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Review

Biointerface engineering nanoplatforms for cancer-targeted drug delivery



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ABSTRACT

Over the past decade, nanoparticle-based therapeutic modalities have become promising strategies in cancer therapy. Selective delivery of anticancer drugs to the lesion sites is critical for elimination of the tumor and an improved prognosis. Innovative design and advanced biointerface engineering have promoted the development of various nanocarriers for optimized drug delivery. Keeping in mind the biological framework of the tumor microenvironment, biomembrane-camouflaged nanoplatforms have been a research focus, reflecting their superiority in cancer targeting. In this review, we summarize the development of various biomimetic cell membrane-camouflaged nanoplatforms for cancer-targeted drug delivery, which are classified according to the membranes from different cells. The challenges and opportunities of the advanced biointerface engineering drug delivery nanosystems in cancer therapy are discussed.

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1. Introduction

Cancer morbidity and mortality have risen globally in recent decades, with approximately 18.1 million new cancer diagnoses and 9.6 million cancer-related deaths occurring in 2018 [1]. Surgery remains the most effective method for cancer therapy. However, in cases of terminal

cancer, surgery is not always an option for many patients. Meanwhile, conventional treatments, such as chemotherapy, radiotherapy, and molecule targeted therapy, are insufficient. These conventional treatments also generate severe side effects that include hepatotoxicity, renal toxicity, myelosuppression, radiation-induced enteritis, and multidrug resistance, and so forth. Despite the many studies done, these therapeutic formulations remain mostly unchanged, and their

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drawbacks remain. Several alternative approaches for cancer therapy have emerged in recent decades. The most successful example of these is immunotherapy, which has been recommended in many current cancer treatment guidelines [2]. However, with its widespread clinical application, some problems have emerged. They include immunotherapy-associated side effects and relatively lower treatment efficiency [3–5]. Besides, a perplexing issue is the susceptibility of some, but not all, patients to immunotherapy. Another emerging therapeutic approach is phototherapy, which has become very popular in anticancer research and has been proved efficient in cancer suppression [6,7]. However, there are also limitations to phototherapy. For example, only superficial tumors can feasibly be treated using phototherapy. Moreover, the low efficiency of photothermal transition necessitates the further modification of conventional photosensitizers to allow phototherapy to be used more broadly.

With the progress in nanotechnology and increasing research efforts in nanomedicine, nanoparticle-based anti-neoplastic solutions are being considered a superior treatment option [8,9]. To improve anticancer efficiency, a variety of nanocarriers have been invented and rationally designed. These include micelles, liposomes, nanogels, nanocapsules, nanoemulsions, nanocomplexes, and other designs [10–22]. Some of these nanoformulations have been employed in clinical anticancer treatment [23–26]. Typically, various nanocarriers are administered as drug vehicles that function to deliver their payload to the tumor with various anticancer agents loaded in the nanocarriers or chemically conjugated to the surface [27–30]. Certain types of nanomedicines are also capable of inhibiting tumors due to their physical and chemical characteristics [27,31].

The primary therapeutic capability of the various types of nanomedicines relies on their local accumulation at the tumor site, where target specificity remains a challenge. The nonspecific distribution of nanocarriers in other major organs and healthy cells always blunts the therapeutic outcomes and causes severe systematic side effects. The goal of many ongoing types of research is to develop strategies that enhance the intratumor accumulation of various nanomedicines, either passively or actively.

Due to the abnormal leakage of tumor vessels and cacoethic lymphatic drainage, the enhanced permeability and retention (EPR) effect passively facilitates the local accumulation of nanoparticles at the targeted areas [32–34]. However, because most nanoparticle-based drug delivery systems are artificial, the recipient biological organisms enable the accurate and efficient identification of the “non-self” nanoparticles. These nanomaterials, therefore, are rapidly removed through the reticuloendothelial system [35,36]. Thus, proper modifications that increase biocompatibility and extend the circulation half-time enhance the EPR effect, thereby improving the passive accumulation of various nanoparticles. The use of poly(ethylene glycol) (PEG) to modify the biointerfaces of nanoparticles was once considered an effective means to increase the biocompatibility and circulation half-time of the nanoparticles. However, repeated administration of PEG-modified nanocarriers was demonstrated to stimulate the secretion of anti-PEG antibodies and induce immune responses against

PEGylated nanomedicines, in turn accelerating the premature clearance of anti-neoplastic agents from the body [37,38].

Another strategy that is being explored is the targeting strategy. Apart from the means of embellishing nanocarriers with biological ligands [39–43], or endowing them with internal/external stimuli-responsive properties [44–47], nanomedicine researchers have developed the cell membrane-engineered nanoplatfroms. Different cells have various and specific functions within biological microenvironments based on their intrinsic membrane proteins and saccharides. Thus, by coating nanoparticles with various cell membranes, the biomimetic strategy aims at disguising nanoparticles as different types of living cells. Accordingly, the membrane-enshrouded nanoparticles carry out the defined functions of the source cells to some extent, as depicted in Fig. 1. In living organisms, specific cells enable the immune escape and have a long circulation half-life while others communicate with tumor cells or biological microenvironment. The communication involves cell recognition, adhesion, and cytokine-induced recruitment, which is facilitated by the activities of membrane adhesion molecules or secreted cytokines [48,49]. Various aspects are summarized in Table 1. Based on the natural affinity between the source cells and tumor cells, the cell-mimetic nanocarriers tend to actively recognize and adhere to the tumor cells in a ligand-receptor manner. Some types of the cell-engineered nanoplatfroms are also recruited by the chemical signals of cytokines in the tumor microenvironment (TME), as the biological behavior of their source cells. Modifying the nanoparticles with such selective cell membranes drives the targeting.

Nowadays, the development of biomimetic membrane-camouflaged nanoplatfroms has become a hot area of research. Moreover, several research groups have been focusing on the membrane-camouflaged nanoplatfroms in cancer theranostics [50–52]. Based on the multiple research, we comprehensively summarized various biomimetic membrane-camouflaged nanoplatfroms that have been applied for cancer-targeted drug delivery. Apart from erythrocyte membrane-camouflaged nanoplatfrom, which is a passively targeted example, all the other researches in this review are actively targeted nanoformulations. The biological targeting mechanism of each type of cell membrane derivation is briefly described and discussed in each section. Relevant research examples we discuss are summarized in Table 2, and the diverse membrane extraction technologies and membrane coating procedures are attached in Table 3.

2. Types of cell-derived nanoplatfroms fabricated for cancer-targeted drug delivery

2.1. Erythrocyte membrane-camouflaged nanoplatfroms

Red blood cells (RBCs), also termed erythrocytes, are the most abundant cells in the blood circulation system. They are responsible for the gas exchange that occurs between the blood and all tissues or organs, including oxygen uptake and carbon dioxide dislodgement [53]. Erythrocytes can be functionally active for up to 120d, because of the presence

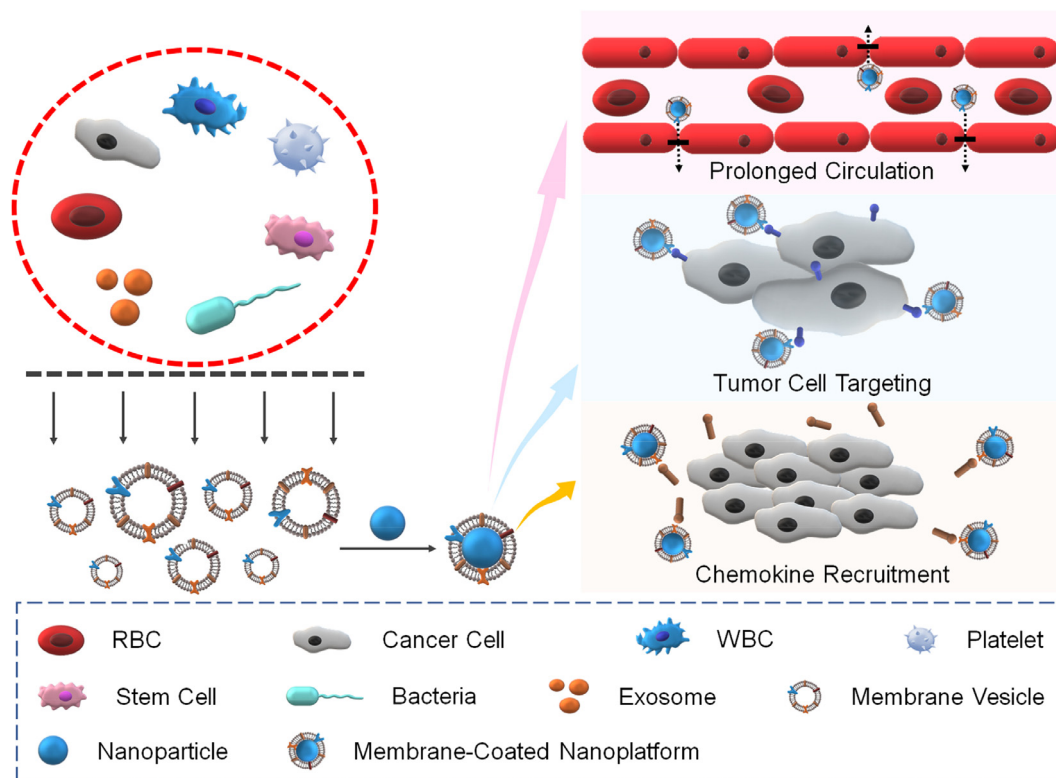


Fig. 1 – Schematic illustration of cell membrane-camouflaged nanoplateforms for cancer-targeted drug delivery.

Table 1 – Synopsis of various cell membrane derivations and their active targeting mechanism.

Cell derivation	Tumor cell targeting	Chemokine recruitment	Targeted region	Cell adhesion molecule for active targeting	Targeted ligand or attractant	Ref.
Cancer cell	+	–	Cancer cell	EpCAM, galectin-3, N-cadherin	EpCAM, galectin-3, N-cadherin	[61–66]
WBC	+	+	Cancer cell/TME	CXCR2, CCL18, $\alpha 4$ integrin, endothelin-B receptor, CSF-1 receptor, EGF, VEGFR, TCR	CXCL1/2/3/4/5/7/8, VCAM-1, GM-CSF ET-2, CSF-1, EGFR, VEGF, Melan-A/MART-1, tyrosinase, gp100, MAGEs, so-called cancer/testis antigens, tumor-restricted antigens	[75–82,90]
Platelet	+	–	Cancer cell	P-selectin	CD44 receptor	[105,106]
Mesenchymal stem cell	+	+	Cancer cell	CXCR4, EGF, integrins, extracellular matrix molecules	SDF-1, EGFR (HER2)	[108–111]
Bacteria	+	–	Cancer cell	HA, engineered anti-HER2 affibody	CD44 receptor, HER2	[119,120]
Exosome	+	–	Cancer cell	Lysosome-associated membrane glycoprotein 2b, GE-11 peptide, lymphocyte function-associated antigen-1, hEGF	Acetylcholine receptor, HER2, CAMs, magnetic field	[121,123–126,129]

+: available; –: not available.

Table 2 – Features of nanoparticles used for cancer-targeted drug delivery.

Membrane derivation	Excipient of nanoparticle	Model drug	Targeted cell line	Ref.
RBC	Methoxy poly(ethylene glycol)-block-poly(D,L-lactide)	PTX, TPC	HeLa	[60]
Cancer cell	PLGA	DOX, Hb	MCF-7	[70]
	PLGA	R837	RM-1	[68]
WBC	PLGA	DOX	MCF-7	[84]
	Bismuth selenide	QE	4T1	[90]
	Dual-end PEGylation of poly(β -amino ester)	PTX	MDA-MB-231	[91]
	PLGA	PTX	MKN-45	[93]
	Lipids 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-dioleoyl-3-trimethylammonium-propane (chloride salt) (DOTAP), cholesterol	DOX	MCF-7	[96]
	PLGA	CFZ	4T1	[103]
Platelet	Acrylamide, N-(3-aminopropyl) methacrylamide, glycerol dimethacrylate	TRAIL, DOX	MDA-MB-231	[107]
Mesenchymal stem cell	PLGA	DOX	MHC97H	[112]
Bacteria	Selenium-PEI	siRNA	HepG2	[119]
	–	siRNA	HCC-1954	[120]
Exosome	Transferrin	DOX	H22	[129]
	–	DOX, ICG	BT474, MDA-MB-468	[126]
WBC/Cancer cell	–	PTX	HN12, B16	[131]
RBC/Cancer cell	CuS	DOX	B16F10	[132]

of a protein called a cluster of differentiation 47 (CD47). CD47 is a transmembrane protein that is exposed on the membrane surface. It is an autologous identification marker that prevents cells from being engulfed and degraded by macrophages [54,55]. Erythrocytes are numerous in blood and easy to collect. Hence, the erythrocyte membrane was the first type of cell membrane used in the manufacture of biomimetic nanoplatforms. Coating erythrocyte membrane to the various nanocarriers was done to prolong residence in the blood and encourage their passive accumulation at the targeted tumor site. To date, erythrocyte membrane-camouflaged nanoplatforms have been the most exploited nanoformulation and have been widely employed in cancer chemotherapy, radiotherapy, molecular targeted therapy, photothermal therapy (PTT), and photodynamic therapy (PDT) [41,56–59].

In one study, Pei and the coworkers designed RBC membrane-camouflaged nanoparticles (RBC(M(TPC-PTX))), loaded with paclitaxel (PTX) dimeric prodrug (PTX2-TK) and photosensitizer 5,10,15,20-tetraphenylchlorin (TPC) for synergistic chemotherapy and PDT (Fig. 2A) [60]. As expected, nanoparticles loaded with PTX or TPC, and those loaded with both drugs had a homogeneous spherical structure. By co-extruding the RBC membrane-derived vesicles with PTX2-TK and TPC encapsulated nanoparticles (M(TPC-PTX)) through a 450 nm pore size polycarbonate membrane, the harvested RBC(M(TPC-PTX)) displayed a spherical core-shell structure. Under the camouflage provided by the RBC membranes, the concentration of the anticancer agent at the tumor site was improved, which illustrated that a prolonged circulation was achieved (Fig. 2B). To further investigate the *in vitro* cytotoxicity, HeLa cells of each group were identified using the established live-dead cell assay. In the control group, which used phosphate-buffered saline (PBS), the cells remained alive. In other groups, markedly more dead cells

were observed in RBC(M(TPC-PTX)) (L+) group than those in the M(TPC-PTX) and M(TPC-PTX) (L+) groups. The outcome illustrated the synergetic inhibition evoked by chemotherapy and PDT. The synergetic anticancer efficacy was also investigated *in vivo*. Animals treated with RBC(M(TPC-PTX)) (L+) displayed more significant tumor ablation compared with other groups (Fig. 2C). The results indicate the potential of RBC(M(TPC-PTX)) nanoformulations in synergistic cancer therapy. As the most popular nanoplatform, the erythrocyte membrane-camouflaged formulations have demonstrated the practicability of biomimetic nanoplatforms in cancer-targeted drug delivery.

2.2. Cancer cell membrane-cloaked nanoplatforms

Cancer cells are one of the most frequently used source cells that have been investigated for biomimetic nanoparticles engineering. Nanoparticles coated with cancer cell membranes reportedly displayed identical surface adhesion molecules, such as epithelial cell adhesion molecule (EpCAM), galectin-3, and N-cadherin, as the source cancer cells. As such, they show a source cell-specific targeting phenomenon [61], which reflected the homologous binding mechanism of multicellular aggregation formation repeatedly noted in cancers [62–66]. Nowadays, various cancer cell membranes have been used to cloak the nanoparticles to direct their targeted drug delivery in cancer therapy [67–71].

In a study by Tian et al., a type of doxorubicin (DOX)/hemoglobin (Hb)-loaded and cancer cell membrane-cloaked nanoparticle (DHCNP) was fabricated (Fig. 3A) [70]. DHCNP was designed to selectively deliver the oxygen-loaded Hb to influence oxygen supply in hypoxia TME and further to overcome hypoxia-induced multidrug resistance. The results confirmed the preservation of the galectin-3, EpCAM,

Table 3 – Typical example of extraction technologies of each membrane and membrane coating process of cell-derived nanoplatfoms.

Membrane derivation	Extraction technologies of different membranes	Membrane coating procedure	Ref.
RBC	The whole blood was centrifuged to collect the RBC, followed by washing with cold PBS. The obtained RBC was put into a cold hypotonic buffer for hemolysis. The free hemoglobin was eliminated by centrifugation at 4 °C. The pink pellet was obtained by washing with cold hypotonic buffer. Afterward, the RBC vesicle was collected by extruding the empty RBC membrane through 450 nm polycarbonate membrane.	The RBC membrane-coated nanoplatfoms were prepared by co-extruding RBC vesicles and nanoparticles through 450 nm porous membrane. Free RBC vesicle was eliminated by centrifugation at 4 °C.	[60]
Cancer cells	The source membranes were obtained by hypotonic lysis of cancer cells, mechanical membrane disruption, and the different speed of centrifuge. Then the intracellular contents of cancer cells were removed, and the cancer cell membrane was collected. Finally, the membrane was extruded through the 220 nm polycarbonate membrane with DSPE-PEG2000.	The cancer cell-coated nanoplatfoms were harvested by extruding the nanoparticles and source membranes with a 220 nm polycarbonate membrane.	[70]
WBCs	Monocytes	Cell membranes of U937 monocytes were obtained by hypotonic lysis, homogenization, and subsequent isolation of the membrane fraction by serial ultracentrifugation.	[84]
	Macrophages	The macrophage ghost was obtained by freezing and thawing in liquid nitrogen of macrophages suspension in 50 nM phenylmethanesulfonyl fluoride (PMSF) added 0.25 × PBS. The lysate was washed with the buffer and centrifuged to obtain the macrophage ghost.	[91]
	hCTLs	Lymphocytes were washed with PBS and lysed in hypotonic lysis buffer. The cells were disrupted on ice by the homogenizer. The homogenized cells were centrifuged at 4 °C. The supernatant was saved, then the pellet was resuspended in hypotonic lysis buffer and made another 20 passes and centrifuged again. The process was repeated until no intact cells remain. All the supernatants were subjected to sucrose density gradient ultracentrifugation at 4 °C. The collected membranes were retained, lyophilized, weighed, resuspended in 0.9% saline solution, and stored at 4 °C.	[93]
	NK cells	Source cells were washed with PBS and centrifuged. The purified pellet was suspended in homogenization buffer and homogenized on ice. The homogenized mixture was collected and subjected to sucrose density gradient ultracentrifugation at 4 °C. The collected gradients were ultra-centrifuged 4 °C. Then, the obtained membrane fractions were diluted with saline and ultracentrifuged for purification. The isolated membranes were lyophilized, weighed, and stored at 4 °C.	[96]
	Neutrophils	Neutrophils were suspended in the ice-cold isolation buffer, and were homogenized using a homogenizer. The homogenate was then centrifuged at 4 °C. The supernatant was then collected and centrifuged at 4 °C to remove the mitochondria. The collected supernatant was then centrifuged at 4 °C. The cell membranes containing pellets were washed. After freeze-drying and weighting, the obtained membranes were stored at –80 °C for further use.	[103]

(continued on next page)

Table 3 (continued)

Membrane derivation	Extraction technologies of different membranes	Membrane coating procedure	Ref.
Platelets	Platelets were isolated by gradient centrifugation from whole blood. After that, the collected platelets were added into a lysis buffer for dissociation. Then, the solution was centrifuged to acquire the purified platelets membrane.	The nanoparticles and platelet membranes were sonicated together. Then, the mixture was stirred and maintained overnight to coat the platelet membranes onto nanoparticles.	[107]
MSCs	The MSC membranes were washed with ice-cold PBS and put into lysis buffer. Afterward, the suspension was centrifuged, and the cell pellet was then collected, homogenized in solution, which contains mannitol, sucrose, bovine serum albumin, EDTA, Tris, and phosphatase and protease inhibitor cocktail. The collected solution was centrifuged at 4 °C. The supernatant was then ultracentrifuged at 4 °C. The resulting pellet was obtained for further use.	The obtained MSC membrane pellet solution was mixed with the prepared nanoparticles and ultrasonicated together. The mixture was centrifuged, and the MSC membrane-coated nanoparticles were obtained.	[112]
Bacteria	The OMVs were purified by multiple centrifugation and filtration steps to ensure complete elimination of parent bacterial debris and free endotoxins. The crude OMVs collected were further separated by sequential density sucrose gradient ultracentrifugation. After that, the removal of free endotoxin was completed using endotoxin-removing columns. Then, the obtained OMVs were resuspended in 15% glycerol, filtered by 0.20 μm cellulose acetate filter, and stored at –80 °C.	–	[120]
Exosomes	The cell surface was induced to bud and generate giant plasma membrane vesicles (GPMVs) with the function of sodium deoxycholate. Then, GPMVs were purified under the low power of ultrasonic vibration to generate nanosized exosomes.	–	[126]
RBC/Cancer cells	Apart from the manufacture of RBC membrane vesicles, as shown above, the cancer cells were washed with PBS at 4 °C and suspended in membrane protein extraction reagent A containing PMSF. The mixture was incubated in an ice bath and then centrifuged. The collected supernatant was further centrifuged to obtain the membrane. Moreover, the membrane was lyophilized and stored at –80 °C for further use. After that, RBC membrane vesicle was added to the cancer cell membrane. Then, they were sonicated at 37 °C to complete the fusion of different membranes.	The nanoparticles solution was added to the hybrid membrane solution. Then the mixture was sonicated to achieve the membrane-coated nanoplatforms. The resulting solution was centrifuged to get rid of the excess membrane. At last, the nanoplatforms were resuspended in deionized water for future use.	[132]

and N-cadherin proteins from the source MCF-7 cell line. To demonstrate the homologous targeting ability of the functionalized nanoplatforms, DHCNPs were incubated with various cell lines, and cell internalization was visualized through the fluorescence intensity detection of DOX. The fluorescence intensity in MCF-7 cells was much stronger than those in other groups, which verified the source cell-specific targeting behavior (Fig. 3B). *In vivo* anticancer efficacy data were also provided. As shown in Fig. 3C, compared with other groups, the DHCNP group displayed the lowest relative tumor volume, which demonstrated the promise of oxygen interference strategy in overcoming hypoxia-induced multidrug resistance. The results indicated the broad prospect of cancer cell membrane-derived nanoplatforms in cancer-targeted drug delivery.

In another example, Li et al. fabricated the multiantigenic nanoparticles (MANPs) using the cancer cell membrane (Fig. 4A) [72]. Through the coating of the cancer cell membrane, the resulting nanoparticles exhibited multiple tumor-associated antigens and were administered as the anticancer vaccines. The R837-loaded MANPs with different particle diameters were prepared, and their capability of immune stimulation was investigated. *In vivo* prophylactic effects on cancer revealed that, after prophylactic vaccination with different nanovaccine formulations, MANP/R837 with the size of 83 nm (MANP83/R837) displayed the most efficient antigen presentation through activating mature of dendritic cells (DCs), and showed the best efficacy of tumor prevention (Fig. 4B). At the same time, the median survival of MANP83/R837 group was the most extended compared with those of the

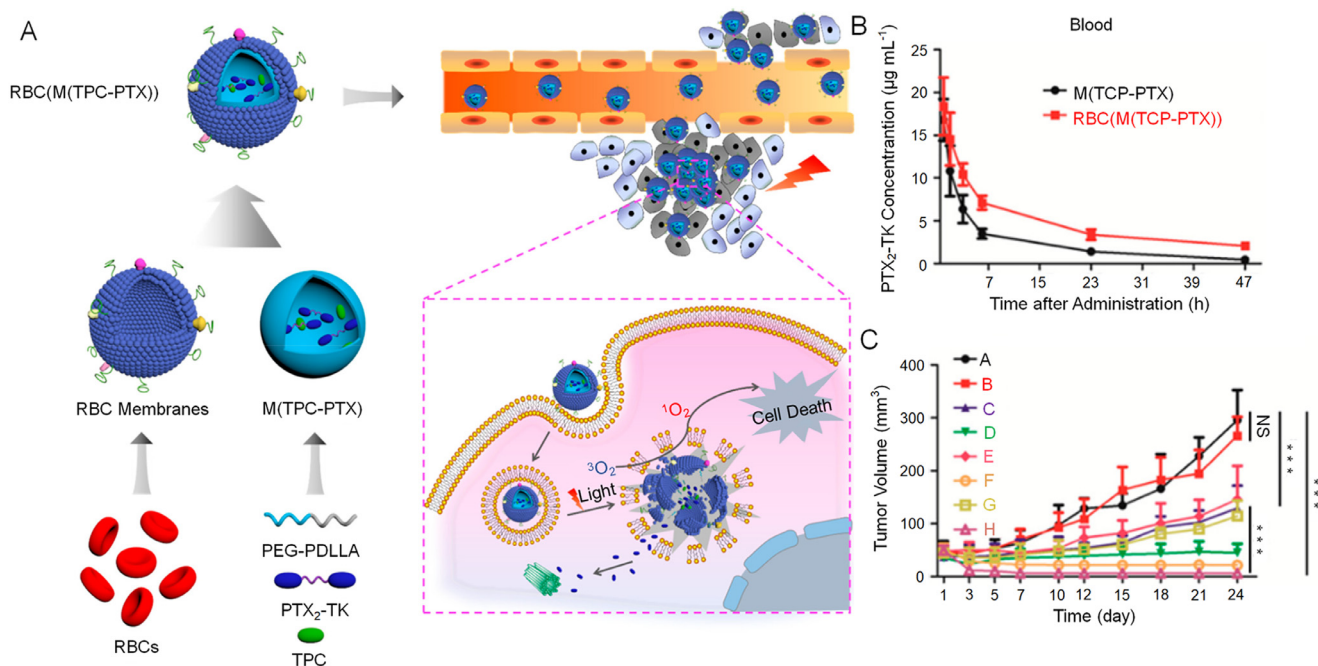


Fig. 2 – Manufacture of RBC(M(TPC-PTX)), brief mechanism in cancer therapy, pharmacokinetics performance, and inhibition of tumor growth. (A) Fabrication of RBC membrane-camouflaged nanoparticles for synergistic photodynamic/chemotherapy. (B) Pharmacokinetics data of PTX₂-TK in RBC(M(TCP-PTX)) and M(TCP-PTX) groups. (C) Tumor suppression curve of subcutaneous xenografts in different groups. (A: PBS B: PBS(L+) C: M(PTX) D: M(PTX) (L+) E: M(TPC-PTX) F: M(TPC-PTX) (L+) G: RBC(M(TPC-PTX)) H: RBC(M(TPC-PTX)) (L+)). Reproduced with permission from [60]. Copyright 2018 American Chemical Society.

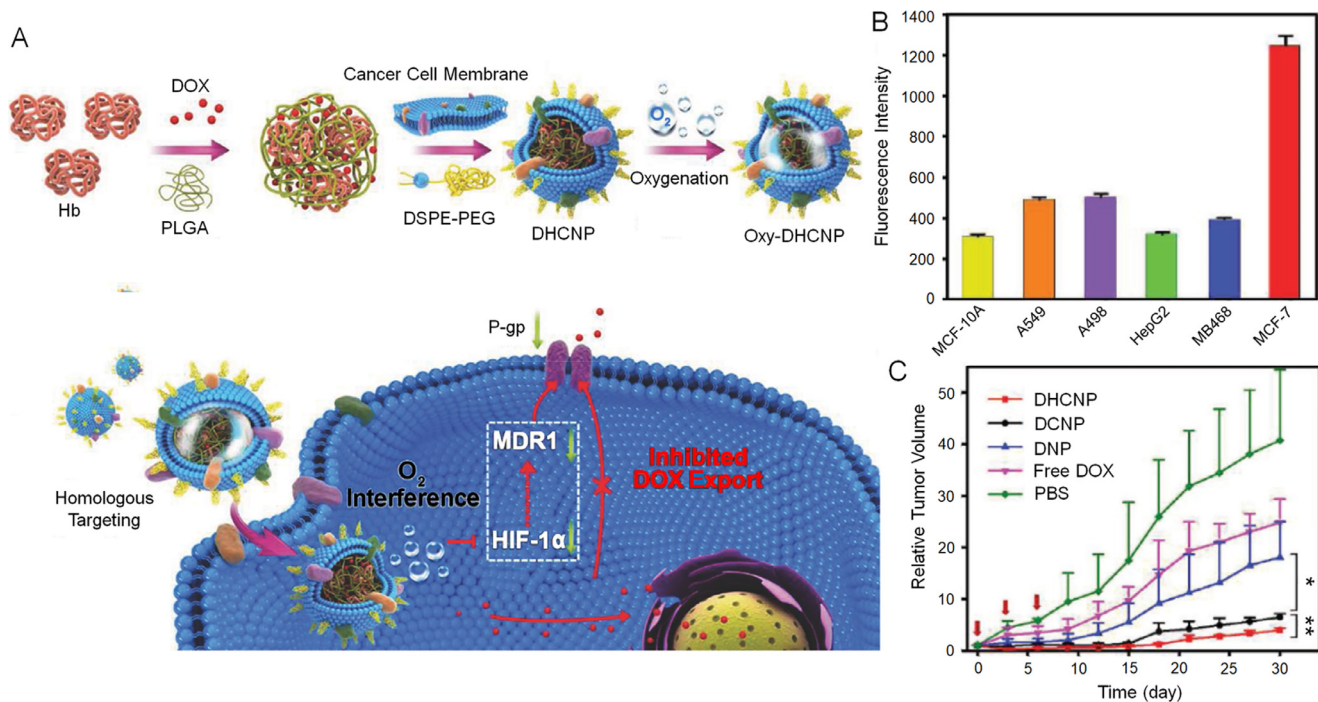


Fig. 3 – Preparation of Oxy-DHCNP, characterization of homologous targeting property, and inhibition of tumor growth. (A) Fabrication process of DHCNP and therapeutic mechanism in overcoming hypoxia-induced multidrug resistance. (B) Homologous targeting behavior of DHCNP toward source MCF-7 cells, verified by fluorescence intensity. (C) Relative tumor volumes of different groups treated, respectively, with DHCNP, DCNP, DNP, free DOX, and PBS. Reproduced with permission from [70]. Copyright 2017 John Wiley & Sons.

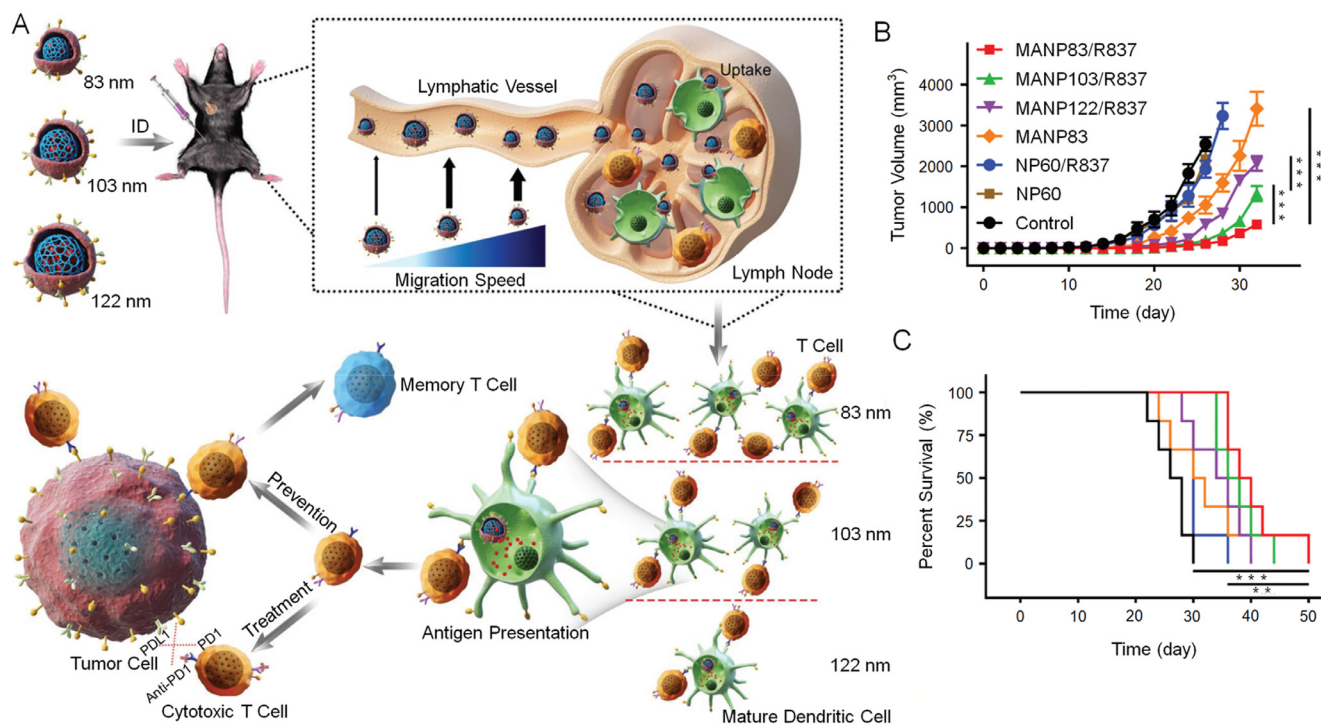


Fig. 4 – Brief mechanism in tumor suppression, in vivo prophylactic effects on tumor growth, and median survival data. (A) Process of immune stimulation by MANPs and mechanism in cancer prevention and treatment. (B) Tumor volumes of different groups vaccinated by MANP83/R837, MANP103/R837, MANP122/R837, MANP83, NP60/R837, NP60, or PBS. (C) Median survival of different treatment groups. ID, intradermal injection. Reproduced with permission from [72]. Copyright 2019 John Wiley & Sons.

other groups (Fig. 4C). Subsequent studies on cancer cell membrane-engineered nanoplatforms have been reported, although considerable progress is still required before these will be ready for clinical applications.

2.3. White blood cell membrane-coated nanoplatforms

White blood cells (WBCs) constitute essential cells in the blood, with diameters ranging from 7 to 20 μm [73]. According to their different functions, WBCs are divided into numerous subtypes, including monocytes, macrophages, lymphocytes, neutrophils, eosinophils, basophilic granulocytes, and mastocytes. WBCs are crucial in the immune system, and protect the body against infection and foreign aggression [74]. When the body is infected or invaded, WBCs are recruited from the blood circulation to the injured site, at which point inflammation occurs together with the secretion of various cytokines [75]. Considering that the chronic inflammatory response is a primary characteristic of tumor tissue [76], and based on the inflammatory chemotactic properties of WBCs, many subtypes of WBCs are susceptible to the tumor-derived chemoattractants. These chemoattractants include chemokine (C–X–C motif) ligand (CXCL)1/2/3/4/5/7/8, vascular cell adhesion molecule-1 (VCAM-1), granulocyte-macrophage colony-stimulating factor (GM-CSF), endothelin-2 (ET-2), colony-stimulating factor-1 (CSF-1), and so forth [77–81]. Besides, through activation of the T cell receptors, T cells recognize and attack tumor cells [82]. Various WBCs have

already been utilized in nanoparticle engineering for drug delivery. Notably, such WBC membrane-coated nanoparticles exhibit superior active targeting toward neoplastic cells with the minimal nonspecific distribution of the loaded drugs.

2.3.1. Monocyte membrane-wrapped nanoplatforms

Monocytes originate from hematopoietic stem cells of the bone marrow and are the precursors of macrophages. As the biggest WBCs, monocytes serve as a significant component of the body's defense system. They are capable of engulfing damaged and aging cells and the cell fragments with apparent deformational movements. They participate in the immune response by presenting the engulfed antigenic determinants to lymphocytes for the induction of specific immune responses. Under pathological conditions, the secretion of chemokine (C–C motif) ligand 2 (CCL2) by the tumor or stroma cells serves to recruit inflammatory monocytes, which express the chemokine (C–C motif) receptor 2 (CCR2), resulting in their accumulation at the tumor sites. Moreover, the presence of tumor-specific monocytes is often related to tumor metastasis and progression, along with poor clinical prognosis [83].

To exploit the binding mechanism between monocytes and tumor cells, Krishnamurthy et al. synthesized the DOX-loaded biodegradable nanoparticle, which had a poly(lactic-co-glycolic acid) (PLGA) core wrapped by monocyte membrane [84]. In this nanoplatform, the membrane protein pattern was consistent between monocyte (U937) membrane and the shell of the prepared nanoparticle, verifying the preservation of

cell membrane conjugating proteins. In addition, monocyte membrane-coated nanoparticle avidly targeted MCF-7 cells, better than bare PLGA NP, further demonstrating the cell receptor-specific binding phenomenon. In another example, Li et al. developed a nanoparticle-based drug delivery system against an astrocytoma cell line incorporating a bone marrow-derived monocyte membrane coating as a shell [85]. The monocyte membrane shell protected the nanoparticle from being eliminated by the mononuclear phagocyte system, with the chemokine receptor CXCR4 on monocyte membrane able to promote the active tumor-tropism of the nanoparticle-based drug delivery system. The outcomes from these two studies revealed that the monocyte membrane-wrapped nanoparticles have great potential for cancer-targeted drug delivery. Further studies will explore this potential.

2.3.2. Macrophage membrane-biomimetic nanoplatfoms

Macrophages are categorized as a type of functionalized immune cells that are derived from monocytes [86]. They are widely distributed in various tissues and organs of the body and are capable of recognizing and engulfing foreign invaders or other non-self-materials. The engulfed antigens can then be presented to DCs or T cells after phagocytosis, and the step is essential in antigen-specific immune responses. Similar to monocyte, macrophage membranes have been extracted and used in the manufacture of nanoparticle-based drug delivery systems, and have proven to be crucial in cancer therapy owing to their inherent cell membrane proteins [87–90]. For example, Zhao et al. reported the development of macrophage membrane-coated quercetin (QE)-loaded bismuth selenide nanoparticles (M@BS-QE NPs) for the inhibition of breast cancer lung metastasis [90]. The recruitment of M@BS-QE NPs was through the way of CCL2/CCR2 chemokine interaction. Besides, tumor recognition of M@BS-QE NPs was realized via $\alpha 4$ /VCAM-1 interaction. QE encapsulated in nanoparticles acted as a synergistic PTT-sensitive agent by inhibiting the expression of heat shock protein 70 and preventing tumor progression through the reduction of p-Akt/matrix metalloproteinase-9 pathway signaling. The therapeutic effect against lung metastasis of breast cancer was shown in a BALB/c mouse model, which further indicated the synergistic inhibition efficacy associated with M@BS-QE NPs.

As reported in most recent studies, different types of cell membrane-engineered nanoparticles are integrally endocytosed by the targeted cells, including both the internal core and the outer cell membranes. However, a newly published study reported that prior to the endocytosis, the outer envelope membrane surface was removed, which was termed the membrane escape phenomenon [91]. The phenomenon, also termed the “proton sponge” effect [92], is based on the ability of cationic polymer nanoplatfoms to cause an influx of extra electrolytes and water into the acidic late endosome, which obtains an internal balance of ionic strength and electrical neutrality. This process caused the surface membrane rupturing with the overflow of the internal core. Owing to the membrane escape phenomenon, the macrophage membrane-coated nanoparticles actively targeted the TME and then displayed a step-by-step release of anticancer agents following the removal of the outer membrane when the pH value changed in the extracellular

and intracellular TME [91]. This work inspired the rational design of membrane-biomimetic nanoplatfoms in cancer-targeted drug delivery, although additional verification and exploration are required for further biomedical application.

Furthermore, because of the fluid character of lipid bilayers in living cells, we hypothesize that during the endocytosis of nanoparticles, the outer shell of the nanoparticle is likely to interact with the targeted cell membranes through the partial exchange of lipid bilayers. Thus, this process might be utilized for tumor cell membrane-specific drug delivery and therapy, similar to that afforded by the small molecule programmed cell death-ligand 1 inhibitors. However, there is as yet no relevant research evidence in support of this hypothesis. Such studies are warranted.

2.3.3. Lymphocyte membrane-covered nanoplatfoms

Lymphocytes are essential components in the human body's immune response, although they are the smallest WBCs. Depending on their occurrence, surface molecules, and individual functions, lymphocytes are categorized as T cells, B cells, and natural killer (NK) cells. Both T cells and B cells are antigen-specific lymphocytes, as they become mature and functional after encountering an antigen trigger, thereby producing a cytotoxic effect or secretion of the corresponding antibodies. NK cells have cytotoxic effects without relying on antigen stimulation and have wide-ranging effects on targets.

Taking advantage of the capability of lymphocyte antigen recognition, several lymphocyte membrane-covered nanoplatfoms have been developed and applied for cancer-targeted drug delivery. In the work of Zhang et al., membrane vesicles were extracted from human cytotoxic T lymphocytes (hCTLs) [93]. The vesicles used to cover PTX-loaded PLGA NP to form an hCTL-inspired nanoformulation. Low-dose irradiation (LDI) promotes local infiltration of intratumoral CD8⁺ T cells [94], resulting from the upregulation of membrane adhesion molecule expression on tumor vasculature and the enhanced release of chemoattractants [95]. As such, LDI was administered in the study to facilitate targeting of the hCTL-inspired nanoformulations toward the tumor site. In addition, through the synergistic chemotherapeutic inhibition mediated by the encapsulated PTX, therapeutic efficacy against a subcutaneous gastric cancer xenograft model was also amplified.

NK cells, the crucial effector cells in innate immunity, have also been utilized for nanoparticle-based research. The NK cell membranes were employed to coat DOX-loaded nanoparticle for cancer-targeted treatment [96]. Notably, the lipid bilayer of the membrane-coated nanoparticle and targeted tumor cells fused prior to the discharge of the DOX from the nanoparticle inside the tumor cells, with the membrane-covered nanoparticle not being integrally engulfed. B cells have not yet been used in the design of biomimetic nanoformulations, although additional anticancer studies are expected to be conducted based on other types of lymphocytes.

2.3.4. Neutrophil membrane-enveloped nanoplatfoms

Typically, neutrophils serve as a crucial barrier against foreign intruders. Early studies described that neutrophils were cytotoxic to malignant cells [97,98]. However, other

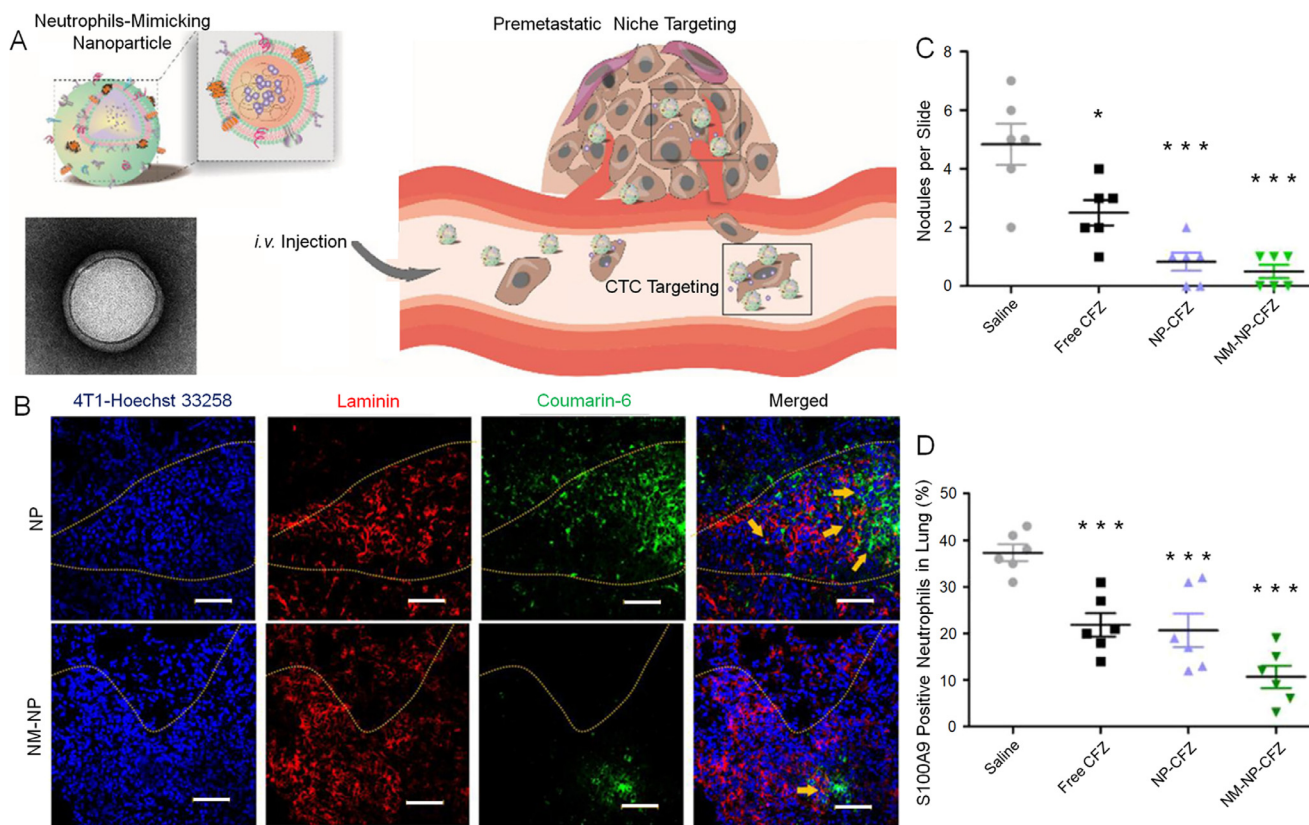


Fig. 5 – Fabrication of neutrophil-mimicking nanoparticle (NM-NP), assessment of pre-metastatic niche targeting, and application in lung metastasis therapy. (A) NM-NP for targeting CTCs and pre-metastatic niche. (B) Targeting property of NM-NP compared with naked nanoparticle in the pre-metastatic region as displayed by confocal microscopy. Scale bar: 50 μm. (C) Quantification of metastasis nodules in lung tissue slides of different groups. (D) S100A9 positive neutrophil level in different treating groups. Reproduced with permission from [103]. Copyright 2017 American Chemical Society.

studies showed that tumor-associated neutrophils isolated from both tumor-bearing mice and patients with gastric cancer were not cytotoxic to the tumor cells [99,100]. Instead, these neutrophils contributed to tumor progression and metastasis, with adhesion molecules exposed on the neutrophil membranes implicating in the adherence to cancer cells [101,102]. Kang et al. designed a neutrophil membrane-enveloped nanoparticle (NM-NP) that was capable of actively targeting circulating tumor cells and inhibiting the pre-metastatic niche (Fig. 5A) [103]. In an animal model of tumor pre-metastasis, different mice were intravenously injected with coumarin-6-labeled nanoparticles or NM-NPs. As shown in the outcome, the neutrophil membrane coating resulted in better targeting to the pre-metastatic region in the lung (Fig. 5B). Moreover, after loading with carfilzomib (CFZ), the nanoplatforms demonstrated the enhanced therapeutic capability to reduce the metastatic foci. Moreover, the quantification of metastasis nodules in lung tissue slides revealed the fewest metastasis nodules in the CFZ-loaded NM-NP group (Fig. 5C). S100A9, expressed by neutrophils, is a metastatic niche-promoting molecule. The recruitment of S100A9-expressing neutrophils to metastatic sites was also investigated [103]. Dramatically reduced expression of S100A9 in the lung was noted after administration of CFZ-

loaded NM-NPs compared to those in the other groups, and lung sections from the CFZ-loaded NM-NP group revealed the lowest level of S100A9-positive neutrophils (Fig. 5D). These results demonstrated the marked potential for treating metastatic tumors and regulating the TME through the bioengineering of various nanoparticles with neutrophil membranes.

2.4. Platelet membrane-masquerading nanoplatforms

Platelets are generically derived from mature megakaryocytes. Their primary physiological function is participation in hemostasis. When blood vessels are injured and leaking, platelets are quickly recruited around the damaged vascular endothelial cells and aggregate into clusters to form a thrombus, thereby blocking the leakage and benefiting the recovery of the body. However, a recent study revealed their contribution to tumor progression and metastasis [104]. Typically, the membrane protein P-selectin on platelets combines with the CD44 receptor, which is overexpressed on tumor cell membranes. The combination facilitates interaction and adherence of platelets around the circulating tumor cells and promotes the formation of distant metastatic lesions [105,106]. Based on this distinct adherence mechanism

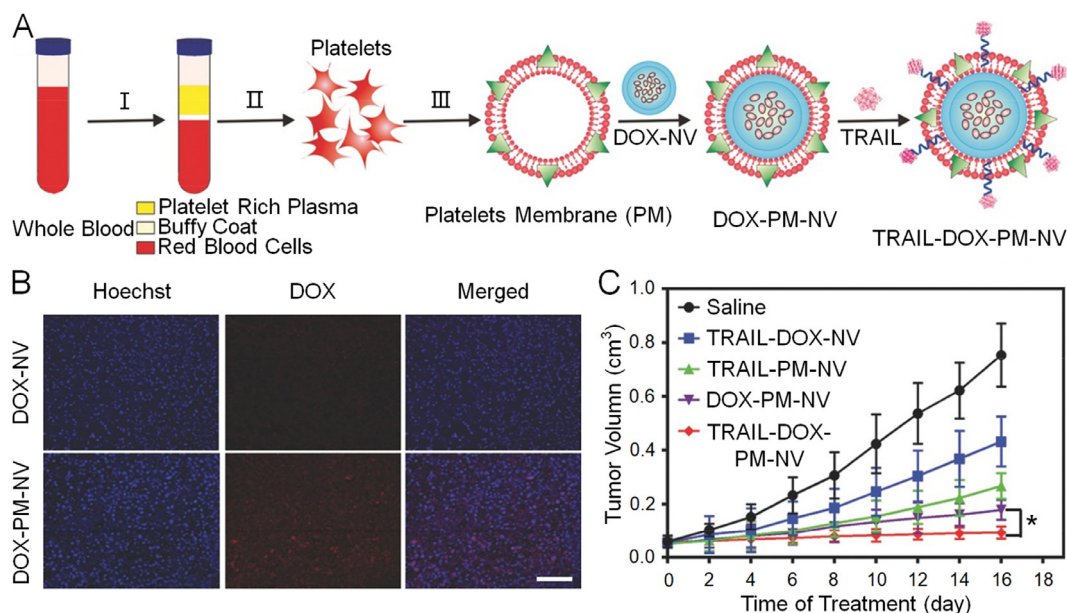


Fig. 6 – Fabrication process of TRAIL-DOX-PM-NV, active targeting property, and inhibition of tumor growth. (A) Schematic illustration of preparation of TRAIL-DOX-PM-NV. (B) Fluorescence distribution of tumors treated with TRAIL-DOX-NV and TRAIL-DOX-PM-NV. Scale bar: 100 μm . (C) Tumor volume following administration of saline, TRAIL-DOX-NV, TRAIL-PM-NV, DOX-PM-NV, and TRAIL-DOX-PM-NV. Reproduced with permission from [107]. Copyright 2015 John Wiley & Sons.

between platelets and cancer cells, Hu et al. fabricated a platelet-mimicking nanovehicle, which was further modified by decoration with tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and loading with DOX (Fig. 6A) [107]. Masked by the platelet membranes, the synthetic platelets membrane-mimicking nanovehicles exhibited a favorable performance with respect to hemodynamics, and active targeting capability was observed (Fig. 6B). The platelet-mimicking nanovehicles also displayed enhanced anticancer efficacy due to TRAIL decoration and DOX loading, as shown in Fig. 6C. Other studies have identified the key determinant of the platelet membrane in targeted drug accumulation. Further studies will be needed before this potential translates to clinical applications.

2.5. Mesenchymal stem cell membrane-shrouded nanoplatforms

Mesenchymal stem cells (MSCs) are multipotent cells that can differentiate into a variety of cell types. Additionally, they exhibit immunomodulatory properties in pathological situations, including tumor occurrence, and often show a high affinity toward neoplastic cells [108]. Consequently, they are widely applied in cancer and immune-related research. Considering that MSCs express specific cell adhesion molecules, such as CXCR4, epidermal growth factor (EGF), integrins, and extracellular matrix, they are easily attracted by the tumoral chemoattractants that include stromal cell-derived factor 1 or directly interact with the targeted ligands like human epidermal growth factor receptor-2 (HER2) [108–111]. Moreover, taking advantage of the property of their

affinities with neoplastic cells, MSCs have been utilized to decorate nanoparticles for cancer-targeted drug delivery.

In a recent study, Yang et al. functionalized synthetic PLGA NPs with the biological properties of MSCs [112]. The PLGA NPs harboring DOX were coated with MSC membranes and administered intravenously for active tumor-specific drug delivery (Fig. 7A). A tumor-specific tropism assay was conducted *in vivo* between the liposome-coated nanoparticles and MSC membrane-coated nanoparticle groups. Twenty hours after administration, distinct fluorescence distribution was noted between the two groups, which illustrated that tumor-specific tropism was inherited from the source MSCs (Fig. 7B). The tumor inhibition assay was also carried out. After four administrations over 15 days, tumor growth was inhibited best in mice who received MSC membrane-coated nanoparticles containing DOX (Fig. 7C). In two other studies, MSC membrane-shrouded nanoparticles also displayed active tumor targeting and efficacious treatment of cancer-based on PDT and chemotherapy *in vitro* and *in vivo* [113,114].

2.6. Bacteria-based nanoplatforms

The human body hosts many microbes that are essential to metabolism and other biological activities. These microbes include bacteria, fungi, rickettsia, and viruses. Bacteria are unicellular organisms that lack both organelles and a membrane-bound nucleus [115]. While some bacteria are pathogenic, others can be very beneficial for preventing or treating diseases, and there are many ongoing studies on the potential use of bacteria in nanoparticle engineering for cancer-targeted drug delivery.

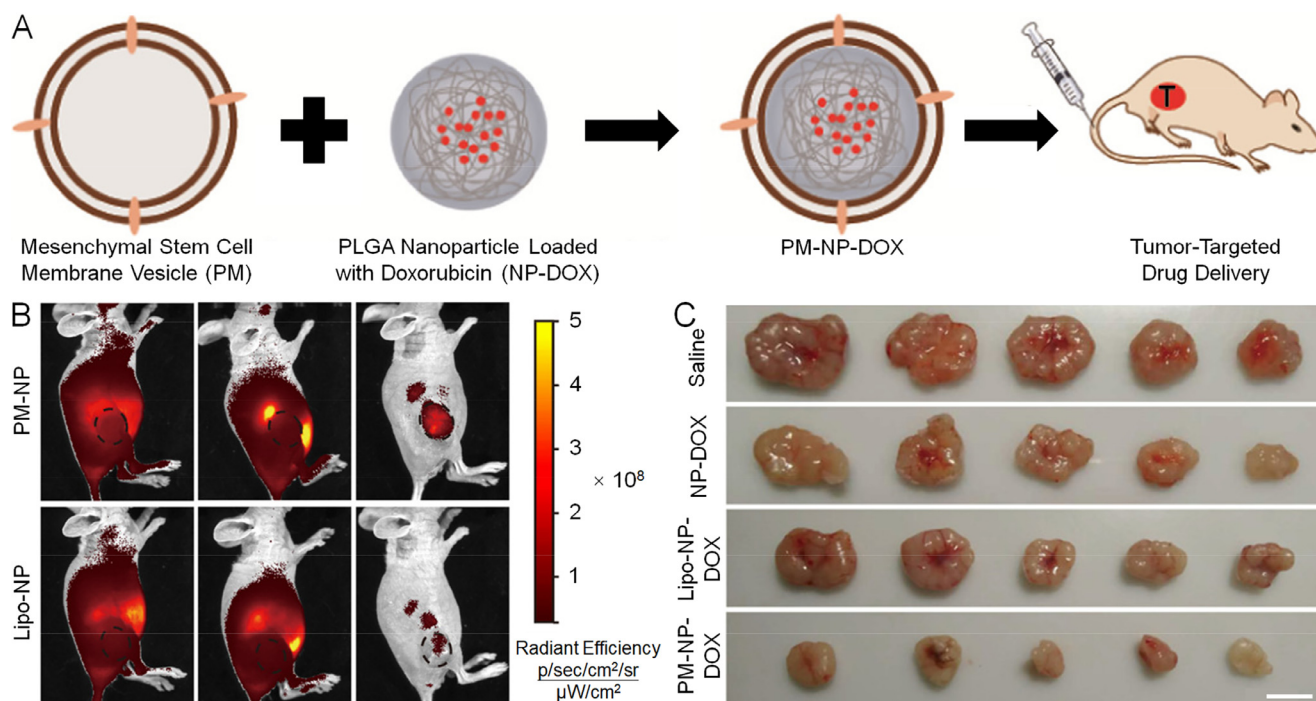


Fig. 7 – Preparation of PM-NP-DOX, evaluation of tumor-specific targeting ability, and inhibition of tumor growth. (A) MSC membrane-shrouded polymeric PLGA nanopatform for tumor-specific DOX delivery. (B) Tumor-specific targeting capability between lipo-NP and PM-NP groups. (C) Tumor inhibition efficacy after different treatments. PM: cell plasma membrane. Reproduced with permission from [112]. Copyright 2018 American Chemical Society.

Typically, bacteria-based nanoparticles are constructed to replicate a particular bacterial cell component, such as the S-layer, bacterial ghosts, outer membrane vesicles (OMVs), endospores, and magnetosomes. Each bacterium has unique properties and different biologically active components, which may be useful for active tumor targeting. For example, the *Streptococcus* bacteria contains a bacterial polymer called hyaluronic acid (HA) targeting the cell membrane protein CD44 receptor and then produces HA-based nanoparticles that are effective cargo carriers for drug delivery [116–118]. Xie et al. reported that siRNA-loaded nanoparticles ornamented with HA displayed enhanced inhibition of hepatocellular carcinoma. Due to this property of HA, it has been widely employed to decorate nanoparticles in order to improve drug delivery [119]. In another example, bacterial OMVs have also been utilized for cancer-targeted drug delivery (Fig. 8A) [120]. OMV-based nanoparticles are cytotoxic to tumor cells *in vitro*, and they are able to actively target HER2-overexpressed tumor cells and induce inhibition of tumor growth *in vivo* after being modified with an engineered anti-HER2 antibody (Fig. 8B and C). Despite the numerous benefits of using bacteria-based drug delivery vectors, it is essential to recognize the risk for potential infections or antibiotic infections in clinical trials.

2.7. Exosome-mimicking nanoplatforms

The exosomes are multifunctional vehicles that transfer biological information between cells upon stimulation. They are the smallest types of extracellular vehicles with particle

sizes ranging from 40 to 100 nm [121]. Although once regarded as the transporters of waste materials from cells, exosomes are currently thought to be multifunctional vehicles that transfer biological information between diverse cells [122]. After being externally secreted, exosomes usually move toward the binding molecules, such as acetylcholine receptor, HER2, and endothelial cell adhesion molecules on the surface of the targeted cells [121,123–126]. They are internalized by these targeted recipient cells, with the loaded cargos. These cargos include mRNAs or miRNAs, which cause the targeted gene silencing or the production of certain encoded proteins [127,128].

Due to this active targeting property, exosomes have been studied for their potential applications in cancer therapeutics. Qi et al. isolated transferrin receptor-expressing exosomes from blood plasma and loaded them with DOX. These nanosized exosomes were then modified with engineered transferrin, giving them a super-paramagnetic property. Under an external magnetic field, the super-paramagnetic nanoparticles actively targeted and inhibited tumor growth [129]. In another study, Zhang et al. genetically engineered biofunctionalized liposome-like nanovesicles (BLNs) to express human EGF on their biointerface as targeting moieties and loaded them with DOX (Fig. 9A) [126]. These BLNs displayed better-targeting capabilities than artificial liposome nanovesicles covalently combined with hEGF and marked with fluorescein isothiocyanate (Fig. 9B). Moreover, they even exhibited better anticancer efficacy than clinically approved liposomal doxorubicin (Doxil®) when administered

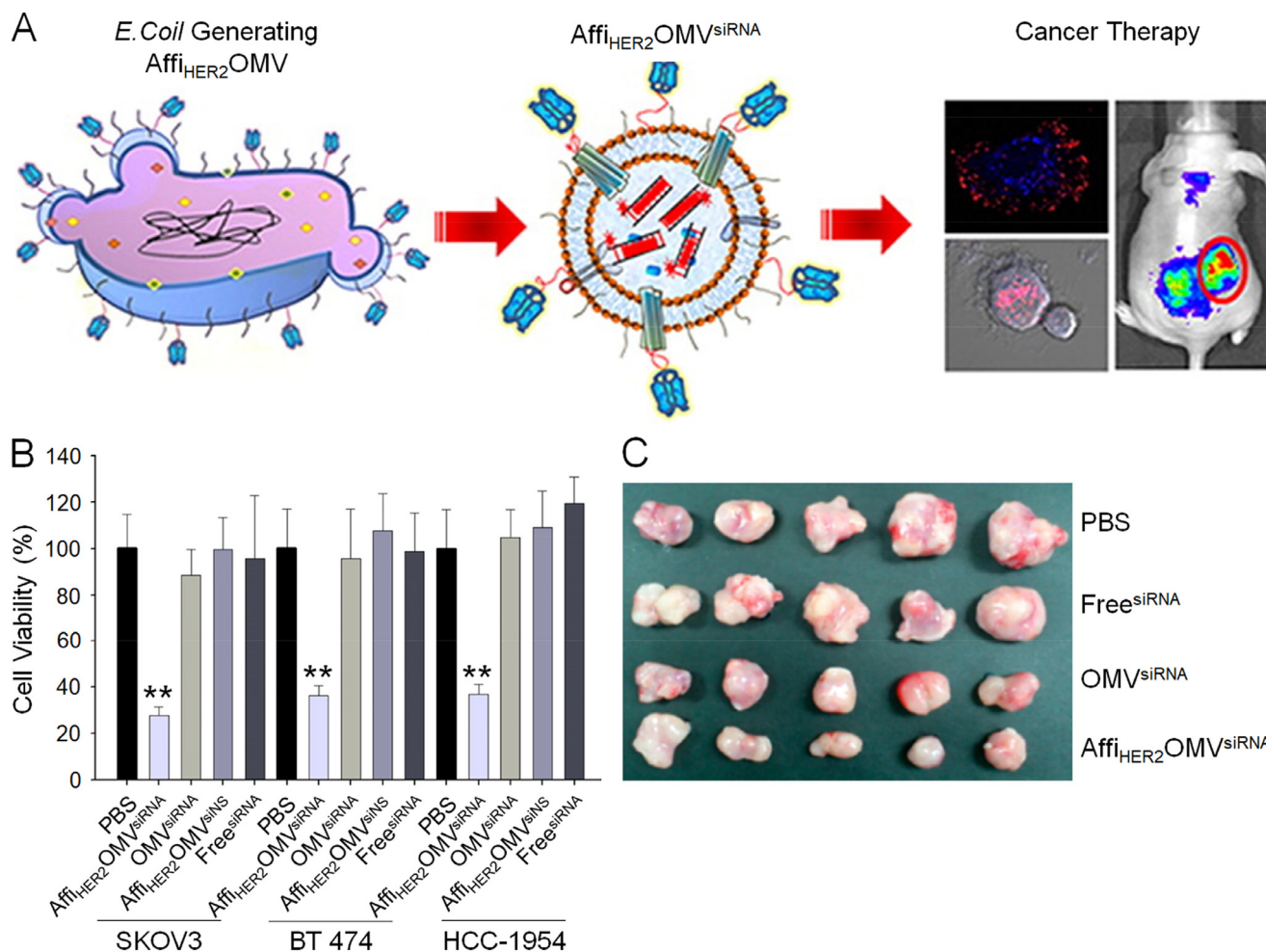


Fig. 8 – Fabrication of Escherichia coli (*E. coli*) generating OMV and assessment of *in vitro* and *in vivo* efficacy. (A) *E. coli* generating OMV displaying HER2-specific affibody and loaded siRNA for cancer therapy. (B) *In vitro* cell viability evaluation among different groups. (C) Excised tumor tissues of different groups after therapy. Reproduced with permission from [120]. Copyright 2014 American Chemical Society.

in HER2-overexpressing tumor xenograft models (Fig. 9C). These studies demonstrated that with excellent targeting property and smart engineering strategies, exosome-based nanoparticles have considerable potential for future clinical applications.

2.8. Hybrid membrane-veiled nanoplatforms

Various cell membrane sources have been utilized in nanoparticle engineering since the original use of RBC membranes. The shell of the nanoparticles displayed unitary cell-derived formulations in most cases. In order to harness the distinct characteristics from different cells, Dehaini et al. fabricated an erythrocyte-platelet hybrid membrane-veiled nanoparticle as a proof-of-concept [130]. Notably, the researchers demonstrated that the dual-membrane formulation was realized with the inheritance of both source cell properties. Subsequently, hybrid membrane-veiled nanoparticles were further developed for cancer-targeted drug delivery. He et al. reported a composite cell

membrane modality wherein leukocytes, and cancer cells were employed as the source cells [131]. Because of the dual-membrane extraction, both the preeminent homing toward the tumor site and prolonged circulation were realized compared with the single source cell formulation. Moreover, the encapsulation of PTX improved the anticancer efficacy without inducing severe side effects. In another example, a similar method was adopted based on RBCs and B16F10 cancer cells as the membrane sources [132]. The hollow copper sulfide nanoparticles were prepared and encapsulated with DOX (DCuS NPs), followed by hybrid membrane coating (Fig. 10A). Because of the membrane camouflage, DCuS NPs exhibited active tumor-specific tropism together with prolonged blood retention. The composite membrane-veiled nanoparticles (DCuS@[RBC-B16] NPs) also showed near-total inhibition of tumor growth with synergistic PTT and chemotherapy (Fig. 10B). Systematic toxicity was also investigated. No obvious body weight loss was observed in the DCuS@[RBC-B16] NPs-treated animals (Fig. 10C).

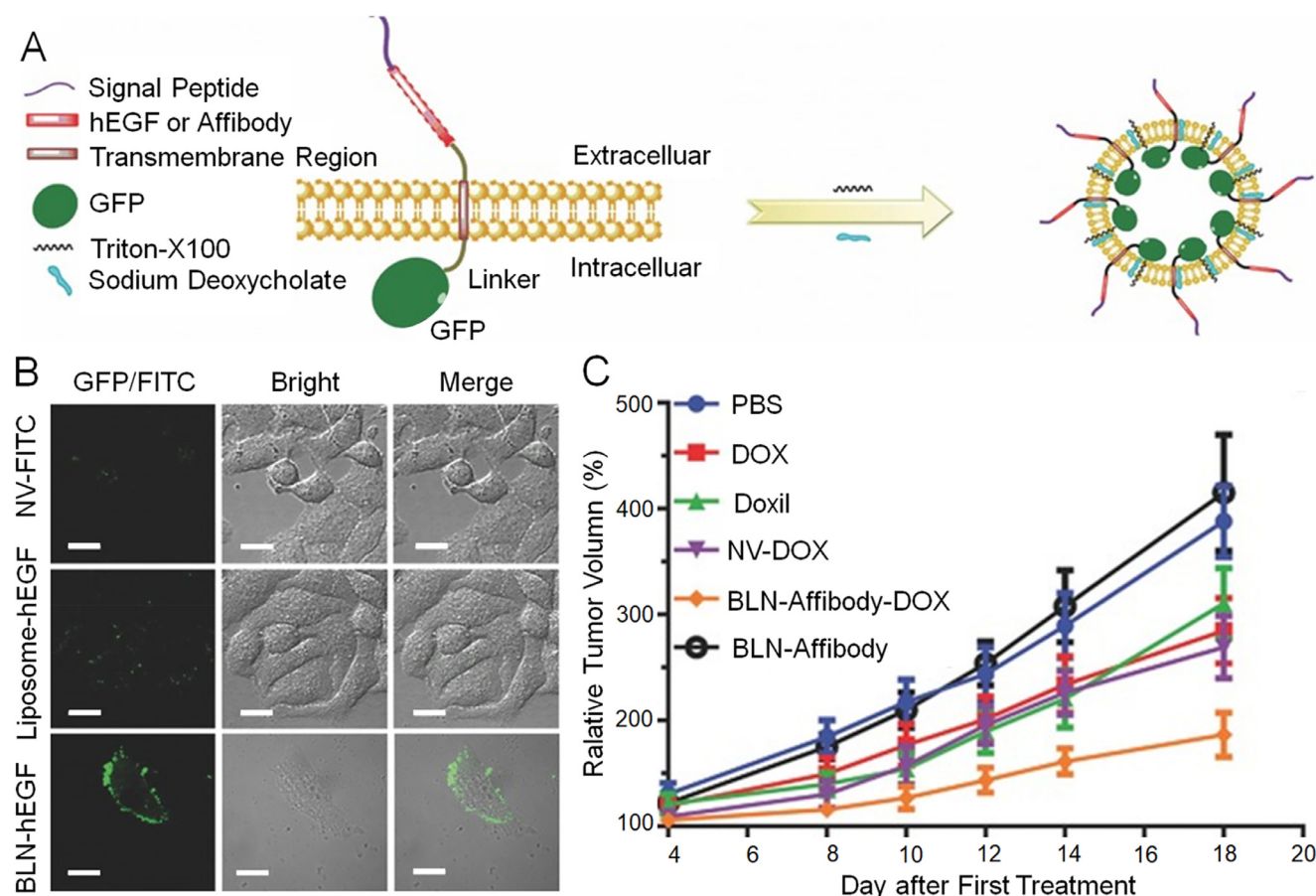


Fig. 9 – Illustration of forming process of BLN, characterization of targeting performance, and inhibition of tumor growth. (A) By induction of surfactants, BLN budding from cell surface was completed. (B) Superior targeting performance of BLN-hEGF. (C) Relative tumor volume of different groups. Reproduced with permission from [126]. Copyright 2017 John Wiley & Sons.

3. Discussion and outlook

We have summarized different paradigms of membrane-camouflaged nanoplatforms that have been extensively developed for cancer-targeted drug delivery. This new biointerface engineering strategy leverages the interaction between the modified biomimetic nanomaterials and the organism itself, the targeted neoplastic cells, or the TME. Numerous cell types have been explored for the engineering of nanoparticle-based drug delivery systems, including RBCs, tumor cells, WBCs, platelets, and stem cells. As well, material and medical science have been advancing encouragingly. This progress has synergistically advanced cancer therapy and improved the therapeutic outcomes of these biofunctionalized nanoplatforms.

Nevertheless, additional efforts are necessary, and many issues deserve further exploration. For example, most studies have established that in the metabolism of these biomimetic nanocarriers, the outer biofilms were endocytosed by the targeted cancer cells together with the inner cores. However, considering that certain functions of membrane proteins are preserved after membrane coating, it is possible that the properties of the phospholipid bilayer itself, such as membrane fluidity, may be retained after being extracted and

coated onto the nanoparticles, along with the occurrence of membrane exchange between the nanoparticles and targeted cells during endocytosis activity. This process, if confirmed by additional studies, might be used to targeted deliver anticancer drugs from the shell of the nanoparticles to tumor cell membranes and fulfill cancer cell membrane-specific drug delivery. In addition, as indicated in one study, the outer membranes of nanoparticles were removed in the acidic TME before endocytosis [91]. However, relevant data are scant, and more studies are required. If confirmed, anticancer drugs loaded in outer membranes and inner nanoparticles can be respectively delivered to different target sites.

Clinical transformations and applications are the goals of cancer-associated research, including cell membrane-engineered nanomedicines. Several issues remain to be solved. For example, cancer cell membrane-coated nanoparticles are popular in targeted anticancer research on animals. However, patients may not accept the use of the tumor-derived components that need to be administered back into their bodies for therapy. Clinical trials in this area will be challenging in terms of approval and execution. The use of standardized cell lines in cancer research is usually done. Nevertheless, heterogeneity is a principal attribute of cancer, which often results in treatment failure. As a result,

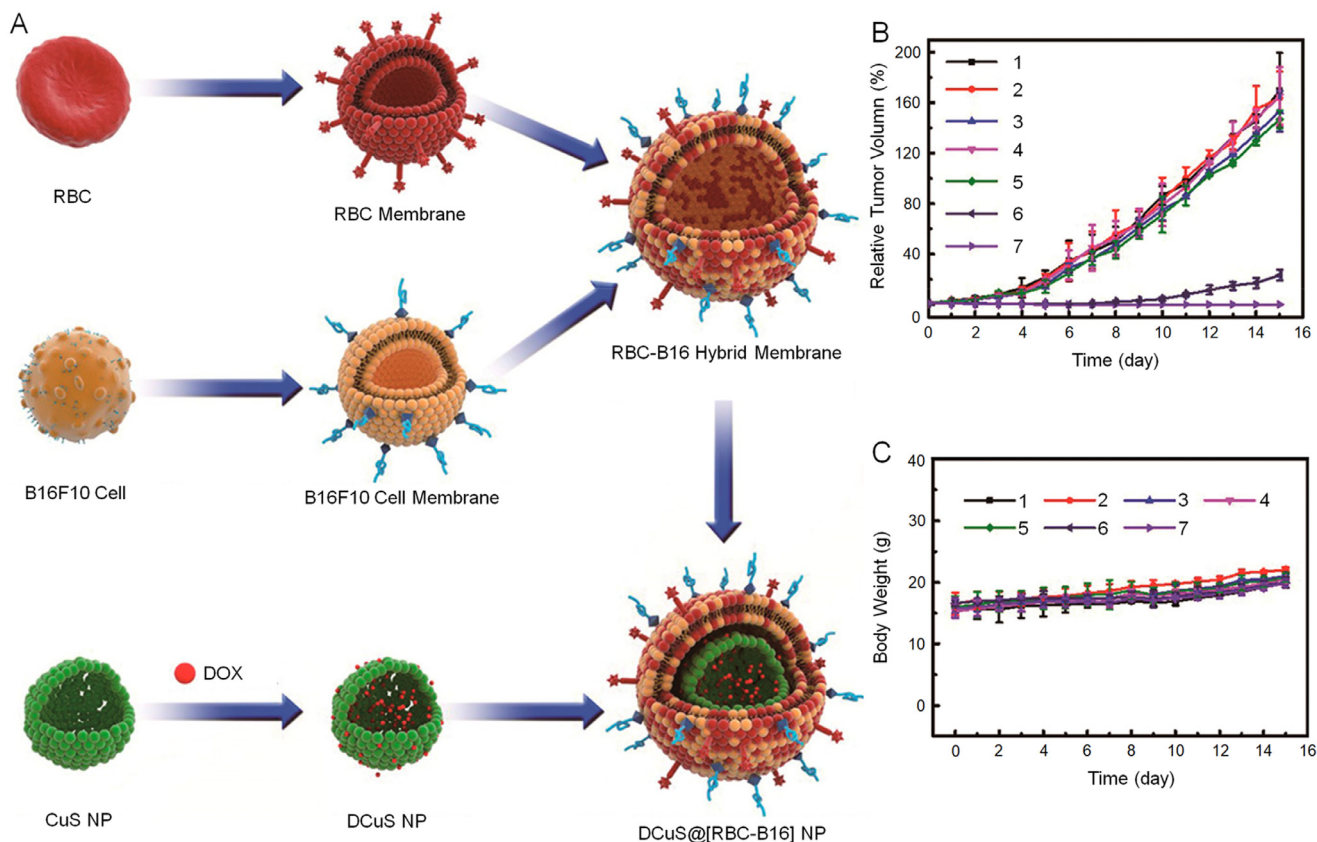


Fig. 10 – Manufacture of DCuS@[RBC-B16] NP, inhibition of tumor growth, and systematic safety assessment. (A) Schematic presentation of DCuS@[RBC-B16] NP synthesis. (B) Relative tumor volume following administration of each groups (1: NS, 2: CuS@[RBC-B16], 3: DOX, 4: NIR laser (1064 nm, 1.0 W/cm²), 5: DCuS@[RBC-B16], 6: CuS@[RBC-B16] with NIR laser (1064 nm, 1.0 W/cm²), 7: DCuS@[RBC-B16] with NIR laser (1064 nm, 1.0 W/cm²)). (C) Follow-up investigation of body weight in each group. Reproduced with permission from [132]. Copyright 2018 American Chemical Society.

bench-to-bedside individualized treatment based on cancer heterogeneity is the most critical challenge to be solved.

In conclusion, there are still many opportunities for additional studies, especially on the mechanisms of tumorigenesis and progression. Moreover, additional opportunities ought to exist for the application of nanotechnology in targeted oncological research and clinical translation. The myriad innovative advances in the future will promote the development of accurate and efficient nanomedicine and will hopefully solve the crucial problems of cancer-targeted drug delivery to benefit human health.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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