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Review article

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Targeting drugs to tumours using cell membrane-coated nanoparticles

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Abstract

Traditional cancer therapeutics, such as chemotherapies, are often limited by their non-specific nature, causing harm to non-malignant tissues. Over the past several decades, nanomedicine researchers have sought to address this challenge by developing nanoscale platforms capable of more precisely delivering drug payloads. Cell membrane-coated nanoparticles (CNPs) are an emerging class of nanocarriers that have demonstrated considerable promise for biomedical applications. Consisting of a synthetic nanoparticulate core camouflaged by a layer of naturally derived cell membranes, CNPs are adept at operating within complex biological environments; depending on the type of cell membrane utilized, the resulting biomimetic nanoformulation is conferred with several properties typically associated with the source cell, including improved biocompatibility, immune evasion and tumour targeting. In comparison with traditional functionalization approaches, cell membrane coating provides a streamlined method for creating multifunctional and multi-antigenic nanoparticles. In this Review, we discuss the history and development of CNPs as well as how these platforms have been used for cancer therapy. The application of CNPs for drug delivery, phototherapy and immunotherapy will be described in detail. Translational efforts are currently under way and further research to address key areas of need will ultimately be required to facilitate the successful clinical adoption of CNPs.

Sections

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Key points

- Cell membrane-coated nanoparticles (CNPs) are an emerging class of nanocarriers that are inherently multifunctional, combining the properties of synthetic nanoparticle cores with the bio-interfacing properties of cell membranes.
- The type of membrane that is utilized is usually reflected in the biological properties of the resulting CNP, which can be further fine-tuned or augmented using various engineering approaches.
- CNP technology has the potential to be applied in several therapeutic areas of oncology, including drug delivery, phototherapy and immunotherapy.
- Efforts to translate promising CNPs into approved therapies are currently under way and will require the development of large-scale production methods and novel assays to facilitate the clinical adoption of CNPs.

Introduction

A lack of specificity, leading to adverse effects that must be carefully managed by clinicians, is a major limitation of traditional cancer therapies such as chemotherapy[1–3]. The narrow therapeutic window that is characteristic of many cancer therapies requires a careful balance between antitumour activity and patient safety, often allowing cancer cells to develop resistance[4,5]. Researchers have long sought to overcome this key challenge using a variety of strategies[6,7]. Among these strategies, nanomedicine has an important role and has resulted in the development of drug formulations with improved therapeutic indices[8–10]. In comparison with their unmodified counterparts, nanoformulations can be more specifically delivered to tumours, either by passive or active targeting mechanisms[11,12]. Nanocarriers can also be leveraged to enhance the bioavailability of drugs that otherwise have limited clinical efficacy[13]. Liposomal doxorubicin was first approved for clinical use in the USA in 1995 by the FDA and is currently still used as first-line therapy for patients with certain cancers[14]. A considerable number of clinically approved nanoformulations are available, such as nab-paclitaxel[15] and liposomal cytarabine-daunorubicin[16], and many others are being actively investigated in clinical trials[17].

Despite the continued evolution of biomedical nanotechnology for oncological applications over the past several decades, further improvements can be made in several important areas. In order to avoid detection and clearance by the immune system, many nanocarriers now include a 'stealth coating' consisting of polyethylene glycol (PEG)[18]. This PEGylation has proven to be effective in prolonging the plasma half-life of most nanoparticles to at least several hours, although antibodies can be elicited against the polymer[19]. This acquired immunity can result in accelerated clearance after multiple administrations, thus leading to reduced performance over time. First-generation nanocarriers, such as liposomal doxorubicin, rely exclusively on passive targeting via the enhanced permeation and retention (EPR) effect[20]; however, considerable research efforts have since been focused on the use of active targeting moieties to enhance tumour specificity[11]. This approach necessitates the identification, characterization and production of specific targeting ligands, which can require a considerable investment of both time and other resources[21–23]. Furthermore, modification of nanocarriers using conventional approaches becomes exceedingly difficult to control as greater levels of functionality are included, thus making the clinical translation of such platforms particularly challenging.

Owing to these challenges, considerable research interest has emerged in developing new nanoparticle-based platforms using biomimetic designs[24]. Cell membrane-coated nanoparticles (CNPs) are an emerging class of nanocarriers that have demonstrated considerable potential (Fig. 1). Nanoparticles of this type are generally fabricated by camouflaging synthetic cores with a layer of naturally derived cellular membranes, which results in a core–shell nanostructure with cell-mimicking properties[25,26]. These biomimetic nanoparticles and other similar cell membrane-derived platforms[27,28] excel at interacting with biological substrates, or bio-interfacing, thus enabling them to effectively navigate complex biological environments by avoiding immune clearance and specifically accumulating at disease sites[29]. Cell membrane coating provides an effective top-down nanoparticle functionalization strategy, thus potentially streamlining the development of nanocarrier platforms with desirable properties that can be custom-tailored for a wide range of applications. In this Review, we describe the development of CNPs for the treatment of cancer. The application of CNPs in anticancer drug delivery, phototherapy and immunotherapy will be examined in detail. Considerations for the

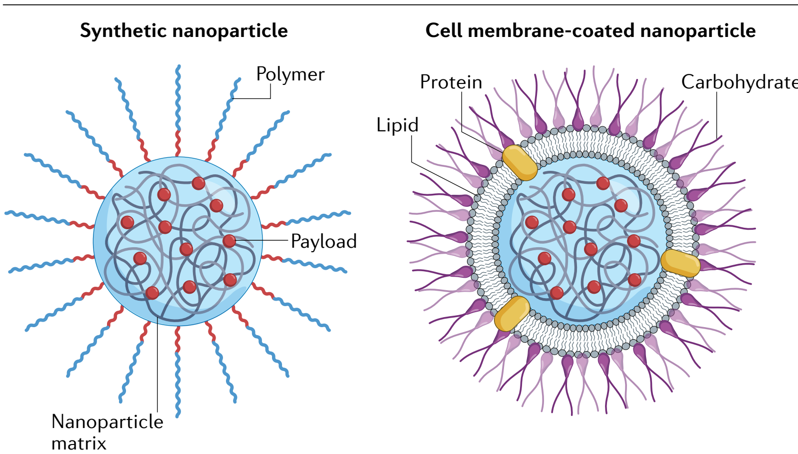

Fig. 1 | Traditional synthetic nanocarriers versus cell membrane-coated nanoparticles. Synthetic nanoparticle platforms generally consist of a nanomaterial matrix enabling payload encapsulation that is coated with a polymer layer to prevent rapid clearance by the immune system. By contrast, cell membrane-coated nanoparticles are functionalized with naturally derived cell membranes, which typically contain various lipids, carbohydrates and proteins that can potentially delay clearance by the immune system and/or provide an additional level of cell-mimicking functionality.

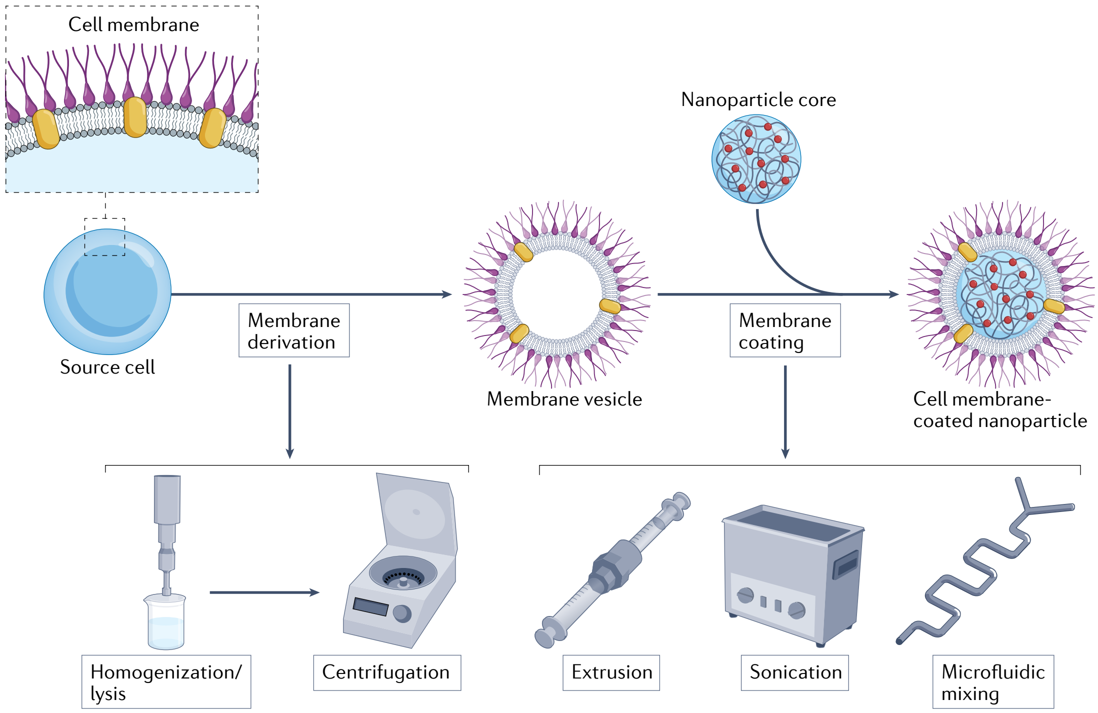

Fig. 2 | Fabrication of cell membrane-coated nanoparticles. Membrane materials are derived from source cells and then coated around synthetic nanomaterial cores using techniques such as extrusion, sonication or microfluidic mixing. The resulting cell membrane-coated nanoparticles have a characteristic core–shell structure and the faithful transfer of cell membranes onto their surface bestows these nanoparticles with cell-mimicking functions that reflect the cell membrane source material.

future translation of promising CNP platforms into the clinic will also be discussed.

Overview of CNP technology

A CNP generally consists of two key components: a synthetic core and an outer layer of a naturally derived cellular membrane (Fig. 2). This hybrid design enables CNPs to exploit many of the advantages of each constituent part. The core can function as a matrix into which anticancer payloads can be incorporated or that can be adapted for immunostimulatory or photoresponsive functions. Certain nanomaterials can also be utilized for their environmental responsiveness or endosomal escape properties[30]. At the same time, the cell membrane layer enables CNPs to effectively interact with surrounding proteins, cells and other biological substrates after in vivo administration[29]. In contrast to synthetic PEG coatings, cell membranes can incorporate various cell-surface proteins that confer nanoparticles with certain properties such as the ability to avoid rejection by the immune system[31,32]. CNPs often exhibit the same tropisms as the cells from which their membrane is sourced[33,34]; depending on the type of membrane coating, the nanoparticles can also serve as effective antigen sources or present immunostimulatory signals for immunotherapeutic applications[33–36]. In an early report describing the use of CNP technology, red blood cell (RBC) membranes were used to camouflage a poly(lactic-*co*-glycolic acid) (PLGA) nanoparticle core[37]. Following this initial proof-of-concept study, CNP platforms have been developed using cell membranes sourced from a variety of different cell types to functionalize a wide range of synthetic nanomaterials[25].

Sources of membrane coatings

Depending on the source of the cell membrane, the corresponding CNP will typically have a unique set of properties that can be leveraged for oncological applications (Fig. 3). RBCs are natural long-circulating carrier cells that transport oxygen throughout the body. These cells lack organelles and contain mostly haemoglobin, making the purification of membranes that contain a high density of self-markers, such as CD47 and complement regulatory proteins, relatively straightforward[31,38]. Accordingly, RBC membranes have been widely used for applications in which non-specific interactions need to be minimized, thus providing an effective substitute for synthetic PEG coatings, which can be recognized as foreign by the immune system[39]. Owing to their non-immunogenic nature, RBC membrane-coated nanoparticles are naturally suited for situations in which prolonged in vivo retention is crucial as they are unaffected by the accelerated blood clearance sometimes seen with PEG coatings and can thus maintain consistent performance even after repeated administrations[40]. A long plasma half-life is particularly important for passively targeted CNPs that are designed to accumulate via the EPR effect as this increases the possibility of tumour contact.

Platelets are another type of anucleated blood cell that has been widely used as a cell membrane source for the surface coating of nanoparticles. These cells are less abundant and more fragile than RBCs but share many of the same immunoevasive properties[41]. Owing to the central role of platelets in haemostasis and their ability to respond to inflammatory cues, platelet membranes can be utilized for targeted delivery applications[34]. For example, the ability

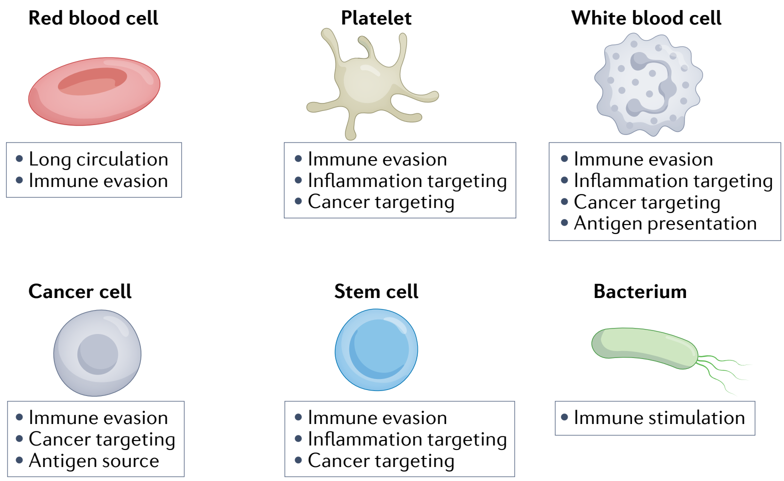

Fig. 3 | Common membrane sources for the fabrication of cell membrane-coated nanoparticles. Cell membrane-coated nanoparticles can be fabricated using cell membrane materials sourced from red blood cells, platelets, immune cells, cancer cells, stem cells or bacteria. Each type of membrane coating confers specific properties that can be leveraged for anticancer applications.

of platelet membrane-coated nanoparticles to localize to the subendothelium, sites of thrombosis and activated endothelial cells makes them suitable for the targeting of tumours during various stages of progression[42,43]. Additionally, certain circulating tumour cells have been reported to directly bind to platelets as a method of immune evasion[42,43].

In terms of nucleated cells, macrophages, dendritic cells, neutrophils, natural killer cells and T cells have all been used as sources of membrane material for CNP fabrication despite having a more complex cellular structure than RBCs and platelets. Immune cells are known to have a major role in tumorigenesis, with certain subsets capable of either promoting or suppressing cancer growth and progression[44,45]. Such cells are typically able to accumulate at sites of inflammation, which is often a driving force for cancer development. Established tumours can also recruit immune cells into their microenvironment to promote immunosuppression.

Besides cells originating from the blood, cancer cells are another unique source of cell membrane coating material. CNPs fabricated using cancer cell membranes have been widely investigated for their potential anticancer applications as they demonstrate a range of cancer cell-mimicking properties[33,46,47]. In particular, many cancer cells have an affinity to adhere to each other, which is thought to aid in tumour development and metastatic dissemination[48]. This homotypic binding enables cancer cell membrane-coated nanoparticles to be used as a targeted carrier for delivering payloads to tumours[46]. Cancer cell membranes are also a rich source of tumour-associated antigens and neoantigens, which are potentially useful for cancer vaccines and related applications[49]. Indeed, CNPs are an ideal platform for nanovaccine development as a cancer membrane coating can be combined with an immunostimulatory nanoparticle core in order to elicit strong antitumour immunity. For most preclinical studies, cancer cell membranes are sourced from established cell lines although the potential also exists to derive autologous material from a patient's resected tumour material[50]. Other types of nucleated cells, such as stem cells[51,52] and fibroblasts[53], have also been used as membrane sources for the development of CNP-based cancer therapeutics.

Other than mammalian sources, CNP formulations have also been successfully generated using membrane material obtained from pathogens[54,55]. In particular, nanoparticles coated using the outer membranes of Gram-negative bacteria have been explored for their ability to promote antitumour immunity[35]. Bacterial membranes contain a wide range of pathogen-associated molecular patterns, including endotoxins, that are highly effective at stimulating immune responses via pattern recognition receptors found predominantly on innate immune cells[56]. Stimulating innate immunity is generally considered a safety concern that precludes clinical use; however, the immunostimulatory properties of bacterial membranes might, under certain conditions, provide a useful method of reinvigorating endogenous antitumour immunity[54]. For example, the introduction of immune adjuvants can turn an immunologically 'cold' tumour into a 'hot' tumour and thus improve responsiveness to immunotherapies such as immune-checkpoint inhibitors[57]; this could also be useful in combination with other therapeutic modalities such as chemotherapy, radiotherapy or surgery[58]. The basic principle of using bacteria to promote antitumour immunity is over a century old[59]; nonetheless, this remains an active area of research that holds considerable potential[60]. Various methods are also available for improving the safety of bacteria-derived membranes[61], which might facilitate more widespread use of this approach.

Methods of preparation

In order to fabricate CNPs, cell membrane material first needs to be obtained from a suitable source. For primary blood cells, such as RBCs, platelets and immune cells, the availability of existing infrastructures for blood collection and processing makes the acquisition from commercial sources reasonably straightforward. Cell lines or bacterial strains can be cultured at a moderate scale in a laboratory setting, which is generally sufficient to support preclinical studies. Suspension cells can be grown volumetrically in shaker or spinner flasks[62], making them simpler to harvest than adherent cells, which require either enzymatic or physical detachment. In vitro methods of culturing engineered RBCs or platelets have also been reported[63,64], and this type of approach might be used for future CNPs.

After obtaining a sufficient number of source cells, the next step is to derive the membrane material. For anucleate cells, this can easily be done by subjecting them to hypotonic treatment or freeze–thaw cycles in order to release their intracellular contents[34,37]. This cellular lysis is then followed by high-speed centrifugation in order to form a pellet containing the membrane. The membrane derivation process is more complex for nucleated cells, requiring the separation of the plasma membrane from intracellular organelles and proteins[33]. After cell lysis, which can be accomplished using mechanical homogenization, sonication or nitrogen cavitation, the resulting homogenate is subjected to either differential or gradient centrifugation, which enables plasma membrane isolation. Extracellular vesicles[65], which can be derived from most of the cell sources described above, have also been explored as an alternative source of membrane coating material[66]. Although large-scale production is a challenge that has yet to be adequately addressed, extracellular vesicles share many similarities with plasma membranes and contain a variety of functional markers. Outer membrane vesicles from Gram-negative bacteria have been utilized in a similar manner[55].

After purification, cell membrane material can then be coated onto the surface of nanoparticles. Initially, the membrane coating process was conducted by repeatedly extruding cell membrane vesicles and synthetic nanoparticle cores together, back and forth, through a membrane with pores of a few hundred nanometres in diameter[37]. The temporary disruption of the membrane structure as it is being mechanically extruded enables it to reform around a nanoparticulate substrate in a stable core–shell configuration, yielding a CNP with surface proteins that largely match those found on the source cells[34]. Evidence suggests that the coated membrane generally has a right-side-out orientation, which might be facilitated by the nanoparticle core and how it interacts with the inherently asymmetric charge profile between the inner and outer membrane leaflets[32]. This asymmetry is important as it ensures that the membrane-bound moieties responsible for bestowing cell-mimicking properties remain functional. As an alternative to physical extrusion, another method involves the introduction of ultrasonic energy into a membrane and core mixture to achieve membrane coating[67]. Sonication is less labour intensive, particularly for laboratory-scale synthesis, and is believed to serve a similar purpose as extrusion by destabilizing the membrane structure. However, owing to the intense localized energy associated with the process, care must be taken to maintain the structural integrity and function of the biological membrane and its constituents. As such, physical extrusion is often the preferred method of membrane coating when dealing with samples that cannot tolerate excessive disruption. Subsequently, an approach using microfluidics combined with electroporation was reported, which might enable finer control over the membrane coating process via tunable parameters such as the mixing channel geometry, flow rate, voltage and electric field pulse rate[68]. Another benefit of microfluidic technology is the potential to provide predictable scalability when running multiple devices in parallel. After coating, the final CNPs can be isolated using ultracentrifugation as the core material is often denser than the cell membrane; the intrinsic properties of certain nanomaterials can also be leveraged for purification purposes, such as when using a magnetic field to separate out cell membrane-coated iron oxide nanoparticles[69]. Transmission electron microscopy, western blotting or mass spectrometry protein analysis, stability assays, and binding exclusion assays are all commonly used methods of evaluating the completeness and integrity of the membrane coating, both of which must be optimized in order for CNPs to function as intended[33,34,70,71].

Strategies for augmenting functionality

Since the first RBC membrane-coated nanoparticle formulation was reported, a wide range of CNP platforms has been developed for different biomedical applications based on various cell membrane and core combinations[25]. Cell membrane coating provides a facile approach for recapitulating the bio-interfacing properties of cells, and the results of this highly streamlined approach to nanoparticle functionalization cannot be easily replicated using traditional synthesis techniques. Researchers attempting to develop new CNPs can take a function-driven approach, selecting the type of membrane based on its known tropisms and how well its unique properties can serve the end goal. In relying on natural biomolecules that have been honed by evolution, cell membrane coating circumvents the often lengthy and time-consuming processes of developing artificial ligands.

Certain properties of natural cell membrane coatings can limit their utility. Cells can potentially express thousands of surface markers, not all of which will be useful for a given application, and those that are most relevant might not be expressed in the desired quantities or ratios. Targeted nanodelivery, in which the purpose is usually to enhance affinity towards a specific receptor of interest found on the target cell, provides an example of how this factor can become an issue. While natural membrane coatings might express the cognate ligand, such expression might not be at a density that is sufficient to facilitate a strong targeting effect. To overcome this challenge, a variety of strategies have been developed to fine-tune the function of CNPs by further engineering the cell membrane coating (Fig. 4). Owing to the biological origins of the cell membrane, traditional chemical conjugation strategies are generally avoided as the reagents and reaction conditions involved in such processes might impair protein function. Thus, researchers have turned to other, less disruptive strategies for introducing additional functionality. One such approach involves anchoring ligands using a lipid, which can be passively inserted into the cell membrane via hydrophobic interactions[72]. This method has been utilized for components ranging from small molecules, such as folate, to large biomacromolecules such as aptamers. Another method involves hybrid membrane coatings, in which membranes from two different cell types are fused together[73]. The resulting CNP formulations exhibit properties that are characteristic of both source cells, and the degree to which specific functionalities can be recapitulated is dependent on the ratio between the two membranes.

Genetic engineering is a powerful approach for modifying cell-membrane protein expression and has been used to generate CNPs with enhanced levels of functionality[36]. An advantage of this method is that it enables researchers to work directly with membrane-bound proteins, which would otherwise be a difficult task with other nanoparticle functionalization techniques. Modulating cell-surface protein expression can enable major alterations in function, including modifications in cellular-level or organ-level tropism. For example, CNPs targeting vascular cell adhesion molecule 1 (VCAM1, a protein expressed on inflamed endothelial cells) can be generated through genetic modification of the source cells to constitutively express very late antigen 4 (VLA4, which has an affinity for VCAM1)[74]. In another example, source cells were engineered to express the influenza envelope protein haemagglutinin, which substantially enhanced the ability of the resulting CNPs to escape endosomes after cellular uptake and thus deliver a greater proportion of their mRNA payload directly into the cytoplasm[75].

Metabolic engineering, in which the source cells are cultured with modified sugars that are then displayed via surface glycans, provides another strategy for altering CNP function[76]. The modified membrane can then be further engineered using high-efficiency and non-disruptive conjugation chemistries to introduce exogenous ligands. For example, CNPs have been engineered using this approach to express azide groups on their surface, enabling the facile attachment

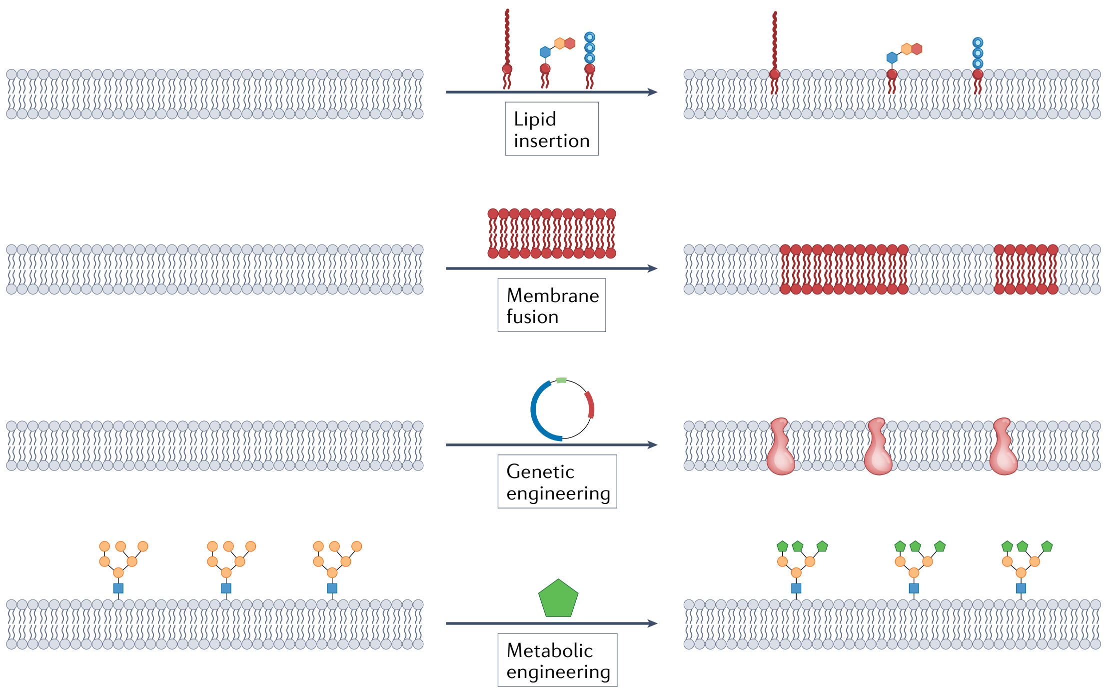

Fig. 4 | Approaches for cell membrane modification. Cell membranes can be modified using various approaches to synthesize cell membrane-coated nanoparticles with enhanced functionality. Lipid insertion leverages the natural affinity of lipid molecules for cell membranes to anchor ligands onto the nanoparticle surface. Membrane fusion produces hybrid membranes that combine the surface properties of two different cell types. Genetic engineering enables the expression and presentation of membrane proteins that would otherwise be difficult to employ using traditional synthesis techniques. Metabolic engineering modifies the surface glycans of cells to include functional groups that can participate in efficient and non-disruptive conjugation reactions.

of dibenzocyclooctyne-modified ligands by copper-free click chemistry[76]. Overall, cell membrane engineering opens the door for the development of next-generation CNP platforms with custom-tailored functionality that goes beyond what is naturally available.

Targeting tumours using CNPs

CNP platforms are being explored extensively for anticancer applications in preclinical models owing to their unique bio-interfacing properties (Tables 1–5). A common theme has been to leverage the enhanced tumour-binding affinity of CNPs to enhance the delivery of various cytotoxic, phototherapeutic and/or immunomodulatory payloads (Fig. 5). Here, we describe the major areas of research in which CNPs are actively being investigated and highlight notable examples of their utilization in oncology.

Drug delivery

As a foundational facet of nanomedicine, the central goal of nanodelivery is to effectively localize one or more payloads to a site of interest[8–10]. Owing to their inherent biological and immunological compatibility, CNPs fabricated using an RBC membrane have a longer circulation half-life than PEGylated nanoparticles and can therefore be used to enhance the passive targeting of therapeutics to tumours via the EPR effect[32,37]. Doxorubicin was one of the first chemotherapies to be encapsulated into a CNP formulation[77]. In this approach, doxorubicin was incorporated into a PLGA matrix, either by physical encapsulation or chemical conjugation, followed by coating with an RBC membrane. Since the initial proof-of-concept study[77], researchers have leveraged the modularity of the core–shell structure of CNPs to design several cancer drug nanoformulations. Self-assembled polymeric cores are commonly utilized in such formulations as they enable passive drug loading via hydrophobic or charge-based interactions[77–79]. Porous silica cores are well suited for the encapsulation of hydrophilic payloads and can subsequently be coated with cell membranes for tumour targeting[80]. Nanoscale metal–organic frameworks (MOFs) excel at the delivery of biomacromolecules owing to their facile synthesis and high loading yields[81,82], and various payloads can be encapsulated into crosslinked nanogels whose mechanical properties can be finely tuned[83,84]. Besides the use of preformed nanoparticle cores, drug crystals can be formed directly within cell membrane vesicles by remote loading, whereby a pH gradient is used to drive cross-membrane transport[85]. Liquid cores, such as those based on perfluorocarbons, have also been utilized in CNP formulations[86,87]. The stiffness of CNPs can have important implications for their in vivo performance: particles that best mimic the natural deformability of healthy RBCs are the least likely to be cleared by the immune system[88].

To further improve the cancer specificity of CNP-based nanoformulations, certain modifications can be made to both the membrane and the core components. In one of the first examples describing the use of membrane modifications to enhance the affinity of CNPs for cancer cells, RBC membrane-coated nanoparticles were functionalized with either folate or the aptamer AS1411 using a lipid anchor attached to a PEG-based tether[72]. Similar approaches have been used to functionalize CNPs, for example, with the tripeptide Arg-Gly-Asp (RGD) or the angiopep 2 peptide, which have improved the delivery of payloads to tumour tissues[78,89]. Cell membrane modification to display streptavidin enables further functionalization via the ligation of various biotinylated molecules[90]. This strategy was used to functionalize RBC membrane-coated nanoparticles with a cyclic RGD peptide, thus enhancing the accumulation of docetaxel in a mouse orthotopic model of glioma.

The cores of CNP nanoparticles are often also engineered for improved specificity, for example, through the introduction of triggered release mechanisms[30]. The stimulus for release (the trigger) can be applied externally, such as when a photoresponsive dye or nanomaterial is used to generate localized heat upon near-infrared (NIR) irradiation. An example is provided by the incorporation of the NIR dye chlorine e6 into RBC membrane-coated mesoporous silica nanoparticles, which facilitated the light-triggered release of a co-loaded drug payload[80]. Similarly, CNPs fabricated using gelatin nanogels have been co-loaded with cisplatin and methylene blue, the latter of which helped to improve the extent of drug accumulation upon irradiation[91]. In another example, graphene quantum dots were used as the photoresponsive element to trigger accelerated drug release[92]. For local stimuli, CNPs can be engineered such that they are responsive to features of the tumour microenvironment. Along these lines, nanoparticles fabricated using poly(l-γ-glutamyl-carbocistein)–paclitaxel, an acid-labile prodrug conjugate that is converted into its active form at a typical intratumoural pH (~6.5), can be coated with RBC membranes[93]. Another tumour pH-responsive CNP platform was fabricated using UV-crosslinked nanogels incorporated with paclitaxel[94]; the nanoparticles were further coated with IL-2 for concurrent chemotherapy and immunotherapy.

In order to achieve active tumour targeting, CNPs have been fabricated using the membranes from platelets and certain immune cell subsets, both of which are often implicated in tumorigenesis[42–45]. For example, platelet membranes conjugated with TNF-related apoptosis-inducing ligand (TRAIL) were used to camouflage acid-sensitive nanogels loaded with doxorubicin[95]. Leveraging the natural expression of P-selectin on platelets to target CD44 found on tumour cells, the final formulation had considerable antitumour activity in a mouse model of breast cancer[95]. A similar platform using silica particles coated with a TRAIL-functionalized platelet membrane to target circulating cancer cells attenuated the development of lung metastases in a mouse xenograft model[96]. In another example, platelet membranes were modified using tissue plasminogen activator to reduce the extent of thrombosis, which can occur in patients receiving immunomodulatory agents plus proteasome inhibitors for multiple myeloma[97]. The membranes were then targeted to accumulate in bone marrow using alendronate and coated around a polymeric core loaded with bortezomib. Similarly, platelet membranes have been used to camouflage silica nanoparticles loaded with tirapazamine, a hypoxia-activated prodrug, and 5,6-dimethylxanthenone-4-acetic acid, a vessel-disrupting agent used to further amplify the targeting effect of the nanoformulation in a mouse model of colorectal cancer[98]. Platelet vesicles can also be remotely loaded via a pH gradient with doxorubicin nanocrystals to enhance the antitumour accumulation of the drug as demonstrated using a mouse breast cancer model[99]. For nucleic acid delivery, a survivin-silencing small interfering RNA (siRNA) can be loaded into platelet membrane-coated MOFs[82]. After uptake by cancer cells, the MOF cores

Table 1 | Examples of RBC membrane-coated nanoparticles

Core material	Encapsulated payloads	Surface functionalizations	Application notes	Ref.
PLGA	Doxorubicin	–	Passive delivery	79
Doxorubicin nanocrystal	Doxorubicin	–	Passive delivery	85
PEG nanogel	Doxorubicin	–	Passive delivery	88
Mesoporous silica	Doxorubicin; chlorin e6	–	Light-triggered drug release	80
MOF (ZIF-8)	Glucose oxidase; tirapazamine	–	Tumour starvation-assisted therapy	81
Perfluorohexane	Glucose oxidase	–	Tumour starvation and immune cell recruitment	86
Gold nanocage	–	–	Photothermal therapy	112
Iron oxide	–	–	Photothermal therapy	68
Iron oxide	–	–	Photothermal therapy	113
Gelatin nanogel	Cisplatin; methylene blue	–	Hyperthermia, photodynamic therapy and light-triggered drug release	91
Manganese oxide	Bovine serum albumin-bound chlorin e6; glucose oxidase	–	Tumour starvation and photodynamic therapy	121
Mesoporous silica	Graphene quantum dots; docetaxel	Cetuximab	Photothermal therapy and light-triggered drug release	92
Docetaxel nanocrystal	Docetaxel	cRGD peptide	Tumour-targeted delivery	90
Acetylated dextran	Doxorubicin; lexiscan	Angiopep 2 peptide	Brain-targeted delivery	89
PLGA	Human gp100; monophosphoryl lipid A	Mannose	Antigen-presenting cell-targeted tumour antigen delivery	140
Chitosan-based nanogel with cyclodextrin	Paclitaxel	IL-2	pH-sensitive drug release and immunotherapy	94

cRGD, cyclic Arg-Gly-Asp; MOF, metal–organic framework; PEG, polyethylene glycol; PLGA, poly(lactic-co-glycolic acid); RBC, red blood cell; ZIF, zeolitic imidazolate framework.

Table 2 | Examples of platelet membrane-coated nanoparticles

Core material	Encapsulated payloads	Surface functionalizations	Application notes	Ref.
Doxorubicin nanocrystal	Doxorubicin	–	Tumour-targeted delivery	99
MOF (ZIF-8)	Anti-survivin siRNA	–	Tumour-targeted delivery	82
Mesoporous silica	Tirapazamine; 5,6-dimethylxanthenone-4-acetic acid	–	Tumour-targeted delivery and vasculature disruption	98
Iron oxide	–	–	Tumour-targeted photothermal therapy	115
Polylactic acid	Resiquimod	–	Local immune stimulation	135
Polyacrylamide nanogel	Doxorubicin	TRAIL	Tumour-targeted delivery	95
Silica	–	TRAIL	Circulating tumour cell-targeted delivery	96
Acetylated dextran	Bortezomib	Tissue plasminogen activator; alendronate	Bone-targeted delivery and thrombolysis	97

MOF, metal–organic framework; siRNA, small interfering RNA; TRAIL, TNF-related apoptosis-inducing ligand; ZIF, zeolitic imidazolate framework.

are able to dissociate and facilitate endosomal release to enhance the bioactivity of the siRNA.

Similar to platelet membrane-coated CNPs, unique cancer-targeting CNP platforms have also been developed using membrane coatings derived from various immune cells. In an early example, liposomes incorporating emtansine were coated with macrophage membranes in an attempt to target lung metastases via interactions with upregulated VCAM1 in a mouse model of breast cancer lung metastasis[100]. Similarly, macrophage-based CNPs carrying paclitaxel have been designed to destabilize under the slightly acidic conditions found in most tumours, thus releasing individual small nanoparticles with ligands promoting enhanced tumour cell uptake via the insulin-like growth factor 1 receptor[101]. While some payload accumulation was observed in other organs, the macrophage membrane coating enabled the payload to predominantly localize to the tumour. Neutrophil membranes have also been utilized for their cancer-targeting properties, including in a CNP formulation loaded with the proteasome inhibitor carfilzomib, which depleted circulating tumour cells and inhibited the formation of metastases in a mouse model of breast cancer[102]. In another interesting example, neutrophil membranes were used to coat MOFs embedded with glucose oxidase and chloroperoxidase, enabling them to mimic the ability of native neutrophils to kill target cells by producing hypochlorous acid, with antitumour activity demonstrated in a mouse model of metastatic breast cancer[103].

The use of cancer cells as a source of membrane coatings provides a novel approach for the development of tumour-targeting CNP formulations by leveraging the homotypic binding properties of cancer cells[48]. This concept was first demonstrated using polymeric nanoparticles coated with membranes derived from a breast cancer cell line (MDA-MB-435); the resulting CNPs were found to be much more effective at targeting the source cells compared with control nanoparticles coated with RBC membranes[33]. The utility of this approach was further confirmed using paclitaxel-loaded CNPs developed from the 4T1 mouse breast cancer cell line[104]. When administered in vivo in mice, this nanoformulation was able to effectively target established 4T1 tumours, leading to reduced tumour growth and metastasis. In another study, the specificity of homotypic targeting was evaluated using a panel of cancer cell lines; CNPs developed using either UM-SCC-7 or HeLa cells were much more effective at targeting their own source cells in vitro compared with heterologous cell lines[105]. This effect was further confirmed in vivo using a bilateral tumour model, in which only tumours grown from the source cell could be successfully targeted. Cancer cell membranes have also been used to coat redox-responsive mesoporous silica nanoparticles loaded with cytotoxic protein payloads such as RNase enzymes[106]. The same platform can also be loaded with doxorubicin, with drug release triggered by X-ray irradiation leading to the cleavage of diselenide bonds within the nanoparticle core[107]. In another approach, tumour-derived extracellular vesicles containing anti-miRNA targeting miR-21 (designed to modulate the expression of BCL-2 and several other apoptosis-related proteins) coated onto gold–iron oxide cores have been developed[108]. In a final example, cancer cell membranes were used to facilitate the tumour-targeted delivery of glucose oxidase-loaded mesoporous silica nanoparticles designed to deplete cancer cells of glucose, which was successfully combined with immune-checkpoint inhibition to improve antitumour activity in a mouse model of melanoma[109].

Phototherapy

Nanoparticle-based phototherapeutic platforms have become increasingly popular and are an active area of research within nanomedicine[110]. There are two main approaches to phototherapy: photothermal therapy (PTT) and photodynamic therapy (PDT). PTT involves the conversion of light into heat by a photothermal agent, resulting in the physical ablation of nearby cells, whereas PDT relies on photosensitizers to facilitate the production of reactive oxygen species that can cause targeted cell death[111]. In comparison with traditional regimens, phototherapies provide an extra layer of specificity owing to the need for an external stimulus to be applied at the tumour site, thus potentially improving the safety profile relative to systemically administered therapies. CNPs have been used as targeted delivery vehicles to enhance the intratumoural accumulation of a wide range of phototherapeutic payloads.

For PTT applications, CNPs have been developed using various metallic, inorganic and dye-loaded nanoparticle platforms capable of efficient photothermal conversion. For example, RBC membranes have been used to coat gold nanocages, and the resulting nanoformulation has been shown to induce local hyperthermia in tumour tissues upon NIR irradiation[112]. RBC membranes have also been used to coat iron oxide nanoparticles[113] and copper selenide nanoparticles[114], with each of the resulting nanoformulations enabling effective PTT in mouse models. The latter CNPs are able to absorb light of wavelengths ≥1,000 nm (also known as the NIR II window)[114], allowing much deeper tissue penetration.

In terms of active targeting, the coating of iron oxide nanoparticles with platelet membranes has been shown to facilitate their accumulation in MCF-7 breast cancer xenografts[115]. Similarly, cancer cell membranes have been used to bestow homotypic targeting properties to PLGA nanoparticle cores loaded with indocyanine green[116]. In a unique approach, T cell membranes were metabolically labelled with azide groups and used to coat a dye-loaded PLGA core[117]. Prior to in vivo administration of this nanoformulation, tumours in mouse models were modified to display bicyclo[6.1.0]nonyne groups, which served as artificial receptors capable of reacting with the azides without noticeable adverse effects on the general health of mice. Hybrid membranes from RBCs and cancer cells have been used to coat doxorubicin-loaded hollow copper sulfide nanoparticles, conferring both an improved circulation half-life associated with RBCs and the tumour-targeting properties of cancer cells[118]. Finally, bacterial membrane-coated gold nanoparticles have been developed and designed to aggregate via hydrophobic interactions after being taken up by phagocytic immune cells in vivo, with the cells subsequently able to target tumours based on inflammatory cues[119].

In terms of PDT, CNPs have demonstrated considerable utility for the tumour-specific delivery of photosensitizers. A common theme has been to combine the delivery of a photosensitizing agent with supplemental functionality in order to augment therapeutic efficacy. In an early example of this type of approach, cancer cell membranes were used to coat a MOF-based platform, PCN-224, containing the photosensitizer tetrakis(4-carboxyphenyl)porphyrin[120]. The CNPs were also loaded with glucose oxidase for starvation therapy and catalase to facilitate the production of oxygen from hydrogen peroxide for enhanced PDT, which requires sufficient oxygen levels to generate enough free radicals to kill target cells. In another example, a catalytically active manganese oxide core was incorporated alongside glucose oxidase and the photosensitizer chlorine e6 prior to RBC membrane coating[121]. This platform was able to self-supply H^+, enabling the accelerated generation of oxygen radicals. Similarly, cancer cell membrane-coated gold–rhodium core–shell nanoparticles have been reported to have catalase-like activity, facilitating the generation of oxygen, thus reducing tumour hypoxia and increasing the PDT activity of an encapsulated indocyanine green payload[122]. Mesoporous copper–manganese silicate nanospheres camouflaged with cancer cell membranes have been shown to facilitate localized oxygen production and glutathione depletion, both of which enhanced the therapeutic activity of singlet oxygen radicals generated upon light irradiation both in vitro and in vivo[123]. A unique nanobullet structure with a disulfide-containing mesoporous organosilica body and a magnetic head has also been coated with cancer cell membranes for homotypic binding[124]. The photosensitizer chlorine e6 was loaded within the body of the nanobullet and could be released in response to glutathione. Upon irradiation, the generation of reactive oxygen species combined with hyperthermia promoted immunogenic cell death that could be further amplified using systemically administered anti-CTLA4 antibodies. In another example of the ability of a cancer-mimicking CNP to engage in PDT, PCN-224 MOFs were loaded with the VEGFR2 inhibitor apatinib for its anti-angiogenic effects and were further functionalized by the addition of a layer of manganese oxide to scavenge glutathione[125].

Immunotherapy

As a result of the understanding of cancer as a disease with an important immunological component[44,45], a great deal of emphasis has been placed on manipulating the immune system to better elicit antitumour

Table 3 | Examples of immune cell membrane-coated nanoparticles

Core material	Encapsulated payloads	Cell type	Surface functionalizations	Application notes	Ref.
Liposome	Emtansine	Macrophage	–	Metastatic tumour-targeted delivery	100
PEGylated poly(β-amino ester) with CSKC peptide	Paclitaxel	Macrophage	–	Tumour-targeted, environmentally responsive delivery	101
MOF (ZIF-8)	Anti-indoleamine 2,3-dioxygenase-1 siRNA; mitoxantrone	Macrophage	–	Local immune stimulation	130
PLGA	Carfilzomib	Neutrophil	–	Metastatic tumour-targeted delivery and circulating tumour cell depletion	102
MOF (ZIF-8)	Glucose oxidase; chloroperoxidase	Neutrophil	–	Inflammation-targeted, hypochlorous acid-mediated tumour cell killing	103
PLGA	4,4′,4″,4‴-(Porphine-5,10,15,20-tetrayl) tetrakis(benzoic acid)	Natural killer cell	–	Tumour-targeted photodynamic therapy and M1 macrophage polarization	129
Iron oxide nanocluster	–	Macrophage	SIINFEKL-loaded MHC I; anti-CD28 antibody	Ex vivo T cell expansion and magnetically guided tumour delivery	149
Iron oxide nanocluster	–	Macrophage	SB505124; anti-PD-1 antibody	Magnetically guided immune stimulation and ferroptosis	128
PLGA	Imiquimod	Dendritic cell	Anti-CD3 antibody; naturally presented tumour antigens; upregulated co-stimulatory markers	Local immune stimulation and T cell-targeted direct tumour antigen presentation	151
Crosslinked bovine serum albumin	ORY-1001	T cell	PD-1; macrolittin 70	Tumour-targeted immune stimulation	133

MHC I, major histocompatibility complex class I; MOF, metal–organic framework; PEG, polyethylene glycol; PLGA, poly(lactic-co-glycolic acid); siRNA, small interfering RNA; ZIF, zeolitic imidazolate framework.

Table 4 | Examples of cancer cell membrane-coated nanoparticles

Core material	Encapsulated payloads	Surface functionalizations	Application notes	Ref.
Polycaprolactone	Paclitaxel	–	Homotypic tumour-targeted delivery	104
Iron oxide	Doxorubicin	–	Homotypic tumour-targeted delivery	105
Diselenide-bridged mesoporous silica	RNase A	–	Homotypic tumour-targeted, environmentally responsive delivery	106
Mesoporous organosilica	Doxorubicin	–	Homotypic tumour-targeted delivery and X-ray-triggered drug release	107
Mesoporous silica	Glucose oxidase	–	Homotypic tumour-targeted starvation	109
Porous rhodium-coated gold	Indocyanine green	–	Homotypic tumour-targeted photodynamic therapy	122
MOF (PCN-224)	Glucose oxidase; catalase	–	Homotypic tumour-targeted photodynamic therapy and starvation	120
Mesoporous copper–manganese silicate	–	–	Homotypic tumour-targeted photodynamic therapy and chemodynamic therapy	123
Manganese oxide-coated MOF (PCN-224)	Apatinib	–	Homotypic tumour-targeted photodynamic therapy and anti-angiogenesis	125
PLGA	CpG 1826	–	Tumour antigen delivery and immune stimulation	49
Black phosphorous quantum dot	–	–	Local antigen delivery and photothermal-assisted immune stimulation	50
PLGA	Indocyanine green	PEG	Homotypic tumour-targeted photothermal therapy	116
PLGA	–	CD80	Direct tumour antigen presentation	36
Iron oxide	–	SIRPα	Magnetically guided immune stimulation and M1 macrophage polarization	131
PLGA	Imiquimod	Mannose	Antigen-presenting cell-targeted tumour antigen delivery and stimulation	143
Gold–iron oxide	Anti-miR-21	Indocyanine green	Homotypic tumour-targeted delivery	108

MOF, metal–organic framework; PLGA, poly(lactic-co-glycolic acid); PEG, polyethylene glycol; SIRPα, signal regulatory protein-α.

responses. The initial success of immune-checkpoint inhibitors has demonstrated the feasibility and power of interventions that disinhibit the immune system for cancer treatment[126], and many types of immunotherapies are now being studied in clinical settings[127]. Along these lines, CNP platforms have demonstrated an ability to modulate the immune system in basic research settings. One general approach has been to utilize the unique properties of CNPs to provide immunostimulatory signals to the immune system. This immunostimulation has been accomplished by formulating RBC membrane-coated nanogels with a cytokine payload capable of synergizing with a co-loaded chemotherapy agent to promote more robust antitumour activity[94]. In another example, leukocyte membrane-coated nanoparticles were loaded with a small-molecule TGFβ inhibitor, and the membrane was further functionalized using click chemistry to conjugate an anti-PD-1 antibody to the CNP surface[128]. Instead of delivering exogenous immunomodulatory payloads, CNPs have been used to directly promote M1 macrophage polarization by leveraging proteins naturally presented via a natural killer cell membrane coating[129]. When combined with PDT, the platform was able to generate a robust immune response that prevented the growth of distant tumours in a mouse model of breast cancer. An alternative to stimulating antitumour immunity is to inhibit oncogene expression. As an example, siRNAs targeting indoleamine-pyrrole 2,3-dioxygenase have been delivered using macrophage membrane-coated nanoparticles as a means of overcoming immune evasion in mouse models of glioblastoma[130]. Genetic modification is a common method of generating membrane coatings with immunomodulatory functions. This approach has been used to develop CNPs expressing high-affinity signal regulatory protein-α (SIRPα) variants that do not activate downstream signalling but competitively inhibit CD47 (ref.[131]) or expressing PD-1 to abrogate the immunosuppressive effects of PD-L1 signalling[132–134]. Finally, platelet membrane-coated CNPs have been demonstrated to be a useful tool capable of facilitating the retention of the TLR agonist resiquimod following intratumoural injections[135]. When this strategy was used in mice bearing MC38 colorectal tumours, a curative effect was observed with resistance to subsequent rechallenge with injections of the same cell line.

Vaccines act by priming the immune system to respond to specific antigens and have been very successful in the prevention of various infectious diseases[136]. Over the past 15 years, vaccination against cancer in patients with active disease has been a topic of considerable research interest, and the first therapeutic formulation, sipuleucel-T, was approved by the FDA in 2010 (ref.[137]). However, the success of this and other vaccines has since been limited, largely owing to the technical difficulties associated with generating robust antitumour immunity in patients with advanced-stage tumours that often have only limited immunogenicity and a strongly immunosuppressive microenvironment[138]. Various CNP-based nanovaccines have been developed in an attempt to address this challenge[139]. To enhance the delivery of tumour antigen-functionalized nanoparticles, mannose-modified RBC membranes were used for the more specific delivery to dendritic cells via their mannose receptors[140]. In another study, RBC membranes were modified to display *N*-glycolylneuraminic acid, a tumour-associated carbohydrate antigen that is not naturally produced by humans but can be derived from dietary sources and that accumulates on cancer cells[141]. To overcome the limited immunogenicity of tumour antigens found naturally on cancer cell membranes, CNP nanovaccines have been developed using adjuvant-loaded nanoparticle cores[49] as well as nanomaterials that have inherently immunostimulatory properties[142]. Similar to RBC membranes, the membranes of cancer cells can also be functionalized with mannose to facilitate more effective delivery to antigen-presenting cells (APCs)[143]. Another approach designed to promote immunogenicity involves fusing cancer cell membranes with outer membrane vesicles derived from bacteria, which are naturally immunostimulatory[144]. To develop personalized vaccine formulations, researchers have fabricated CNPs using membrane material derived from surgically resected tumours[50]. A more generalized approach for prophylactic vaccination involves the use of induced pluripotent stem cell membranes, which contain antigens expressed by many cancer cells that are not found on differentiated adult cells[145].

Instead of providing the immune system with exogenous antigenic material, the goal of in situ vaccination is to stimulate immunity against endogenous antigens that are released as a result of treatment[146]. In one example, an immunostimulatory CNP was developed by coating a core consisting of a TLR agonist and an endosomal escape polymer with a bacteria-derived membrane[147]. The surface of the nanoformulation was further functionalized by the addition of maleimide groups, which were used to capture tumour antigens released following radiotherapy and deliver them to APCs. In another example, investigators utilized magnesium-based micromotors (small synthetic particles capable of autonomous movement) coated with a layer of bacterial membrane[35]. When injected intratumourally, the motors caused substantial physical disruption of the tumour structure, which synergized with the immunostimulatory coating to promote robust anticancer immunity in mouse models of colorectal cancer and melanoma.

Similar to vaccines, nanoscale artificial APCs (aAPCs) are capable of stimulating antigen-specific immune responses against tumours in mouse models[148]. However, instead of delivering unprocessed antigenic material, these platforms bypass the need for endogenous antigen uptake, processing and presentation by presenting tumour antigens directly to T cell precursors. As an example of a CNP-based aAPC, a magnetic core was coated with an azide-functionalized cell membrane followed by conjugation with peptide-loaded major histocompatibility complex class I (MHC I) molecules and anti-CD28 as a co-stimulatory signal[149]. The final formulation was used to expand antigen-specific T cells in vitro, which were subsequently infused into tumour-bearing mice. Instead of chemically conjugating pre-loaded MHC I and co-stimulatory factors to CNPs, later CNP platforms leveraged cell sources that present these components prior to membrane derivation. For example, dendritic cell membranes were fused with cancer cell membranes, thus providing the requisite signals for effective tumour antigen presentation[150]. The hybrid membrane was then coated onto a photosensitizer-loaded MOF core, which was used to induce immunogenic cell death via PDT. In another example, dendritic cells were incubated with tumour-derived antigens to facilitate their cross-presentation on MHC I followed by further stimulation using a cocktail of cytokines and lipopolysaccharides[151]. The membranes of these dendritic cells were subsequently used to coat an adjuvant-loaded PLGA core and further functionalized with anti-CD3 antibodies for T cell targeting. Instead of relying on membranes sourced from dendritic cells, cancer cells have been genetically engineered to express co-stimulatory factors, such as CD80, alongside endogenous MHC I to promote more effective T cell priming[36]. When the membranes from these engineered cancer cells were used to coat a nanoparticle core, the resulting aAPC formulation was effective at eliciting antitumour immunity in vivo and synergized effectively with immune-checkpoint inhibitors to control tumour growth in mouse models.

Future clinical translation

Over the past decade, cell membrane coating technology has become a thriving topic of research within the field of nanomedicine. As researchers continue to explore how the technology can be leveraged for biomedical applications, efforts to translate CNP platforms into the clinic

Table 5 | Miscellaneous examples of cell membrane-coated nanoparticles

Core material	Encapsulated payloads	Cell type	Surface functionalizations	Application notes	Ref.
Human serum albumin-stabilized perfluorotributylamine	Sinoporphyrin sodium	Epithelial cell	PD-1	Photodynamic therapy and immune stimulation	134
Gelatin nanogel	Doxorubicin	Stem cell	–	Tumour-targeted delivery	84
Poly(cyclopentadithiophene-*alt*-benzothiadiazole)	–	Fibroblast	–	Tumour-targeted photothermal therapy and photodynamic therapy	53
Hollow copper sulfide	Doxorubicin	RBC; cancer cell (hybrid)	–	Homotypic tumour-targeted delivery and photothermal therapy	118
MOF (PCN-224)	–	Cancer cell; dendritic cell (hybrid)	–	Homotypic tumour-targeted antigen delivery, immune stimulation and photodynamic therapy	150
PLGA	Indocyanine green	Cancer cell; bacteria (hybrid)	–	Local antigen delivery, photothermal therapy and immune stimulation	144
Gold with β-cyclodextrin or adamantane	–	Bacteria	–	Inflammation-targeted photothermal therapy	119
Titanium dioxide-coated magnesium Janus micromotor	–	Bacteria	–	Local tumour disruption and immune stimulation	35
PC7A	CpG 1826	Bacteria	Maleimide	Local antigen capture and immune stimulation	147

MOF, metal–organic framework; PLGA, poly(lactic-co-glycolic acid); RBC, red blood cell.

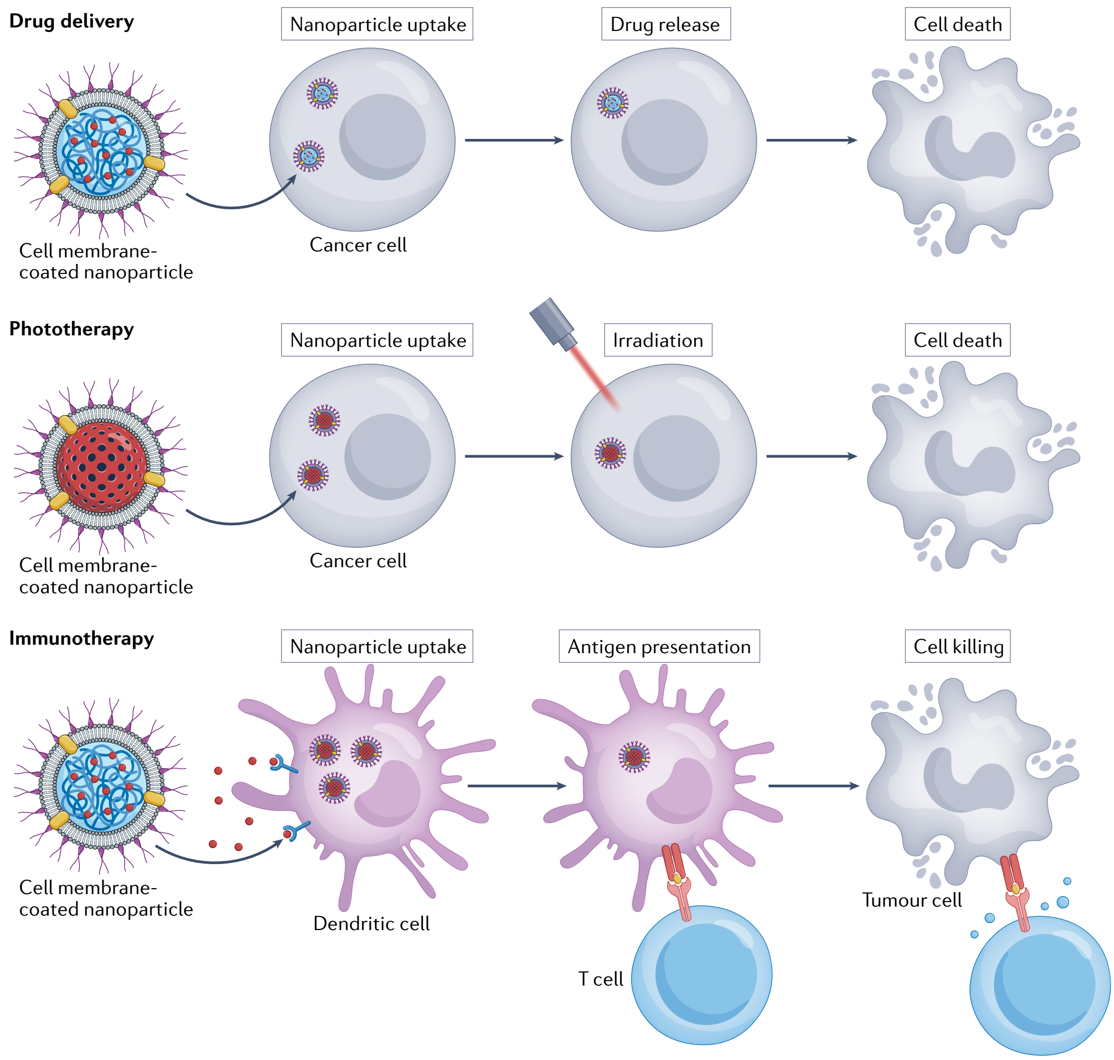

Fig. 5 | Anticancer applications of cell membrane-coated nanoparticles. Leveraging their tumour tropism, biocompatibility and immunomodulatory functions, cell membrane-coated nanoparticle platforms have been developed for different applications, with some successes observed in animal models. For cancer drug delivery, long-circulating and targeted formulations utilizing coatings derived from red blood cells, platelets and cancer cell membranes localize strongly to tumours, thus enhancing therapeutic efficacy while reducing the risk of adverse events. Likewise, for phototherapy applications, cell membrane-coated nanoparticles are excellent vehicles for the delivery of photothermal and photosensitizing agents specifically to tumours, thus enhancing their effects upon irradiation. For immunotherapies, cell membrane-coated nanoparticles can be used to deliver immunostimulatory agents, serve as antigen sources or directly interface with immune cells to promote antitumour immunity.

have commenced. These efforts have attracted the attention of at least one biotech company with a dedicated oncology pipeline[135] and at least one other company is applying this technology for the development of therapeutics for other indications, such as infectious diseases and inflammatory diseases, with substantial progress towards clinical trials. CNPs are a new class of biosynthetic hybrids; therefore, many factors need to be considered for their successful translation. Substantial input will be required from the FDA or equivalent agencies in order to determine the most appropriate pathways for regulatory approval. Because cell membranes are an integral component of CNPs, new drug candidates will probably be treated as biologics. In this regard, lessons can be learned from ongoing efforts to translate extracellular vesicle-based drug-delivery vehicles, especially with regards to overcoming issues related to CNP heterogeneity and batch-to-batch variability[152]. Even though various methods of CNP fabrication have been reported, additional work is needed to scale-up production towards clinically relevant quantities of CNPs while consistently meeting strict quality requirements to ensure both effectiveness and safety. As various metallic, inorganic and polymeric nanoparticles have already been approved for human use or are in late-stage clinical trials[153], most of the focus will probably be on the cell membrane derivation and coating processes. Fortunately, many existing industrial-scale techniques could be readily adapted for high-yield production[154,155]. Microfluidic devices could also be used to facilitate reliable and cost-effective scale-up while still providing the ability to accurately manipulate the membrane coating process[68]. To prevent any potentially deleterious effects associated with the administration of free cell membranes[156], large-scale purification methods will be required to separate the final CNP product from any unincorporated raw materials.

Regarding the cell membrane source, RBCs, platelets and primary immune cells are all readily available either from commercial vendors or from blood banks. Furthermore, most CNP formulations can be lyophilized for long-term storage[34], and thus the use of blood products that are just about to expire and are therefore not suited for direct clinical application should be feasible, which would help to reduce wastage of these precious resources. For cell types that require in vitro culture, such as cancer cells or immortalized immune cells, large bioreactors can be used for volumetric propagation[157]. For such cells, continuous genotyping and phenotyping as well as the establishment of master cell banks will help to ensure batch-to-batch consistency. All cell sources would need to be carefully screened for transmissible diseases. Steps will also be required to ensure immunocompatibility with patients, particularly as the majority of patients will probably receive CNPs manufactured from allogeneic source materials. RBCs and platelets are commonly infused in non-autologous settings[158], and any undesirable immunogenicity can be readily managed through the matching of donor and recipient blood types. However, greater care will be required for other cell types owing to the immunogenicity that can result from MHC mismatches[159]. One potential avenue for addressing this concern is to engineer universal cell lines in which potentially immunogenic antigens are genetically knocked out[160]; subsequent expression of the minimally polymorphic HLA-E could help prevent unwanted clearance by innate immune cells[161]. From a safety perspective, the non-living nature of CNPs should eliminate concerns regarding graft-versus-host disease, possibly justifying the use of mismatched formulations in short-term situations in which adaptive immunity is unlikely to affect CNP performance.

Analytical assays will need to be developed to ensure CNP quality at various stages of the production process. For cell membranes, the presence and integrity of key protein markers as well as the total protein and lipid content should be tested for every batch to ensure compliance with pre-established specifications. Likewise, the final CNP products should be evaluated for their potency, physicochemical properties, bioburden (an indication of microorganism contamination in a product), endotoxin levels and stability, among other factors. Certain membrane coating methods can be more disruptive than others; therefore, the impact of each method on membrane sidedness and integrity will need to be tested. The development of sophisticated label-free techniques to distinguish between uncoated nanoparticle cores, unbound membrane vesicles and CNPs would provide important information to support further optimization of the membrane coating process. All CNP fabrication steps would need to be conducted under aseptic conditions. Nonetheless, an effective strategy for post-synthesis sterilization can serve as a backstop to minimize the potential effects of bacterial or viral contamination. Overall, many considerations need to be addressed before CNPs can be deemed ready for widespread clinical adoption, and a concerted effort by scientists and engineers working in both industry and academia will help to make this a reality.

Conclusions

In this Review, we have provided a detailed overview of the development and application of CNPs in oncology. CNP technology leverages the unique bio-interfacing capabilities of cell membranes as a means to augment the performance of traditional nanoparticle platforms. The type of membrane coating dictates CNP functionality, and specific source cells can be chosen depending on the desired application. Cell membranes can also be modified using various engineering approaches, thus providing additional flexibility to create custom-tailored formulations. With regards to cancer treatment, CNPs for drug delivery, phototherapy and immunotherapy have been extensively studied in preclinical models. Further efforts to elucidate the relevance of specific features to CNP performance in biological environments will enable researchers to purposefully design new platforms with enhanced effectiveness. Likewise, an improved understanding of the biophysics dictating the membrane coating process will result in better fabrication methods with tighter control over CNP properties. Considerable collaboration between industry, academia and government agencies will be required to successfully bring CNP technology into the clinic. To better facilitate this clinical translation, a premium will be placed on simple and elegant platforms that can be easily adapted for streamlined large-scale production. Ultimately, the outlook is bright as continued research on CNP technology will undoubtedly lead to more effective cancer treatments and improved patient care.

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References

1. Gangadhar, T. C. & Vonderheide, R. H. Mitigating the toxic effects of anticancer immunotherapy. *Nat. Rev. Clin. Oncol.* **11**, 91–99 (2014).
2. Bower, J. E. Cancer-related fatigue—mechanisms, risk factors, and treatments. *Nat. Rev. Clin. Oncol.* **11**, 597–609 (2014).
3. Stone, J. B. & DeAngelis, L. M. Cancer-treatment-induced neurotoxicity — focus on newer treatments. *Nat. Rev. Clin. Oncol.* **13**, 92–105 (2016).
4. Holohan, C., Van Schaeybroeck, S., Longley, D. B. & Johnston, P. G. Cancer drug resistance: an evolving paradigm. *Nat. Rev. Cancer* **13**, 714–726 (2013).
5. Vasan, N., Baselga, J. & Hyman, D. M. A view on drug resistance in cancer. *Nature* **575**, 299–309 (2019).
6. Drago, J. Z., Modi, S. & Chandarlapaty, S. Unlocking the potential of antibody-drug conjugates for cancer therapy. *Nat. Rev. Clin. Oncol.* **18**, 327–344 (2021).
7. Llovet, J. M., Montal, R., Sia, D. & Finn, R. S. Molecular therapies and precision medicine for hepatocellular carcinoma. *Nat. Rev. Clin. Oncol.* **15**, 599–616 (2018).
8. Davis, M. E., Chen, Z. G. & Shin, D. M. Nanoparticle therapeutics: an emerging treatment modality for cancer. *Nat. Rev. Drug Discov.* **7**, 771–782 (2008).
9. Wilhelm, S. et al. Analysis of nanoparticle delivery to tumours. *Nat. Rev. Mater.* **1**, 16014 (2016).
10. Peer, D. et al. Nanocarriers as an emerging platform for cancer therapy. *Nat. Nanotechnol.* **2**, 751–760 (2007).
11. Rosenblum, D., Joshi, N., Tao, W., Karp, J. M. & Peer, D. Progress and challenges towards targeted delivery of cancer therapeutics. *Nat. Commun.* **9**, 1410 (2018).
12. Mitchell, M. J. et al. Engineering precision nanoparticles for drug delivery. *Nat. Rev. Drug Discov.* **20**, 101–124 (2021).
13. Patra, J. K. et al. Nano based drug delivery systems: recent developments and future prospects. *J. Nanobiotechnol.* **16**, 71 (2018).
14. Barenholz, Y. Doxil® — the first FDA-approved nano-drug: lessons learned. *J. Control. Rel.* **160**, 117–134 (2012).
15. Yardley, D. A. *nab*-Paclitaxel mechanisms of action and delivery. *J. Control. Rel.* **170**, 365–372 (2013).
16. Lancet, J. E. et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. *J. Clin. Oncol.* **36**, 2684–2692 (2018).
17. Shi, J., Kantoff, P. W., Wooster, R. & Farokhzad, O. C. Cancer nanomedicine: progress, challenges and opportunities. *Nat. Rev. Cancer* **17**, 20–37 (2017).
18. Suk, J. S., Xu, Q. G., Kim, N., Hanes, J. & Ensign, L. M. PEGylation as a strategy for improving nanoparticle-based drug and gene delivery. *Adv. Drug Deliv. Rev.* **99**, 28–51 (2016).
19. Abu Lila, A. S., Kiwada, H. & Ishida, T. The accelerated blood clearance (ABC) phenomenon: clinical challenge and approaches to manage. *J. Control. Rel.* **172**, 38–47 (2013).
20. Torchilin, V. Tumor delivery of macromolecular drugs based on the EPR effect. *Adv. Drug Deliv. Rev.* **63**, 131–135 (2011).
21. Wu, C. H., Liu, I. J., Lu, R. M. & Wu, H. C. Advancement and applications of peptide phage display technology in biomedical science. *J. Biomed. Sci.* **23**, 8 (2016).
22. Little, M., Kipriyanov, S. M., Le Gall, F. & Moldenhauer, G. Of mice and men: hybridoma and recombinant antibodies. *Immunol. Today* **21**, 364–370 (2000).

23. Darmostuk, M., Rimpelova, S., Gbelcova, H. & Ruml, T. Current approaches in SELEX: an update to aptamer selection technology. *Biotechnol. Adv.* **33**, 1141–1161 (2015).
24. Yoo, J. W., Irvine, D. J., Discher, D. E. & Mitragotri, S. Bio-inspired, bioengineered and biomimetic drug delivery carriers. *Nat. Rev. Drug Discov.* **10**, 521–535 (2011).
25. Fang, R. H., Kroll, A. V., Gao, W. & Zhang, L. Cell membrane coating nanotechnology. *Adv. Mater.* **30**, 1706759 (2018).
26. Fang, R. H., Jiang, Y., Fang, J. C. & Zhang, L. Cell membrane-derived nanomaterials for biomedical applications. *Biomaterials* **128**, 69–83 (2017).
27. Molinaro, R. et al. Biomimetic proteolipid vesicles for targeting inflamed tissues. *Nat. Mater.* **15**, 1037–1046 (2016).
28. Toledano Furman, N. E. et al. Reconstructed stem cell nanoghosts: a natural tumor targeting platform. *Nano Lett.* **13**, 3248–3255 (2013).
29. Jiang, Y., Chekuri, S., Fang, R. H. & Zhang, L. Engineering biological interactions on the nanoscale. *Curr. Opin. Biotechnol.* **58**, 1–8 (2019).
30. Krishnan, N., Fang, R. H. & Zhang, L. Engineering of stimuli-responsive self-assembled biomimetic nanoparticles. *Adv. Drug Deliv. Rev.* **179**, 114006 (2021).
31. Oldenborg, P. A. et al. Role of CD47 as a marker of self on red blood cells. *Science* **288**, 2051–2054 (2000).
32. Hu, C.-M. J. et al. 'Marker-of-self' functionalization of nanoscale particles through a top-down cellular membrane coating approach. *Nanoscale* **5**, 2664–2668 (2013).
33. Fang, R. H. et al. Cancer cell membrane-coated nanoparticles for anticancer vaccination and drug delivery. *Nano Lett.* **14**, 2181–2188 (2014).
34. Hu, C. M. et al. Nanoparticle biointerfacing by platelet membrane cloaking. *Nature* **526**, 118–121 (2015).
35. Zhou, J. et al. Physical disruption of solid tumors by immunostimulatory microrobots enhances antitumor immunity. *Adv. Mater.* **33**, 2103505 (2021).
36. Jiang, Y. et al. Engineered cell-membrane-coated nanoparticles directly present tumor antigens to promote anticancer immunity. *Adv. Mater.* **32**, 2001808 (2020).
37. Hu, C. M. et al. Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform. *Proc. Natl Acad. Sci. USA* **108**, 10980–10985 (2011).
38. Noris, M. & Remuzzi, G. Overview of complement activation and regulation. *Semin. Nephrol.* **33**, 479–492 (2013).
39. Fang, R. H., Hu, C. M. J. & Zhang, L. F. Nanoparticles disguised as red blood cells to evade the immune system. *Expert Opin. Biol. Ther.* **12**, 385–389 (2012).
40. Rao, L. et al. Red blood cell membrane as a biomimetic nanocoating for prolonged circulation time and reduced accelerated blood clearance. *Small* **11**, 6225–6236 (2015).
41. Olsson, M., Bruhns, P., Frazier, W. A., Ravetch, J. V. & Oldenborg, P. A. Platelet homeostasis is regulated by platelet expression of CD47 under normal conditions and in passive immune thrombocytopenia. *Blood* **105**, 3577–3582 (2005).
42. Gay, L. J. & Felding-Habermann, B. Contribution of platelets to tumour metastasis. *Nat. Rev. Cancer* **11**, 123–134 (2011).
43. Schlesinger, M. Role of platelets and platelet receptors in cancer metastasis. *J. Hematol. Oncol.* **11**, 125 (2018).
44. Zamarron, B. F. & Chen, W. J. Dual roles of immune cells and their factors in cancer development and progression. *Int. J. Biol. Sci.* **7**, 651–658 (2011).
45. Gonzalez, H., Hagerling, C. & Werb, Z. Roles of the immune system in cancer: from tumor initiation to metastatic progression. *Genes Dev.* **32**, 1267–1284 (2018).
46. Harris, J. C., Scully, M. A. & Day, E. S. Cancer cell membrane-coated nanoparticles for cancer management. *Cancers* **11**, 1836 (2019).
47. Rao, L. et al. Cancer cell membrane-coated upconversion nanoprobes for highly specific tumor imaging. *Adv. Mater.* **28**, 3460–3466 (2016).
48. Glinsky, V. V. et al. Intravascular metastatic cancer cell homotypic aggregation at the sites of primary attachment to the endothelium. *Cancer Res.* **63**, 3805–3811 (2003).
49. Kroll, A. V. et al. Nanoparticulate delivery of cancer cell membrane elicits multiantigenic antitumor immunity. *Adv. Mater.* **29**, 1703969 (2017).
50. Ye, X. et al. Surgical tumor-derived personalized photothermal vaccine formulation for cancer immunotherapy. *ACS Nano* **13**, 2956–2968 (2019).
51. Wang, M. et al. Recent advances in mesenchymal stem cell membrane-coated nanoparticles for enhanced drug delivery. *Biomater. Sci.* **9**, 1088–1103 (2021).
52. Zhang, W. & Huang, X. Stem cell membrane-camouflaged targeted delivery system in tumor. *Mater. Today Bio* **16**, 100377 (2022).
53. Li, J. et al. Cell membrane coated semiconducting polymer nanoparticles for enhanced multimodal cancer phototheranostics. *ACS Nano* **12**, 8520–8530 (2018).
54. Krishnan, N. et al. Bacterial membrane vesicles for vaccine applications. *Adv. Drug Deliv. Rev.* **185**, 114294 (2022).
55. Gao, W. W. et al. Modulating antibacterial immunity via bacterial membrane-coated nanoparticles. *Nano Lett.* **15**, 1403–1409 (2015).
56. Mogensen, T. H. Pathogen recognition and inflammatory signaling in innate immune defenses. *Clin. Microbiol. Rev.* **22**, 240–273 (2009).
57. Zemek, R. M. et al. Sensitizing the tumor microenvironment to immune checkpoint therapy. *Front. Immunol.* **11**, 223 (2020).
58. Drake, C. G. Combination immunotherapy approaches. *Ann. Oncol.* **23**, viii41–viii46 (2012).
59. McCarthy, E. F. The toxins of William B. Coley and the treatment of bone and soft-tissue sarcomas. *Iowa Orthop. J.* **26**, 154–158 (2006).
60. Holay, M. et al. Bacteria-inspired nanomedicine. *ACS Appl. Bio Mater.* **4**, 3830–3848 (2021).
61. Zariri, A. et al. Meningococcal outer membrane vesicle composition-dependent activation of the innate immune response. *Infect. Immun.* **84**, 3024–3033 (2016).
62. Moore, G. E. & Ulrich, K. Suspension cultures of mammalian cells: a review. *J. Surg. Res.* **5**, 270–282 (1965).
63. Baek, E. J. et al. In vitro clinical-grade generation of red blood cells from human umbilical cord blood CD34[+] cells. *Transfusion* **48**, 2235–2245 (2008).
64. Ito, Y. et al. Turbulence activates platelet biogenesis to enable clinical scale *ex vivo* production. *Cell* **174**, 636–648.e18 (2018).
65. van Niel, G., D'Angelo, G. & Raposo, G. Shedding light on the cell biology of extracellular vesicles. *Nat. Rev. Mol. Cell Biol.* **19**, 213–228 (2018).
66. Holay, M. et al. Organotropic targeting of biomimetic nanoparticles to treat lung disease. *Bioconjug. Chem.* **33**, 586–593 (2022).
67. Copp, J. A. et al. Clearance of pathological antibodies using biomimetic nanoparticles. *Proc. Natl Acad. Sci. USA* **111**, 13481–13486 (2014).
68. Rao, L. et al. Microfluidic electroporation-facilitated synthesis of erythrocyte membrane-coated magnetic nanoparticles for enhanced imaging-guided cancer therapy. *ACS Nano* **11**, 3496–3505 (2017).
69. Sherwood, J. et al. Cell-membrane coated iron oxide nanoparticles for isolation and specific identification of drug leads from complex matrices. *Nanoscale* **11**, 6352–6359 (2019).
70. Luk, B. T. et al. Interfacial interactions between natural RBC membranes and synthetic polymeric nanoparticles. *Nanoscale* **6**, 2730–2737 (2014).
71. Gao, W. et al. Surface functionalization of gold nanoparticles with red blood cell membranes. *Adv. Mater.* **25**, 3549–3553 (2013).
72. Fang, R. H. et al. Lipid-insertion enables targeting functionalization of erythrocyte membrane-cloaked nanoparticles. *Nanoscale* **5**, 8884–8888 (2013).
73. Dehaini, D. et al. Erythrocyte–platelet hybrid membrane coating for enhanced nanoparticle functionalization. *Adv. Mater.* **29**, 1606209 (2017).
74. Park, J. H. et al. Genetically engineered cell membrane-coated nanoparticles for targeted delivery of dexamethasone to inflamed lungs. *Sci. Adv.* **7**, eabf7820 (2021).
75. Park, J. H. et al. Virus-mimicking cell membrane-coated nanoparticles for cytosolic delivery of mRNA. *Angew. Chem. Int. Ed. Engl.* **61**, e202113671 (2022).
76. Ai, X. et al. Surface glycan modification of cellular nanosponges to promote SARS-CoV-2 inhibition. *J. Am. Chem. Soc.* **143**, 17615–17621 (2021).
77. Aryal, S. et al. Erythrocyte membrane-cloaked polymeric nanoparticles for controlled drug loading and release. *Nanomedicine* **8**, 1271–1280 (2013).
78. Fu, Q. et al. Programmed co-delivery of paclitaxel and doxorubicin boosted by camouflaging with erythrocyte membrane. *Nanoscale* **7**, 4020–4030 (2015).
79. Luk, B. T. et al. Safe and immunocompatible nanocarriers cloaked in RBC membranes for drug delivery to treat solid tumors. *Theranostics* **6**, 1004–1011 (2016).
80. Su, J. et al. Enhanced blood suspensibility and laser-activated tumor-specific drug release of theranostic mesoporous silica nanoparticles by functionalizing with erythrocyte membranes. *Theranostics* **7**, 523–537 (2017).
81. Zhang, L. et al. Erythrocyte membrane cloaked metal–organic framework nanoparticle as biomimetic nanoreactor for starvation-activated colon cancer therapy. *ACS Nano* **12**, 10201–10211 (2018).
82. Zhuang, J. et al. Targeted gene silencing in vivo by platelet membrane–coated metal-organic framework nanoparticles. *Sci. Adv.* **6**, eaaz6108 (2020).
83. Zhang, Y. et al. Erythrocyte membrane-coated nanogel for combinatorial antivirulence and responsive antimicrobial delivery against *Staphylococcus aureus* infection. *J. Control. Rel.* **263**, 185–191 (2017).
84. Gao, C. et al. Stem cell membrane-coated nanogels for highly efficient in vivo tumor targeted drug delivery. *Small* **12**, 4056–4062 (2016).
85. Zhang, X. et al. Remote loading of small-molecule therapeutics into cholesterol-enriched cell-membrane-derived vesicles. *Angew. Chem. Int. Ed. Engl.* **56**, 14075–14079 (2017).
86. Zou, M. Z. et al. Artificial natural killer cells for specific tumor inhibition and renegade macrophage re-education. *Adv. Mater.* **31**, 1904495 (2019).
87. Zhuang, J. et al. Biomimetic nanoemulsions for oxygen delivery in vivo. *Adv. Mater.* **30**, 1804693 (2018).
88. Miao, Y. et al. Cell membrane-camouflaged nanocarriers with biomimetic deformability of erythrocytes for ultralong circulation and enhanced cancer therapy. *ACS Nano* **16**, 6527–6540 (2022).
89. Zou, Y. et al. Effective and targeted human orthotopic glioblastoma xenograft therapy via a multifunctional biomimetic nanomedicine. *Adv. Mater.* **30**, 1803717 (2018).
90. Chai, Z. et al. Ligand-modified cell membrane enables the targeted delivery of drug nanocrystals to glioma. *ACS Nano* **13**, 5591–5601 (2019).
91. Zhai, Y. et al. Traceable bioinspired nanoparticle for the treatment of metastatic breast cancer via NIR-trigged intracellular delivery of methylene blue and cisplatin. *Adv. Mater.* **30**, 1802378 (2018).
92. Sung, S. Y. et al. Graphene quantum dots-mediated theranostic penetrative delivery of drug and photolytics in deep tumors by targeted biomimetic nanosponges. *Nano Lett.* **19**, 69–81 (2019).
93. Gao, L. et al. Erythrocyte membrane-wrapped pH sensitive polymeric nanoparticles for non-small cell lung cancer therapy. *Bioconjug. Chem.* **28**, 2591–2598 (2017).
94. Song, Q. et al. Tumor microenvironment responsive nanogel for the combinatorial antitumor effect of chemotherapy and immunotherapy. *Nano Lett.* **17**, 6366–6375 (2017).
95. Hu, Q. et al. Anticancer platelet-mimicking nanovehicles. *Adv. Mater.* **27**, 7043–7050 (2015).

96. Li, J. et al. Targeted drug delivery to circulating tumor cells via platelet membrane-functionalized particles. *Biomaterials* **76**, 52–65 (2016).
97. Hu, Q. et al. Engineered nanoplatelets for enhanced treatment of multiple myeloma and thrombus. *Adv. Mater.* **28**, 9573–9580 (2016).
98. Zhang, M. et al. Platelet-mimicking biotaxis targeting vasculature-disrupted tumors for cascade amplification of hypoxia-sensitive therapy. *ACS Nano* **13**, 14230–14240 (2019).
99. Ying, M. et al. Remote-loaded platelet vesicles for disease-targeted delivery of therapeutics. *Adv. Funct. Mater.* **28**, 1801032 (2018).
100. Cao, H. Q. et al. Liposomes coated with isolated macrophage membrane can target lung metastasis of breast cancer. *ACS Nano* **10**, 7738–7748 (2016).
101. Zhang, Y. et al. Macrophage-membrane-coated nanoparticles for tumor-targeted chemotherapy. *Nano Lett.* **18**, 1908–1915 (2018).
102. Kang, T. et al. Nanoparticles coated with neutrophil membranes can effectively treat cancer metastasis. *ACS Nano* **11**, 1397–1411 (2017).
103. Zhang, C. et al. Artificial super neutrophils for inflammation targeting and HClO generation against tumors and infections. *Adv. Mater.* **31**, 1901179 (2019).
104. Sun, H. et al. Cancer-cell-biomimetic nanoparticles for targeted therapy of homotypic tumors. *Adv. Mater.* **28**, 9581–9588 (2016).
105. Zhu, J. Y. et al. Preferential cancer cell self-recognition and tumor self-targeting by coating nanoparticles with homotypic cancer cell membranes. *Nano Lett.* **16**, 5895–5901 (2016).
106. Shao, D. et al. Bioinspired diselenide-bridged mesoporous silica nanoparticles for dual-responsive protein delivery. *Adv. Mater.* **30**, 1801198 (2018).
107. Shao, D. et al. Biomimetic diselenide-bridged mesoporous organosilica nanoparticles as an X-ray-responsive biodegradable carrier for chemo-immunotherapy. *Adv. Mater.* **32**, 2004385 (2020).
108. Bose, R. J. C. et al. Tumor cell-derived extracellular vesicle-coated nanocarriers: an efficient theranostic platform for the cancer-specific delivery of anti-miR-21 and imaging agents. *ACS Nano* **12**, 10817–10832 (2018).
109. Xie, W. et al. Cancer cell membrane camouflaged nanoparticles to realize starvation therapy together with checkpoint blockades for enhancing cancer therapy. *ACS Nano* **13**, 2849–2857 (2019).
110. Chitgupi, U., Qin, Y. & Lovell, J. F. Targeted nanomaterials for phototherapy. *Nanotheranostics* **1**, 38–58 (2017).
111. Li, X., Lovell, J. F., Yoon, J. & Chen, X. Clinical development and potential of photothermal and photodynamic therapies for cancer. *Nat. Rev. Clin. Oncol.* **17**, 657–674 (2020).
112. Piao, J. G. et al. Erythrocyte membrane is an alternative coating to polyethylene glycol for prolonging the circulation lifetime of gold nanocages for photothermal therapy. *ACS Nano* **8**, 10414–10425 (2014).
113. Ren, X. et al. Red blood cell membrane camouflaged magnetic nanoclusters for imaging-guided photothermal therapy. *Biomaterials* **92**, 13–24 (2016).
114. Liu, Z. et al. Fabrication of red blood cell membrane-camouflaged $Cu_{2-x}Se$ nanoparticles for phototherapy in the second near-infrared window. *Chem. Commun.* **55**, 6523–6526 (2019).
115. Rao, L. et al. Antitumor platelet-mimicking magnetic nanoparticles. *Adv. Funct. Mater.* **27**, 1604774 (2017).
116. Chen, Z. et al. Cancer cell membrane-biomimetic nanoparticles for homologous-targeting dual-modal imaging and photothermal therapy. *ACS Nano* **10**, 10049–10057 (2016).
117. Han, Y. et al. T cell membrane mimicking nanoparticles with bioorthogonal targeting and immune recognition for enhanced photothermal therapy. *Adv. Sci.* **6**, 1900251 (2019).
118. Wang, D. et al. Erythrocyte–cancer hybrid membrane camouflaged hollow copper sulfide nanoparticles for prolonged circulation life and homotypic-targeting photothermal/chemotherapy of melanoma. *ACS Nano* **12**, 5241–5252 (2018).
119. Gao, C. et al. In vivo hitchhiking of immune cells by intracellular self-assembly of bacteria-mimetic nanomedicine for targeted therapy of melanoma. *Sci. Adv.* **8**, eabn1805 (2022).
120. Li, S. Y. et al. Cancer cell membrane camouflaged cascade bioreactor for cancer targeted starvation and photodynamic therapy. *ACS Nano* **11**, 7006–7018 (2017).
121. Yang, X. et al. Biomimetic hybrid nanozymes with self-supplied H^+ and accelerated O_2 generation for enhanced starvation and photodynamic therapy against hypoxic tumors. *Nano Lett.* **19**, 4334–4342 (2019).
122. Wang, J. P. et al. A porous Au@Rh bimetallic core–shell nanostructure as an H_2O_2-driven oxygenerator to alleviate tumor hypoxia for simultaneous bimodal imaging and enhanced photodynamic therapy. *Adv. Mater.* **32**, 2001862 (2020).
123. Liu, C. et al. Biodegradable biomimic copper/manganese silicate nanospheres for chemodynamic/photodynamic synergistic therapy with simultaneous glutathione depletion and hypoxia relief. *ACS Nano* **13**, 4267–4277 (2019).
124. Wang, Z. et al. Janus nanobullets combine photodynamic therapy and magnetic hyperthermia to potentiate synergetic anti-metastatic immunotherapy. *Adv. Sci.* **6**, 1901690 (2019).
125. Min, H. et al. Biomimetic metal–organic framework nanoparticles for cooperative combination of antiangiogenesis and photodynamic therapy for enhanced efficacy. *Adv. Mater.* **31**, 1808200 (2019).
126. Ribas, A. & Wolchok, J. D. Cancer immunotherapy using checkpoint blockade. *Science* **359**, 1350–1355 (2018).
127. Esfahani, K. et al. A review of cancer immunotherapy: from the past, to the present, to the future. *Curr. Oncol.* **27**, S87–S97 (2020).
128. Zhang, F. et al. Engineering magnetosomes for ferroptosis/immunomodulation synergism in cancer. *ACS Nano* **13**, 5662–5673 (2019).
129. Deng, G. et al. Cell-membrane immunotherapy based on natural killer cell membrane coated nanoparticles for the effective inhibition of primary and abscopal tumor growth. *ACS Nano* **12**, 12096–12108 (2018).
130. Zhang, J. et al. Immunostimulant hydrogel for the inhibition of malignant glioma relapse post-resection. *Nat. Nanotechnol.* **16**, 538–548 (2021).
131. Rao, L. et al. Activating macrophage-mediated cancer immunotherapy by genetically edited nanoparticles. *Adv. Mater.* **32**, 2004853 (2020).
132. Zhang, X. et al. PD-1 blockade cellular vesicles for cancer immunotherapy. *Adv. Mater.* **30**, 1707112 (2018).
133. Zhai, Y. et al. T lymphocyte membrane-decorated epigenetic nanoinducer of interferons for cancer immunotherapy. *Nat. Nanotechnol.* **16**, 1271–1280 (2021).
134. Zhang, Y., Liao, Y., Tang, Q., Lin, J. & Huang, P. Biomimetic nanoemulsion for synergistic photodynamic-immunotherapy against hypoxic breast tumor. *Angew. Chem. Int. Ed. Engl.* **60**, 10647–10653 (2021).
135. Bahmani, B. et al. Intratumoral immunotherapy using platelet-cloaked nanoparticles enhances antitumor immunity in solid tumors. *Nat. Commun.* **12**, 1999 (2021).
136. Pollard, A. J. & Bijker, E. M. A guide to vaccinology: from basic principles to new developments. *Nat. Rev. Immunol.* **21**, 83–100 (2021).
137. Higano, C. S. et al. Sipuleucel-T. *Nat. Rev. Drug Discov.* **9**, 513–514 (2010).
138. van der Burg, S. H., Arens, R., Ossendorp, F., van Hall, T. & Melief, C. J. Vaccines for established cancer: overcoming the challenges posed by immune evasion. *Nat. Rev. Cancer* **16**, 219–233 (2016).
139. Zhou, J., Kroll, A. V., Holay, M., Fang, R. H. & Zhang, L. Biomimetic nanotechnology toward personalized vaccines. *Adv. Mater.* **32**, 1901255 (2020).
140. Guo, Y. Y. et al. Erythrocyte membrane-enveloped polymeric nanoparticles as nanovaccine for induction of antitumor immunity against melanoma. *ACS Nano* **9**, 6918–6933 (2015).
141. Reuven, E. M. et al. Biomimetic glyconanoparticle vaccine for cancer immunotherapy. *ACS Nano* **13**, 2936–2947 (2019).
142. Fontana, F. et al. Multistaged nanovaccines based on porous silicon@acetalated dextran@cancer cell membrane for cancer immunotherapy. *Adv. Mater.* **29**, 1603239 (2017).
143. Yang, R. et al. Cancer cell membrane-coated adjuvant nanoparticles with mannose modification for effective anticancer vaccination. *ACS Nano* **12**, 5121–5129 (2018).
144. Chen, Q. et al. A hybrid eukaryotic-prokaryotic nanoplatform with photothermal modality for enhanced antitumor vaccination. *Adv. Mater.* **32**, 1908185 (2020).
145. Zhai, Y. W. et al. A splenic-targeted versatile antigen courier: iPSC wrapped in coalescent erythrocyte-liposome as tumor nanovaccine. *Sci. Adv.* **7**, eabi6326 (2021).
146. Hammerich, L., Binder, A. & Brody, J. D. In situ vaccination: cancer immunotherapy both personalized and off-the-shelf. *Mol. Oncol.* **9**, 1966–1981 (2015).
147. Patel, R. B. et al. Development of an in situ cancer vaccine via combinational radiation and bacterial-membrane-coated nanoparticles. *Adv. Mater.* **31**, 1902626 (2019).
148. Eggermont, L. J., Paulis, L. E., Tel, J. & Figdor, C. G. Towards efficient cancer immunotherapy: advances in developing artificial antigen-presenting cells. *Trends Biotechnol.* **32**, 456–465 (2014).
149. Zhang, Q. B. et al. Biomimetic magnetosomes as versatile artificial antigen-presenting cells to potentiate T-cell-based anticancer therapy. *ACS Nano* **11**, 10724–10732 (2017).
150. Liu, W. L. et al. Expandable immunotherapeutic nanoplatforms engineered from cytomembranes of hybrid cells derived from cancer and dendritic cells. *Adv. Mater.* **31**, 1900499 (2019).
151. Xiao, P. et al. Engineering nanoscale artificial antigen-presenting cells by metabolic dendritic cell labeling to potentiate cancer immunotherapy. *Nano Lett.* **21**, 2094–2103 (2021).
152. Herrmann, I. K., Wood, M. J. A. & Fuhrmann, G. Extracellular vesicles as a next-generation drug delivery platform. *Nat. Nanotechnol.* **16**, 748–759 (2021).
153. Anselmo, A. C. & Mitragotri, S. Nanoparticles in the clinic: an update. *Bioeng. Transl. Med.* **4**, e10143 (2019).
154. Busatto, S. et al. Tangential flow filtration for highly efficient concentration of extracellular vesicles from large volumes of fluid. *Cells* **7**, 273 (2018).
155. Ganesan, P., Karthivashan, G., Park, S. Y., Kim, J. & Choi, D. K. Microfluidization trends in the development of nanodelivery systems and applications in chronic disease treatments. *Int. J. Nanomed.* **13**, 6109–6121 (2018).
156. Wortzel, I., Dror, S., Kenific, C. M. & Lyden, D. Exosome-mediated metastasis: communication from a distance. *Dev. Cell* **49**, 347–360 (2019).
157. Jensen, C. & Teng, Y. Is it time to start transitioning from 2D to 3D cell culture? *Front. Mol. Biosci.* **7**, 33 (2020).
158. Szczepiorkowski, Z. M. & Dunbar, N. M. Transfusion guidelines: when to transfuse. *Hematol. Am. Soc. Hematol. Educ. Program* **2013**, 638–644 (2013).
159. Shlomchik, W. D. Graft-versus-host disease. *Nat. Rev. Immunol.* **7**, 340–352 (2007).
160. Ren, J. et al. Multiplex genome editing to generate universal CAR T cells resistant to PD1 inhibition. *Clin. Cancer Res.* **23**, 2255–2266 (2017).
161. Gornalusse, G. G. et al. HLA-E-expressing pluripotent stem cells escape allogeneic responses and lysis by NK cells. *Nat. Biotechnol.* **35**, 765–772 (2017).

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