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Cell membrane coated nanoparticles as a biomimetic drug delivery platform for enhancing cancer immunotherapy

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Cancer immunotherapy, a burgeoning modality for cancer treatment, operates by activating the auto-immune system to impede the growth of malignant cells. Although numerous immunotherapy strategies have been employed in clinical cancer therapy, the resistance of cancer cells to immunotherapeutic medications and other apprehensions impede the attainment of sustained advantages for most patients. Recent advancements in nanotechnology for drug delivery hold promise in augmenting the efficacy of immunotherapy. However, the efficacy is currently constrained by the inadequate specificity of delivery, low rate of response, and the intricate immunosuppressive tumor microenvironment. In this context, the investigation of cell membrane coated nanoparticles (CMNPs) has revealed their ability to perform targeted delivery, immune evasion, controlled release, and immunomodulation. By combining the advantageous features of natural cell membranes and nanoparticles, CMNPs have demonstrated their unique potential in the realm of cancer immunotherapy. This review aims to emphasize recent research progress and elucidate the underlying mechanisms of CMNPs as an innovative drug delivery platform for enhancing cancer immunotherapy. Additionally, it provides a comprehensive overview of the current immunotherapeutic strategies involving different cell membrane types of CMNPs, with the intention of further exploration and optimization.

1. Introduction

Immunotherapy, a promising cancer treatment, activates the host immune system to combat solid tumors and circulating tumor cells.[1] In recent years, immunotherapy has been used clinically as an adjuvant treatment after surgery, radiotherapy, and chemotherapy.[2,3] Current cancer immunotherapies include cancer vaccines, immune checkpoint blockade (ICB) therapy, cytokine therapy, and adoptive immunotherapy.[4] Despite their potential, issues like low tumor antigen expression, abnormal cytokine secretion, inadequate immune cell activation, and the complex immunosuppressive tumor microenvironment (TME) lead to drug resistance and adverse reactions.[5,6] Together with the accompanying toxic and inflammation reactions during therapy, the clinical efficacy is limited.[7] Hence, the imperative challenges lie in precisely targeting drug delivery to tumor sites, ameliorating the immuno-

suppressive TME, augmenting immune responsiveness, and mitigating systemic immunotoxicity.[8]

Nanotechnology has introduced innovative approaches to cancer immunotherapy.[9] Nanoparticles (NPs) have demonstrated considerable utility in delivering singular or multiple drugs to tumor sites, significantly impacting diagnostic imaging, photoimmunotherapy, chemotherapy, and gene therapy.[10–13] Their systemic delivery leverages the enhanced penetration and retention (EPR) effect,[14] and their controlled properties and low toxicity ensure prolonged drug retention and compatibility, mitigating delivery challenges in cancer immunotherapy.[15] However, NPs face challenges in immunotherapy due to recognition and clearance by the reticuloendothelial system (RES), leading to low effectiveness.[16,17] Prior attempts to enhance NP circulation and targeting with modifications like polyethylene glycol (PEG) or antigenic peptides have limitations due to immune response and complex synthesis process.[18–20] The ideal NPs should possess immune evasion, extended retention, targeted delivery, biosafety, and scalability.[21,22]

Cell membrane coating technology presents a solution by encapsulating natural cell membranes on NPs. These synthesized CMNPs are endowed with both NPs' properties and

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those of the coated cell membranes.[23–25] Various cell membrane types, such as erythrocyte, leukocyte, platelet, cancer cell, immune cell, and hybrid cell membranes, have been utilized, resulting in CMNPs with immune evasion, targeted delivery, controlled release, and immunomodulation. These advances have found applications in diagnostic imaging,[26,27] infection,[28,29] inflammation,[30–32] cancer chemotherapy,[33] and immunotherapy. This review provides an overview of the applications of CMNPs in enhancing cancer immunotherapy (Fig. 1). It delineates the process of cancer immunotherapy and the synthesis of CMNPs, while emphasizing the latest research progress and the underlying mechanisms of CMNPs concerning different cell membrane types and delivery components. Furthermore, it discusses the challenges and prospects of this technology.

2. Cancer immune cycle and cancer immunotherapy

The immune system recognizes cancer cells as foreign entities, triggering innate and adaptive immune responses to eliminate them. This process, termed the "cancer immune cycle", was conceptualized by Chen and Mellman in 2013.[34] Dendritic cells (DCs) act as specialized antigen-presenting cells (APCs) to capture antigens released by tumors (step 1), and then express
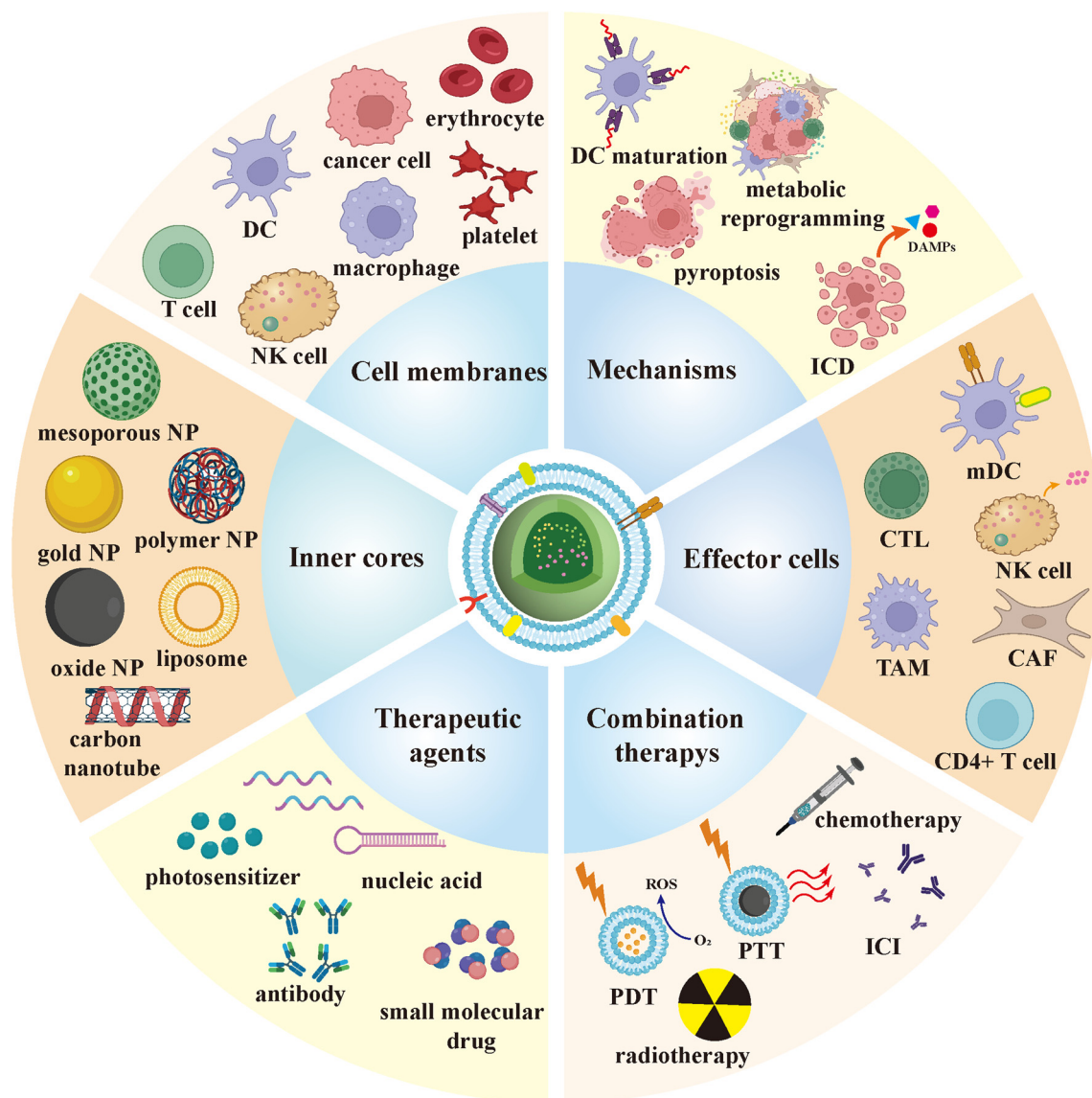

Fig. 1 Graphical abstract of CMNPs delivering different therapeutic agents for enhancing cancer immunotherapy. NP: nanoparticle; NK cell: natural killer cell; DC: dendritic cell; ICD: immunogenic cell death; DAMP: damage associated molecular pattern; CTL: cytotoxic T lymphocytes; mDC: mature dendritic cell; TAM: tumor associated macrophage; CAF: cancer associated fibroblasts; PTT: photothermal therapy; PDT: photodynamic therapy; ICIs: immune checkpoint inhibitors.

the captured antigens as major histocompatibility complex (MHC)-antigen peptide complexes on cell membranes (step 2). After DCs deliver the complexes to the secondary lymphoid organs (step 3), T cells are activated by the interactions between T cell receptors (TCRs) and the MHC-antigen peptide complexes along with other ligands and receptors. Activated tumor-specific cytotoxic T cells (CTLs) migrate to the tumor sites, guided by chemokines in TME (step 4), and gradually infiltrate the tumor tissues (step 5). Specific recognition and binding of TCRs to MHC-antigen peptide complex on associated tumor cells (step 6) lead to tumor cell destruction, releasing more tumor-associated antigens (TAAs), and perpetuating the cycle (step 7). Each step has checkpoints or inhibitors to finely regulate tumor immunity.[35,36] Consequently, cancer immunotherapy aims to enhance and amplify the cancer immune cycle to achieve a heightened immune response without inducing autoimmune-associated inflammation (Fig. 2).[37,38]

Cancer immunotherapy has made substantial advancements, representing a pivotal development in the realm of cancer treatment. Immune checkpoint inhibitors (ICIs) are notable for restoring immune cells' capacity to counter cancer cells by blocking inhibitory molecules (*e.g.*, PD-1, PD-L1, CTLA-4) on immune cells.[39] These inhibitors have gained FDA approval for melanoma, lung cancer, renal cancer, and other conditions, yielding noteworthy therapeutic outcomes.[40–44]

Adoptive cell therapy, such as CAR-T cell therapy, primarily targets hematological malignancies (like leukemia and lymphoma). It involves genetically modifying T cells with specific antigen receptor genes, enabling them to release substances like perforin and granzyme B to directly eliminate identified tumor cells.[45,46] Cancer vaccines, in contrast, aim to activate the patient's immune system against tumor cells. Notable vaccine types include TAA vaccines, individualized cancer vaccines, viral vector vaccines, and combination vaccines with immunostimulants or antitumor drugs.[47–49] Cytokine therapy regulates the growth, differentiation, and function of immune cells within TME, enhancing immune cell activity and alleviating immunosuppression.[50] Several cytokines, including IL-2, IL-7, IL-12, IL-15, interferon (IFN), and tumor necrosis factor (TNF), are partially utilized in cancer immunotherapy.[51–55] Each of these immunotherapeutic approaches reinitiates the cancer immune cycle by acting on one or more stages, effectively controlling tumor progression, metastasis, and recurrence, thereby representing significant progress for cancer patients.

Despite being at the forefront of cancer treatment, immunotherapy's clinical efficacy remains suboptimal, primarily due to patient resistance to immunotherapeutic drugs. Various mechanisms contribute to cancer cells developing resistance after immunotherapy.[6,56] Tumor cells evade immune cell recognition by down-regulating TAA expression, diminish immune
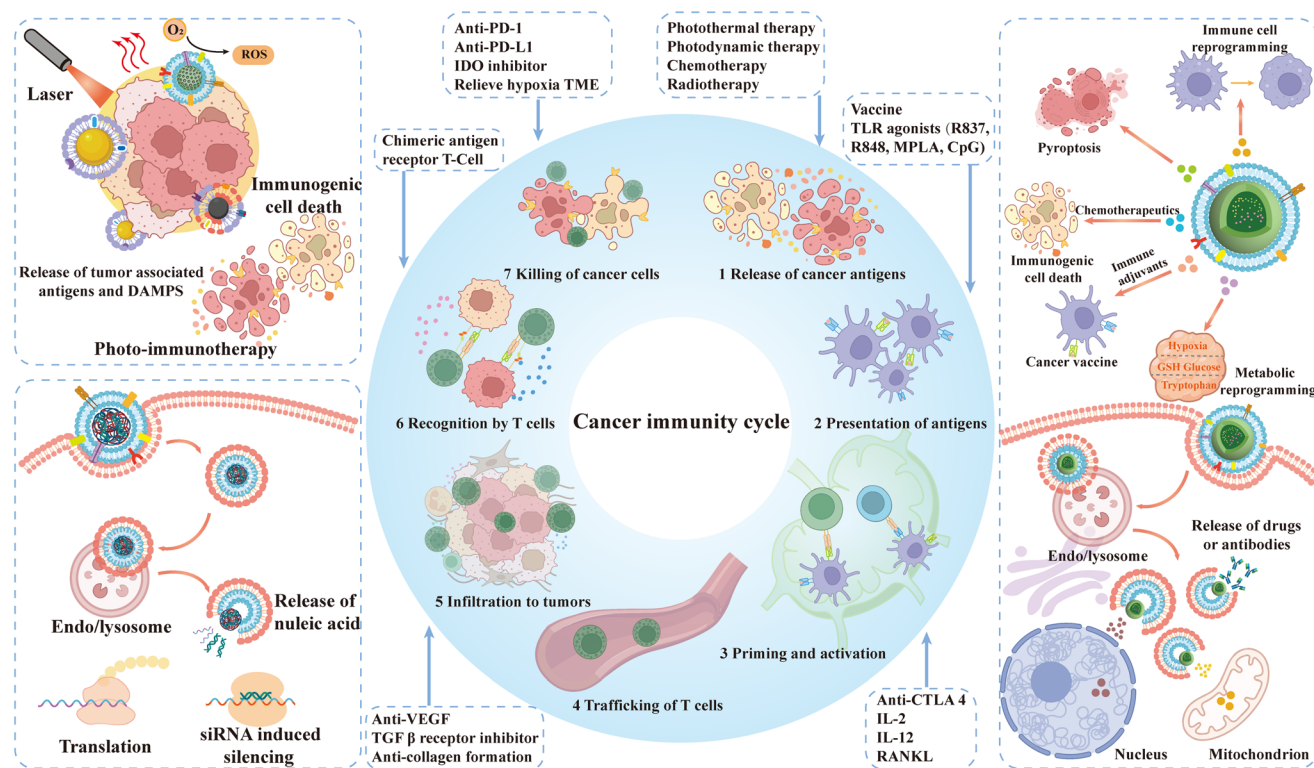

Fig. 2 Schematic of the cancer immunity cycle and mechanisms of CMNPs loaded with different therapeutic agents and common immunotherapies for enhancing the anti-cancer immunity.

clearance by expressing immunosuppressive molecules (PD-L1 and CTLA-4), and develop resistance to immunotherapy, as seen in tumor cells treated with photo-immunotherapy that up-regulate heat shock proteins (HSPs) to counteract thermal ablation effects.[57,58] Additionally, multiple factors in the intricate TME, such as immune-suppressing cells (Tregs, M2-type macrophages, and CAFs), immunosuppressive cytokines (TGF-β, IL-10), physical barriers like dense extracellular matrix, and signaling pathways promoting anti-apoptotic and anti-inflammatory responses, hinder immune cell function.[59] Moreover, high-frequency gene mutations in tumor cells during proliferation can result in the expression of neoantigens or mutant tumor antigens, leading to a low or no response to immunotherapeutic drugs.[60] A sustained anti-tumor immune response also leads to impaired function, inactivation, or death of immune cells.[5,61–63] These intricate and interconnected mechanisms collectively contribute to the development of drug resistance. Besides, the limitations of cancer immunotherapy, including low response rates, limited durability, and immune-related adverse events (irAEs), pose challenges for its rapid development.[64,65] Consequently, it has become a challenge to develop new immunotherapeutic strategies to provide patients with safe, durable, and specific cancer immunotherapy.

3. Applications of nanoparticles in cancer immunotherapy

The emergence of nanoparticles has provided new ideas to address these challenges of cancer immunotherapy approaches described above. Nanotechnology has significantly improved drug delivery by utilizing drug-loaded NPs that enhance penetration, retention, and accumulation of immunotherapy drugs in cancer tissues, leading to safer and more efficient drug delivery.[14,15] For instance, Xu et al. have loaded melanoma TAAs and adjuvants into lipid calcium phosphate (LCP) NPs to develop a cancer vaccine. This approach stimulated an effective anti-melanoma T cell response by enhancing phagocytosis and presentation of DCs.[66] Another study involved combining mRNA with lipid-based NPs to create an mRNA vaccine. The nanoparticles protected mRNA from degradation and clearance, thereby increasing its accumulation in DCs and enhancing the expression of specific tumor antigens, resulting in effective T cell responses in models of melanoma and lung cancer.[67]

Certain nanomaterials with photosensitive properties, such as gold nanocages and copper sulfide, can enhance the effectiveness of immunotherapy. They achieve this by inducing immunogenic cell death (ICD) in tumor cells through photodynamic or photothermal therapy, releasing pro-inflammatory factors to promote APC maturation, and enhancing the depth of the cancer immune cycle.[68,69] For instance, Wang et al. demonstrated that polyethanolated gold nanostructures, when exposed to near-infrared (NIR) light, prolonged blood circulation time, accumulated at tumor sites, and exhibited signifi-

cant therapeutic effects in a breast cancer mouse model by converting light into thermal energy.[70] Another study utilized mesoporous silica-coated up-conversion NPs loaded with photosensitizers, resulting in the generation of a large amount of reactive oxygen species (ROS) upon 980 nm laser irradiation, showcasing the photodynamic effect in a colon cancer mouse model.[71]

Additionally, novel nano-delivery systems can enhance immunotherapy effectiveness by targeting neovascularization, fibroblasts, and immunosuppressive factors in TME to reshape its immunosuppressive nature. Ferumoxytol, an iron oxide NP, has been found to induce the repolarization of M2-type macrophages to M1-type, initiating a pro-inflammatory immune response that inhibits tumor growth.[72] Lipid NPs loaded with anti-angiogenic drugs and other chemotherapeutics have been designed to normalize tumor blood vessels, bolster endothelial resistance, and promote vascular normalization.[73]

However, despite the promising future of NPs in cancer immunotherapy, there exist limitations that hinder their application. While NPs accumulate in tumor tissues based on their specific properties, they can also permeate normal tissues, potentially leading to toxic reactions.[74] Furthermore, NPs are often recognized as foreign entities by the immune system, resulting in expedited clearance and reduced efficacy. Despite some advances in delivery, the issue of tumor resistance to immunotherapeutic agents remains unresolved.[75] Consequently, the development of safe, controlled, and targeted NPs has become a paramount challenge for advancing cancer immunotherapy.

To address the limitations of individual nanoparticles in cancer therapy, different types of CMNPs have been investigated and applied across various fields. Undoubtedly, CMNPs, leveraging the biological functionalities inherent in cell membranes, have significantly enhanced the versatility of nanoparticles in cancer immunotherapy, catalyzing a spectrum of innovative advancements. Primarily, CMNPs leverage natural cells as encapsulating agents, endowing them with surface characteristics reminiscent of native cells, thereby facilitating enhanced interactions with the immune system.[76] By modulating the surface proteins or ligands of nanoparticles, CMNPs can precisely target specific tumor cells, facilitating accurate delivery and controlled release of therapeutic agents.[77] Moreover, CMNPs exhibit the capability to not only transport chemical drugs but also incorporate immunomodulators, nucleic acid drugs, and other therapeutic agents, thereby creating a multifunctional therapeutic platform.[78] This multifaceted approach enables simultaneous engagement of multiple immunotherapeutic mechanisms, consequently augmenting the overall efficacy of tumor treatment strategies. In fact, CMNPs are not independent of the current rapidly evolving cancer immunotherapy modalities, but rather a complementary form of drug delivery that undoubtedly provides a theoretically safer and more efficient platform for the applications of for ICIs, CAR-T cell therapy, cytokine therapy, cancer vaccines, and other immunotherapeutic approaches.[79,80]

4. Characterization and synthesis of CMNPs

Since Hu *et al.* formed CMNPs by co-extruding erythrocyte membranes with PLGA nanoparticles in 2011, the biomimetic strategy of CMNPs began to flourish and provided a perfect platform for cancer therapy.[23] The combinations of different cell membranes with nanoparticle cores have given CMNPs the functions of membrane-derived cells and the unique advantages of nanoparticles in cancer immunotherapy. Multiple cell membranes are currently used in this biomimetic strategy, including the membranes of erythrocytes, platelets, cancer cells, immune cells, stem cells, bacteria, and even hybrid cell membranes.[81,82]

The complex functions of cell membranes enable CMNPs to adapt to the intricate tumor microenvironment. After wrapping membranes on NPs as carriers, and loading with drugs or engineering on the surface, CMNPs exhibit diverse characteristics, particularly in targeted drug delivery and immune evasion that conventional therapies lack, presenting a novel concept for cancer immunotherapy.[24]

4.1. Unique functions of CMNPs from different cell membrane sources

Following the coating of cell membranes, the proteins, signaling molecules, and antigens on the cell membrane surface remain intact, thereby ensuring the seamless transfer of these biologically functional constituents to CMNPs. The specialized functions that CMNPs derive from original cells are outlined next, based on the different cell types.

4.1.1. Erythrocyte membranes. Erythrocytes are highly abundant blood cells within the circulatory system with favorable circulatory properties, enabling efficient oxygen transport to tissues. The long survival time of erythrocytes in the bloodstream (approximately 120 days) is attributed to CD47, a marker on membrane surface that interacts with glycoprotein signal-regulated protein alpha (SIRPα) found on phagocyte membranes to provide a "don't eat me" signal. This signal evades the clearance by immune organs and cells to achieve prolonged circulation and sustain oxygenation.[83] Mature erythrocytes lack nuclei and other organelles, resulting in membranes more readily isolated and purified.[23] Compared to PEG NPs, erythrocyte membrane coated NPs exhibit an extended half-life and enhanced capacity to evade phagocytosis and clearance by RES.[84]

4.1.2. Platelet membranes. Platelets, originating from mature bone marrow macrophages, are essential for hemostasis and tissue repair in the physiological state. Activated platelets can also participate in adaptive immunity by releasing antimicrobial peptides, defensins, and proteases.[85] Similar to erythrocytes, platelets have no organelles, making them suitable as coatings for NPs. Furthermore, platelets express CD47 on their surfaces, allowing them to evade macrophage phagocytosis and extend their circulation within the bloodstream. Certain molecules on the platelet membrane, such as CD55 and CD59, can inhibit attacks from the complement system, thus protecting platelet-coated nanoparticles in circulation within blood vessels.[86] Unlike erythrocytes, platelets express p-selectin, αIIbβ3, and GPIbα, which are linked to cancer development, indicating that they can specifically bind and interact with cancer cells.[87] For instance, p-selectin expressed on platelets during activation could selectively bind to CD44 on cancer cell surfaces, conferring platelet membrane coated NPs to target cancer tissues and circulating cancer cells in the bloodstream.[88] Evidence also indicates that platelets aggregate within tumor tissues depending on the surface expression of GPIb and GPIIb/IIIa molecules, providing new insights into the development of platelet-derived CMNPs with enhanced tumor affinity.[89]

4.1.3. Cancer cell membranes. In the process of cancer development, cancer cells employ intricate mechanisms to evade immune surveillance. For instance, the presence of specific molecules on cancer cell membranes, such as CD47, lay the foundation for cancer cell membrane coated NPs to achieve immune evasion. Notably, Thomsen-Friedenreich glycoantigen (T antigen), galectin-3, epithelial cell adhesion molecule (EpCAM) on membranes facilitate the homotypic adhesion among cancer cells, endowing resulting coated NPs with the ability to selectively target homotypic cancer cells, thus achieving precise drug delivery.[90] Additionally, the antigens present on membranes can be effectively presented to T cells by APCs, triggering an effective immune response.[91] Biomimetic nanoparticles coated with cancer cell membranes retain tumor-specific antigens and homologous targeting capabilities, enriching the drug delivery strategies for cancer immunotherapy. Therefore, cancer cell membranes hold substantial promise as coating materials for NPs in cancer immunotherapy. However, it is essential to consider the impact of cancer cell heterogeneity, phenotypic differences between cell lines used for membrane extraction and tumor cell models in animal studies, and phenotypic mutations during tumor progression, all of which may affect the specificity of drug delivery.

4.1.4. Immune cell membranes. Leukocytes possess the ability to traverse physiological barriers, evade immune evasion, target inflammatory sites, and secrete various cytokines and chemokines to mitigate inflammation.[92] Given that tumors exhibit chronic inflammatory characteristics, leukocytes are closely related to tumor development and antitumor immune response. Consequently, immune cell membranes (such as DCs, macrophages, NK cells, T cells, *etc.*) coated NPs play an indispensable role in cancer immunotherapy.[93]

Macrophages are versatile innate immune cells widely distributed in tissues. In adult individuals, they predominantly originate from hematopoietic stem cells/monocytes in the bone marrow. Macrophages could assume diverse functional states depending on their local microenvironment. M1-type macrophages are activated by interferon, bacterial lipopolysaccharide (LPS), or granulocyte-macrophage colony-stimulating factor (CM-CSF), and promote inflammatory processes and adaptive immunity. Conversely, M2-type macrophages are pri-

marily activated by elevated levels of cytokines such as IL-4, and IL-13, and are involved in tissue repair, angiogenesis, and the suppression of inflammation.[94] As a natural immune barrier, macrophages express integrins on the membranes to contact with vascular cell adhesion molecules (VCAM-1) on tumor cells, thus enabling them to target tumor sites and realize prolonged circulation time.[95] Macrophages in TME can transform into TAM under the influence of chemokines.[96] As the most abundant immune cell population in the TME, M1-type TAMs secrete pro-inflammatory cytokines and enhance their ability to combat tumors. Conversely, most TAMs exhibit M2-type characteristics, which can inhibit the function of CD4^{+} and CD8^{+} T cells, recruit Tregs, suppress the anti-tumor immune response, and facilitate tumor cell proliferation, infiltration, and metastasis.[97,98] Thus, modulating macrophage polarization is an ideal approach to reverse immunosuppression of TME.[99]

Dendritic cells, being the primary APCs in the body, play a pivotal role in recognizing, internalizing, and presenting antigens, which are essential for activating specific T cell immune responses. Since mature DCs expressing MHC-antigen peptide complexes on the surfaces are key players in the tumor immune process, DC membrane coated NPs are poised to amplify the cancer immune cycle by inheriting their antigen-presenting and T cell activation abilities, thereby offering novel possibilities for CMNPs-based immunotherapy.[100]

NK cells can generate non-specific anti-tumor responses without prior antigen sensitization or antibody involvement. This is mainly accomplished by perforin and tumor necrosis factor secreted by activated NK cells. Additionally, NK cells release various cytokines to play immunomodulatory roles, such as promoting the maturation of APCs and inducing M1-type macrophage polarization. Moreover, NK cells can target tumor cells through surface activation receptors CD16 and NKG2D. Consequently, NK CMNPs hold promise for enhancing targeted drug delivery and regulating the immune microenvironment.[101]

4.1.5. Hybrid membranes. Apart from using single-cell membranes for nanoparticle coating, the emerging focus has been on hybrid cell membranes. Hybrid membranes offer a more convenient and flexible option for designing biomimetic nanodrug delivery systems. In cases where single-cell membrane coatings are insufficient for designing CMNPs, fusion of two or more cell membranes retains the surface markers of original cell membranes, resulting in a combination of multiple functions.[102] Hybrid membranes are obtained by blending different types of cell membranes through methods such as agitation, ice-bathing, or sonication, and are coated onto nanoparticles using the aforementioned techniques.[103] For instance, Zhang et al. merged erythrocyte membranes with melanoma cell membranes for coating, leading to prolonged circulation time and specific targeting of homologous melanoma cells.[104] Another study combined DC membranes with cancer cell membranes, resulting in the expression of both tumor antigens and co-stimulatory molecules, effectively activating T cells.[105] Research has also utilized hybridization of

tumor stem cell membranes and platelet membranes, significantly reducing the uptake of nanoparticles by RAW264.7 macrophages, demonstrating enhanced biocompatibility.[106] Additionally, various combinations of hybrid cell membranes are being developed for cancer therapy, such as macrophages with cancer cells, and cancer cells with activated fibroblasts.[107,108] Surface modification of nanoparticle-coated hybrid membranes can also enhance active targeting capabilities. For instance, research has shown effective targeting of circulating tumor cells by modifying anti-epithelial cell adhesion molecules on hybrid membranes of platelets and leukocytes.[109] This membrane hybridization technology confers a more comprehensive biological function to CMNPs and demonstrates considerable research significance.

4.1.6. Other membranes. Besides the common cell membranes mentioned above, various membrane types find increasing use in designing CMNPs. Mesenchymal stem cells, owing to their potential for multidirectional differentiation and expression of various chemokine receptors, enable CMNPs to migrate specifically toward cancer cells.[110] Fibroblasts, constituting a key component of TME, play important roles in tumor angiogenesis, proliferation, and metastasis. Utilizing activated fibroblast membranes as coatings facilitates the homologous targeting of fibroblasts in tumor mesenchyme, thus inhibiting tumor growth.[108] Recently, organelle membranes (mitochondria, endoplasmic reticulum, etc.) are emerging coating materials. Subcellular organelle membranes assist NPs in achieving immune escape, and some studies have fused cellular membranes with organelle membranes to realize the synergistic effect of targeting specific cells and then subcellular organelles.[111] Intriguingly, some bacterial cell membranes are rich in pathogen-associated molecular patterns, and the resulting CMNPs can activate innate immune responses and promote DC maturation by serving as "adjuvants".[112]

4.2. Engineering strategies of cell membranes

There are inevitable limitations in using natural cell membranes as the biological function source for CMNPs. With the increasing comprehensiveness and stringency of CMNP requirements, there's a gradual shift in the coating materials from natural to engineered cell membranes (Fig. 3).[113] To achieve multifunctional modification, engineering strategies are gaining attention to modify the cell membrane by inserting specific ligands, functional proteins, or directly at the cellular level.[114,115] Hybrid cell membranes, discussed earlier, represent a mature engineering technique for physical fusion, overcoming the inherent limitations of single-cell membranes and achieving functional compatibility.[103]

Chemical modification is widely employed for engineering cell membranes. The phospholipid bilayer structure allows the embedding amphiphiles containing diverse functional groups into the cell membrane via a non-covalent manner by hydrophobic interactions. For instance, DSPE-PEG-Man, inserted into the phospholipid bilayers, increased the ability to target APCs in lymph nodes or macrophages in tumor sites through mannose introduction.[116,117] Recognizing the low stability of
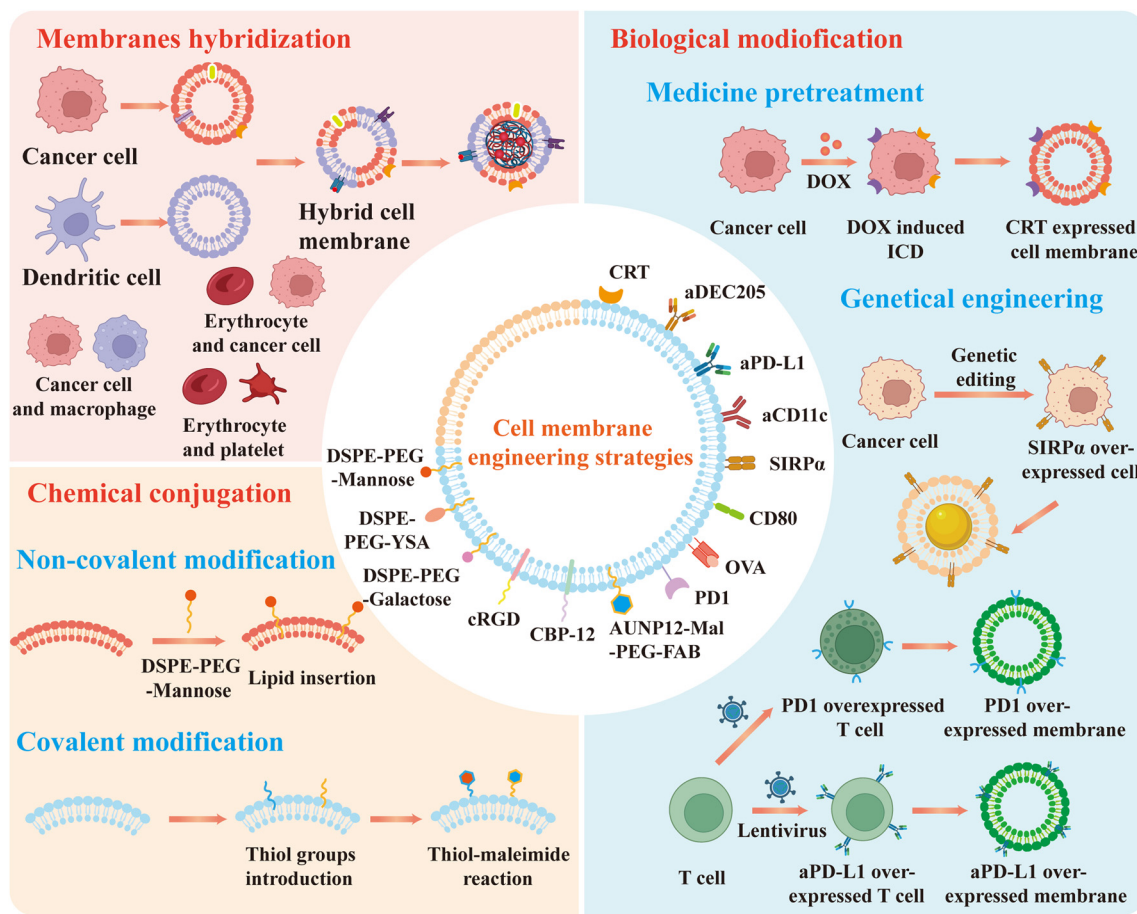
Fig. 3 Engineering strategies of cell membranes *via* membrane hybridization, chemical conjugation, and biological modification. aDEC205: anti-DEC205; aSIRPα: signal regulatory protein alpha; OVA: ovalbumin; AUNP12-Mal-PEG-FAB: AUNP12(anti-PD1 peptide)-maleimide-polyethylene glycol-formyl benzoic acid; CBP-12: 12-mer Clec9a binding peptide; cRGD: cyclo (Arg-Gly-AspD-Tyr-Lys) peptide; YSA: ephrin-A2 receptor-specific peptide.

non-covalent binding, researchers prefer chemical bonding for the stable attachment of active molecules like peptides or proteins to membrane surfaces.[118]

Biological modification of cell membranes is a favorable and promising approach. One study employed DOX pretreatment to obtain cell membranes overexpressing CRT for promoting the active uptake of nanovaccines by DCs.[119] Genetic engineering techniques enable precise control of cellular biosynthesis at the gene level, resulting in cell membranes that stably express the desired functional molecules. For instance, Rao and co-workers realized overexpression of the SIRPα variants on cancer cell membranes by lentiviral transfection, heightening the affinity for CD47.[120] Similarly, Tang *et al.* genetically engineered a HEK293T cell line stably overexpressing M-αPD-L1 to encapsulate NPs to enhance immunotherapy.[121]

4.3. The synthesis of CMNPs

The process of acquiring cell membrane materials involves two key stages: cell membrane lysis and subsequent purification (Fig. 4). Current methodologies for cell membrane lysis

encompass hypotonic solution, freeze–thaw cycling, and ultrasound techniques. Hypotonic lysis necessitates the preparation of a suitable hypotonic lysis buffer (pH 7.4), typically composed of Tris, $MgCl_2$, among others, with the addition of the protease inhibitor PMSF (excluding EDTA) on ice to prevent the degradation of crucial functional proteins on the cell membrane surface. Subsequently, cell pellets are harvested *via* centrifugation and subjected to washing for further processing.[122] Freeze–thaw cycling involves the iterative freezing of cell suspensions in liquid nitrogen for about 20 minutes, succeeded by thawing in a water bath (37 °C) for 5 minutes, until substantial disruption of cell morphology is achieved, accompanied by the disappearance of intact nuclei and perinuclear structures, as visualized under a microscope. Subsequent centrifugation is performed to eliminate dense cell nuclei and a fraction of undamaged cells.[123] Although ultrasound-assisted cell lysis is a convenient and rapid method, the potential for membrane protein damage and protein denaturation due to ultrasound-induced heating underscores the necessity for meticulous control over ultrasound parameters. Presently, researchers commonly employ the former two methods for cell lysis,
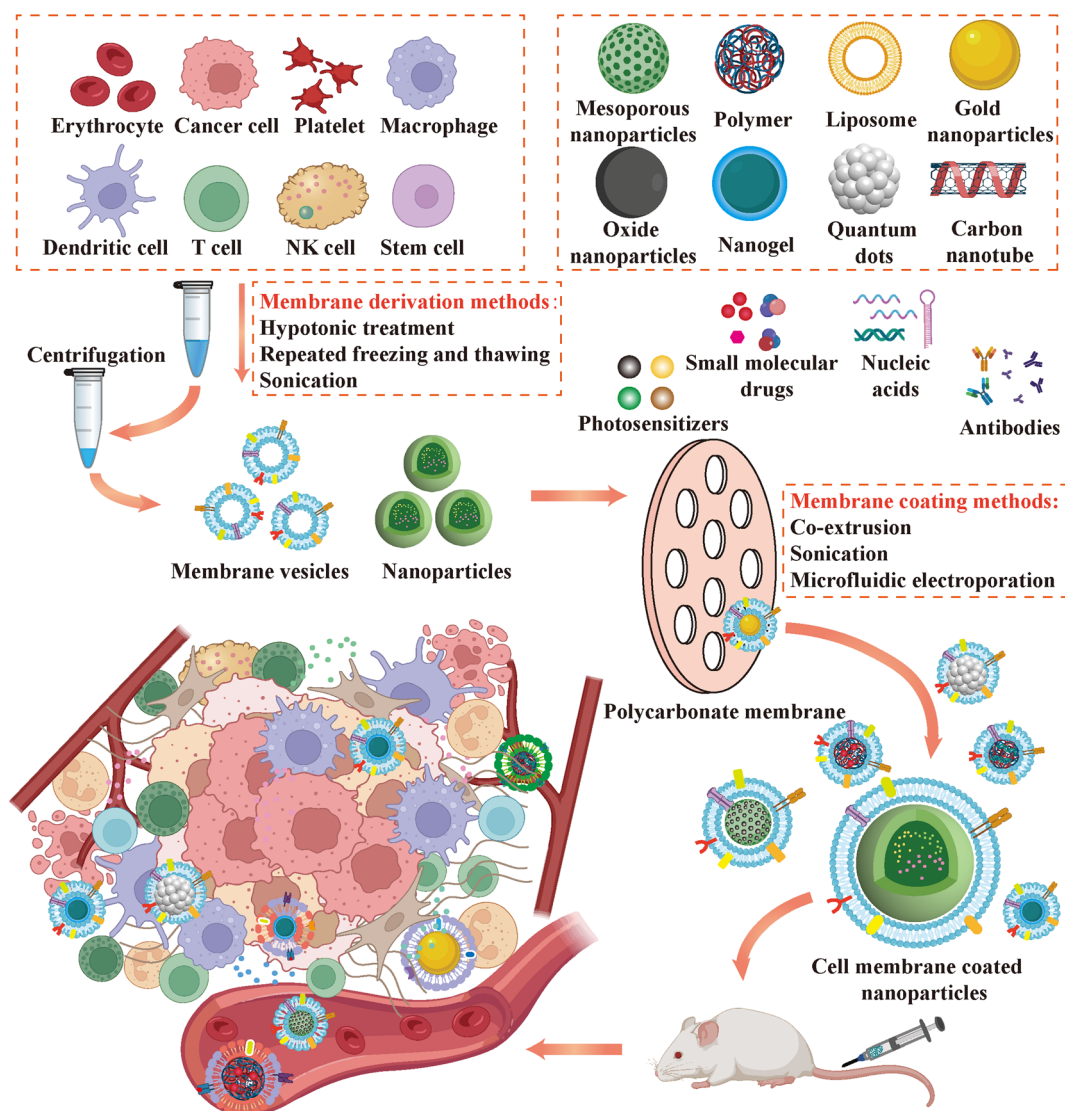
Fig. 4 Schematic of sources and synthesis process of cell membrane coated nanoparticles for cancer immunotherapy.

adapting protocols as needed to preserve the integrity of cell membrane surface proteins and ion channel structures and functionalities.[105] Following lysis, further processing of the obtained cell suspension is required to obtain purified cell membrane fragments. For nucleus-free cells such as red blood cells and platelets, purification of cell membranes is relatively straightforward through high-speed centrifugation. However, for nucleated cells like tumor cells and immune cells, the presence of intracellular organelles and complex protein and enzyme components presents challenges to membrane material acquisition.[124] Typically, a discontinuous sucrose gradient centrifugation method is employed to segregate and purify cell membranes. This is followed by low-speed centrifugation to eliminate residual cell nuclei and organelles, prior to subjecting the resulting supernatant to high-speed centrifugation for the precipitation of cell membrane fractions.[125]

The selection of a coating technique for CMNPs significantly influences their functionality. Physical extrusion emerges as the preferred method in most investigations, entailing the repeated extrusion of purified cell membranes and nanoparticles through porous polycarbonate membranes with diameters in the hundreds of nanometers.[126] Mechanical force transiently disrupts membrane fluidic structures, facilitating the reassembly of protein-laden membrane fragments around nanoparticle cores. This approach enables the production of uniformly sized and coated CMNPs by adjusting membrane pore sizes, thereby ensuring consistency with the surface proteins of the source cells.[25] Nonetheless, this method is primarily suitable for laboratory-scale production and entails considerable time and labor. The inherent asymmetric charge interactions between nanoparticle cores and the inner and outer layers of cell membranes culminate in the formation of shell–core structures with specific right-side-out

membrane orientation subsequent to coating.[127] This phenomenon is crucial for preserving the integrity of various ion channels and functional protein components on the cell membrane surface. Ultrasound, based on acoustic principles, is another coating method where ultrasound energy can disrupt membrane stability, leading to self-assembly of membranes and nanoparticles into shell–core structures, facilitating large-scale production.[128] However, careful consideration is warranted regarding potential alterations in biological membrane component functionality attributable to excessive local ultrasound energy and drug deformation and leakage. Microfluidic electroporation represents an innovative coating approach wherein membranes and nanoparticles traverse distinct channels within a microfluidic chip, achieving thorough mixing before fusing at the electroporation region between two electrodes under the influence of electrical pulses.[129] Various parameters such as mixing velocity, voltage, and pulse intensity can be finely tuned within the device, thereby advancing membrane coating technology towards heightened efficiency and precision. The attainment of comprehensive coverage of cell membranes onto nanoparticle surfaces holds pivotal importance in constructing proficient drug delivery systems.[130]

Ensuring complete coverage of cell membranes on the surface of nanoparticles is crucial for constructing drug delivery systems. Many studies characterize the physicochemical properties and biological characteristics of CMNPs to verify the successful encapsulation. The encapsulation process, owing to the negative charge of cell membranes, elicits alterations in nanoparticle surface charge and particle size. Consequently, dynamic light scattering (DLS) analyzers serve as prevalent tools for quantifying and contrasting the particle size and zeta potential of nanoparticles pre- and post-coating. Moreover, transmission electron microscopy (TEM) enables direct visualization of the shell–core architecture of CMNPs, with discernible density disparities between lipid bilayers and nanoparticles evident upon staining, manifesting as a halo encircling effectively coated nanoparticles.[131] Spectroscopic techniques are employed to scrutinize the optical characteristics and surface chemistry of CMNPs. For instance, UV-visible absorption spectroscopy enables the discrimination between absorption spectra originating from cell membranes and nanoparticle cores. This differentiation facilitates the characterization and authentication of CMNPs by discerning between individual nanoparticles exhibiting either dual or single absorption modes.[132,133] Furthermore, X-ray diffraction, Fourier transform infrared spectroscopy, and nuclear magnetic resonance spectroscopy are utilized to probe the structural configuration and compositional makeup of CMNPs.[134]

An indispensable facet of characterization experiments involves the analysis of surface proteomics and lipidomics of synthesized CMNPs. Conventionally, sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) is deployed to confirm distinct membrane protein profiles, while western blot analysis evaluates the retention of coated proteins. Notably, for engineered cell membrane coated nanoparticles, Coomassie Brilliant Blue staining and western blotting targeting coupled or overexpressed proteins assume critical importance.[135] Mass spectrometry emerges as a robust tool for identifying surface biological functional constituents. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) facilitates the analysis of surface protein constituents and their amino acid sequences, along with the identification and quantification of lipid species and contents on the membrane surface.[136] Immunological detection methodologies, such as immunoblotting and immunofluorescence staining, are instrumental in examining the presence, spatial distribution, and relative abundance of specific components on CMNP surfaces, especially for overexpressed engineered cell membranes, where localization of overexpressed proteins by spotlight confocal microscopy is essential.[77]

In summary, recent years have witnessed significant advancements in the preparation techniques for CMNPs. Alongside conventional blood cells and tumor cells, diverse cell membrane sources such as T cells, stem cells, and hybrid membranes have emerged as promising coating materials owing to their distinct advantages.[137] The rapid progress in engineered cell membrane technologies, encompassing chemical conjugation and genetic engineering, has introduced diverse strategies to enhance the functionalities of coated membranes. Given the reliance of CMNPs on straightforward top-down fabrication methods, stringent requirements for core nanomaterials are not imperative.[25] Various materials including polymers, metallic substances, and oxides can serve as drug carriers, greatly expanding the repertoire of shell–core structures.[138,139] On the synthesis front, besides conventional physical extrusion and sonication methods, innovative techniques such as microfluidic electroporation have been developed to yield more stable and homogeneous CMNPs. Collectively, these advancements contribute to the ongoing progress of CMNPs in the realm of cancer immunotherapy, and ongoing optimization of synthesis processes promises to expand its applicability for the treatment of cancer and other diseases.

5. Classification of CMNPs delivery components

CMNPs, as a nascent drug delivery platform, possess distinctive drug-loading capabilities. Encasing NPs in cell membranes provides a biocompatible shield, reducing toxicity and immunogenicity, preventing premature drug clearance and degradation, and enhancing drug bioavailability and patient adherence. Cell membranes derived from specific cell types enable targeted delivery through protein binding and surface modification, augmenting their biological functions. This biocompatible, targeted, stable, and versatile platform opens new avenues for precise drug delivery and therapy. These delivered therapeutic agents can be broadly classified into the following groups shown in Table 1.[88,107,116,121,140–162]

Table 1 Classification of CMNP delivery components

Type	Therapeutic agents	Core nanoparticles	Membrane types	Ref.
Photosensitizers	Gold nanoparticles	Au@Carbon	Human oral adenosquamous carcinoma cell	140
	Black phosphorus	Black phosphorus quantum dots	4T1 and B16F10 cancer cell	141
	Polydopamine	Polydopamine	4T1 cancer cell	142
	Indocyanine green	Fe_3O_4	Hybrid membrane (erythrocyte and ID8 cell membrane)	143
	Protoporphyrin IX	Copper peroxide	Erythrocyte	144
	Chlorin e6	DGL-G3	Platelet	145
	TCPP	Metal–organic frameworks	Hybrid membrane (DC and 4T1 cell membrane)	146
Small molecule compounds				
Targeting immune cells	R837	PLGA	B16-OVA cell	116
	R848	CuS	4T1 cell	147
	Monophosphoryl lipid A	PLGA	B16F10 cell	148
	cGMP-AMP	PLGA	B16-OVA cell	149
	IL-15	PLGA	NK cell	150
	Acetaminophen	Nanogel	Panc02 cell	151
	Magnetic nanoparticles	Fe_3O_4	M1 macrophage	152
Targeting cancer cells	Doxorubicin	Mesoporous organosilica nanoparticles	4T1 cell	153
	Paclitaxel	Hollow manganese dioxide nanoparticles	Mesenchymal stem cell	154
	Sorafenib	Hollow mesoporous silica nanoparticles	HepG2 cell	88
	Gemcitabine	PEG-PDPA	4T1 cell	155
	Docetaxel	PLGA	4T1 cell	156
Targeting cancer metabolic mechanisms	Glucose oxidase	Zeolitic imidazolate framework	4T1 cell	157
	Indoximode	Gold nanocage	M1 macrophage	158
	Catalase	Zeolitic imidazolate framework	B16F10 cell	159
Nucleic acid	Fibrinogen-like protein 1 siRNA	PLGA	Hybrid membrane (macrophage and 4T1 cell membrane)	107
	IL-1α siRNA	Black phosphorus	Erythrocyte	160
	Protein tyrosine phosphatase non-receptor type 2 shRNA	HA-DOX	M1 macrophage	161
	IL-12 mRNA	Calcium carbonate	GL261 cell	162
Antibody	aPD-L1	Barium titanate nanoparticle	293T cell	121
	aPD-L1	Hollow mesoporous silica nanoparticles	Platelet	88

5.1. Photosensitizers

Photothermal therapy (PTT) is a novel, non-invasive tumor thermal ablation technology. After the materials with high photothermal conversion efficiency are injected into the body, they can convert external near-infrared light into heat, inducing tumor cell ICD. The apoptotic tumor cells release massive new antigens and damage-associated molecular patterns (DAMPs), initiating the first step of the tumor immune cycle, recruiting APCs, and mobilizing T cells to amplify the immunotherapy.[163] Currently, various photothermal agents are being incorporated into CMNPs to address issues like inadequate accumulation at the target site, limited circulation time, and potential toxic reactions.

Nanoparticles with inherent photothermal properties, such as gold NPs utilizing localized surface plasmon resonance (LSPR), have been employed in the treatment of prostate cancer. In one study, Au@C NPs were synthesized through one-step hydrothermal method using gold perchlorate

$(HAuCl_4{\cdot}3H_2O)$ and glucose as the carbon source, while Au@C-CCM was produced by coating CAL-27 cancer cell membranes. The encapsulation provided stable photothermal properties to gold NPs, achieving 44.2% photothermal conversion efficiency, potentially improving PTT efficacy coupled with cancer cell membrane-based targeting.[140] Black phosphorus (BP), a 2D material with superior photothermal conversion efficiency, is a preferred photothermal agent in PTT applications. In a study, black phosphorus Quantum Dots (BPQDs) were prepared using a modified liquid stripping technique, forming BPQD-CCNVs after coating them with cancer cell membranes. These NPs exhibited rapid surface temperature increase under near-infrared light within 2 min.[141] Polydopamine (PDA) is a melanin-like substance with excellent physicochemical properties. CPCaNPs were pH-responsive and imaging-guided PTT platforms, which were synthesized by dopamine-mediated biomineralization and 4T1 cell membrane coating (Fig. 5). Upon targeting the acidic microenvironment, CPCaNPs decomposed to produce CO_2 bubbles that signifi-
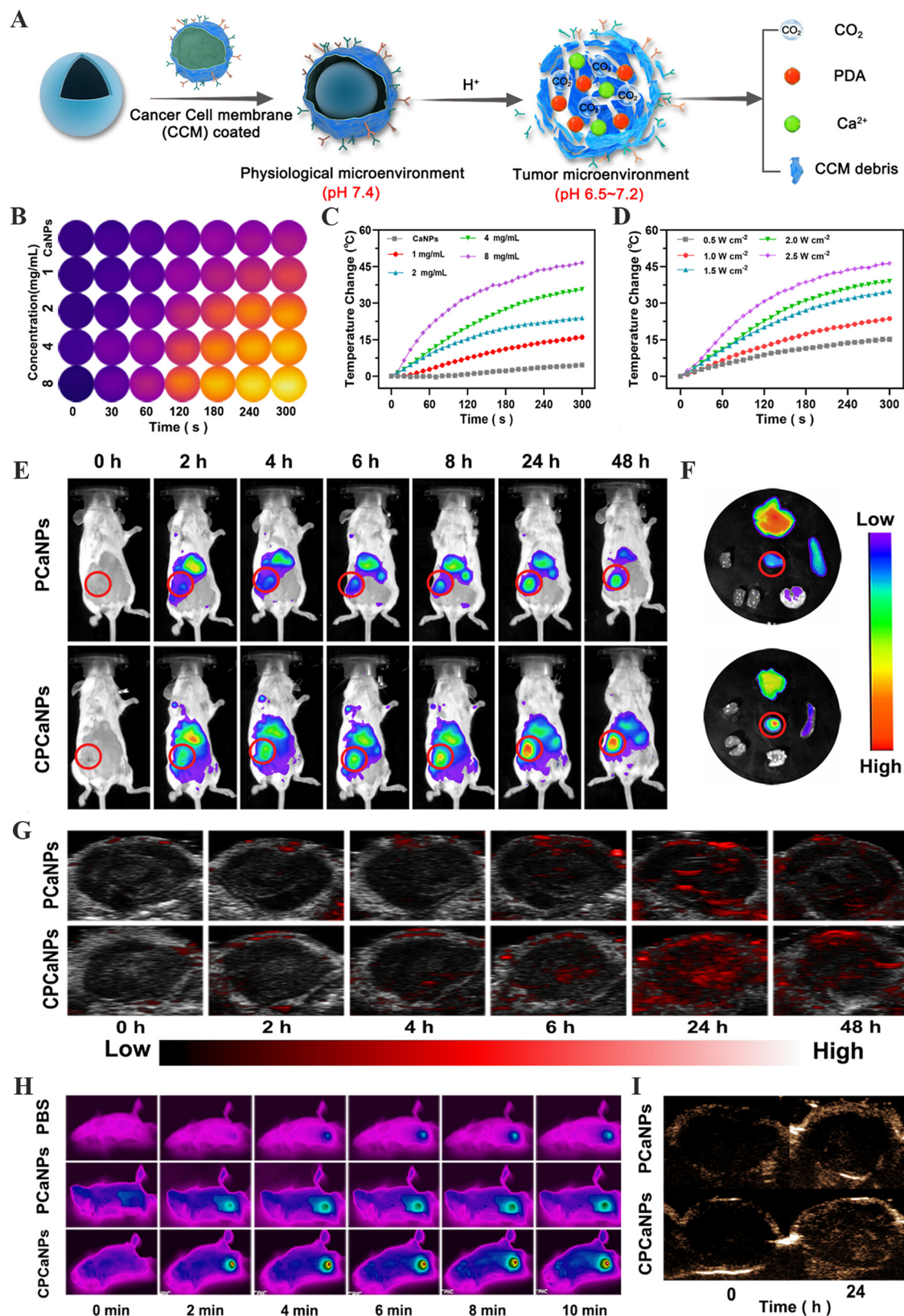
Fig. 5 CMNPs for cancer multimodal imaging and photothermal immunotherapy.[142] (A) Schematic of the synthesis of CPCaNPs. (B) Thermal infrared images at different concentrations. (C) Temperature change curve at different concentrations. (D) Temperature variation curve under different power densities of the 808 nm laser. (E) *In vivo* distribution and tumor targeting examination. (F) Tissue distribution in the removed organs and tumors. (G) PA imaging of the tumor after injection. (H) Photothermal images of laser-irradiated tumors after injection. (I) CEUS imaging of the tumor after injection. Copyright 2022 American Chemical Society.

cantly enhance the ultrasound signal for imaging. These NPs exhibited concentration-dependent heating ability with a 36.7% photothermal conversion efficiency and enabled photoacoustic (PA) imaging.[142]

Many other photosensitizers have been incorporated into CMNPs to exert photothermal effects, including indocyanine green (ICG), IR-797, *etc*. For instance, ICG was loaded into Fe_3O_4 coated with hybrid cell membranes (erythrocyte and ID8 cell membranes), achieving a desirable photothermal effect. This combination reached a temperature of 55.5 °C when exposed to 808 nm near-infrared light, demonstrating promising potential for tumor ablation.[143,164] Moreover, organic NPs, such as porphyrin compounds and specific organic polymers, can regulate the photothermal effects through molecular structure and functional unit adjustments.[165]

In the realm of photodynamic therapy (PDT), a range of photosensitizers can be selected to generate ROS or other active substances upon excitation by laser light at specific wavelengths, enabling selective damage to tumor cells. ICG, as mentioned earlier in PTT, serves as a notable representative and an FDA-approved imaging reagent for near-infrared PDT.[12] Commonly used photosensitizers include protoporphyrin IX (PpIX), methylene blue (MB), chlorin e6 (Ce6), and low-wavelength photosensitizers.[144,166,167] Despite its potential for highly effective and non-invasive cancer therapy, PDT's progress remains hindered by the limited availability of suitable photosensitizers and delivery challenges.

The emergence of CMNPs offers a new strategy for photosensitizer delivery. Metal–organic frameworks (MOFs) containing photosensitizers can overcome the self-combustion disadvantage and enhance the diffusion of the generated ROS. For example, a study employed TCPP to synthesize porphyrin-based Zr-MOF (PCN-224) and coated it with hybrid membrane composed of 4T1 cell and DC membranes *via* ultrasonication in an ice bath. This assembly was then irradiated with 660 nm light to generate ROS.[146] Ce6, similar to most photosensitizers, exhibits hydrophobicity and tends to aggregate in solution. To address this, non-covalent interactions were harnessed to load Ce6 into OVA NPs encapsulated with cancer cell membranes, enhancing stability and efficient ROS generation under laser irradiation.[145]

Additionally, photosensitizers can be embedded into the surface of biological membranes to mediate PDT. For instance, through the chimeric peptide with electrostatic interaction and hydrophobic effect, PpIX was inserted into the erythrocyte membranes tightly, forming a multifunctional nanoplatform CP@mRBC-PpIX after coating copper peroxide (CP) NPs.[144]

Given the variability in materials with distinct absorption spectra and phototherapeutic properties, the selection of photosensitizers should be customized based on disease characteristics, patient conditions, and research or clinical treatment objectives.

5.2. Small molecule compounds

In the realm of cancer immunotherapy, immune-modulating drugs have been widely researched and applied. Since cytokines such as IL-2 were applied in immunotherapy, the development of various small molecule immunotherapy drugs such as cell growth inhibitors, cytokines, chemokines, and metabolism modulators has been spurred.[50] Despite tremendous progress, small molecule drugs often encounter resistance and adverse reactions in clinical applications, prompting innovations in drug delivery strategies. CMNPs, with superior delivery properties, are extensively employed in research to overcome drug resistance and enhance targeted drug delivery efficiency. The following section will provide an overview of several widely used immunotherapeutic drugs loaded into CMNPs.

5.2.1. Drugs targeting immune cells. Toll-like receptor (TLR) homologous molecules are all type I transmembrane proteins with significant recognition and regulatory roles in acquired immunity.[168] TLR agonists often act as immune adjuvants to promote DC maturation or TAM polarization in immunotherapy.[169] For example, Yang *et al.* synthesized a biomimetic vaccine (NP-R@M-M) by loading the TLR 7 agonist imiquimod (R837) into PLGA NPs and coating B16-OVA cancer cell membranes with mannose inserted.[116] Similarly, the TLR 7/8 agonist resiquimod (R848), functions as an adjuvant in a cancer vaccine encapsulating 4T1 tumor cell membranes within DLMSN@CuS *via* physical uptake and intermolecular interactions.[147] Monophosphoryl lipid A (MPLA) is another FDA-approved TLR4 agonist, and research has explored its value in enhancing immune responses when incorporated into PLGA NPs encapsulating B16F10 cell membranes.[148]

Alongside TLR agonists, interferon gene-stimulating factor (STING) agonists can also activate innate immunity as adjuvants.[149] DNA fragments from lysed tumor cells activate STING *via* cGMP-AMP synthase (cGAS) within APCs and T cells, leading to downstream IFN-dependent antitumor immunity. Combining PC7A (activating STING pathway) with TLR-9 agonist CpG has been investigated for its vaccine adjuvant properties. The PH-responsive PC7A multimer formed cores with CpG loaded and coated with Mycobacterium smegmatis (MS) membranes containing pathogen-associated molecular patterns. This synthesized structure, known as BNP, was further modified with imine moieties (Mal) to enhance antigen uptake.[112]

Additionally, cytokine therapy, a classical form of immunotherapy, can also benefit from improved drug delivery through CMNPs. In a recent study, IL-15, known for its activation of T cell and NK cell functions, was loaded into PLGAs and enveloped by cRGD peptide-modified NK cell membranes (referred to as R-NKm@NPs). This approach improved cytokine delivery and enabled pH-responsive drug release (Fig. 6). NK cell membrane components, NKG2D and DNAM1, facilitated the NPs in crossing the blood–brain barrier (BBB) to target GBM cells. Their ability to target glioma TME was further amplified after modification with the brain tumor-targeting ligand cGRD, which exhibited a high affinity with $\alpha_v\beta_3$ on GBM cell surfaces.[101]

Conventional anti-inflammatory drugs have also demonstrated a modulatory effect on immune cells. In one study,
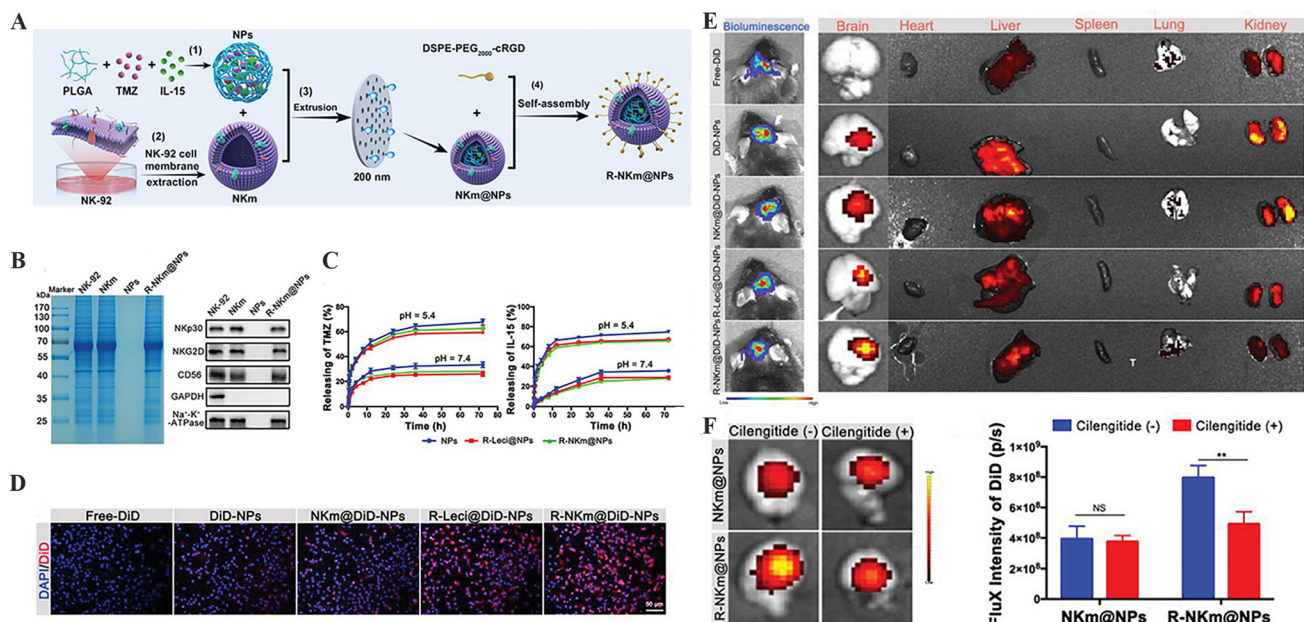
Fig. 6 NK cell membrane coated NPs delivered cytokine and chemotherapeutics for targeted GBM chemo-immunotherapy.[150] (A) Schematic of the synthesis of R-NKm@NPs. (B) SDS-PAGE and western blotting analysis. (C) Drug releasing profile. (D) Confocal images of the permeability in the *in vitro* BBB model. (E) *In vivo* bioluminescence imaging and *ex vivo* fluorescence imaging of the major organs. (F) *Ex vivo* fluorescence imaging of the brain and the semiquantitative biodistribution of DiD. Copyright 2023 Wiley.

Panc02 cell membranes (PCM) were employed to coat pH/oxidation-responsive nanogels for delivering the cyclooxygenase inhibitor Acetaminophen (APAP) to modulate NK cell function.[151] Beyond drug loading, nanoparticles themselves can serve as immune cell modulators. For example, Rao *et al.* encapsulate magnetic nanoparticles (MNs) with membranes derived from genetically engineered cells that overexpress SIRPα, effectively reprogramming TAMs.[120] Commonly used nanoparticles, such as iron oxide NPs (Fe_3O_4), have been encapsulated with various cell membranes, including M1 membranes and hybrid cell membranes, to participate in the regulation of immune processes.[143,152] Furthermore, there is a growing trend of combining traditional immunotherapeutic drugs with NPs, offering new avenues for cancer immunotherapy.

5.2.2. Drugs targeting cancer cells. Despite the significant advancements in regulating immune cells, traditional anticancer medications remain integral in cancer treatment. In addition to loading drugs with immunotherapeutic properties, chemotherapeutic agents can be co-loaded into CMNPs. These drugs facilitate immunotherapy by targeting tumor cells directly. Their cytotoxic effects on cancer cells can induce ICD, thereby stimulating innate and adaptive immune responses. This amplified the cancer immune cycle, leading to more favorable therapeutic outcomes.

For instance, doxorubicin (DOX), a non-specific anticancer agent, which inhibits DNA and RNA synthesis, has been incorporated into various CMNPs. In one study, DOX was loaded into mesoporous organosilica nanoparticles (MONs) coated with 4T1 cell membranes, allowing for controlled release

through ray-responsive diselenide bonding.[153] Another study loaded DOX with IND and Ce6 into M1 membrane coated bilirubin NPs (BPs) through stirring and centrifugation to exert synergistic effects.[158]

Paclitaxel (PTX), the first discovered drug that inhibits cancer cell mitosis by interacting with microtubules, can be precisely delivered using hollow manganese dioxide NPs coated with human umbilical cord-derived mesenchymal stem cell membranes, as demonstrated by Xie *et al.*[154] Various other classic anticancer drugs, including docetaxel, gemcitabine, and sorafenib, have also been integrated into nanoplatforms for cancer immunotherapy.[88,155,156]

5.2.3. Drugs targeting cancer metabolic mechanisms. The intricate metabolic mechanisms in TME leading to immunosuppression due to the accumulation of various metabolites, an important factor for tumor development. Targeting these processes can remodel the TME, inducing tumor cell apoptosis and reversing immunosuppression.

The robust proliferative capacity of tumor cells relies on the high-energy supply, leading to enhanced glycolysis and glutaminolysis for energy and biosynthesis. To address this, CMNP with glucose oxidase (Gox) as the major body was developed. Gox solution was centrifuged by mixing and stirring with 2-MI solution so that Gox was co-loaded with EPI and hemin on zeolitic imidazolate framework (ZIF-8). Ultrasound encapsulation in 4T1 membrane enabled the simultaneous reduction of glucose and glutathione (GSH) levels at the tumor site.[157]

Tryptophan metabolism in tumors, regulated by enzymes tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO), generates immunosuppressive metabolites such

as kynurenine. Tryptophan deficiency and metabolite accumulation inhibit effector T cell function, promoting the development of Treg and myeloid-derived suppressor cells (MDSCs). To disrupt tumor cell tryptophan metabolism, IDO1 inhibitor indoximode (IND) was loaded into various CMNPs, such as M1 macrophage coated gold nanocages and GL261 cell membrane coated $Cu_{2-x}Se$ NPs.[158,170]

Hypoxia, another significant feature of TME, results from excessive oxygen consumption by proliferating tumors and insufficient oxygen supply from abnormal blood vessels. Researchers have utilized CMNPs to alleviate tumor hypoxia to reverse immunosuppressive TME. For example, they incorporated catalase (CAT) for hydrogen peroxide breakdown into ZIF-8 with B16F10 cell membranes to create mZCD.[159] Another study developed manganese dioxide multifunctional biomimetic nanoparticles, HM-BPT NPs, with hybrid cell membrane encapsulation (MSC membranes and pH-sensitive liposomes) to leverage manganese oxides' catalase-like function through Mn^{2+}-mediated Fenton-like reactions.[171] Moreover, drugs targeting the arginine and adenosine metabolic pathways are also expected to amplify their effects based on CMNPs.

5.3. Nucleic acid agents

Nucleic acid therapy, a rapidly evolving biotechnology, is widely applied in addressing infectious diseases, cancer, autoimmune disorders, and related fields through regulating intracellular gene expression.[172] Distinct from traditional small molecule and antibody drugs, nucleic acid drugs primarily function through base complementary pairing, enabling specific targeting of intracellular and extracellular proteins by modulating protein-coding genes. Nucleic acids, which carry a negative charge, require binding to auxiliary agents to facilitate cellular uptake. However, their clinical translation faces challenges, including the risk of degradation by nucleases, transmembrane transport difficulties, immunogenicity, and instability. Consequently, innovation in nucleic acid drugs concentrates on improving their delivery systems. Traditional viral vector delivery strategies, due to their limitations, are being replaced by alternative methods like GalNac (N-acetylgalactosamine) modification and liposomal delivery technologies.[173] Several notable drugs have been introduced using these approaches. Similarly, CMNPs, characterized by multiple advantageous features, have garnered attention as drug delivery platforms for acid-based drugs to enhance cancer immunotherapy.

Small interfering RNAs, a prominent class of small nucleic acid drugs, are favored by researchers for their precise gene silencing capabilities. For example, Gong et al. employed a double emulsion technique to co-encapsulate fibrinogen-like protein 1 siRNA (siFGL1) and Met-CO$_2$ into PLGA and coated with a hybrid membrane derived from RAW264.7 and 4T1 cells using ultrasound. siFGL1 effectively downregulated FGL1 expression in tumor cells, reducing its binding to lymphocyte activation gene 3.[107] In another study, IL-1α siRNA disrupted inflammation-associated IL-1α expression and regulated Treg

cells through BP NPs coated with erythrocyte membranes.[160] Yang et al. used CMNPs to deliver short hairpin RNAs (shRNAs) targeting protein tyrosine phosphatase non-receptor type 2 (Ptpn2) for gene therapy. They co-assembled Ptpn2-targeted shRNA plasmids with iRGD and DOX via electrostatic adsorption and co-extruded them with M1 macrophage membranes to downregulate Ptpn2 gene expression.[161]

Furthermore, the delivery of mRNAs can also be improved through CMNPs. For example, IL-12 is a kind of cytokine with significant activation of anti-tumor immunity but difficult to achieve by intravenous administration. Zhao et al. utilized reverse microemulsion to load IL-12 mRNA onto calcium carbonate ($CaCO_3$) and synthesized mRNA@CMCaCO$_3$ NPs by co-extrusion with GL261 cell membranes in 200 nm polycarbonate membranes, enabling BBB penetration and cytoplasmic transfection of IL-12 mRNA (Fig. 7).[162]

As research advances, nucleic acid delivery strategies like exosomes and peptide nanomaterials are under development. Combining these approaches with cell membrane coating technology holds promise for enhancing nucleic acid drug delivery efficiency in future research.

5.4. Antibody agents

Since the first introduction of therapeutic anti-CD3 antibodies in clinical practice in 1986, antibody-based drugs have rapidly proliferated and found widespread applications in areas like chronic inflammation, autoimmune disorders, and cancer treatment. In cancer therapy, these antibodies fall into three categories: monoclonal antibodies (mAbs), bispecific antibodies, and antibody–drug conjugates (ADCs).[174] They function by modulating various signaling pathways within cancer cells. Notably, ICIs, predominantly targeting PD-1/PD-L1 and CTLA-4 with monoclonal antibodies, have gained prominence as classical immunotherapeutic agents in cancer treatment.

Despite the benefits of ICIs, such as high specificity, relatively low side effects, and extended half-lives, there is ongoing research focused on enhancing their therapeutic effectiveness using CMNPs. For instance, to enhance the precision of anti-PD-L1 therapy, a genetically engineered aPD-L1 with MMP2 activation properties was expressed on the surface of HEK 293T cells. The membranes were obtained through low-permeability lysis and cyclic freezing and thawing, which were then coated onto ultra-small barium titanate (BTO) NPs (Fig. 8). The N-terminal binding domain of aPD-L1 was concealed by the MMP2 substrate peptide, allowing its inhibitory effect to be exerted specifically within MMP2-rich tumor tissues.[121] Additionally, research has explored improving the delivery of aPD-L1 with CMNPs, such as by mixing aPD-L1 with synthesized platelet membrane-encapsulated hollow mesoporous silica NPs at room temperature and subjecting them to high-speed centrifugation to facilitate the co-delivery of aPD-L1 and antitumor drugs.[88] In fact, ICIs are more frequently used as a combination immunotherapy regimen, co-administered with CMNPs to achieve synergistic therapeutic effects.
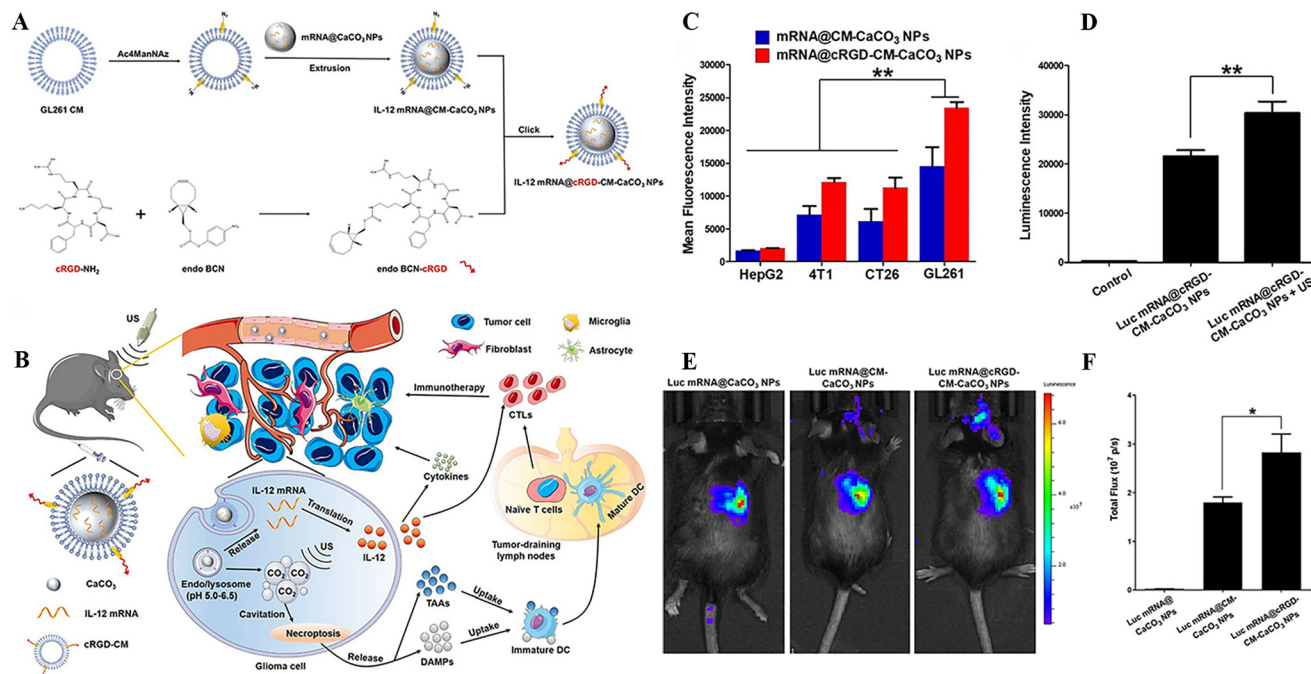
Fig. 7 Cancer cell membrane coated NPs delivered IL-12 mRNA for targeted GBM immunotherapy.[162] (A) Schematic of the synthesis of IL-12 mRNA@cRGD-CM-CaCO$_3$ NPs. (B) Proposed mechanism of NPs for BBB penetration, TME navigation and sono-immunotherapy synergistic anti-tumor effects in GBM. (C) Homotypic targeting through fluorescence measurement. (D) Luminescence intensity of NPs. (E) *In vivo* luminescence imaging of brain tumor model. (F) Quantitative bioluminescence signal intensity. Copyright 2022 BioMed Central.
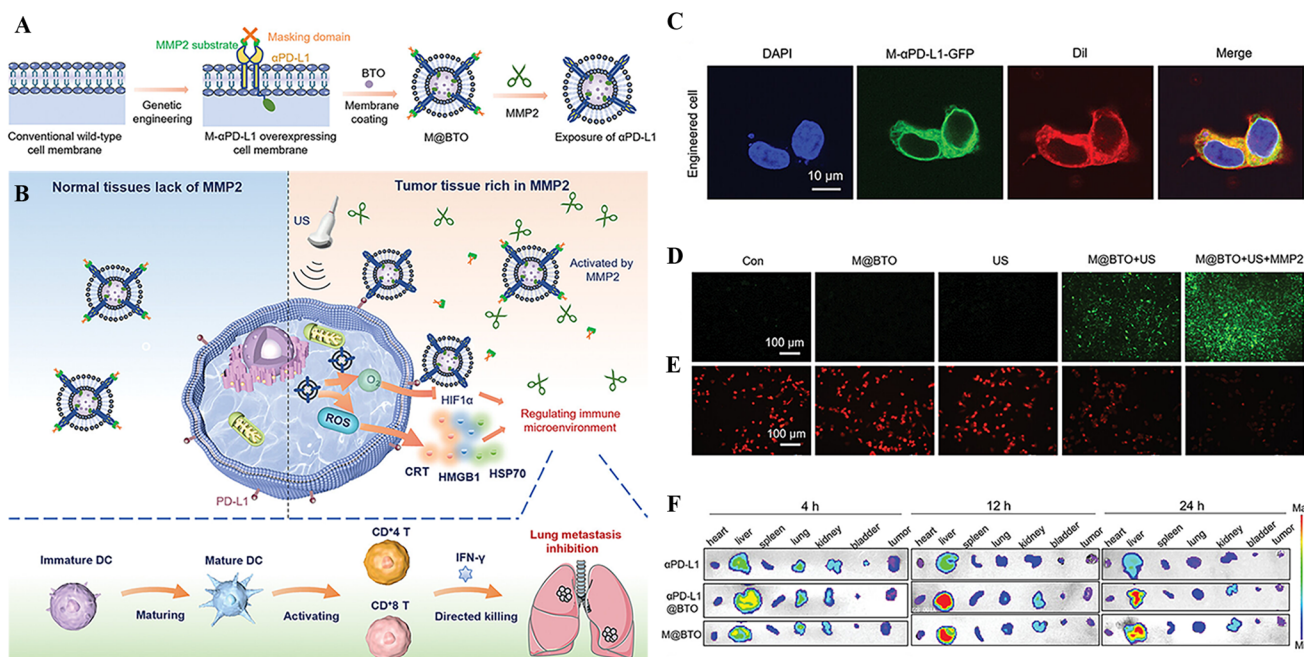

Fig. 8 Genetically engineering CMNPs for MMP2-activated immunotherapy. (A) Schematic of synthesis of M@BTO.[121] (B) Schematic of mechanism of MMP2-activated piezocatalysis-immunotherapy. (C) Fluorescence images of genetically engineered cells. (D) Fluorescence images of DCFH-DA in B16F10 cells. (E) Fluorescence images of oxygen probe in B16F10 cells. (F) Fluorescence imaging of organs collected after different injections. Copyright 2023 Wiley.

In parallel with CMNPs, numerous drug delivery systems have undergone extensive investigation. Among these, liposomes represent an early-developed system characterized by one or more phospholipid bilayers forming spherical vesicles. Typically, liposomes consist of cationic lipids, helper lipids, cholesterol, and PEGylated lipids. They excel in encapsulating

hydrophobic drugs within their lipid bilayer, thereby enhancing drug solubility and prolonging residence time.[175] Lipid nanoparticle formulations have been extensively employed in clinical trials for delivering various therapeutic agents, including anticancer, anti-inflammatory, antibiotic, antifungal, and gene therapies, notably in nucleic acid drug delivery, such as mRNA vaccine development.[176,177] Nevertheless, liposomes encounter challenges such as reduced stability and limited biocompatibility compared to CMNPs, especially in scenarios where effective penetration of biological barriers like the blood–brain barrier remains elusive. The majority of nanoparticles available commercially are simplistic liposomal structures, underscoring the need for more sophisticated designs to enhance patient outcomes *via* nanodelivery systems.[178]

Extracellular vesicles (EVs) represent another class of membranous vesicles secreted by cells into the extracellular matrix, playing crucial roles in intercellular communication.[179] Similar in size and structure to liposomes, EVs harbor various bioactive molecules such as proteins and lipids on their surface, along with internal nucleic acids. This feature endows EVs with the potential for complex drug delivery functionalities. EVs are commonly categorized into exosomes, microvesicles, and apoptotic bodies based on their cellular origin.[180] Their low immunogenicity and distinctive advantages in intercellular signaling render them promising candidates as drug carriers in cancer therapy.[181] In addition, EVs can efficiently load proteins, nucleic acids, cytokines, and other substances *via* endogenous expression within cells, utilizing the cell's inherent expression machinery.[182] Nonetheless, despite these advantages, EVs exhibit certain limitations compared to CMNPs. For example, in terms of pharmacokinetics, externally introduced EVs may undergo rapid hepatic clearance, resulting in a shortened half-life.[183] Furthermore, achieving clinical translation of extracellular vesicle delivery necessitates elevated standards of isolation and characterization. Moreover, the purification of extracellular vesicles typically involves intricate methodologies and specialized equipment, and is susceptible to contamination, thereby posing challenges in large-scale production and purification processes.[184]

Consequently, in comparison to analogous drug delivery systems, CMNPs, with their intricate surface biomolecular composition, heightened biocompatibility and stability, and more sophisticated design strategies, demonstrate superior potential for advancement in the realm of tumor immunotherapy.

6. Applications of CMNPs in cancer immunotherapy

This review article surveys various types of CMNPs aimed at augmenting the efficacy of tumor immunotherapy, as depicted in Table 2.[80,88,100,101,105,107,116,117,120,128,139,141,143–149,151–153,155,157–162,164,166,170,185–211] The predominant mechanisms underlying most CMNPs are twofold: (1) delivering photosensitizers or capitalizing on the optical properties of NPs, facilitating photoimmunotherapy under near-infrared light irradiation. This process directly induces ICD through PTT or PDT for tumor ablation and the release of a significant quantity of tumor-associated antigens to reinitiate the cancer immune cycle. (2) Delivering small molecule immunotherapeutic drugs, immune modulators, chemical agents, or signaling molecules that induce tumor cell apoptosis, enhancing the immune system's response to tumor tissue. These compounds also act either on immune cells, immunosuppressive factors in TME, or both, thereby reshaping the immunosuppressive TME and bolstering anti-tumor immunity.

Many types of CMNPs exhibit a multifaceted approach to tumor clearance, combining various immunotherapy techniques and even traditional cancer treatments like chemotherapy and radiotherapy. The following sections categorize CMNP applications based on key immunotherapeutic agents and their impact on anti-tumor immunotherapy.

6.1. Photoimmunotherapy based on photosensitizer delivery

Photoimmunotherapy involves the accumulation of photosensitizers at the tumor site, achieved through active or passive targeting strategies. By irradiating with specific light wavelengths, the phototherapeutic agent transitions from an inactive to an active state, inducing ICD in tumor cells and releasing DAMPs including CRTs, high-mobility group box 1 (HMGB1), and adenosine triphosphate, which trigger an enhanced anti-tumor immune response.[212]

The effectiveness of photothermal therapy relies on selecting NPs with high photothermal conversion efficiency and facilitating their localized aggregation at the tumor site. To boost the efficacy of photoimmunotherapy, researchers employ strategies such as the application of BPQDs with photothermal properties. For instance, Liang *et al.* designed BPQD-RM, comprising BPQDs at its core and encapsulated with erythrocyte membranes (Fig. 9). BPQDs exhibit a high photothermal conversion efficiency of 28.4% and excellent loading capabilities. Additionally, the presence of erythrocyte membranes reduces *in vivo* degradation and prolongs circulation time, with a half-life of 23.91 ± 0.2 h. A 10 min exposure to 808 nm NIR irradiation during BPQD-RM treatment raised 4T1 tumor temperatures to 52.5 °C, resulting in PTT-induced tumor cell apoptosis, DCs aggregation, and significant infiltration of $CD4^+$ and $CD8^+$ T cells at the tumor sites. However, tumor cells upregulated PD-1 expression, depleting infiltrating T cells. To address this, the study employed a combination of BPQD-RMNVs, NIR, and aPD-1, which enhanced T cell function, showing promise in treating triple-negative breast cancer.[189]

Efficient delivery of photothermal materials to the tumor site is crucial. To achieve this, researchers synthesized Gel-BPQD-CCNV by encapsulating BPQD with cancer cell membranes and loading them into a heat-sensitive hydrogel containing GM-CSF and LPS. This facilitated the sustained release of GM-CSF and LPS upon heating, effectively recruiting DCs to promote antigen cross-presentation. Similarly, this platform

Table 2 Summary of the applications of CMNPs in cancer immunotherapy

Types of membrane	Core nanoparticles	Modification of CMNPs	Delivered drugs	Animal tumor models	Applications	Ref.
Erythrocyte	PLGA	DSPE-PEG-Mannose inserted	hgp100 peptides, MPLA	Breast cancer	• Biomimetic vaccine: co-delivered antigen peptide and adjuvant to APCs	185
	PLGA	DSPE-PEG-Mannose inserted	PLB, DIH, NH_4HCO_3	Hepatoma	• Delivered PLB and DIH to induce ICD to reverse the immunosuppressive TME	186
	PLGA	DSPE-PEG-Mannose inserted	hgp peptides, MPLA	Melanoma	• Biomimetic vaccine: co-delivered antigen peptide and MPLA to APCs • Combined with DOX induced ICD	187
	Mesoporous TiO$_2$	Hb on the NP surface	RRx-001	Breast cancer	• Reactive nitrogen species (RNS) induced ICD	188
	BP	YSA anchored onto membrane	IL-1α siRNA, PTX	Colorectal cancer	• Deliver siRNA to block IL1 expression and restrict Treg cell accumulation	160
	BPQDs			Breast cancer	• PTT induced ICD and synergized with aPD-1 therapy	189
	CP	PpIX inserted		Melanoma	• PDT induced ICD and CP induced reverse of immunosuppressive TME	144
Platelet	PLA		R848	Colorectal cancer and breast cancer	• Delivered immunostimulatory R848 to TME	128
	Fe$_3$O$_4$		SAS	Breast cancer	• Delivered SAS to induce ferroptosis and M1 macrophage polarization	190
	DGL-G3		Ce6, DTX	Melanoma	• PDT and delivery of DTX induced ICD	166
	MOF		Lox, Oxa	Breast cancer	• Delivered Lox to consume lactate and Oxa to amplify ICD-induced immunotherapy	191
Cancer cell	HMSNs	aPD-L1 coupled to membrane	SO	Hepatoma	• Delivered aPD-L1 and SO to CTCs effectively	88
	MNs	SIRPα variant overexpressed on membrane		Melanoma and breast cancer	• Blocked CD47-SIRPα pathway and repolarized TAMs to M1-type to enhance macrophage immune response	120
B16F10	PLGA	OVA and CD80 overexpressed on the membrane		Melanoma	• Delivered antigen and costimulatory signals to stimulate T cells directly	192
	PEI25k	CRT induced and CD47 knockout	CpG	Melanoma	• Biomimetic vaccine: co-delivered antigen and CpG to stimulate DCs and combined with ICIs	193
	PLGA		MPLA	Melanoma	• Biomimetic vaccine: co-delivered antigen and MPLA to APCs effectively	148
	ZIF-8		CAT, DOX	Melanoma	• Delivered CAT to relieve hypoxia in TME and enhance the aPD1 therapy	159
	MSN		CpG, Pro	Melanoma	• Delivered Pro to block β-AR to reverse suppressive effects on T cells • Delivered CpG to promote DC maturation	139
B16-OVA	OVA NPs		Ce6	Melanoma	• PDT induced ICD	145
	PLGA	CBP-12 peptide inserted	2′3′-cGAMP	Melanoma and breast cancer	• Delivered antigen and STING agonist to DCs to enhance IFN-stimulated expression of genes and antigen cross-presentation	149
	PLGA	DSPE-PEG-Mannose inserted	R837	Melanoma	• Biomimetic vaccine: co-delivered antigen and R837 to stimulate DCs and combined with aPD1 therapy	116
	1G$_3$-Cu		Toy	Melanoma	• Delivered 1G3-Cu and Toy to induce ICD through amplifying ER stress and mitochondrial dysfunction and combined with aPD-L1 therapy	194
4T1	MPDA		R848	Breast cancer	• Biomimetic vaccine: co-delivered antigen and R848 to activate APCs and combined with aPD-L1 therapy	195
	MONs		DOX	Breast cancer	• Delivered DOX to induce ICD and combined with aPD-L1 therapy	153
	ZIF-8	Calreticulin over-expressed on the membrane	EPI, Gox, hemin	Breast cancer	• Delivered EPI, Gox, and hemin to induce ICD and enhance ICI therapy	157
	PLGA	^{D}PPA-1 anchored to the membrane	AFT, 2-BP	Breast cancer	• Delivered AFT and 2-BP to induce apoptosis and proliferation inhibition • Delivered DPPA-1 for PD-1/PD-L1 blockade	196
	DLMSNs	Thiol functional groups; AUNP-12	CuS, R848	Breast cancer	• PTT induced ICD and R848 induced T lymphocyte activation	147
	DMSNs and Au NPs	Membrane mixed with PEOz liposome	R837	Breast cancer	• PTT induced ICD • Delivered R837 to enhance immunotherapy	197
	BPQDs	Loaded into thermosensitive hydrogel with GM-CSF and LPS		Melanoma and breast cancer	• PTT enhanced recruitment and migration of DCs and combined with aPD1 therapy	141
AML	PLGA		CpG	Acute myeloid leukemia	• Biomimetic vaccine: co-delivered AML-associated antigen and CpG to APCs effectively	80
K7M2	Hollow MnO$_2$	ALD	Ginsenosides Rh2	Osteosarcoma	• Delivered ginsenosides Rh2 and Mn^{2+} to induce immuno-chemo-dynamic therapy	198
Panc02	pH/oxidation nanogels		APAP	Pancreatic cancer	• Delivered APAP to enhance the activation of NK cells and NK cells-dependent DCs recruitment, combined with ICIs	151
GL261	CaCO$_3$	cRGD inserted	IL-12 mRNA	Glioma	• CO$_2$ induced necroptosis of GBM cells under US irradiation • Delivered IL-12 mRNA to stimulate the proliferation and activation of CTLs	162
	AMNPs		CLP002	Glioma	• PTT induced ICD • Delivered CLP002 to amplify ICB therapy	199
	Cu$_{2-x}$Se		IND and JQ1	Glioma	• PDT induced ICD • Delivered IND, JQ1 to remodel immunosuppressive TME	170
LLC	Iron(II)-CpG	Cell membrane pre-treated with DOX to over-express ICD-related proteins	CpG	Lewis lung carcinoma	• Delivered ICD-related proteins and CpG to promote DC maturation	200
Dendritic cell	PLGA	DC membrane was pre-pulsed with CCM-coated NPs		Melanoma	• Cross-primed T cells directly for immunotherapy and combined with ICIs	201
	PLGA	DC membrane was preactivated to present tumor antigens	RAPA	Glioblastoma	• Delivered tumor antigen and RAPA to promote DC maturation	100
	DSPE-PEG		IR-797	Breast cancer	• PTT induced ICD and enhanced T cell activation	164

Table 2 *(Contd.)*

Types of membrane	Core nanoparticles	Modification of CMNPs	Delivered drugs	Animal tumor models	Applications	Ref.
NK cell	PLGA		TCPP	Breast cancer	• PDT induced ICD and M1 macrophage polarization	202
	PLGA	cRGD inserted	TMZ, IL-15	Glioma	• Delivered TMZ and IL-15 to stimulate NK cell proliferation and activation	101
Macrophage	PLGA and Fe$_3$O$_4$	Lipopolysaccharide treated	R837	Breast cancer	• Enhanced M1 phenotype polarization	152
	PLGA		R837, DOX, lansoprazole	Breast cancer	• Delivered DOX to induce ICD and R837 to induce macrophage repolarization	203
	PEG-PDPA		Gem	Breast cancer	• Delivered Gem to promote lymphocyte infiltration	155
	AuNCs		DOX, Ce6, IND	Breast cancer and melanoma	• PDT and delivery of DOX and IND induced ICD and reversed immunosuppressive TME	158
	UCNP	CSF1R overexpressed on the membrane and PMMA modified	RB	Breast cancer	• PDT induced ICD • Blocked CSF1–CSF1R axis	204
	FFVLK-PEG		Ce6, PTX, IND	Breast cancer	• PDT and delivery of PTX induced ICD • Delivered IND to induce inhibition of IDO pathway to reverse the immunosuppressive TME	205
	SiO$_2$		DOX, R848, CAT	Hepatoma and colorectal cancer	• Delivered DOX and R848 to induce ICD and promote DC maturation • Delivered Cat to alleviate A2AR pathway to reverse immunosuppressive TME	206
	SiO$_2$	DSPE-PEG-Mannose inserted	PFC, Ce6, PTX	Breast cancer	• PDT induced ICD • Delivered PTX to induce the M2 to M1 reprogramming	117
	HA-DOX	iRGD inserted and PEI condensed shRNA-Ptpn2	shRNA, DOX	Melanoma	• Delivered DOX to induce ICD and shRNA for M1 macrophage polarization and DC maturation	161
T cell	MSNs	CAR-T cell	IR780	Hepatoma	• PTT induced ICD	207
	BSA	PD-1 overexpressed on membrane	ORY-1001	Breast cancer and colorectal cancer	• Delivered ORY-1001 to upregulate IFNs and downstream MHC I and PDL1 • Delivered PD-1 to block PD-L1	208
Hybrid membrane						
DC and cancer cell	PLGA		CpG-ODN	Colorectal cancer and glioma	• Delivered antigens, costimulatory signals, and CpG-ODN to T cells	105
	PLGA		CpG-ODN	Ovarian cancer	• Delivered antigens and CpG-ODN to stimulate T cells	209
	NS		DTX	Glioblastoma	• Delivered antigen to stimulate T cell and DTX to induce apoptosis	210
	PCN-224			Breast cancer	• Delivered antigen and co-stimulating factors to DCs and T cells • PDT induced ICD	146
	SPN			Breast cancer	• Delivered antigen and T cell stimulating factors to DCs and T cells • PTT induced ICD	211
RBC and cancer cell	Fe$_3$O$_4$		ICG	Ovarian cancer	• PTT induced ICD	143
Macrophage and cancer cell	PLGA		Met-CO$_2$, siFGL1	Breast cancer	• Delivered Met and siRNA to induce PD-L1 blockade and FGL1 gene silencing	107

PLGA: poly(lactic-*co*-glycolic acid); PLB: plumbagin; DIH: dihydrotanshinone I; Hb: hemoglobin; YSA: ephrin-A2 receptor-specific peptide; BP: black phosphorus; BPQDs: black phosphorus quantum dots; PTX: paclitaxel; CP: copper peroxide; PpIX: protoporphyrin IX; PLA: polylactic acid; SAS: sulfasalazine; DGL-G3: third-generation poly-L-lysine dendrimer; Ce6: chlorin e6; DTX: docetaxel; MOF: metal organic framework; Lox: lactate oxidase; Oxa: oxaliplatin; HMSNs: hollow mesoporous silica nanoparticles; SO: sorafenib; MNs: magnetic nanoparticles; OVA: ovalbumin; ZIF-8: zeolitic imidazolate framework; CAT: catalase; DOX: doxorubicin; MSNs: mesoporous silica nanoparticles; Pro: propranolol; CBP-12: 12-mer Clec9a binding peptide; 1G3-Cu: phosphorus dendrimer–copper(II) complexes; Toy: toyocamycin; MPDA: mesoporous polydopamine; EPI: epirubicin; Gox: glucose oxidase; DPPA-1: D-peptide antagonist; AFT: afatinib; 2-BP: 2-bromopalmitate; DLMSNs: dendritic large-pore mesoporous silica nanoparticles; AUNP12: anti-PD1 peptide; GM-CSF: granulocyte-macrophage colony-stimulating factor; LPS: lipopolysaccharide; ALD: alendronate; APAP: acetaminophen; TCPP: 4,4′,4″,4‴-(porphine5,10,15,20-tetrayl) tetrakis (benzoic acid); cRGD: cyclo (Arg-Gly-AspD-Tyr-Lys) peptide; AMNPs: allomelanin nanoparticles; IND: indoximod; RAPA: rapamycin; TMZ: temozolomide; Gem: gemcitabine; AuNCs: gold nanoclusters; UCNP: upconversion-nanoparticle; HA: hyaluronic acid; NS: nanosuspensions; PCN-224: porphyrin-based Zr-MOF; SPN: semiconducting polymer nanoparticles; Met: metformin; siFGL1: fibrinogen-like protein 1 siRNA.

significantly enhanced CD8$^+$ and CD4$^+$ T cell infiltration and remarkably increased IFN-γ and TNF-α levels in a recurrent tumor model when combining PTT and aPD-1, offering a novel idea for treating residual and metastatic tumors following primary tumor resection.[141]

Moreover, small-molecule photosensitizers, similar to photothermal NPs, can be used for comprehensive photoimmunotherapy based on CMNPs. However, the method of enhancing photothermal effects by increasing the photothermal conversion rate may inadvertently harm immune cells while improving tumor ablation. In one study, DCs were activated in a controlled environment through co-cultivation with 4T1 tumor antigen and a TLR-3 agonist. These activated DCs exhibited a heightened expression of key co-stimulatory signals on membranes, notably MHC molecules, CD80, and CD86. Subsequently, an intelligent dendritic cell (iDC) was synthesized by encapsulating DC membrane with NPs carrying IR-797. The administered iDC effectively migrated to the lymph nodes, where it stimulated the proliferation of T cells and the secretion of pro-inflammatory cytokines, such as TNF-α, IL-2, and IFN-γ. This, in turn, led to the suppression of HSP family expression in cancer cells and diminished their ability to adapt to high temperatures. Under the increased sensitivity to heat stress, maintaining a temperature range of 42–45 °C through 808 nm laser induced ICD in 4T1 cells, further increasing the activation percentage of CD8$^+$ and CD4$^+$ T cells.[164]

Additionally, another study involved the fusion of ID8 cell and erythrocyte membranes at a 1 : 1 ratio, achieved through sonication at 37 °C for 10 min. This composite was then coated onto Fe$_3$O$_4$ NPs loaded with ICG to enhance its targeting ability toward ovarian cancer tissues and reduce RES phagocytosis. The resulting Fe$_3$O$_4$-ICG@IRM composite displayed tumor-inhibiting properties, even in the absence of NIR treat-
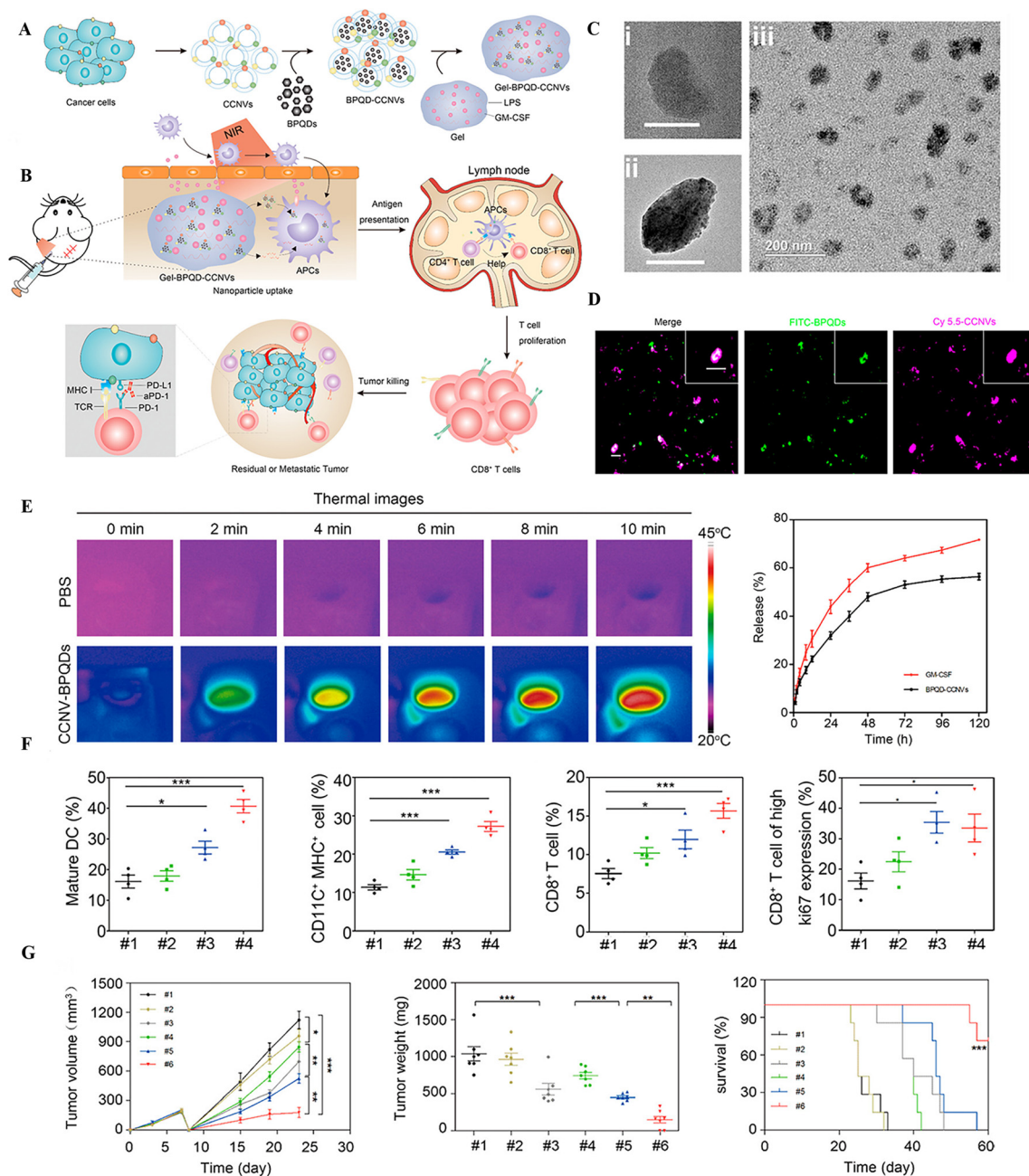
Fig. 9 Cancer cell membrane coated BPQDs for cancer photothermal immunotherapy. (A) Schematic of synthesis of Gel-BPQD-CCNVs.[189] (B) Schematic of mechanism for cancer immunotherapy. (C) TEM image of empty CCNV, single BPQD-CCN, and BPQD-CCNVs. (D) Confocal images indicating the membrane coated successfully. (E) IR thermographic maps and *in vitro* collective release of GM-CSF and BPQD-CCNVs. (F) Quantitative analysis of cells in draining lymph nodes; PBS (#1), Gel-BPQD-CCNVs + NIR (GM-CSF free, #2), Gel-BPQD-CCNVs (#3), Gel-BPQD-CCNVs + NIR (#4). (G) Tumor growth curves, weights of tumors, and survival curves; (#1) PBS, (#2) CCNV, (#3) a-PD1, (#4) Gel-BPQD-CCNVs, (#5) Gel-BPQD-CCNVs + NIR, (#6) Gel-BPQD-CCNVs + NIR + a-PD1. Copyright 2019 American Chemical Society.

ment. Upon applying NIR irradiation at 2.0 W cm^{-2} for 10 min, the tumor site's temperature rose significantly, reaching 58.7 °C. Sufficient PTT led to an increased proportion of CD4$^+$ and CD8$^+$ T cells, accompanied by a reduction in immunosuppressive Foxp3$^+$ T cells.[143]

In the context of enhancing PDT-mediated photoimmunotherapy, researchers have developed some multifunctional nanoplat-

forms such as PCN@FM. This platform exhibited targeted specificity for 4T1 tumors and inherited DC-like characteristics, including the ability to migrate to lymph nodes and express co-stimulatory molecules required for T cell activation. Under laser irradiation, PCN@FM triggered the release of ROS, inducing ICD. As a result, the PCN@FM group achieved enhanced activation of DCs and CTLs compared to other experimental groups.[146]

Since the mentioned strategy involves delivering antigens and stimulation signals to T cells, which can be challenging to prepare and apply, some studies have explored the use of cell membranes capable of modulating immune cells without prior sensitization to deliver photosensitizers. Deng *et al.* reported NK cell membrane-based biomimetic systems (NK-NPs) loaded with TCPP for PDT against 4T1 tumors. NK-NPs also triggered the polarization of M1-type macrophages through surface-bound proteins like IRGM1 and RAB 10.[202]

The cell membrane's phospholipid bilayer structure facilitates the integration of functional molecules, offering novel possibilities for photosensitizer applications. For instance, CP@mRBC-PpIX, embedded within the erythrocyte membrane, generated substantial ROS upon 630 nm laser irradiation, leading to pronounced cytotoxicity in just two min. Additionally, copper peroxide reacted with hydrogen ions to raise the pH at the tumor site, mitigating the acidic and hypoxic TME. The results demonstrated that CP@mRBC-PpIX enhanced the expression of STING, CRT, and HMGB1 proteins, promoted macrophage polarization toward the M1-type, and effectively recruited $CD8^+$ T cells through the immunomodulatory effects of PDT and CP.[144]

6.2. Immunotherapy based on small molecular drug delivery

6.2.1. Modulation of immune cells. DC-based immunotherapy plays a crucial role in cancer treatment due to DCs being potent APCs that initiate specific CTL responses. Provenge is the first FDA-approved prostate cancer therapeutic vaccine that matures autologous DCs *in vitro* and reintroduces them into patients to activate T cells against cancer. While effective, this therapy is expensive and complex due to *in vitro* DC culture. Therefore, various immune adjuvants are loaded into CMNPs to provide sustained stimulatory signals to promote DC maturation in patients. Guo *et al.* constructed a nanovaccine co-loading the soluble antigenic peptide hgp100 and MPLA into PLGA, improving APC migration to lymph nodes *via* mannose modification. Man-RBC-NP$_{hgp}$ reduced blood clearance and enhanced lymph node accumulation, elevating CD86 expression in DCs and inflammatory factor levels such as TNF-α and IFN-γ. Abundant IFN-γ activated antigen-specific $CD8^+$ T cells, resulting in a durable CTL response with 76.6% melanoma inhibition 21 days post-vaccination.[185]

In recent years, CMNPs undoubtedly provide a new platform for enhancing biomimetic cancer vaccines by delivering specific tumor antigens on cell membranes to improve the body's immune response. The introduction of immune adjuvants further strengthens the function of immune cells such as DCs. Yang *et al.* created a melanoma tumor vaccine called NP-R@M-M using PLGA NPs loaded with the R837 and mannose-modified B16-OVA cell membranes. Similarly, this combination promoted DC maturation and induced CTL to control tumor progression and metastasis. Combining this approach with ICIs further enhanced its therapeutic potential.[116]

In addition to cancer vaccines comprising tumor antigens and adjuvants, various pharmaceuticals and NPs are available for direct modulation of immune cells within TME based on CMNPs. Deng and colleagues introduced a nanogel coated with Panc02 cell membranes (PCM@RNGs). Given the high expression of prostaglandin E2 (PGE2) in malignant tumors, which directly inhibits DC maturation and NK cell function, they incorporated the cyclooxygenase inhibitor APAP (PCM@APAP@RNG) to counteract PGE2's suppressive effects. The PCM@APAP@RNG promptly released APAP in the acidic, glutathione-rich TME, promoting NK cell activation. Activated NK cells produced IFN-γ to induce cancer cell apoptosis, released CCL5 and XCL1 to influence the migration of BMDCs, and in combination with aPD-L1 therapy, enhanced $CD8^+$ T cell infiltration, significantly suppressing pancreatic tumor growth and postoperative tumor recurrence.[151]

Considering that TAMs can drive tumor invasion and metastasis by adopting an immunosuppressive M2-type, and due to the plasticity of TAMs under the influence of inflammatory factors, their polarization towards the M1-type has become a prominent immunotherapeutic strategy. A study introduced gene-edited NPs (gCM-MNs) where SIRPα variants over-expressed on the cell membrane exhibited a 50 000-fold increase in affinity for CD47, substantially enhancing macrophage uptake of gCM-MNs through competitive binding. Meanwhile, ROS generated by MNs *via* the Fenton reaction induced TAM repolarization towards an anti-tumor M1-type. The results demonstrated an increase in $CD8^+$ T cell infiltration at the tumor site, accompanied by elevated secretion of IFN-γ and TNF-α, resulting in a noteworthy inhibitory effect on melanoma.[120]

6.2.2. Depletion of cancer cells. Chemotherapeutic agents are pivotal in combined immunotherapy treatments due to their ability to activate anti-tumor immunity by directly clearing tumor cells. In a study, 4T1 cell membranes were encapsulated with DOX-loaded MONs (CM@MON@DOX). DOX aggregated at the tumor site elevated the $CD8^+/CD4^+$ T cell ratio, promoted CTL infiltration, and increased pro-inflammatory cytokine production (TNF-α, IFN-γ, and IL-6) by inducing ICD.[153]

Similarly, HMnO$_2$-MSC-TAT@PTX further optimized the delivery of lung cancer-associated chemotherapeutic agents by facilitating the accumulation of Mn^{2+} and PTX in tumor cell nucleus *via* TAT peptides (Fig. 10). This led to enhanced PTX-mediated DNA damage, coupled with Mn^{2+}-mediated activation of cyclic adenosine monophosphate synthase (cCAS) and STING, promoting DC maturation and T cell infiltration for a synergistic therapeutic effect on non-small cell lung cancer.[154] Additionally, studies also explored the combined effects of chemotherapeutic agents with photosensitizers and nucleic acid drugs.[167]

6.2.3. Intervention of cancer metabolism. Aside from cellular components in TME, many non-cellular components contribute to the proliferation of tumor cells and result in immunosuppression. Several crucial enzymes essential for tumor metabolism have emerged as promising targets for boosting
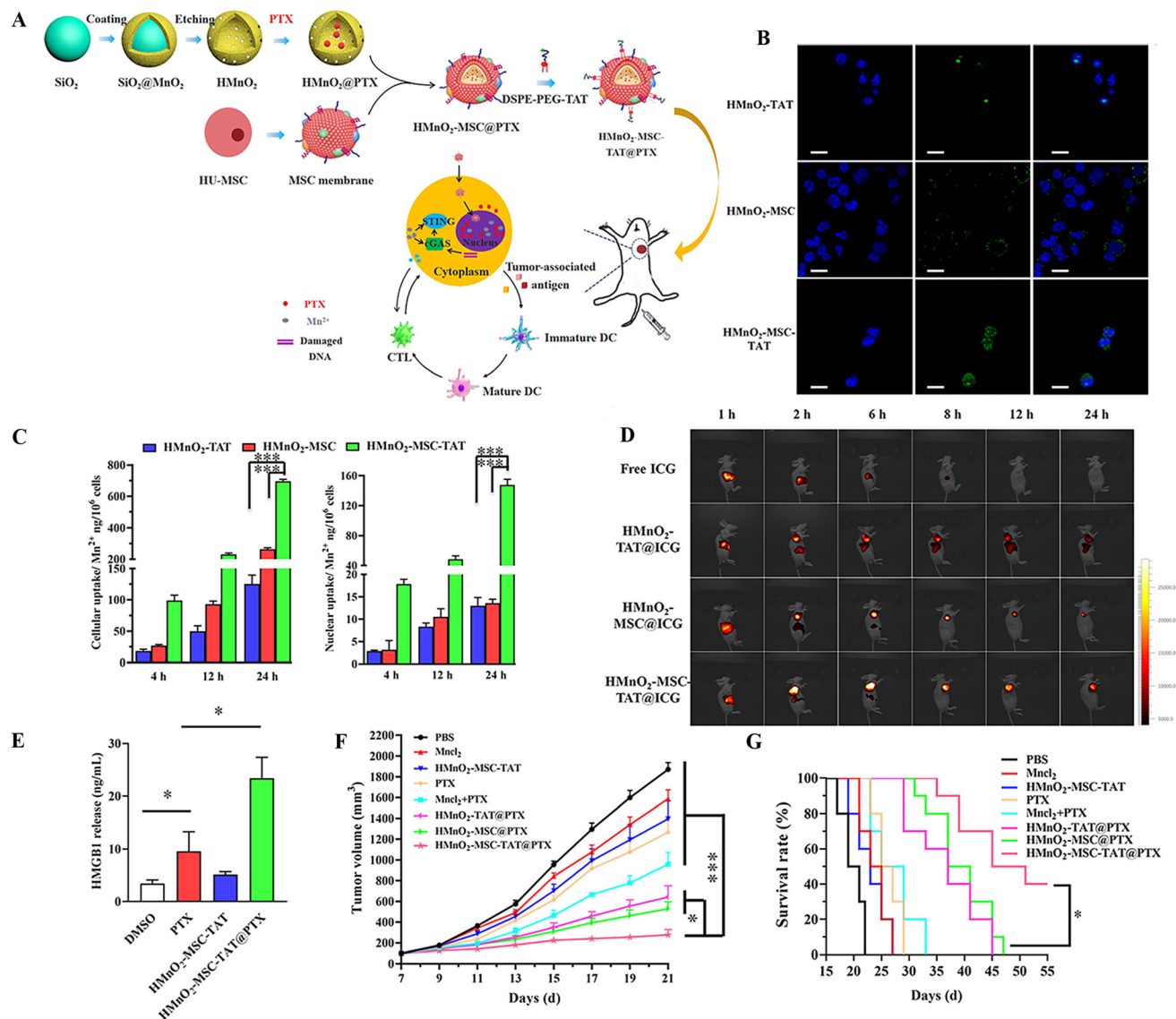
Fig. 10 Mesenchymal stem cell membrane coated MnO_2 delivered PTX for nucleus–targeted combination cancer therapy.[154] (A) Schematic of synthesis of $HMnO_2$-MSC-TAT NPs and schematic illustration of chemo-immunotherapy. (B) CLSM images of A549 cells incubated with different NPs. (C) Amount of cellular and nuclear uptake of NPs. (D) *In vivo* imaging of A549 tumor-bearing mice. (E) Amount of released HMGB1. (F) LLC tumor growth curves in mice. (G) Percentages of surviving mice treated with different formulations. Copyright 2023 American Chemical Society.

immunotherapy. Nonetheless, drugs specifically targeting tumor metabolism often struggle to achieve comprehensive anti-tumor effects and are frequently employed as supplementary or complementary therapies alongside other treatments in recent investigations. For instance, a study developed a self-amplifying biomimetic nanocarrier system known as mEHGZ to effectively deplete glucose and GSH required for tumor cell proliferation. This system involved co-loading EPI, Gox, and hemin into ZIF-8, along with overexpressing CRT on 4T1 cell membrane surfaces. Gox could oxidize glucose in tumor cells, leading to gluconic acid and H_2O_2 production. This reduced glucose supply to starve tumor cells while generating hydroxyl radicals ($^\bullet OH$) and depleting intracellular GSH *via* the Fenton reaction. This combination enhanced endoplasmic reticulum

stress and exacerbated ICD in tumors. Besides inducing DC maturation and $CD8^+$ T cell infiltration, this system also improved the sensitivity of tumor cells to anti-PD-L1 therapy.[159]

Another study aimed to reverse the immunosuppressive effects of adenosine accumulation in TME, often caused by hypoxia. Adenosine binds to the G-protein-coupled A2A receptor (A2AR) and suppresses immune cell function, including the recruitment of Tregs. To address this, Wen *et al.* co-encapsulated Cat, Dox, and R848 in mesoporous silica (Cat@SiO_2-M) to promote the uptake of NPs by hepatocellular carcinoma cells through macrophage membrane encapsulation (Fig. 11). The encapsulated Cat converted H_2O_2 into oxygen, relieving hypoxia and alleviating immunosuppression associated with
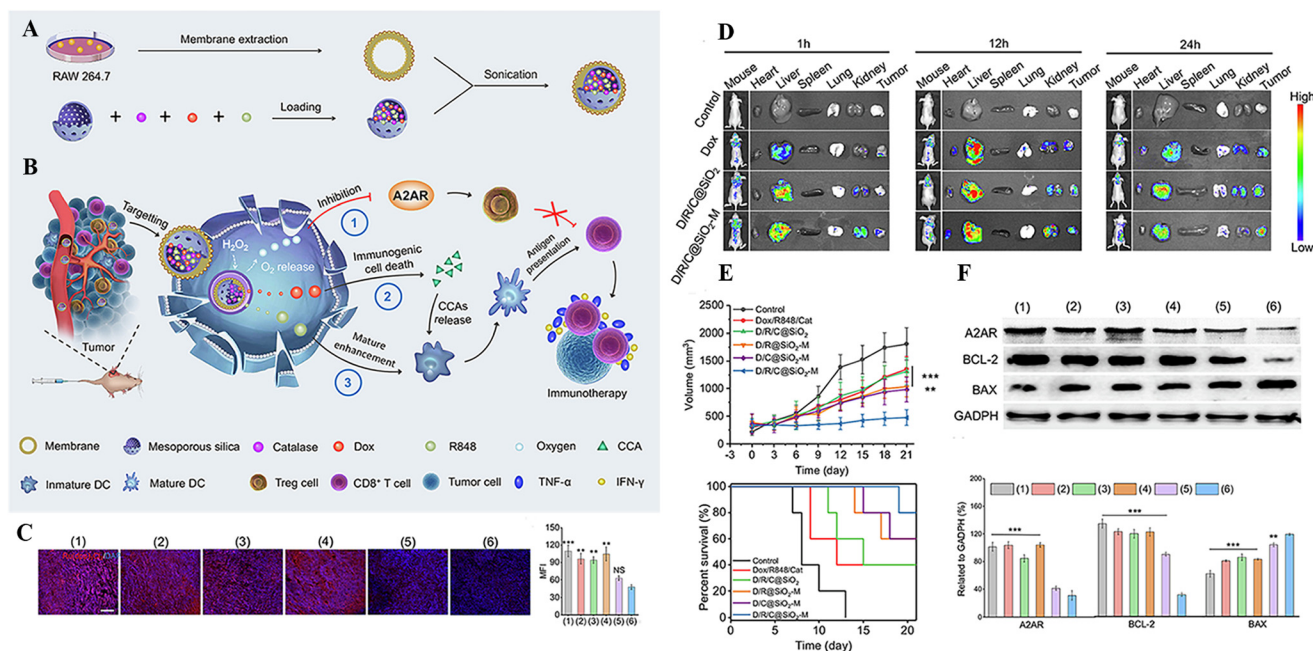
Fig. 11 Macrophage membrane coated mesoporous silica nanoplatform inhibiting adenosine A2AR *via in situ* oxygen supply for immunotherapy.[206] (A) Schematic of synthesis of D/R/C@SiO₂-M. (B) The mechanism of D/R/C@SiO₂-M mediated immunotherapy. (C) Fluorescence images and the MFI of tumor tissue. (D) *In vivo* bioluminescence images of tumor–bearing mice and *in vitro* tissues. (E) Tumor growth curves and percentages of surviving mice treated with different formulations. (F) Western blot analysis and average gray value in mice tumor tissue 2 days after the last treatment. Copyright 2023 Elsevier.

the adenosine-A2AR pathway. Additionally, the ICD and DC maturation effects of DOX and R848 reduced the population of Tregs by 90.21% while increasing CD8⁺ T cells, effectively counteracting immune cell dysfunction caused by adenosine accumulation.[206]

6.3. Immunotherapy based on nucleic acid delivery

The inherent stability of nucleic acid drugs necessitates innovative delivery systems, such as CMNPs, widely employed in studies for enhancing cancer immunotherapy through nucleic acid-based drug delivery. In a study, Ou *et al.* utilized poly-L-histidine (H)-grafted BP to carry PTX and IL-1α siRNA (ILsi) for combined cancer therapy (Fig. 12). The BP-H-ILsi-X@EM-YSA system, synthesizing an erythrocyte membrane shell embedded with Ephrin-A2 receptor-specific peptide (YSA), selectively targeted MC38 tumor tissues. Upon NIR exposure, ROS production degraded the erythrocyte membrane shell, releasing ILsi and PTX into the cytoplasm. ILsi notably silenced IL-1α expression, reducing CCL22 secretion, hindering Treg migration to the tumor site, and in combination with PTX, enhancing CD8⁺ T cell infiltration.[160]

In another study, nanopolymers encapsulated in M1 macrophage membranes were used to deliver shRNA-Ptpn2 with DOX. Polarized M1 macrophage membranes facilitated DOX accumulation and targeted intranuclear delivery of shRNA, significantly down-regulating Ptpn2 mRNA expression, and enhancing T cell responsiveness to IFN-γ. The combi-

nation with DOX increased CD8⁺ T cell ratios in the TME, augmenting the immunotherapeutic impact on melanoma.[161]

6.4. Immunotherapy based on antibody delivery

ICIs, following extensive research, have been successfully integrated into clinical practice and demonstrate remarkable tumor suppression capabilities. With the introduction of CMNPs in cancer immunotherapy, ICIs are frequently combined with CMNPs loaded with immunotherapeutic agents. Additionally, ICIs can also realize more effective therapeutic outcomes through CMNPs.

For instance, in the context of treating intracerebral glioblastoma, one study employed CLP002, a low molecular weight PD-L1 inhibitor, loaded into allomelanin NPs (AMNPs) – a melanin analogue with photothermal properties (Fig. 13). AMNPs were encapsulated with GL261 membranes (AMNP@CLP@CCM) to enhance BBB and targeting precision. Subsequent laser irradiation at 808 nm and 0.5 W cm⁻² allowed for effective photothermal therapy in glioblastoma tissues. The combined action of *in situ* PTT and ICIs led to DC maturation, CD8⁺ T cell infiltration, and long-term immune memory T cell generation, achieving therapeutic effects against intracranial tumors.[199]

The non-specific distribution of ICIs *via* injection contributes to their limited efficacy and adverse effects. Alongside CMNP-mediated targeted delivery, research has harnessed MMP2 found in TME to enhance the precision of ICI therapy. For instance, BTO was encapsulated in genetically engineered membranes with aPD-L1 overexpressed. The helical peptides
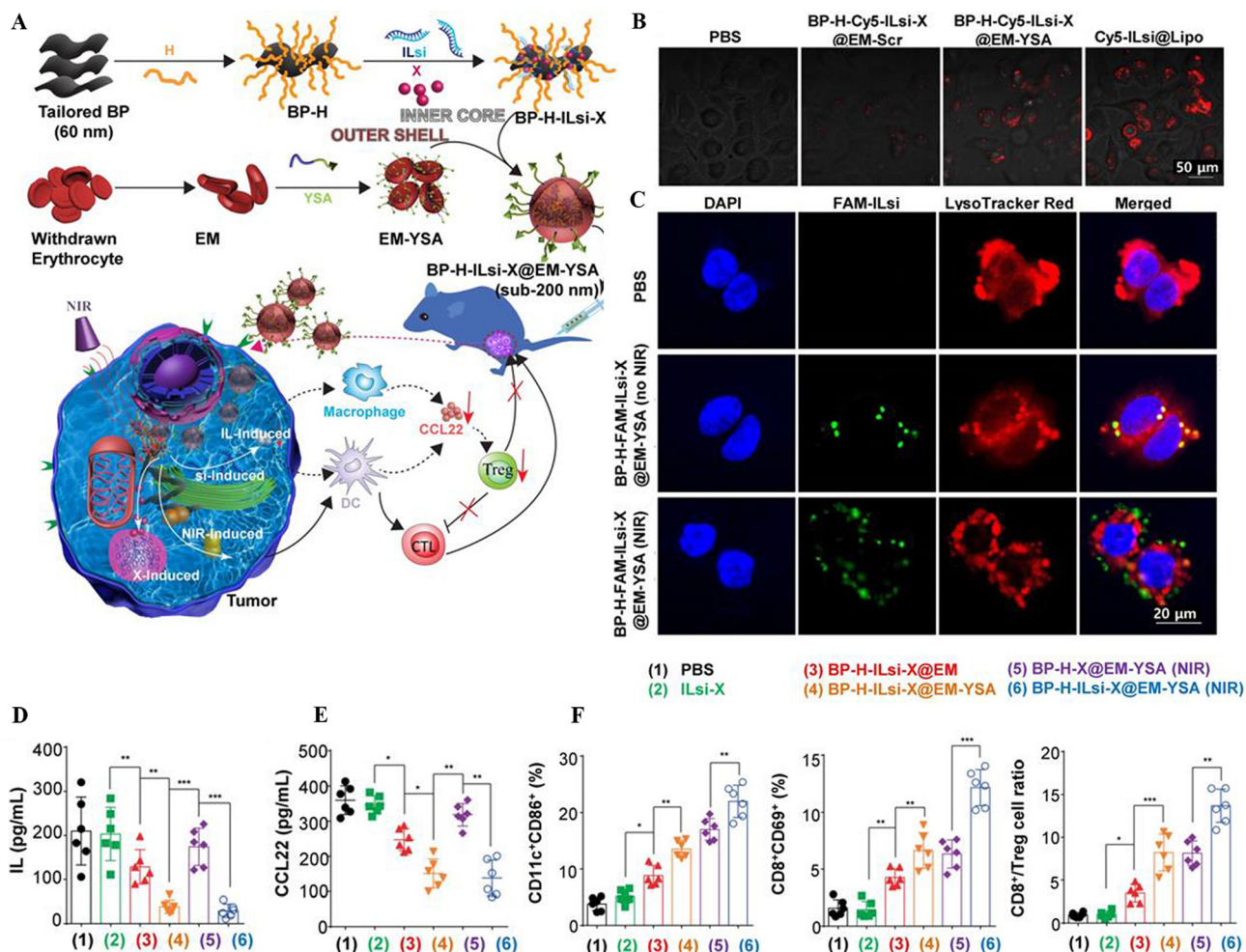
Fig. 12 Erythrocyte membrane coated NPs delivered IL-1α siRNA and paclitaxel for targeted and combination cancer therapy.[160] (A) Schematic of synthesis of BP-H-ILsi-X@EM-YSA and schematic illustration of immunotherapy. (B) Confocal images and flow cytometry data of cellular uptake levels. (C) Confocal analysis of endosomal escape of ILsi from MC-38 cells. (D) ELISA analysis of IL levels in MC-38 tumors. (E) ELISA analysis of intra-tumor CCL22 levels. (F) Flow cytometry analysis of the percentages of DCs and T cells and ratio between CD8+ and Treg in the treated tumor. Copyright 2019 Theranostics.

on aPD-L1 were specifically cleaved by MMP2 to realize specific anti-PD-L1 therapy. The synergistic effects of BTO and ROS-induced ICD not only boosted intracellular oxygen levels but also enhanced the aggregation of immune-suppressive cells in the hypoxic TME, facilitating the transformation of "cold" tumors into "hot" tumors.[121]

Various strategies have also been devised for ICI delivery through CMNPs, including lipid nanoparticles loaded with RNA editing enzyme ADAR1 siRNA (siAdar) enclosed by PD1 over-expressed membranes. This approach achieved immune check-point inhibition and promoted interferon production *via* gene silencing.[213] As CMNP technology advances, new avenues for effectively regulating immune checkpoint axis will continue to emerge.

6.5. Combination therapy

To enhance therapeutic outcomes and overcome limitations in immunotherapy, immunotherapeutic approaches based on CMNPs are typically combined with other modalities in oncol-

ogy. For instance, ICIs, as a matured immunotherapeutic, often administered systemically, are used in conjunction with CMNP-mediated photoimmunotherapy or cancer nanovaccines.[189,193,195] This combined therapeutic approach has the potential for comprehensive immune system acti-vation, displaying promising clinical translational prospects. Surgical intervention remains an effective treatment for many early-stage solid tumors. However, residual lesions or metasta-sized tumor cells significantly impact surgical efficacy. Studies have explored utilizing extracted cell membranes from excised tumor tissues to encapsulate NPs loaded with immune adju-vants, compensating for surgical limitations.[141] Moreover, tra-ditional systemic radiotherapy and chemotherapy can syner-gize or amplify CMNP-mediated immunotherapy by directly killing tumor cells.[214,215] Ongoing research and advancement of these combinational therapeutic strategies hold the promise of offering more effective treatment options for cancer patients.
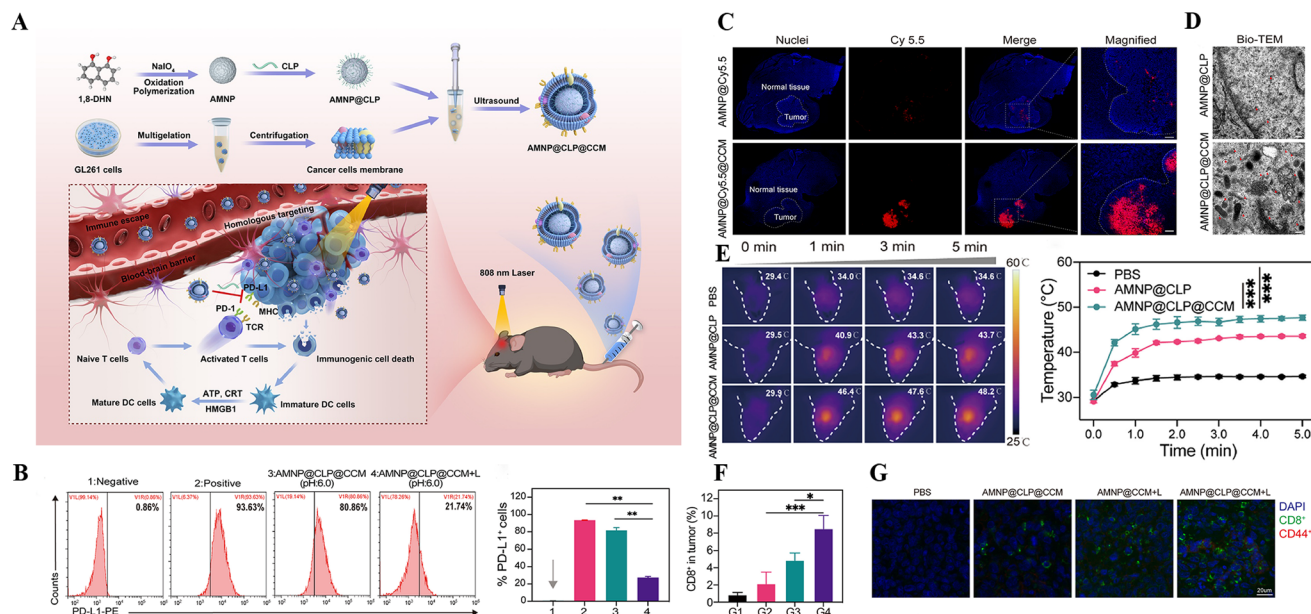
Fig. 13 Cancer cell membrane coated AMNPs delivered ICIs for targeted photothermal immunotherapy.[199] (A) Schematic of synthesis and therapeutic mechanism of AMNP@CLP@CCM for immunotherapy. (B) Flow histogram and corresponding quantification analysis of the blocking effect of PD-L1 on the surface of GL261 cells. (C) Representative fluorescence images of frozen brain sections. (D) Bio-TME images of the tumor tissue after being administrated for 12 h. (E) *In vivo* infrared thermal imaging in orthotopic GBM-bearing mice. (F) Flow cytometric quantification of activated CTL from the tumor. (G) Immunofluorescence images of CD8^{+} CD44^{+} T cells in glioma tumor sections. Copyright 2023 Elsevier.

7. Conclusions and future perspectives

This review highlights the application of different CMNPs in cancer immunotherapy. Recent advances in cancer therapy have led to the increasing popularity of immunotherapy, which activates the immune system to combat cancer cells. However, the effectiveness of immunotherapy varies depending on factors like cancer cell resistance. The introduction of new nanotechnology in cancer treatment has opened up avenues for enhancing cancer immunotherapy depending on its excellent drug delivery capacity or photothermal property. The arrival of biomimetic nano-platforms allows a wider application of NPs in cancer immunotherapy. Due to the inheritance of unique characteristics of both cell membranes and NPs, CMNPs enable prolonged circulation in the bloodstream, precise drug delivery, and interaction with components in TME, making them a superior platform for immunotherapy. Consequently, CMNPs can enhance PTT or PDT by delivering photosensitizers to tumor tissues. They can also stimulate the innate and adaptive immune system against tumors and reverse the immunosuppressive TME by delivering immunomodulatory agents.

While CMNPs show promise in cancer immunotherapy and demonstrate significant anti-tumor effectiveness in studies, their clinical application faces numerous challenges and limitations. The synthesis process of CMNPs is critical for their anti-tumor effectiveness. Extracting intact and functional cell membranes poses a pressing issue, as the loss and inactivation of proteins

during membrane extraction compromise CMNPs' therapeutic effectiveness.[216] Heterogeneity in cell membranes expanded *in vitro* can trigger inflammatory responses, necessitating the isolation of blood cells or autologous tumor cells, increasing operational complexity. Current purification methods, mainly using differential centrifugation, can lead to immune reactions and self-damage due to the retention of complex components like nucleic acids and cytoplasm, potentially causing cell carcinogenesis. Improving the cell membrane extraction process is essential to maintain CMNPs' quality. Furthermore, the challenge of achieving mass production hinders the clinical adoption of CMNPs. The current methods, such as physical extrusion and ultrasonication, suffer from inefficiency, complexity, and uneven coating. Although production methods are improving, they are still in the early stages of research, posing challenges for scaling up to clinical needs.[217]

As a novel anti-tumor strategy, CMNPs must address biosafety concerns to determine their clinical viability. The stability of the membrane coating impacts *in vivo* metabolism and is critical for achieving favorable pharmacokinetics in the case of CMNPs. The evolving field of NPs provides diverse core options for CMNPs, raising considerations about potential immune responses, organism toxicity, degradation kinetics, and metabolite toxicity associated with NPs. Moreover, the intricate protein composition on CMNPs' surfaces can lead to hypersensitivity reactions in allergic individuals or adverse interactions with normal cells.

In current research, various cell membranes, including organelle membranes, have been explored to emulate the bio-

mimetic function of CMNPs. Future investigations into novel cell membrane types, like B cell membranes, hold promise for improving CMNPs. Targeted drug delivery is a primary focus in CMNP research. While existing studies mention the use of different cell membrane coatings for drug targeting toward tumor or immune cells, most approaches are essentially "passive" targeting, lacking specificity. Engineered cell membranes have enabled precise drug delivery to specific components in TME, such as targeting macrophages with mannose or crossing BBB for homologous targeting of brain tumor cells through cRGD modification.[162] Genetically engineered cell membranes are emerging as a promising strategy for active targeting in cancer therapy. For instance, NPs enclosed within the membranes of T cells with PD-1 overexpressed allow for specific interactions with tumor cells exhibiting high levels of PD-L1.[208] In general, engineered CMNPs represent a burgeoning area of interest for active targeting and enhancing the efficacy of cancer immunotherapy.

The amalgamation of biofilm functions and nanoparticle properties in CMNPs presents significant potential in cancer therapy. Efforts in future research should focus on developing bionanosystems with enhanced multifunctionality and precise targeting capabilities, while prioritizing biosafety. This will enable the full utilization of their unique advantages in clinical cancer immunotherapy.

Abbreviations

CMNPs	Cell membrane coated nanoparticles
ICB	Immune checkpoint blockade
TME	Tumor microenvironment
NPs	Nanoparticles
RES	Reticuloendothelial system
PEG	Polyethylene glycol
DC	Dendritic cell
APC	Antigen-presenting cell
CTL	Cytotoxic T cell
TAA	Tumor-associated antigen
ICI	Immune checkpoint inhibitor
IFN	Interferon
TNF	Tumor necrosis factor
PD-1	Programmed cell death 1
PD-L1	Programmed cell death 1 ligand 1
CTLA-4	Cytotoxic T lymphocyte-associated antigen-4
Treg	Regulatory T cell
CAF	Cancer associated fibroblast
ICD	Immunogenic cell death
NIR	Near-infrared
ROS	Reactive oxygen species
CAR-T	Chimeric antigen receptor T-cell immunotherapy
PLGA	Poly(lactic-co-glycolic acid)
SIRPα	Signal-regulated protein alpha
NK cell	Natural killer cell
CRT	Calreticulin
PTT	Photothermal therapy

DAMPs	Damage-associated molecular patterns
BP	Black phosphorus
PDA	Polydopamine
PDT	Photodynamic therapy
PpIX	Protoporphyrin IX
MOF	Metal organic framework
Ce6	Chlorin e6
TLR	Toll-like receptor
STING	Interferon gene-stimulating factor
BBB	Blood–brain barrier
MNs	Magnetic nanoparticles
DOX	Doxorubicin
MONs	Mesoporous organosilica nanoparticles
PTX	Paclitaxel
ZIF	Zeolitic imidazolate framework
GSH	Glutathione
IDO	Indoleamine 2,3-dioxygenase
MDSC	Myeloid-derived suppressor cells
siFGL1	Fibrinogen-like protein 1 siRNA
shRNA	Short hairpin RNA
MMP	Matrix metalloproteinases
EV	Extracellular vesicle
HMGB1	High-mobility group box 1

Author contributions

Zichen Zhong and Wen Deng wrote the original draft. Jian Wu, Haojie Shang and Yonghua Tong completed the recombination and arrangement of figures. Yu He, Qiu Huang and Xiaozhuo Ba collected information and organized materials. Zhiqiang Chen and Kun Tang came up with the overall structure of the manuscript. All authors reviewed and edited this manuscript.

Data availability

No data was used in the research and all related researches were referenced.

Conflicts of interest

There exist no conflicts in the review.

Acknowledgements

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