińska A, Tarek M, Kulbacka J. Lipid composition of the cancer cell membrane. *J Bioenerg Biomembr* 2020;**52**:321−42.
110. Dustin ML, Groves JT. Receptor signaling clusters in the immune synapse. *Annu Rev Biophys* 2012;**41**:543−56.
111. Zhang T, Hu W, Chen W. Plasma membrane integrates biophysical and biochemical regulation to trigger immune receptor functions. *Front Immunol* 2021;**12**:613185.
112. Fan D, Cao Y, Cao M, Wang Y, Cao Y, Gong T. Nanomedicine in cancer therapy. *Signal Transduct Targeted Ther* 2023;**8**:293.
113. Wang HX, Zuo ZQ, Du JZ, Wang YC, Sun R, Cao ZT, et al. Surface charge critically affects tumor penetration and therapeutic efficacy of cancer nanomedicines. *Nano Today* 2016;**11**:133−44.
114. Chen L, Zhao T, Zhao M, Wang W, Sun C, Liu L, et al. Size and charge dual-transformable mesoporous nanoassemblies for enhanced drug delivery and tumor penetration. *Chem Sci* 2020;**11**:2819−27.
115. Gitlin I, Carbeck JD, Whitesides GM. Why are proteins charged? Networks of charge-charge interactions in proteins measured by charge ladders and capillary electrophoresis. *Angew Chem Int Ed Engl* 2006;**45**:3022−60.
116. Ikeda-Imafuku M, Wang LL, Rodrigues D, Shaha S, Zhao Z, Mitragotri S. Strategies to improve the EPR effect: a mechanistic perspective and clinical translation. *J Controlled Release* 2022;**345**:512−36.
117. Du JB, Cheng Y, Teng ZH, Huan ML, Liu M, Cui H, et al. pH-triggered surface charge reversed nanoparticle with active targeting to enhance the antitumor activity of doxorubicin. *Mol Pharm* 2016;**13**:1711−22.
118. Bi D, Zhao L, Yu R, Li H, Guo Y, Wang X, et al. Surface modification of doxorubicin-loaded nanoparticles based on polydopamine with pH-sensitive property for tumor targeting therapy. *Drug Deliv* 2018;**25**:564−75.

119. Souri M, Golzaryan A, Soltani M. Charge-switchable nanoparticles to enhance tumor penetration and accumulation. *Eur J Pharm Biopharm* 2024;**199**:114310.
120. Triantafyllopoulou E, Pippa N, Demetzos C. Protein−liposome interactions: the impact of surface charge and fluidisation effect on protein binding. *J Liposome Res* 2023;**33**:77−88.
121. Veider F, Sanchez Armengol E, Bernkop-Schnurch A. Charge-reversible nanoparticles: advanced delivery systems for therapy and diagnosis. *Small* 2024;**20**:e2304713.
122. Liang Y, Iqbal Z, Lu J, Wang J, Zhang H, Chen X, et al. Cell-derived nanovesicle-mediated drug delivery to the brain: principles and strategies for vesicle engineering. *Mol Ther* 2023;**31**:1207−24.
123. Das CK, Jena BC, Banerjee I, Das S, Parekh A, Bhutia SK, et al. Exosome as a novel shuttle for delivery of therapeutics across biological barriers. *Mol Pharm* 2019;**16**:24−40.
124. Yun S, Kim S, Kim K. Cellular membrane components-mediated cancer immunotherapeutic platforms. *Macromol Biosci* 2023;**23**: e2300159.
125. Reuven EM, Leviatan Ben-Arye S, Yu H, Duchi R, Perota A, Conchon S, et al. Biomimetic glyconanoparticle vaccine for cancer immunotherapy. *ACS Nano* 2019;**13**:2936−47.
126. Cheung AS, Koshy ST, Stafford AG, Bastings MM, Mooney DJ. Adjuvant-loaded subcellular vesicles derived from disrupted cancer cells for cancer vaccination. *Small* 2016;**12**:2321−33.
127. Ochyl LJ, Moon JJ. Dendritic cell membrane vesicles for activation and maintenance of antigen-specific T cells. *Adv Healthcare Mater* 2019;**8**:e1801091.
128. Liu WL, Zou MZ, Liu T, Zeng JY, Li X, Yu WY, et al. Cytomembrane nanovaccines show therapeutic effects by mimicking tumor cells and antigen presenting cells. *Nat Commun* 2019;**10**:3199.
129. Liu C, Liu X, Xiang X, Pang X, Chen S, Zhang Y, et al. A nanovaccine for antigen self-presentation and immunosuppression reversal as a personalized cancer immunotherapy strategy. *Nat Nanotechnol* 2022;**17**:531−40.
130. Pack CD, Bommireddy R, Munoz LE, Patel JM, Bozeman EN, Dey P, et al. Tumor membrane-based vaccine immunotherapy in combination with anti-CTLA-4 antibody confers protection against immune checkpoint resistant murine triple-negative breast cancer. *Hum Vaccines Immunother* 2020;**16**:3184−93.
131. Pan Y, Wu X, Liu L, Zhao C, Zhang J, Yang S, et al. Genetically engineered cytomembrane nanovaccines for cancer immunotherapy. *Adv Healthcare Mater* 2024;**13**:e2400068.
132. Meng QF, Zhao Y, Dong C, Liu L, Pan Y, Lai J, et al. Genetically programmable fusion cellular vesicles for cancer immunotherapy. *Angew Chem Int Ed Engl* 2021;**60**:26320−6.
133. Zhang L, Zhao X, Niu Y, Ma X, Yuan W, Ma J. Engineering high-affinity dual targeting cellular nanovesicles for optimised cancer immunotherapy. *J Extracell Vesicles* 2023;**12**:e12379.
134. Rao L, Wu L, Liu Z, Tian R, Yu G, Zhou Z, et al. Hybrid cellular membrane nanovesicles amplify macrophage immune responses against cancer recurrence and metastasis. *Nat Commun* 2020;**11**:4909.
135. Wang C, Sun W, Ye Y, Hu Q, Bomba HN, Gu Z. *In situ* activation of platelets with checkpoint inhibitors for post-surgical cancer immunotherapy. *Nat Biomed Eng* 2017;**1**:11.
136. Li L, Miao Q, Meng F, Li B, Xue T, Fang T, et al. Genetic engineering cellular vesicles expressing CD64 as checkpoint antibody carrier for cancer immunotherapy. *Theranostics* 2021;**11**:6033−43.
137. Jung M, Kang M, Kim BS, Hong J, Kim C, Koh CH, et al. Nanovesicle-mediated targeted delivery of immune checkpoint blockades to potentiate therapeutic efficacy and prevent side effects. *Adv Mater* 2022;**34**:e2106516.
138. Zhao C, Pan Y, Liu L, Zhang J, Wu X, Liu Y, et al. Hybrid cellular nanovesicles block PD-L1 signal and repolarize M2 macrophages for cancer immunotherapy. *Small* 2024;**20**:e2311702.
139. Ding L, Zhang X, Yu P, Peng F, Sun Y, Wu Y, et al. Genetically engineered nanovesicles mobilize synergistic antitumor immunity by ADAR1 silence and PDL1 blockade. *Mol Ther* 2023;**31**: 2489−506.
140. Chen R, Kang Z, Li W, Xu T, Wang Y, Jiang Q, et al. Extracellular vesicle surface display of alphaPD-L1 and alphaCD3 antibodies *via* engineered late domain-based scaffold to activate T-cell anti-tumor immunity. *J Extracell Vesicles* 2024;**13**:e12490.
141. Xu F, Jiang D, Xu J, Dai H, Fan Q, Fei Z, et al. Engineering of dendritic cell bispecific extracellular vesicles for tumor-targeting immunotherapy. *Cell Rep* 2023;**42**:113138.
142. Li Y, Zhu T, Chen J, Liu K, Wei C, Fang Q, et al. Dual-targeted engineered bacterial outer membrane vesicles for hepatocellular carcinoma immunotherapy. *Adv Funct Mater* 2024;**34**:2401355.
143. Sun X, Han X, Xu L, Gao M, Xu J, Yang R, et al. Surface-engineering of red blood cells as artificial antigen presenting cells promising for cancer immunotherapy. *Small* 2017;**13**:1701864.
144. Sahin U, Tureci O. Personalized vaccines for cancer immunotherapy. *Science* 2018;**359**:1355−60.
145. Finn OJ. The dawn of vaccines for cancer prevention. *Nat Rev Immunol* 2018;**18**:183−94.
146. Schijns V, Tartour E, Michalek J, Stathopoulos A, Dobrovolskiene NT, Strioga MM. Immune adjuvants as critical guides directing immunity triggered by therapeutic cancer vaccines. *Cytotherapy* 2014;**16**:427−39.
147. Lohmueller J, Finn OJ. Current modalities in cancer immunotherapy: immunomodulatory antibodies, CARs and vaccines. *Pharmacol Ther* 2017;**178**:31−47.
148. Lollini PL, Nicoletti G, Landuzzi L, Cavallo F, Forni G, De Giovanni C, et al. Vaccines and other immunological approaches for cancer immunoprevention. *Curr Drug Targets* 2011;**12**:1957−73.
149. Palladini A, Landuzzi L, Lollini PL, Nanni P. Cancer immunoprevention: from mice to early clinical trials. *BMC Immunol* 2018;**19**:16.
150. Tran T, Blanc C, Granier C, Saldmann A, Tanchot C, Tartour E. Therapeutic cancer vaccine: building the future from lessons of the past. *Semin Immunopathol* 2019;**41**:69−85.
151. Tan AC, Goubier A, Kohrt HE. A quantitative analysis of therapeutic cancer vaccines in phase 2 or phase 3 trial. *J Immunother Cancer* 2015; **3**:48.
152. Shemesh CS, Hsu JC, Hosseini I, Shen BQ, Rotte A, Twomey P, et al. Personalized cancer vaccines: clinical landscape, challenges, and opportunities. *Mol Ther* 2021;**29**:555−70.
153. Wirth TC, Kuhnel F. Neoantigen targeting-dawn of a new era in cancer immunotherapy?. *Front Immunol* 2017;**8**:1848.
154. Liu J, Liew SS, Wang J, Pu K. Bioinspired and biomimetic delivery platforms for cancer vaccines. *Adv Mater* 2022;**34**:e2103790.
155. Ye T, Li F, Ma G, Wei W. Enhancing therapeutic performance of personalized cancer vaccine *via* delivery vectors. *Adv Drug Deliv Rev* 2021;**177**:113927.
156. Jiang X, Wu L, Zhang M, Zhang T, Chen C, Wu Y, et al. Biomembrane nanostructures: multifunctional platform to enhance tumor chemoimmunotherapy *via* effective drug delivery. *J Control Release* 2023;**361**:510−33.
157. Lei J, Qi S, Yu X, Gao X, Yang K, Zhang X, et al. Development of mannosylated lipid nanoparticles for mRNA cancer vaccine with high antigen presentation efficiency and immunomodulatory capability. *Angew Chem Int Ed Engl* 2024;**63**:e202318515.
158. Wen R, Umeano AC, Kou Y, Xu J, Farooqi AA. Nanoparticle systems for cancer vaccine. *Nanomedicine* 2019;**14**:627−48.
159. Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases—elimination, equilibrium and escape. *Curr Opin Immunol* 2014;**27**:16−25.
160. Li Y, Tong F, Wang Y, Wang J, Wu M, Li H, et al. *In situ* tumor vaccine with optimized nanoadjuvants and lymph node targeting capacity to treat ovarian cancer and metastases. *Acta Pharm Sin B* 2024;**14**:4102−17.
161. Wei MM, Wang YS, Ye XS. Carbohydrate-based vaccines for oncotherapy. *Med Res Rev* 2018;**38**:1003−26.
162. Padler-Karavani V. Aiming at the sweet side of cancer: aberrant glycosylation as possible target for personalized-medicine. *Cancer Lett* 2014;**352**:102−12.

163. Kong X, Zhang J, Chen S, Wang X, Xi Q, Shen H, et al. Immune checkpoint inhibitors: breakthroughs in cancer treatment. *Cancer Biol Med* 2024;**21**:451−72.
164. Xia A, Zhang Y, Xu J, Yin T, Lu XJ. T cell dysfunction in cancer immunity and immunotherapy. *Front Immunol* 2019;**10**:1719.
165. Tauriello DVF, Sancho E, Batlle E. Overcoming TGFbeta-mediated immune evasion in cancer. *Nat Rev Cancer* 2022;**22**:25−44.
166. Young A, Quandt Z, Bluestone JA. The balancing act between cancer immunity and autoimmunity in response to immunotherapy. *Cancer Immunol Res* 2018;**6**:1445−52.
167. Qin S, Xu L, Yi M, Yu S, Wu K, Luo S. Novel immune checkpoint targets: moving beyond PD-1 and CTLA-4. *Mol Cancer* 2019;**18**: 155.
168. Khan S, Gerber DE. Autoimmunity, checkpoint inhibitor therapy and immune-related adverse events: a review. *Semin Cancer Biol* 2020; **64**:93−101.
169. Ramos-Casals M, Brahmer JR, Callahan MK, Flores-Chavez A, Keegan N, Khamashta MA, et al. Immune-related adverse events of checkpoint inhibitors. *Nat Rev Dis Primers* 2020;**6**:38.
170. Bai X, Zhou Y, Yokota Y, Matsumoto Y, Zhai B, Maarouf N, et al. Adaptive antitumor immune response stimulated by bio-nanoparticle based vaccine and checkpoint blockade. *J Exp Clin Cancer Res* 2022; **41**:132.
171. He M, Yang T, Wang Y, Wang M, Chen X, Ding D, et al. Immune checkpoint inhibitor-based strategies for synergistic cancer therapy. *Adv Healthcare Mater* 2021;**10**:e2002104.
172. Zhang C, Zhang C, Wang H. Immune-checkpoint inhibitor resistance in cancer treatment: current progress and future directions. *Cancer Lett* 2023;**562**:216182.
173. Doroshow DB, Bhalla S, Beasley MB, Sholl LM, Kerr KM, Gnjatic S, et al. PD-L1 as a biomarker of response to immune-checkpoint inhibitors. *Nat Rev Clin Oncol* 2021;**18**:345−62.
174. Vanhersecke L, Brunet M, Guegan JP, Rey C, Bougouin A, Cousin S, et al. Mature tertiary lymphoid structures predict immune checkpoint inhibitor efficacy in solid tumors independently of PD-L1 expression. *Nat Cancer* 2021;**2**:794−802.
175. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010;**363**:711−23.
176. Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* 2011;**364**:2517−26.
177. Liu Y, Zheng P. Preserving the CTLA-4 checkpoint for safer and more effective cancer immunotherapy. *Trends Pharmacol Sci* 2020; **41**:4−12.
178. Demaria O, Cornen S, Daeron M, Morel Y, Medzhitov R, Vivier E. Harnessing innate immunity in cancer therapy. *Nature* 2019;**574**: 45−56.
179. Liu X, Pu Y, Cron K, Deng L, Kline J, Frazier WA, et al. CD47 blockade triggers T cell-mediated destruction of immunogenic tumors. *Nat Med* 2015;**21**:1209−15.
180. Liu Y, Weng L, Wang Y, Zhang J, Wu Q, Zhao P, et al. Deciphering the role of CD47 in cancer immunotherapy. *J Adv Res* 2024;**63**:129−58.
181. Kuo TC, Chen A, Harrabi O, Sockolosky JT, Zhang A, Sangalang E, et al. Targeting the myeloid checkpoint receptor SIRPalpha potentiates innate and adaptive immune responses to promote anti-tumor activity. *J Hematol Oncol* 2020;**13**:160.
182. van Helden MJ, Zwarthoff SA, Arends RJ, Reinieren-Beeren IMJ, Parade M, Driessen-Engels L, et al. BYON4228 is a pan-allelic antagonistic SIRPalpha antibody that potentiates destruction of antibody-opsonized tumor cells and lacks binding to SIRPgamma on T cells. *J Immunother Cancer* 2023;**11**:e006567.
183. Gutjahr A, Tiraby G, Perouzel E, Verrier B, Paul S. Triggering intracellular receptors for vaccine adjuvantation. *Trends Immunol* 2016;**37**:716.
184. Steinhagen F, Kinjo T, Bode C, Klinman DM. TLR-based immune adjuvants. *Vaccine* 2011;**29**:3341−55.
185. Niu B, Tian T, Wang L, Tian Y, Tian T, Guo Y, et al. CCL9/CCR1 axis-driven chemotactic nanovesicles for attenuating metastasis of SMAD4-deficient colorectal cancer by trapping TGF-β. *Acta Pharm Sin B* 2024;**14**:3711−29.
186. Oyewumi MO, Kumar A, Cui Z. Nano-microparticles as immune adjuvants: correlating particle sizes and the resultant immune responses. *Expert Rev Vaccines* 2010;**9**:1095−107.
187. Gao X, Feng Q, Wang J, Zhao X. Bacterial outer membrane vesicle-based cancer nanovaccines. *Cancer Biol Med* 2022;**19**:1290−300.
188. O'Neill LA, Golenbock D, Bowie AG. The history of toll-like receptors—redefining innate immunity. *Nat Rev Immunol* 2013;**13**: 453−60.
189. Bode C, Zhao G, Steinhagen F, Kinjo T, Klinman DM. CpG DNA as a vaccine adjuvant. *Expert Rev Vaccines* 2011;**10**:499−511.
190. Wen Z, Liu H, Qiao D, Chen H, Li L, Yang Z, et al. Nanovaccines fostering tertiary lymphoid structure to attack mimicry nasopharyngeal carcinoma. *ACS Nano* 2023;**17**:7194−206.
191. Zheng X, Wu Y, Bi J, Huang Y, Cheng Y, Li Y, et al. The use of supercytokines, immunocytokines, engager cytokines, and other synthetic cytokines in immunotherapy. *Cell Mol Immunol* 2022;**19**: 192−209.
192. Kureshi CT, Dougan SK. Cytokines in cancer. *Cancer Cell* 2025;**43**: 15−35.
193. Propper DJ, Balkwill FR. Harnessing cytokines and chemokines for cancer therapy. *Nat Rev Clin Oncol* 2022;**19**:237−53.
194. Markl F, Huynh D, Endres S, Kobold S. Utilizing chemokines in cancer immunotherapy. *Trends Cancer* 2022;**8**:670−82.
195. Bentebibel SE, Hurwitz ME, Bernatchez C, Haymaker C, Hudgens CW, Kluger HM, et al. A first-in-human study and biomarker analysis of NKTR-214, a novel IL2Rbetagamma-biased cytokine, in patients with advanced or metastatic solid tumors. *Cancer Discov* 2019;**9**:711−21.
196. Daud AI, DeConti RC, Andrews S, Urbas P, Riker AI, Sondak VK, et al. Phase I trial of interleukin-12 plasmid electroporation in patients with metastatic melanoma. *J Clin Oncol* 2008;**26**: 5896−903.
197. Kurz E, Hirsch CA, Dalton T, Shadaloey SA, Khodadadi-Jamayran A, Miller G, et al. Exercise-induced engagement of the IL-15/IL-15Ralpha axis promotes anti-tumor immunity in pancreatic cancer. *Cancer Cell* 2022;**40**:720−37.e5.
198. Pujade-Lauraine E, Guastalla JP, Colombo N, Devillier P, Francois E, Fumoleau P, et al. Intraperitoneal recombinant interferon gamma in ovarian cancer patients with residual disease at second-look laparotomy. *J Clin Oncol* 1996;**14**:343−50.
199. Bertrand F, Montfort A, Marcheteau E, Imbert C, Gilhodes J, Filleron T, et al. TNFalpha blockade overcomes resistance to anti-PD-1 in experimental melanoma. *Nat Commun* 2017;**8**:2256.
200. Fousek K, Horn LA, Palena C. Interleukin-8: a chemokine at the intersection of cancer plasticity, angiogenesis, and immune suppression. *Pharmacol Ther* 2021;**219**:107692.
201. Uricoli B, Birnbaum LA, Do P, Kelvin JM, Jain J, Costanza E, et al. Engineered cytokines for cancer and autoimmune disease immunotherapy. *Adv Healthcare Mater* 2021;**10**:e2002214.
202. Lian H, Ma S, Zhao D, Zhao W, Cui Y, Hua Y, et al. Cytokine therapy combined with nanomaterials participates in cancer immunotherapy. *Pharmaceutics* 2022;**14**:2606.
203. Wu Y, Zhu R, Zhou M, Liu J, Dong K, Zhao S, et al. Homologous cancer cell membrane-camouflaged nanoparticles target drug delivery and enhance the chemotherapy efficacy of hepatocellular carcinoma. *Cancer Lett* 2023;**558**:216106.
204. Chen M, Chen M, He J. Cancer cell membrane cloaking nanoparticles for targeted co-delivery of doxorubicin and PD-L1 siRNA. *Artif Cells, Nanomed Biotechnol* 2019;**47**:1635−41.
205. Cui L, Cui Y, Liu J, Li W, Wu M, Wei X, et al. Bioengineered nanovesicles for efficient siRNA delivery through ligand−receptor-mediated and enzyme-controlled membrane fusion. *Nat Commun* 2025;**16**:6174.

206. Bader J, Brigger F, Leroux JC. Extracellular vesicles *versus* lipid nanoparticles for the delivery of nucleic acids. *Adv Drug Deliv Rev* 2024;**215**:115461.
207. Sundaram V, Aryal S. Emerging biomimetic drug delivery nanoparticles inspired by extracellular vesicles. *Wiley Interdiscip Rev Nanomed Nanobiotechnol* 2025;**17**:e70025.
208. Guo Y, Hu G, Xia Y, Li H, Yuan J, Zhang J, et al. Eliminating the original cargos of glioblastoma cell-derived small extracellular vesicles for efficient drug delivery to glioblastoma with improved biosafety. *Bioact Mater* 2022;**16**:204−17.
209. Su Z, Dong S, Chen Y, Huang T, Qin B, Yang Q, et al. Microfluidics-enabled nanovesicle delivers CD47/PD-L1 antibodies to enhance antitumor immunity and reduce immunotoxicity in lung adenocarcinoma. *Adv Sci (Weinh)* 2023;**10**:e2206213.
210. Wang R, Yu Y, Gai M, Mateos-Maroto A, Morsbach S, Xia X, et al. Liposomal enzyme nanoreactors based on nanoconfinement for efficient antitumor therapy. *Angew Chem Int Ed Engl* 2023;**62**:e202308761.
211. Zhou Y, Penny HL, Kroenke MA, Bautista B, Hainline K, Chea LS, et al. Immunogenicity assessment of bispecific antibody-based immunotherapy in oncology. *J Immunother Cancer* 2022;**10**:e004225.
212. Gu Y, Wang Z, Wang Y. Bispecific antibody drug conjugates: making 1+1>2. *Acta Pharm Sin B* 2024;**14**:1965−86.
213. Shapir Itai Y, Barboy O, Salomon R, Bercovich A, Xie K, Winter E, et al. Bispecific dendritic-T cell engager potentiates anti-tumor immunity. *Cell* 2024;**187**:375−89.e18.
214. Wu J, Fu J, Zhang M, Liu D. Blinatumomab: a bispecific T cell engager (BiTE) antibody against CD19/CD3 for refractory acute lymphoid leukemia. *J Hematol Oncol* 2015;**8**:104.
215. Ning S, Shangguan P, Zhu X, Ou X, Wang K, Suo M, et al. Pyridinium rotor strategy toward a robust photothermal agent for STING activation and multimodal image-guided immunotherapy for triple-negative breast cancer. *J Am Chem Soc* 2025;**147**:7433−44.
216. Salunkhe S, Dheeraj Basak M, Chitkara D, Mittal A. Surface functionalization of exosomes for target-specific delivery and *in vivo* imaging & tracking: strategies and significance. *J Controlled Release* 2020;**326**:599−614.
217. Guo ZY, Tang Y, Cheng YC. Exosomes as targeted delivery drug system: advances in exosome loading, surface functionalization and potential for clinical application. *Curr Drug Deliv* 2024;**21**:473−87.
218. Kaymaz SV, Nobar HM, Sarigul H, Soylukan C, Akyuz L, Yuce M. Nanomaterial surface modification toolkit: principles, components, recipes, and applications. *Adv Colloid Interface Sci* 2023;**322**:103035.
219. Xu Y, Fourniols T, Labrak Y, Preat V, Beloqui A, des Rieux A. Surface modification of lipid-based nanoparticles. *ACS Nano* 2022;**16**:7168−96.
220. Zhang M, Cheng S, Jin Y, Zhang N, Wang Y. Membrane engineering of cell membrane biomimetic nanoparticles for nanoscale therapeutics. *Clin Transl Med* 2021;**11**:e292.
221. Christensen D, Korsholm KS, Andersen P, Agger EM. Cationic liposomes as vaccine adjuvants. *Expert Rev Vaccines* 2011;**10**:513−21.
222. Szachniewicz MM, van den Eeden SJF, van Meijgaarden KE, Franken K, van Veen S, Geluk A, et al. Cationic pH-sensitive liposome-based subunit tuberculosis vaccine induces protection in mice challenged with *Mycobacterium* tuberculosis. *Eur J Pharm Biopharm* 2024;**203**:114437.
223. Sugimoto Y, Suga T, Umino M, Yamayoshi A, Mukai H, Kawakami S. Investigation of enhanced intracellular delivery of nanomaterials modified with novel cell-penetrating zwitterionic peptide-lipid derivatives. *Drug Deliv* 2023;**30**:2191891.
224. Lee J, Lee H, Goh U, Kim J, Jeong M, Lee J, et al. Cellular engineering with membrane fusogenic liposomes to produce functionalized extracellular vesicles. *ACS Appl Mater Interfaces* 2016;**8**:6790−5.
225. Musicò A, Zenatelli R, Romano M, Zendrini A, Alacqua S, Tassoni S, et al. Surface functionalization of extracellular vesicle nanoparticles with antibodies: a first study on the protein corona "variable". *Nanoscale Adv* 2023;**5**:4703−17.
226. Ruan H, Li Y, Wang C, Jiang Y, Han Y, Li Y, et al. Click chemistry extracellular vesicle/peptide/chemokine nanocarriers for treating central nervous system injuries. *Acta Pharm Sin B* 2023;**13**:2202−18.
227. Bhatta R, Han J, Liu Y, Bo Y, Lee D, Zhou J, et al. Metabolic tagging of extracellular vesicles and development of enhanced extracellular vesicle based cancer vaccines. *Nat Commun* 2023;**14**:8047.
228. Zhou X, Jaiswal M, Shi J, Guo J, Kundu S, Guo Z, et al. Efficient enzymatic glycan engineering of extracellular vesicles using nanomaterial-interfaced microfluidics. *ACS Appl Mater Interfaces* 2025;**17**:2689−700.
229. Fan Z, Zhou H, Li PY, Speer JE, Cheng H. Structural elucidation of cell membrane-derived nanoparticles using molecular probes. *J Mater Chem B* 2014;**2**:8231−8.
230. Wang H, Mu J, Chen Y, Liu Y, Li X, Li H, et al. Hybrid ginseng-derived extracellular vesicles-like particles with autologous tumor cell membrane for personalized vaccination to inhibit tumor recurrence and metastasis. *Adv Sci (Weinh)* 2024;**11**:e2308235.
231. Fang W, Li L, Lin Z, Zhang Y, Jing Z, Li Y, et al. Engineered IL-15/IL-15Rα-expressing cellular vesicles promote T cell anti-tumor immunity. *Extracellular Vesicle* 2023;**2**:100021.
232. Liao Y, Zhao C, Pan Y, Guo Y, Liu L, Wu J, et al. Genetically engineered cellular nanoparticles loaded with curcuminoids for cancer immunotherapy. *Theranostics* 2024;**14**:6409−25.
233. Rao L, Zhao SK, Wen C, Tian R, Lin L, Cai B, et al. Activating macrophage-mediated cancer immunotherapy by genetically edited nanoparticles. *Adv Mater* 2020;**32**:e2004853.
234. Luo GF, Chen WH, Zeng X, Zhang XZ. Cell primitive-based biomimetic functional materials for enhanced cancer therapy. *Chem Soc Rev* 2021;**50**:945−85.
235. Cheng Q, Kang Y, Yao B, Dong J, Zhu Y, He Y, et al. Genetically engineered-cell-membrane nanovesicles for cancer immunotherapy. *Adv Sci (Weinh)* 2023;**10**:e2302131.
236. Durand S, Cimarelli A. The inside out of lentiviral vectors. *Viruses* 2011;**3**:132−59.
237. Cheng Q, Li R, He Y, Zhu Y, Kang Y, Ji X. Genetically engineered cellular nanovesicles: theories, design and perspective. *Adv Funct Mater* 2024;**34**:2407842.
238. Mondal J, Pillarisetti S, Junnuthula V, Saha M, Hwang SR, Park IK, et al. Hybrid exosomes, exosome-like nanovesicles and engineered exosomes for therapeutic applications. *J Control Release* 2023;**353**:1127−49.
239. Zhu L, Yu X, Cao T, Deng H, Tang X, Lin Q, et al. Immune cell membrane-based biomimetic nanomedicine for treating cancer metastasis. *Acta Pharm Sin B* 2023;**13**:2464−82.
240. Tian Y, Li S, Song J, Ji T, Zhu M, Anderson GJ, et al. A doxorubicin delivery platform using engineered natural membrane vesicle exosomes for targeted tumor therapy. *Biomaterials* 2014;**35**:2383−90.
241. Xie F, Zhang L, Shi S, Zheng A, Di J, Jin S, et al. Liposomal T cell engager and re-director for tumor cell eradication in cancer immunotherapy. *mAbs* 2022;**14**:2115205.
242. Su Q, Wang C, Song H, Zhang C, Liu J, Huang P, et al. Co-delivery of anionic epitope/CpG vaccine and IDO inhibitor by self-assembled cationic liposomes for combination melanoma immunotherapy. *J Mater Chem B* 2021;**9**:3892−9.
243. Tan H, Shen Z, Wang X, Shu S, Deng J, Lu L, et al. Endoplasmic reticulum-targeted biomimetic nanoparticles induce apoptosis and ferroptosis by regulating endoplasmic reticulum function in colon cancer. *J Control Release* 2024;**375**:422−37.
244. Ye J, Yu Y, Li Y, Yao B, Gu M, Li Y, et al. Nanoparticles encapsulated in red blood cell membranes for near-infrared second window imaging-guided photothermal-enhanced immunotherapy on tumors. *ACS Appl Mater Interfaces* 2024;**16**:34607−19.
245. Hu CM, Fang RH, Wang KC, Luk BT, Thamphiwatana S, Dehaini D, et al. Nanoparticle biointerfacing by platelet membrane cloaking. *Nature* 2015;**526**:118−21.

246. Rossi L, Pierige F, Antonelli A, Bigini N, Gabucci C, Peiretti E, et al. Engineering erythrocytes for the modulation of drugs' and contrasting agents' pharmacokinetics and biodistribution. *Adv Drug Deliv Rev* 2016;**106**:73−87.
247. Wu P, Jiang X, Yin S, Yang Y, Liu T, Wang K. Biomimetic recombinant of red blood cell membranes for improved photothermal therapy. *J Nanobiotechnol* 2021;**19**:213.
248. Pasini EM, Mann M, Thomas AW. Red blood cell proteomics. *Transfus Clin Biol* 2010;**17**:151−64.
249. Bryk AH, Wiśniewski JR. Quantitative analysis of human red blood cell proteome. *J Proteome Res* 2017;**16**:2752−61.
250. Wan X, Zhang S, Wang F, Fan W, Wu C, Mao K, et al. Red blood cell-derived nanovesicles for safe and efficient macrophage-targeted drug delivery *in vivo*. *Biomater Sci* 2018;**7**:187−95.
251. Ding L, Wu Y, Wu M, Zhao Q, Li H, Liu J, et al. Engineered red blood cell biomimetic nanovesicle with oxygen self-supply for near-infrared-II fluorescence-guided synergetic chemo-photodynamic therapy against hypoxic tumors. *ACS Appl Mater Interfaces* 2021;**13**:52435−49.
252. Pan Y, He Y, Zhao X, Pan Y, Meng X, Lv Z, et al. Engineered red blood cell membrane-coating salidroside/indocyanine green nanovesicles for high-efficiency hypoxic targeting phototherapy of triple-negative breast cancer. *Adv Healthcare Mater* 2022;**11**:e2200962.
253. Tzounakas VL, Anastasiadi AT, Dzieciatkowska M, Karadimas DG, Stamoulis K, Papassideri IS, et al. Proteome of stored RBC membrane and vesicles from heterozygous beta thalassemia donors. *Int J Mol Sci* 2021;**22**:3369.
254. Rao L, Bu LL, Xu JH, Cai B, Yu GT, Yu X, et al. Red blood cell membrane as a biomimetic nanocoating for prolonged circulation time and reduced accelerated blood clearance. *Small* 2015;**11**:6225−36.
255. Ye X, Liang X, Chen Q, Miao Q, Chen X, Zhang X, et al. Surgical tumor-derived personalized photothermal vaccine formulation for cancer immunotherapy. *ACS Nano* 2019;**13**:2956−68.
256. Ziegler YS, Moresco JJ, Tu PG, Yates 3rd JR, Nardulli AM. Plasma membrane proteomics of human breast cancer cell lines identifies potential targets for breast cancer diagnosis and treatment. *PLoS One* 2014;**9**:e102341.
257. Prasad R, Mendes BB, Gorain M, Chandra Kundu G, Gupta N, Peng B, et al. Bioinspired and biomimetic cancer-cell-derived membrane nanovesicles for preclinical tumor-targeted nanotheranostics. *Cell Rep Phys Sci* 2023;**4**:101648.
258. Lu Y, Fan L, Wang J, Hu M, Wei B, Shi P, et al. Cancer cell membrane-based materials for biomedical applications. *Small* 2024;**20**:e2306540.
259. Go S, Jung M, Lee S, Moon S, Hong J, Kim C, et al. A personalized cancer nanovaccine that enhances T-cell responses and efficacy through dual interactions with dendritic cells and T cells. *Adv Mater* 2023;**35**:e2303979.
260. Xiong J, Wu M, Chen J, Liu Y, Chen Y, Fan G, et al. Cancer-erythrocyte hybrid membrane-camouflaged magnetic nanoparticles with enhanced photothermal-immunotherapy for ovarian cancer. *ACS Nano* 2021;**15**:19756−70.
261. Liu X, Sun Y, Xu S, Gao X, Kong F, Xu K, et al. Homotypic cell membrane-cloaked biomimetic nanocarrier for the targeted chemotherapy of hepatocellular carcinoma. *Theranostics* 2019;**9**:5828−38.
262. Jin J, Bhujwalla ZM. Biomimetic nanoparticles camouflaged in cancer cell membranes and their applications in cancer theranostics. *Front Oncol* 2019;**9**:1560.
263. Basak M, Chaudhary DK, Takahashi RU, Yamamoto Y, Tiwari S, Tahara H, et al. Immunocyte derived exosomes: insight into the potential chemo-immunotherapeutic nanocarrier targeting the tumor microenvironment. *ACS Biomater Sci Eng* 2023;**9**:20−39.
264. Pauwels E, Rutz C, Provinciael B, Stroobants J, Schols D, Hartmann E, et al. A proteomic study on the membrane protein fraction of T cells confirms high substrate selectivity for the ER translocation inhibitor cyclotriazadisulfonamide. *Mol Cell Proteomics* 2021;**20**:100144.
265. Udeshi ND, Xu C, Jiang Z, Gao SM, Yin Q, Luo W, et al. Cell-surface milieu remodeling in human dendritic cell activation. *J Immunol* 2024;**213**:1023−32.
266. Lopes J, Lopes D, Pereira-Silva M, Peixoto D, Veiga F, Hamblin MR, et al. Macrophage cell membrane-cloaked nanoplatforms for biomedical applications. *Small Methods* 2022;**6**:e2200289.
267. Wu Y, Wan S, Yang S, Hu H, Zhang C, Lai J, et al. Macrophage cell membrane-based nanoparticles: a new promising biomimetic platform for targeted delivery and treatment. *J Nanobiotechnol* 2022;**20**:542.
268. Huang X, Wang L, Guo H, Zhang W. Macrophage membrane-coated nanovesicles for dual-targeted drug delivery to inhibit tumor and induce macrophage polarization. *Bioact Mater* 2023;**23**:69−79.
269. Cao H, Wang H, He X, Tan T, Hu H, Wang Z, et al. Bioengineered macrophages can responsively transform into nanovesicles to target lung metastasis. *Nano Lett* 2018;**18**:4762−70.
270. Xu X, Wang Q, Qian X, Wu Y, Wang J, Li J, et al. Spatial-drug-laden protease-activatable M1 macrophage system targets lung metastasis and potentiates antitumor immunity. *ACS Nano* 2023;**17**:5354−72.
271. Kang M, Hong J, Jung M, Kwon SP, Song SY, Kim HY, et al. T-cell-mimicking nanoparticles for cancer immunotherapy. *Adv Mater* 2020;**32**:e2003368.
272. Han Y, Pan H, Li W, Chen Z, Ma A, Yin T, et al. T cell membrane mimicking nanoparticles with bioorthogonal targeting and immune recognition for enhanced photothermal therapy. *Adv Sci (Weinh)* 2019;**6**:1900251.
273. Fornt-Suñé M, Bermejo GL, Gil-Garcia M, Aran A, Garcia-Pardo J, Martí M, et al. Protein-only nanoparticles for T cell expansion and activation. *ACS Appl Nano Mater* 2024;**7**:6669−80.
274. Wu W, Li H, Chen W, Hu Y, Wang Z, She W, et al. CAR T cell membrane camouflaged nanocatalyst augments CAR T cell therapy efficacy against solid tumor. *Small* 2024;**20**:e2401299.
275. Ma W, Zhu D, Li J, Chen X, Xie W, Jiang X, et al. Coating biomimetic nanoparticles with chimeric antigen receptor T cell-membrane provides high specificity for hepatocellular carcinoma photothermal therapy treatment. *Theranostics* 2020;**10**:1281−95.
276. Geissmann F, Manz MG, Jung S, Sieweke MH, Merad M, Ley K. Development of monocytes, macrophages, and dendritic cells. *Science* 2010;**327**:656−61.
277. Romagnoli GG, Zelante BB, Toniolo PA, Migliori IK, Barbuto JA. Dendritic cell-derived exosomes may be a tool for cancer immunotherapy by converting tumor cells into immunogenic targets. *Front Immunol* 2014;**5**:692.
278. Xu J, Liu H, Wang T, Wen Z, Chen H, Yang Z, et al. CCR7 mediated mimetic dendritic cell vaccine homing in lymph node for head and neck squamous cell carcinoma therapy. *Adv Sci (Weinh)* 2023;**10**:e2207017.
279. Wang W, Zou C, Liu X, He L, Cao Z, Zhu M, et al. Biomimetic dendritic cell-based nanovaccines for reprogramming the immune microenvironment to boost tumor immunotherapy. *ACS Nano* 2024;**18**:34063−76.
280. Parodi A, Quattrocchi N, van de Ven AL, Chiappini C, Evangelopoulos M, Martinez JO, et al. Synthetic nanoparticles functionalized with biomimetic leukocyte membranes possess cell-like functions. *Nat Nanotechnol* 2013;**8**:61−8.
281. Blanchard N, Lankar D, Faure F, Regnault A, Dumont C, Raposo G, et al. TCR activation of human T cells induces the production of exosomes bearing the TCR/CD3/zeta complex. *J Immunol* 2002;**168**:3235−41.
282. Dong C, Wei L, Zhu W, Kim JK, Wang Y, Omotara P, et al. Mature dendritic cell-derived extracellular vesicles are potent mucosal adjuvants for influenza hemagglutinin vaccines. *ACS Nano* 2025;**19**:25526−42.
283. Wang J, Zhu M, Nie G. Biomembrane-based nanostructures for cancer targeting and therapy: from synthetic liposomes to natural biomembranes and membrane-vesicles. *Adv Drug Deliv Rev* 2021;**178**:113974.

284. Hosseinidoust Z, Mostaghaci B, Yasa O, Park BW, Singh AV, Sitti M. Bioengineered and biohybrid bacteria-based systems for drug delivery. *Adv Drug Deliv Rev* 2016;**106**:27−44.
285. Lin X, Jiao R, Cui H, Yan X, Zhang K. Physiochemically and genetically engineered bacteria: instructive design principles and diverse applications. *Adv Sci (Weinh)* 2024;**11**:e2403156.
286. Lu Y, Ma N, Cheng K, Liu G, Liang J, Xu C, et al. An OMV-based nanovaccine as antigen presentation signal enhancer for cancer immunotherapy. *Adv Mater* 2025;**37**:e2413392.
287. Yang QC, Wang YY, Wang S, Song A, Wang WD, Zhang L, et al. Engineered bacterial membrane biomimetic covalent organic framework as nano-immunopotentiator for cancer immunotherapy. *Bioact Mater* 2025;**47**:283−94.
288. Pan J, Wang Z, Huang X, Xue J, Zhang S, Guo X, et al. Bacteria-derived outer-membrane vesicles hitchhike neutrophils to enhance ischemic stroke therapy. *Adv Mater* 2023;**35**:e2301779.
289. Xiang S, Khan A, Yao Q, Wang D. Recent advances in bacterial outer membrane vesicles: effects on the immune system, mechanisms and their usage for tumor treatment. *J Pharm Anal* 2024;**14**:101049.
290. Tenchov R, Bird R, Curtze AE, Zhou Q. Lipid nanoparticles—from liposomes to mRNA vaccine delivery, a landscape of research diversity and advancement. *ACS Nano* 2021;**15**:16982−7015.
291. Anthiya S, Öztürk SC, Yanik H, Tavukcuoglu E, Şahin A, Datta D, et al. Targeted siRNA lipid nanoparticles for the treatment of KRAS-mutant tumors. *J Control Release* 2023;**357**:67−83.
292. Barenholz Y. Doxil®—The first FDA-approved nano-drug: lessons learned. *J Control Release* 2012;**160**:117−34.
293. Estapé Senti M, García Del Valle L, Schiffelers RM. mRNA delivery systems for cancer immunotherapy: lipid nanoparticles and beyond. *Adv Drug Deliv Rev* 2024;**206**:115190.
294. van Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. *Nat Rev Mol Cell Biol* 2018;**19**:213−28.
295. Seung E, Xing Z, Wu L, Rao E, Cortez-Retamozo V, Ospina B, et al. A trispecific antibody targeting HER2 and T cells inhibits breast cancer growth *via* CD4 cells. *Nature* 2022;**603**:328−34.
296. Tapia-Galisteo A, Alvarez-Vallina L, Sanz L. Bi- and trispecific immune cell engagers for immunotherapy of hematological malignancies. *J Hematol Oncol* 2023;**16**:83.
297. Zhang Y, Luo J, Gui X, Zheng Y, Schaar E, Liu G, et al. Bioengineered nanotechnology for nucleic acid delivery. *J Control Release* 2023;**364**:124−41.
298. Chen Y, Li W, Wang Z, Yu Y, Li J, Ding Y, et al. A transformable supramolecular bispecific cell engager for augmenting natural killer and T cell-based cancer immunotherapy. *Adv Mater* 2024;**36**:e2306736.
299. Liu Y, Zhang Y, Li H, Hu TY. Recent advances in the bench-to-bedside translation of cancer nanomedicines. *Acta Pharm Sin B* 2025;**15**:97−122.
300. Elena M, Eleftheria G, Yiannis S, Lefteris ZC, Michael P, Georgios A, et al. Clinical trials of nanovesicles for drug delivery applications. In: Amit Kumar Nayak MSH, Aminabhavi Tejraj M, Torchilin Vladimir P, editors. *Applications of nanovesicular drug delivery*. Elsevier; 2022. p. 467−86.
301. Fais S, O'Driscoll L, Borras FE, Buzas E, Camussi G, Cappello F, et al. Evidence-based clinical use of nanoscale extracellular vesicles in nanomedicine. *ACS Nano* 2016;**10**:3886−99.
302. *A single-center, prospective trial of the safety and efficacy of UCMSC-Exo in consolidation chemotherapy-induced myelosuppression in patients with acute myeloid leukemia after achieving complete remission*. 2024. Available from: https://clinicaltrials.gov/study/NCT06245746.
303. *Phase I study of mesenchymal stromal cells-derived exosomes with KrasG12D siRNA for metastatic pancreas cancer patients harboring KrasG12D mutation*. 2018. Available from: https://clinicaltrials.gov/study/NCT03608631.
304. Phase 1 study of macrophage reprogramming agent, exoASO-STAT6 (CDK-004). *Patients with advanced hepatocellular carcinoma (HCC) and patients with liver metastases from either primary gastric cancer or colorectal cancer (CRC)*. 2022. Available from: https://clinicaltrials.gov/study/NCT05375604.
305. An open. *dose-escalation clinical study of chimeric exosomal tumor vaccines for recurrent or metastatic bladder cancer*. 2022. Available from: https://clinicaltrials.gov/study/NCT05559177.
306. *Exosomes and resistance to immunotherapy in aggressive non-hodgkin B-cell lymphomas (B-NHL)*. 2019. Available from: https://clinicaltrials.gov/study/NCT03985696.
307. *Phase II trial of a vaccination with tumor antigen-loaded dendritic cell-derived exosomes on patients with unresectable non small cell lung cancer responding to induction chemotherapy*. 2010. Available from: https://clinicaltrials.gov/study/NCT01159288.
308. Liu X, Xiao C, Xiao K. Engineered extracellular vesicles-like biomimetic nanoparticles as an emerging platform for targeted cancer therapy. *J Nanobiotechnol* 2023;**21**:287.
309. Wen Y, Fu Q, Soliwoda A, Zhang S, Zheng M, Mao W, et al. Cell-derived nanovesicles prepared by membrane extrusion are good substitutes for natural extracellular vesicles. *Extracell Vesicle* 2022;**1**:100004.
310. Cheng Y, Hay CD, Mahuttanatan SM, Hindley JW, Ces O, Elani Y. Microfluidic technologies for lipid vesicle generation. *Lab Chip* 2024;**24**:4679−716.
311. Taha MS, Padmakumar S, Singh A, Amiji MM. Critical quality attributes in the development of therapeutic nanomedicines toward clinical translation. *Drug Deliv Transl Res* 2020;**10**:766−90.
312. Lau HC, Passalacqua I, Jung JH, Kwon Y, Zocco D, Park SS, et al. Unraveling the surface marker signature of cell-derived vesicles *via* proteome analysis and nanoparticle flow cytometry. *Sci Rep* 2024;**14**:121.
313. Korchak JA, Wiest EF, Zubair AC. How do we assess batch-to-batch consistency between extracellular vesicle products?. *Transfusion* 2023;**63**:279−87.
314. Nguyen VVT, Witwer KW, Verhaar MC, Strunk D, van Balkom BWM. Functional assays to assess the therapeutic potential of extracellular vesicles. *J Extracell Vesicles* 2020;**10**:e12033.