Biomaterials Science

REVIEW

View Article Online
View Journal | View Issue

Cite this: *Biomater. Sci.*, 2020, **8**, 552

Cell membrane biomimetic nanoparticles for inflammation and cancer targeting in drug delivery

Huaiji Wang,[a] Ying Liu,[a] Ruiqing He,[a] Dailin Xu,[a] Jie Zang,[a] Nopphon Weeranoppanant,[b,c] Haiqing Dong*[a] and Yongyong Li *[a]

Received 30th August 2019,
Accepted 10th November 2019

DOI: 10.1039/c9bm01392j

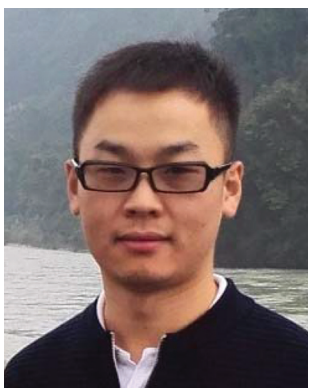
rsc.li/biomaterials-science

Nanoparticle capture and elimination by the immune system are great obstacles for drug delivery. Camouflaging nanoparticles with cell membrane represents a promising strategy to communicate and negotiate with the immune system. As a novel class of nanotherapeutics, such biomimetic nanoparticles inherit specific biological functionalities of the source cells (*e.g.*, erythrocytes, immune cells, cancer cells and platelets) in order to evade immune elimination, prolong circulation time, and even target a disease region by virtue of the homing tendency of the cell membrane protein. In this review, we begin with an overview of different cell membranes that can be utilized to create a biointerface on nanoparticles. Subsequently, we elaborate on the state-of-the-art of cell membrane biomimetic nanoparticles for drug delivery. In particular, a summary of data on circulation capacity and targeting efficiency by camouflaged nanoparticles is presented. In addition to cancer therapy, inflammation treatment, as an emerging application of biomimetic nanoparticles, is specifically included. The challenges and outlook of this technology are discussed.

1. Introduction

Systemic administration of therapeutic agents is presently the most common method for treating many symptoms and diseases, including inflammation and cancer. However, most of the agents show slow circulation and targeting ability.[1] Such problems can be addressed by nanoparticle-based drug delivery. In general, therapeutics are supposed to be encapsulated into

[a]*Shanghai Tenth People's Hospital, The Institute for Biomedical Engineering & Nano Science, Tongji University School of Medicine, Shanghai 200092, P. R. China. E-mail: inano_donghq@tongji.edu.cn, yongyong_li@tongji.edu.cn*
[b]*Department of Chemical Engineering, Burapha University, 169 Longhard Bangsaen, Saensook, Chonburi 20131, Thailand*
[c]*School of Biomolecular Science and Engineering, Vidyasirimedhi Institute of Science and Technology (VISTEC), Wangchan Valley 555 Moo 1 Payupnai, Wangchan, Rayong 21210, Thailand*



Huaiji Wang

Huaiji Wang is currently pursuing his M.S. degree at the School of Medicine, Tongji University. His major research focuses on the development of a cancer cell membrane camouflaging nanoplatform for photo-immunotherapy.

Nopphon Weeranoppanant

Dr Nopphon Weeranoppanant received his B.S. in Chemical Engineering from Columbia University in 2011. Then, he obtained his M.S.CEP. and Ph.D. in Chemical Engineering from Massachusetts Institute of Technology (MIT) in 2013 and 2016, respectively. Currently, he is a lecturer at the Department of Chemical Engineering at Burapha University, Thailand. Also, he holds an adjunct faculty position at the School of Biomolecular Science and Engineering (BSE) at Vidyasirimedhi Institute of Science and Technology (VISTEC) in Thailand. His research lab focuses on flow chemistry, as well as the integration of chemical and biochemical processes.

nanoparticles (*e.g.*, liposomes,[2] polymers[3,4]) in order to improve their pharmacokinetics and biodistribution. Over the decades, researchers have established a standard coating protocol using polyethylene glycol (PEG)[5,6] to enhance the circulation *in vivo*. Further modification of targeting molecules such as folate, peptide Arg-Gly-Asp (RGD) or anti-epidermal growth factor receptor (EGFR) antibodies allows active targeting towards the tumor site and improves the enhanced permeability and retention (EPR) effect.[7–9] Besides drug delivery, another application is the local release of therapeutics through the use of bonds that are activatable in disease environments, such as disulfide bonds,[10] hydrazone bonds,[11] enzyme-sensitive peptides,[12,13] temperature-sensitive modules,[14] *etc*.

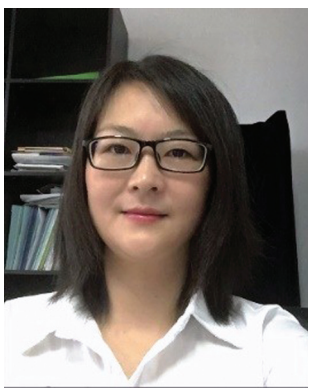
Nevertheless, nanoparticle-based drug delivery is still challenging in many aspects. First, due to 'foreign' compositions, nanoparticles can be cleared rapidly by the immune system, leading to undesirable tumor accumulation.[15,16] Synthetic nanoparticles are easily opsonized by plasma proteins and cleared by the immune system.[17] This usually results in the short half-life of most synthesized nanoparticle delivery system, confined to within hours or even shorter.[18] In some situations, the interaction between the nanoparticles and the immune system induces the production of antibodies that further accelerate their clearance.[19–22] Second, unlike native cells, nanoparticles are usually unable to actively sense and move towards the disease environment, limiting the overall accumulation of nanoparticles. Recent statistical analysis has shown a targeting accumulation efficiency of only 0.7%.[23] An ideal targeting strategy should involve the effectively circulation and accumulation of a material in the targeted region. Consequently, the concept of using cell membrane to camouflage nanoparticles for active delivery provides a new possibility for targeted therapy.[18]

Camouflaging nanoparticles with cell membrane, also known as a 'nanoghost' strategy, utilizes cell membranes such as red blood cell (RBC) membrane, immune cell membrane, cancer cell membrane and platelet membrane. Compared with conventional strategies, this biomimetic strategy exhibits prolonged circulation of the nanoparticles, which are less likely to be recognized by the immune system. For instance, RBC membrane-coated nanoparticles have been designed with prolonged blood circulation time to alleviate clearance by the immune system.[24] Homophilic targeting can also be achieved by cancer cell membrane coating.[25,26] Macrophage cell membrane helps nanoparticles actively target metastatic breast cancer in the lungs by realizing an interaction between the vascular cell adhesion molecule-1 (VCAM-1) of the cancer cells and the α4 integrin of the macrophages.[27] This research proved that the inherent functions of the mother cell membranes make the nanoparticles suitable for use in drug delivery applications.

In this review, we provide an overview of the recent progress in the cell membrane camouflaging of nanoparticles for drug delivery. The advantages of the camouflaged nanoparticles are highlighted with a collection of data on their circulation capacity and targeting efficiency (Table 1). Moreover, the two interesting applications for these nanoparticles, *i.e.* cancer therapy and inflammation treatment, are also covered (Fig. 1). Finally, the challenges and outlook of such biomimetic nanomedicines are presented.

2. Cell membrane isolation and nanoparticle camouflaging

In terms of the isolation of cell membrane, the cells are generally subject to a continuous process to separate the cell membrane from other cellular compartments. The cultivated or primary cells need to be pre-treated using hypotonic buffer to mediate cell death. Subsequently, a discontinuous sucrose-gradient centrifugation, under the protection of protease inhibi-



Haiqing Dong

Haiqing Dong is an Associate Professor at the Institute for Biomedical Engineering & Nano Science (iNANO), Tongji University School of Medicine, China. She received her Ph.D. from the College of Chemistry and Molecular Sciences from Wuhan University in 2009. Then, she joined the Laboratory of Nano Science at Tongji University as a postdoctoral fellow. In 2011, she joined the Advanced Institute of Translational Medicine as an Associate Research Scientist at Tongji University. Since 2013, she has been a faculty member at the Tongji University School of Medicine. Her research areas include supramolecular self-assembly, living cell delivery and their biomedical applications.

Yongyong Li

Yongyong Li is a Professor at the Institute for Biomedical Engineering & Nano Science, Tongji University School of Medicine, China. He received his Ph.D. from the College of Chemistry and Molecular Sciences, Wuhan University, in 2009 and has worked as a faculty member at Tongji University, China, since 2009. He was promoted to a full professor in 2015. His research focuses on bioinstructed materials for therapeutic delivery.

Table 1 Representative examples of cell membrane coated nanoparticles on the circulation and targeting efficiency

Membrane types	Core nanoparticles	$t_{1/2}$ (h)	$t'_{1/2}$ (h)	Targeting efficiency: Relative (times)	Targeting efficiency: Absolute (%ID g^{-1})	Ref.
NK cell	Cationic liposomes of DOTAP/DOPE/Dox	—	18	—	5	32
	mPEG-PLGA/TCPP	5.5	8	6	—	33
Cancer cell	PLGA/ICG	—	—	3.1	—	34
	Diselenide-bridged mesoporous silica nanoparticles/cytotoxic RNase A	7.5–9.7	15.2–20.1	2	—	35
	PLGA/hemoglobin and Dox	—	—	1.3	—	36
	PTX-PCL/PTX	5.9	11.8	4.3	—	37
	Flake-shaped nanocrystals/hydroxycamptothecin	1.0	7.9	2.2	—	38
	Gold nanocages/Dox	—	—	4.2	20–25	39
Leukocyte	SiO_2 nanoparticle modified with polyelectrolyte layers	—	8.4	—	—	40
Neutrophil	PLGA/carfilzomib	0.77	6.59	2.12	—	41
Platelet	Melanin nanoparticles/Dox	5.13	27.6	8/15*	—	42
	Nanogel/Dox and TRAIL	5.6	32.6	1.9	—	43
Macrophage	Liposome/emtansine	—	—	2.8	—	25
	Mesoporous silica nanocapsules/Dox	—	—	4.6	6	44
	DNA tetrahedron dendrimer/Dox	—	—	2.1	—	45
Stem cell	PLGA/Dox	—	2	2	—	46
RBC	Prussian blue-manganese dioxide (PBMn) nanoparticle/Dox	—	—	2	8	47
	ROS-responsive PTX dimer	—	—	4.6	7	48
	Metal–organic framework nanoparticle/glucose oxidase and prodrug tirapazamine	2.4	4.7	2	8	49
	Gelatin nanogel/methylene blue and cisplatin	4.6	26.1	2–3	—	50
	pH-sensitive polymer/Dox and lexiscan	2.4	9.3/7.8#	3.5	3.86/9.66#	51
	Magnetic *O*-carboxymethyl-chitosan/PTX and Dox	—	—	17	—	52
	Upconversion nanoparticles	—	—	9	—	53
Erythrocyte-cancer	Hollow copper sulfide nanoparticles/Dox	1	9.6	2.5	18	54
	Melanin	4	11.2	—	—	55
Leukocyte-cancer	—	4	8.1	9.3	79.1	56

$t_{1/2}$: circulation half-life of the core nanoparticles; $t'_{1/2}$: circulation half-life of biomimetic nanoparticles; relative targeting efficiency (times): the ratio of biomimetic nanoparticles to bare nanoparticles distributed in the tumor; absolute targeting efficiency: the percentage injected dose per gram of tumor; *: cell membrane modified with RGD; #: cell membrane inserted with targeting angiopep-2.

tors, is employed to remove the contents inside the cells, including the nucleus, enzymes and other vesicles. It is important to note that the intercellular lysate of nucleus-free cells (*e.g.* RBCs) can be easily removed by centrifugation. After that, the cell membrane can be finally collected, followed by sonication and extrusion through a porous polycarbonate membrane.

The camouflaging process is performed by extruding the mixture of nanoparticles and extracted cell membrane through a repeated mini-extrusion process, a process adapted from the production of synthetic liposomes.[28] As a versatile and accessible coating approach, cell membrane biomimetic nanotechnology has been implemented to camouflage a wide variety of synthetic or bioderived nanoparticles, including polymer nanoparticles (*e.g.* poly(lactic-*co*-glycolic acid) (PLGA), liposomes), metal nanoparticles (*e.g.* gold, Fe_3O_4, hollow copper sulfide), inorganic non-metal nanoparticles (*e.g.* mesoporous silica), albumin nanoparticles (BSA), nanogels, and so on. Representative examples are summarized in Table 1.

3 Merits of biomimicry

The extracted cell membranes have the inherent characteristics of their mother cells as a result of the protein retained on their surface. Therefore, the cell membrane tends to provide the coated nanoparticles with favourable biological functions, including longer circulation, active targeting capability (Table 1) and even immune capacity.

3.1 Long circulation

3.1.1 RBC membrane. RBCs are responsible for transporting oxygen to tissues or organs,[29] and possess an extremely long lifespan of approximately 115 days in humans.[30,31] CD47, a transmembrane protein expressed on the RBC membrane, acts as a "don't eat me" marker by selectively binding to SIRPα expressed by macrophages. The activation of this signal pathway helps to prevent macrophage uptake. As a result, RBC membrane-camouflaged nanoparticles are likely to have prolonged circulation in the bloodstream, favouring subsequent accumulation at a target site.

3.1.2 Platelet membrane. Platelets are a type of fragment of the cytoplasm that fall from other cells in the blood. Similar to RBCs, platelets also express CD47, so can be utilized with nanoparticles to avoid uptake by macrophages. Moreover, platelet membrane has additional proteins, such as CD55 and CD59 that can suppress the immunological complement system.[43,57] These expressions can further improve nanoparticle circulation in blood vessels.

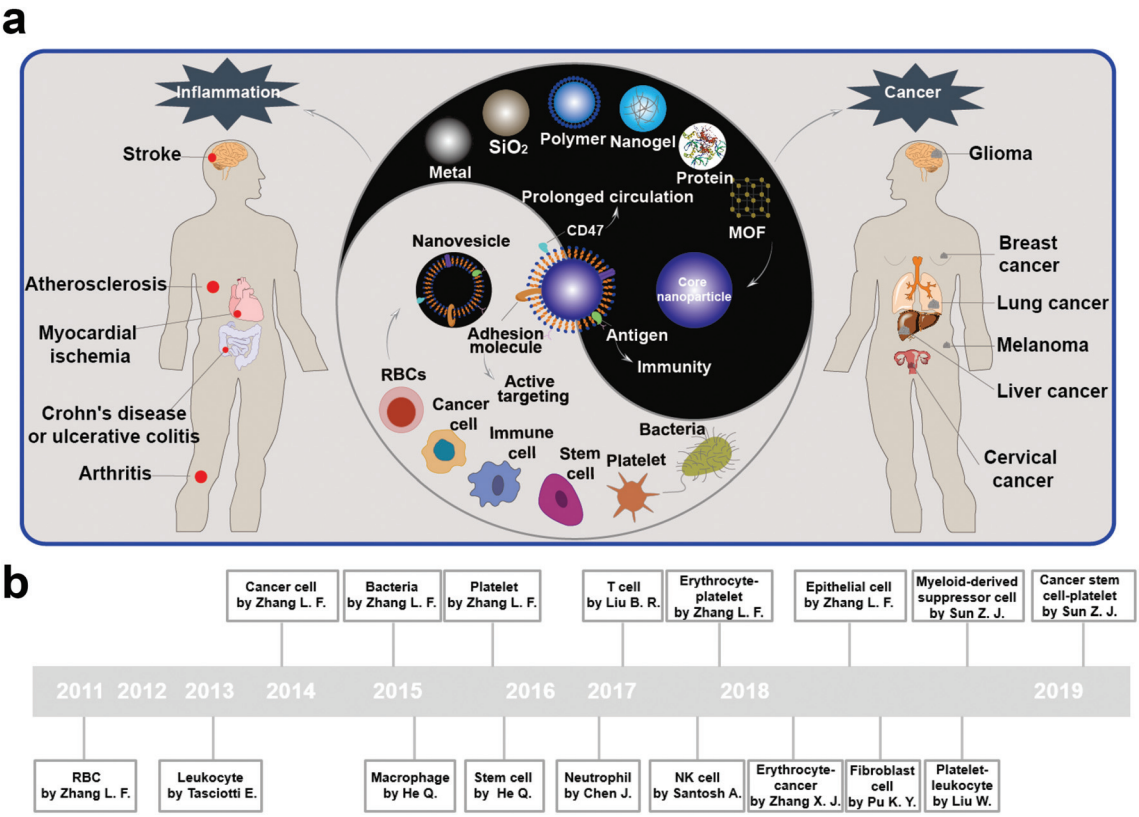


Fig. 1 (a) Cell membrane coated nanoparticles designed for inflammation and cancer therapy. An array of cell membranes from the cell library have been extracted and leveraged to coat a variety of nanoparticles for different diseases. (b) Snapshot of historical trends in cell membrane camouflaging nanomedicine over a span of years.

3.1.3 Immune cell membrane. Immune cells, including macrophages/monocytes, neutrophils, T cells and NK cells, are mainly located in bodily tissues and in the bloodstream. The principle behind the prolonged circulation of nanoparticles coated with macrophage/monocyte or neutrophil membranes lies in the reduced opsonization and self-recognition mechanisms that delay phagocytic uptake.[58] Meanwhile, cytotoxic T cells usually recirculate in the body to hunt for antigens, while NK cells provide host defense. These cells also have effective circulation, and their cell membranes can thus be used to prolong the circulation of nanoparticles *via* a coating process.

3.1.4 Cancer cell membrane. Tumor progression and metastases are mainly caused by immune tolerance towards malignant cells. In the progression of cancer, the cancer cells develop sophisticated mechanisms to neutralize and/or evade immune surveillance. The CD47 molecule overexpressed by the cancer cells plays a major role in immune escape and evasion, particularly in some breast cancer cell lines such as 4T1, MDA-231 and MCF-7.[59] This establishes that nanoparticles camouflaged with CD47 molecules on their surface have the potential to avoid immune elimination.

3.2 Active targeting

3.2.1 RBC membrane. In order to enhance the targeting capability of RBCs, ligands, which specifically bind to inflammation tissue or tumor cells, can be inserted into the RBC membrane to improve targeting accumulation and/or the following cellular uptake. Common targeting ligands include peptides and small molecules, such as angiopep-2, folate, triphenylphosphonium, SHp (CLEVSRKNC), CDX (FKESWREARGTRIERG) and RGD.[51,53,60–63] The incorporation of these new additional properties will definitely expand the native function of RBCs and may profoundly affect the biological outcome. On the other hand, their required further modification complicates the camouflaging process, especially for mass production.

3.2.2 Platelet membrane. Typically, platelets promote coagulation, indicating their tendency to accumulate in injured tissues in order to trigger a repair process.[64] It has been reported that platelets are associated with many diseases, such as Alzheimer's, cancer, tumor growth and metastasis.[65] In addition, research work has evidenced that the surface molecules on platelet membrane such as P-selectin[66] and CD40 ligand[67] modulate a disease process, especially for inflammation and tumors. For instance, P-selectin can bind to CD44 molecules expressed on the surface of tumor cells. Therefore, platelet membrane derived nanoparticles can target and accumulate in tumor tissue.[43] Platelets can also be recruited by vascular damaged components of the subendothelial matrix, including collagen, fibronectin and von Willebrand

factor (vWF).[68] Atherosclerosis targeting has been achieved by platelet membrane coated nanoparticles that can interact with inflamed endothelial cells.[92] A limitation of this platelet membrane camouflaging approach is that the targeting sites of the platelets are mainly located in the subendothelial matrix, which may impede their penetration inside the disease site and further internalization at the cellular level.

3.2.3 Immune cell membrane. Biomimetic nanoparticles with leukocyte membrane are widely used for the treatment of blood vessel injury, inflammation and cancer. Leukocytes have the capability to evade the immune system, cross the biological barriers of the body, recruit and arrive at targeting tissues. The targeting capability relies on a lymphocyte function-associated antigen-1 (LFA-1) molecule that can bind to an intercellular cell adhesion molecule-1 (ICAM-1) on an inflamed endothelium.[69] Similarly, macrophage/monocyte membranes can be utilized because they have a specific membrane protein on their surface that can be recruited to the tumor site by C–C chemokine ligand 2 (CCL2).[70] Neutrophils target circulating tumor cells (CTCs) or inflamed endothelium through combinational binding interactions, namely CD44 with L-selectin, LFA-1 with ICAM-1, and β1 integrin with VCAM-1.[41] Cytotoxic T lymphocytes (CTLs) are more effective in targeting tumor sites due to the higher levels of adhesion molecule expression on CTLs than their naive counterparts.[71] NK cells target tumor cells through inhibitory and activating receptor proteins on their surface, such as DNAM-1 and NKG2D.[33]

3.2.4 Cancer cell membrane. CTCs, derived from local tumors, are resistant to the immune system and capable of targeting homotypic tumors. Cell surface interactions, including Thomsen–Friedenreich antigens and E-cadherin, are responsible for such homotypic aggregation.[37] As a result, the cancer cells tend to exhibit self-adherence, the membranes of which can facilitate the infiltration of nanoparticles into the tissues around carcinoma. Therefore, the adherence between cancer cells offers cancer cell membrane derived nanoparticles a new possibility to actively target tumors, as well as trace and catch cancer cells in the blood. However, the heterogeneity of cancer cells should be considered for desirable homophilic targeting. The mutation in the tumor phenotype during cancer progression affects the targeting effect due to potential phenotype discrepancy between the cell line used in membrane camouflaging and the tumor cells grown in the animal model.

3.2.5 Stem cell membrane. Stem cells have inherent tumoritropic properties, depending on adhesion of the lymphocyte function-associated antigen 1 (LFA-1) binding to the intercellular cell adhesion molecule-1 (ICAM-1), making them fit into cell-based drug delivery.[72] However, stem cells are likely to differentiate into tumor cells, and thereby activate the complement system, compromising their effectiveness in disease treatment. Therefore, stem cell membrane is more suitable for targeting tumors.

3.2.6 Hybrid membrane. In order to enhance the capabilities of the cell membrane coating of nanoparticles, two different cell membranes are integrated to create unique biological features. For example, cell membranes of RBCs were implemented together with cancer cell membranes for improved delivery.[55,73] Such membrane hybridization allows for the development of personalized nanomedicine against different tumors. Longer circulation and enhanced targeting were achieved by fusing erythrocytes with platelets.[74,75] Platelet membrane, which has the ability to evade the immune system, can also be hybridized with cancer stem cell membrane.[76] Platelet and leukocyte membranes can be fused, and further modified with antibodies to enhance the cancer cell binding ability, reducing the homologous leukocyte interaction and promoting the level of specific isolation of circulating tumor cells.[77] In this category of design, it is essential to ensure the optimal distribution and pattern of two types of cell membranes on the nanoparticles.

3.2.7 Other cell membrane. Myeloid-derived suppressor cells rapidly accumulate in the tumor environment, in response to chemokines produced by tumors. This behavior endows cell membrane-coated nanoparticles with the abilities of immune evasion and active targeting of tumor cells.[78] Cancer-associated fibroblast (AF) membrane coated nanoparticles render the homologous targeting of AFs, which is a key component that is a challenge in cancer therapy, as it can promote tumor initiation, angiogenesis, progression, metastasis, and resistance.[79]

3.3 Immunity

Recently, immunotherapy has attracted an intensive amount of attention from researchers. Cell membrane comprises a multitude of immunogenic antigens that can be harnessed to provoke immune response for disease management. Leveraging cancer cell membrane to coat nanoparticles has thus been developed to train the immune system and engineer a vaccine with surface antigenic diversity inherited from source cells. A wealth of membrane-bound proteins (tumor associated antigens) on the cancer cell membrane can be delivered to antigen-presenting cells (APCs) within the tumor.[80,81] NK cell membrane has proteins to induce pro-inflammatory M1-macrophage polarization to modulate the tumor microenvironment, such as immunity-related GTPase family M protein (IRGM1), cannabinoid receptor 1 (CB1), galectin-12, ras-related protein Rab10 (RAB 10), and RANKL.[33] Cell membrane derived nanovesicles (NVs) expressing PD-1 receptors can be exploited as an alternative approach to disrupt the PD-1/PD-L1 immune inhibitory axis for antitumors.[82]

Bacteria membranes with a variety of immunogenic antigens and intrinsic adjuvant properties are also appealing materials. Various pathogen associated-molecular patterns are responsible for the stimulation of innate immunity and the promotion of adaptive immune responses. Bacterial membrane with effective antigen presentation coated nanoparticles has shown robust antibacterial immune responses.[83,84]

4 Recent progress in inflammation and cancer treatment

Inflammation is causally related to many diseases, such as ischemic strokes, ischemic heart disease, rheumatoid arthritis,

atherosclerosis, ulcerative colitis, *etc.*[85] Once inflammation occurs, immune cells rush to the inflamed tissue and are able to cross the biological barriers around the disease region and further penetrate into the tissue. Other cells such as red blood cells and stem cells also play their roles in disease prevention and tissue repair. Additionally, cancer has been recognized as a form of chronic inflammation, involving the participation of a large pool of cell types.[85] As a result, targeting inflammation or tumors based on cell membrane biomimetic nanotechnology provides an opportunity for targeted drug delivery.

4.1 Inflammation

4.1.1 RBC membrane. Recently, studies concerning RBC membrane have been extensively investigated for various types of inflammation therapy. Among these inflammations, atherosclerosis is a progressive inflammatory disease, caused by the aggregation of lipids and immune cells in the artery wall that gradually form an atherosclerotic plaque, hardening and narrowing the arteries. To improve therapy outcome, PLGA nanoparticles have been employed to load rapamycin (RAP) and further cloaked with the RBC membrane (RBC/RAP@PLGA). Importantly, the biomimetic nanoparticles result in less phagocytosis by macrophages *in vitro* and about 31% and 17% overall retention in blood after 24 and 48 h post-injection *in vivo*, respectively, in contrast to the negligible signal of bare PLGA nanoparticles after 4 h post-injection. This prolonged circulation led to an obviously enhanced targeting of atherosclerotic plaques compared to blank nanoparticles, as shown by the *in vivo* fluorescence imaging of ApoE−/− mice. After treatment with free drug, RAP@PLGA and RBC/RAP@PLGA, the lesion area of the plaque was reduced significantly and the area ratio of plaque to the whole aorta declined from 20.13% to 17.8%, and 14.84% and 6.24%, respectively. The longer retention in the blood and stronger targeting of biomimetic nanocomplexes contributed towards significantly attenuating the progression of atherosclerosis.[86]

RBCs camouflaging has also been used to treat acute liver failure, a lethal condition of hepatocyte necrosis and acute deterioration of liver function. Growth factors, such as insulin-like growth factor-1, stromal cell-derived factor-1 and hepatocyte growth factor, were extracted from stem cells and encapsulated with RBC membrane.[87] It has been demonstrated that the RBC coating did not affect the release of growth factor from the RBC coated nanoparticles (MRIN). Moreover, the injected MIRN intravenously showed longer blood retention and more accumulation than that of its nanoparticle counterparts in a mice model with acute liver failure. This study further showed the anti-inflammatory role of MRIN therapy by protecting liver functions effectively and exerting anti-inflammatory effects by reducing the levels of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interleukin-1 beta (IL-1β).

Ischemic stroke, as one of the most serious health diseases, is the injury of neurons due to the upregulated enormous release of toxic reactive oxygen species (ROS) after reperfusion. In order to achieve a long circulation time and specific targeting of ischemic sites, a smart bioengineered drug delivery carrier was developed for ischemic stroke therapy. As shown in Fig. 2a, a boronic ester was introduced to fabricate intelligent ROS-responsive nanoparticles, followed by loading of a neuroprotective agent NR2B9C, RBC membrane was then coated and inserted with a stroke-homing peptide (SHp, CLEVSRKNC).[60] The payloads can be selectively released in neurons upon high levels of intracellular ROS and thus disrupt the interaction between *N*-methyl-D-aspartate receptors and the postsynaptic density protein. *In vitro* results (Fig. 2b) showed that the cumulative NR2B9C release was close to 50% from SHp-RBC-NP groups in the presence of 1 mM H_2O_2, 5-fold higher than the group in the absence of H_2O_2. *In vivo* pharmacokinetic testing (Fig. 2c) demonstrated that the system has a longer circulation time of NR2B9C (over 48 h) with a half-life of 1.38 h, almost 3-fold higher than the control group. The enhanced active targeting of the ischemic area was also demonstrated using middle cerebral artery occlusion (MCAO) rats with reduced ischemic brain damage, as shown in Fig. 2d. The neurological deficit induced by ischemia reperfusion was significantly ameliorated with the treatment with SHp-RBC-NP/NR2B9C compared with that of the MCAO control group. In gene delivery, RBC membrane was introduced onto the surface of gene complexes *via* electrostatic interactions to construct biomimetic gene delivery systems. In this study, the new system exhibited low systemic toxicity and high transfection efficiency towards endothelial cells to enhance its migration ability. Interestingly,

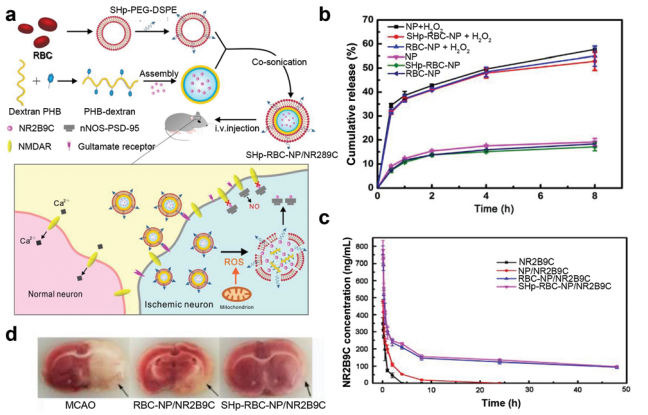


Fig. 2 (a) Schematic design of the RBC coating system (SHp-RBC-NP/NR2B9C) for ischemic stroke therapy. After intravenous injection, the SHp-RBC-NP/NR2B9C could prolong the circulation life with the RBC-mimicking properties and then target to the ischemic brain site *via* stroke homing peptide mediated transcytosis. Upon entry into ischemic neurons, the NR2B9C is released from the PHB-dextran polymer nanoparticles attributable to the high levels of intracellular ROS and then selectively disrupted the NMDARs with PSD-95 to prevent the overproduction of nitric oxide (toxic signaling agent). (b) *In vitro* release profiles of NR2B9C from NP and RBC-NP in PBS (pH 7.4) and PBS with 1 mM H_2O_2 (n = 3). (c) *In vivo* pharmacokinetics of free NR2B9C, NP/NR2B9C, RBC-NP/NR2B9C, and SHp-RBC-NP/NR2B9C (n = 3). (d) Representative tissue slices showing that RBC-NP/NR2B9C and SHp-RBC-NP/NR2B9C group can significantly reduce the infarct volume; the arrows indicated the infarct region as observed. Reproduced from ref. 60. Copyright 2018 American Chemical Society.

the phagocytic rate of the biomimetic system was reduced by 52% compared with that of bare nanoparticles and the circulation time *in vivo* almost doubled.[88]

4.1.2 Platelet membrane. Inspired by the role of platelets as circulating sentinels for invasive microorganisms and vascular damage, platelet membrane cloaked nanoparticles have been designed for immune evasion, subendothelium adhesion and pathogen interactions. Platelet membrane enclosed PLGA nanoparticles have reduced macrophage uptake and avoid complement activation in human plasma. When filled with docetaxel and vancomycin, respectively, it revealed enhanced therapeutic efficacy in both an experimental rat model trial of coronary restenosis and systemic bacterial infection. The unique design takes the advantages of platelet targeting to the injury site and immunomodulatory function and prevents activation of the complement system.[57] In a similar system, a model drug-rapamycin (RA) was loaded into PLGA nanoparticles coated with a PEG inserted platelet membrane for atherosclerotic plaque targeted therapy. After platelet membrane coating, the targeting efficiency towards atherosclerotic arterial trees was promoted to about 4.98-fold higher than control nanoparticles. Also, the progression of atherosclerosis was significantly attenuated and atherosclerotic plaques were stable in ApoE–/– mice.[92]

As for myocardial infarction (MI), cardiac stem cells (CSCs) as a treatment for MI had been investigated in laboratory animal model studies. However, CSCs suffer from low cell retention in the heart. CSCs were therefore fused with platelet nanovesicles (PNVs). Obviously, PNV decoration enhances CSC binding to injured blood vessels *ex vivo*. Moreover, PNV decoration promotes the targeting efficiency of CSCs to the MI injury site and was found to preserve cardiac pump functions and reduce infarct sizes in a rat model of ischaemia/reperfusion.[68]

Inspired by the active role of platelets in the pathogenesis of rheumatoid arthritis, intact platelet membrane was coated onto PLGA nanoparticles for the targeted drug delivery of rheumatoid arthritis, mediated by platelet receptor-mediated adhesion. The studies demonstrated that nanoparticles coated with platelet membrane significantly accumulated in the inflammatory synovial tissue, which may be partly due to the interaction of platelet membrane proteins (GPVI, P-selectin) with collagen IV, and the overexpression of CD44 in rheumatoid arthritis synovial tissue. The arthritis index, micro-CT imaging and histological examination were used to evaluate the therapeutic outcome. Nanoparticles loaded with the model drug FK506 were found to exert a potent anti-arthritic effect.[93]

Synthetic platelets were synthesized and endowed with physical and biological features similar to those of native platelets, such as appropriate size (1 μm), discoidal shape and alternate layers of proteins. Importantly, VWF-A1 was inserted into the particle surface, a key component responsible for the adhesive functions of platelets. These synthetic platelets exhibited high targeting and specificity efficiency, promising to mimic natural platelets to improve targeting efficacy.[94]

4.1.3 Immune cell membrane. Acute pancreatitis (AP) with severe abdominal pain often results in inflammation in regional tissues and even induces life-threatening systemic inflammatory responses. When it comes to therapy, the blood-pancreas barrier is the great hurdle for the management of AP. During inflammation, neutrophils can be quickly recruited and stimulated by cytokines to the site of inflammation. Based on the natural merits of neutrophil membrane, celastro (CTL) loaded PEG-PLGA nanoparticles camouflaged with neutrophil membrane (NNP/CTL) were developed to overcome the blood-pancreas barrier.[95] NNP/CTL can selectively accumulate in inflamed pancreatic tissue. The level of pancreatic myeloperoxidase and serum amylase was downregulated, and the systemic toxicity was obviously improved, as demonstrated in a rat model. The most obvious decrease in the weight of ascites and the wet/dry ratio was observed in the rat model when treated with NNPs/CLT, compared with the other three control groups in which there were no noticeable differences.

To treat ulcerative colitis, neutrophil membrane vesicles were inserted into keratinocyte growth factor (KGF) encapsulated liposomes as neutrophil-like liposomes (KGF-Neus). The KGF-Neus were able to selectively bind to inflammatory human umbilical vein endothelial cells (HUVECs) and home to the inflamed bowel of mice with the fastest and the highest distribution after intravenous injection, which led to the effective recovery of the morphology and functions of the bowel. Compared with free KGF solution and KGF-Lips, KGF-Neus showed the most obvious amelioration of inflammation, comparable to normal mucosa in the control group. The results illustrate that KGF-Neus accumulate widely in the inflamed colons of an ulcerative colitis mice model, leading to a better therapeutic effect on the colitis in the mice.[96] In addition, leukocyte membrane rich in the expression of integrin α4β7 was also used to develop biomimetic nanovesicles for inflammatory bowel disease. When inflammation occurs, α4β7 integrin is overexpressed on the surface of T lymphocytes, which binds to the α4β7 receptor in the gastrointestinal tract and recruits more T lymphocytes to reach the site of inflammation. Thus, this specialized drug delivery system can actively accumulate in the inflamed colon and firmly bind with the activated endothelium in diseased colon tissue, thereby reducing intestinal inflammation.[97]

Based on the close relationship between leukocytes and activated endothelial cells, the researchers reported a strategy to incorporate proteins derived from the leukocyte plasma membrane into lipid nanoparticles, which play an effective role in the regulation of inflammatory environment even without drug loading. They preferentially targeted the inflammatory vasculature, promoted the priority aggregation of leukocytes to inflammatory tissues, reduced neutrophil infiltration, and improved tissue healing, thereby alleviating LPS-induced inflammation models. Upon loading with the anti-inflammatory drug dexamethasone, it was selectively and effectively delivered to the inflamed tissue, and tissue damage was prevented as local inflammation reduced.[98]

Sepsis refers to the systemic inflammatory response syndrome (SIRS) caused by infection. Neutralization and elimination of endotoxin is essential for its treatment. Recently,

researchers have developed a macrophage membrane as a bait to develop a biodegradable PLGA core coated with a macrophage membrane for the control of sepsis. These macrophage-like nanoparticles effectively sequester proinflammatory cytokines and inhibit systemic inflammatory cascade.[99] As mentioned above, rheumatoid arthritis mainly occurs due to inflammatory synovitis. Activation of neutrophils stimulates the synaptic cells to produce chemokines, thereby increasing the recruitment of neutrophils. Researchers have developed neutrophil-like nanoparticles and investigated their use as a broad-spectrum anti-inflammatory agent for rheumatoid arthritis management. By displaying neutrophil plasma membrane on the PLGA nanoparticle surface, the neutrophil-NPs were anticipated to mimic the source cells and thus bind with immunoregulatory molecules that would otherwise target endogenous neutrophils. An *In vivo* study further revealed that such neutrophil membrane-coated nanoparticles inhibit synovial inflammation and alleviate joint damage in inflammatory arthritis.[100]

Similar to cell membrane nanovesicles, outer membrane vesicles also inherit the functionality of source cells. Macrophage-derived outer membrane vesicle coated nanoparticles for targeting rheumatoid arthritis (RA) were established. As shown in Fig. 3a, the macrophages were stimulated with cytochalasin B to induce the outer membrane microvesicle. The membrane protein of the outer membrane microvesicle was similar to the macrophage membrane from the comparative analysis of their proteomic profiles. PLGA was subsequently coated with the microvesicle to prolong the circulation time (Fig. 3b). After loading tacrolimus, a model drug, the system exhibited the most obvious and significant accumulation in the arthritic paw with maximum signal observed 12 h after injection (Fig. 3c–e). Interestingly, the system did not present off-target accumulation in the normal paw and significantly suppressed the severity of RA and mitigated bone erosion with little paw swelling.[101]

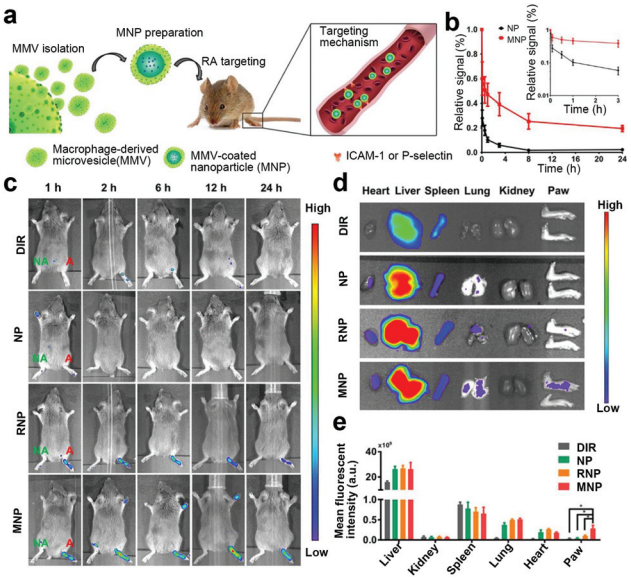


Fig. 3 (a) Schematic illustration of macrophage microvesicle (MMV) coated nanoparticles (MNPs) for rheumatoid arthritis targeting. The MNPs target RA sites through ICAM-1 or P-selectin adhesion. (b) Pharmacokinetics of the NPs or MNPs in mice over 24 h. (c) Representative images of different nanoparticle accumulation in arthritic paws or nonarthritic (NA) paws. (d) Distribution of the MNPs in various organs compared with free DIR, bare NPs, and RNPs. (e) Fluorescence intensity of the MNPs in different organs. Arthritic paws in different groups were compared, and the background was subtracted with the PBS group (n = 3). Reproduced from ref. 101. Copyright 2019 American Chemical Society.

Since membrane properties are dictated by membrane expressions that can be impacted by stimulation, macrophages were subjected to a bacteria stimulation, assuming that membrane is more suitable for the killing of bacteria. The macrophage membrane after bacteria treatment, was separated and coated onto a gold-silver nanocage for bacteria targeting. Consistent with the hypothesis, the expressions of pathogen-related receptors on the macrophage membranes were upregulated *via* stimulation with *Staphylococcus aureus* (Sa) and *Escherichia coli* (Ec) as model Gram positive and negative bacteria, respectively. The nanosystem derived from Sa pretreated macrophage membrane had the strongest antibacterial ability. Regardless of whether the injection method was local or systemic, the nanosystem retained more at the infection site compared to the bare nanoparticles, which was mainly due to the improved bacterial adherence along with prolonged blood circulation time over a span of 24 h.[102]

Loading drug directly into cell membrane derived nanovesicles has been exploited recently. Resolvin D2, capable of binding with G-protein coupled receptor, was carried into neutrophil membrane-derived nanovesicles by convenient mixing to treat ischemia/reperfusion (I/R) injury. The results showed that the administrated nanovesicles (DiR-HVs) exhibited a higher fluorescence intensity compared with the controls. Remarkably, the fluorescence of DiR-HVs remained almost unchanged within 11 h. It was observed that the nanovesicles circulated and then adhered to inflamed brain blood vessels in real-time. The system dramatically enhanced the resolution of inflammation, improved neurological functions and protected brain damage during ischemic strokes in mice.[103]

4.1.4 Other cell membranes. Inspired by the natural adhesion interactions between pathogen and host, plasma membranes of gastric epithelial cells, inherently adherent to *H. pylori* bacteria, were leveraged to coat clarithromycin-loading PLGA nanoparticles (AGS-NPs), so as to combat *H. pylori* infection. *In vitro* binding examination demonstrated that the AGS NPs showed a 10-fold increase in bacteria internalization efficiency, compared with PEG coated PLGA nanoparticles (PEG-NPs). Moreover, the AGS-NPs exhibited superior therapeutic efficacy towards a mouse model of *H. pylori* infection with about 3.08 orders of magnitude reduction compared with the non-targeted nanoparticle control group (only 0.53 order of magnitude reduction).[104]

As a new alternative for treating bacterial infection, bacteria membrane coated nanoparticles hold great promise for designing effective antibacterial vaccines. The bacterial outer mem-

brane vesicle (OMV) of *Escherichia coli*, as a model pathogen, was collected to coat Au nanoparticles (BM-AuNPs) to produce an antibacterial vaccine. Unlike OMV, the AuNPs supported the stability of the outer membrane, which exerted an immune stimulation effect. The BM-AuNPs activated dendritic cells and induce dendritic cell (DC) maturation (upregulated CD40, CD80 and CD86). Besides this, the BM-AuNPs generated a stronger antibody response with IgG titer levels of approximately 3- and 5-fold increase compared with OMV at dosages of 0.2 and 0.02 μg of antigen. Meanwhile, strong Th1 and Th17 based immune responses were induced along with elevated expression of INF-γ and IL-17.[83]

Stem cell therapy has been applied in tissue regeneration and entered clinical investigation. The main mechanism lies in the secretion of paracrine factors and intracellular regenerative pathways triggered by stem cell membranes. Meanwhile, to prevent T cell immune response activation, synthetic stem cells were exploited by loading secretion protein into PLGA nanoparticles camouflaged with stem cell membrane (CMMPs). The CMMPs selectively interacted with injured cells leading to the preservation of viable myocardium and the augmentation of cardiac function in a mouse model of myocardial infarction. The cardiac function was robustly boosted with the highest left ventricular ejection fractions (LVEFs), resembling those of CSC treatment with real CSCs, which also resulted in remuscularization, proliferation of endogenous cardiomyocytes, augmentation of blood flow, and growth of vessel density in the post-MI heart.[105]

4.2 Cancer

4.2.1 RBC membrane. Representative examples of RBC membrane coatings for cancer therapy are listed in Table 2. Actually, the first demonstration of cell membrane biomimetic nanoparticles was established by RBC membrane intended to improve nanoparticle biointerfacing capacity, *i.e.* prolonged circulation time *in vivo*, which was of great importance in bypassing macrophage uptake and systemic clearance.[18] In this pioneering work, the anti-tumor drug doxorubicin (Dox) was encapsulated into PLGA nanoparticles and further coated with RBC membrane. Through this biomimetic approach, an elimination half-life of 40 h was achieved to prolong the circulation of the PLGA nanoparticles, outperforming classic PEGylated control. Moreover, through a lipid tethering technique, the previously identified active targeting ligands with a lipid tail could be conveniently incorporated into nanoparticle systems. For instance, a brain tumor targeting ligand, a neurotoxin-derived peptide, could be efficiently anchored onto cell membrane, based on the lipid tethering technique. Peptide functionalized RBC-camouflaging nanoparticles could be loaded with the chemotherapeutic drug Dox to manage brain glioma. Such nanoparticles possess the properties of RBCs and peptides, providing superior therapeutic efficacy and markedly reduced toxicity, as compared to non-targeted drug formulations.[61] Similarly, RGD with a lipid tail was also inserted into the RBC membrane of magnetic *O*-carboxymethyl-chitosan nanoparticles to encapsulating Dox and paclitaxel (PTX) for programmed delivery and eventually, improved tumor inhibition.[52] The development of RBC membrane camouflaging has attracted a great deal of attention and opened up a new direction in nanoparticle surface functionalization for cancer therapy.

Aside from chemotherapeutic delivery, RBC membrane-based drug delivery systems have been rapidly expanded to other methods of cancer treatment, including photodynamic therapy (PDT), photothermal therapy (PTT), and immunotherapy. By harnessing the unique natural oxygen delivery capacity of RBCs, it has also been elegantly demonstrated that the presence of RBC membrane facilitates the permeation of molecular oxygen and even singlet oxygen for PDT. In this study, precision PDT was actively targeted to a mitochondrial site, at a subcellular level, by combining membrane modified with dual targeting moieties for the selective recognition of cancer cells and mitochondrial targeting.[53] Another active design was realized by coating a RBC membrane onto manganese dioxide nanoparticles, as an oxygen precursor, which generated oxygen and relieved tumor hypoxia. The coating of RBC membrane was found to increase the loading capacity of Dox, and the Dox release was accelerated by the RBC membrane disruption resulting from the generated oxygen. Combination therapy of PTT and chemotherapy was realized by incorporating Prussian blue, a good photothermal agent. The multifunctional RBC coated nanoparticles exerted a synergistic effect on tumor growth inhibition.[47] Inspired by the natural killing mechanism of cytotoxic T lymphocytes (CTLs), artificial cells were recently developed by coating a nanogel (loaded with methylene blue (MB) and cisplatin) with RBC membrane. In principle, the artificial cells behave like CTLs, generating pores on the tumor cell surface *via* the photo-heating of MB upon irradiation, and then releasing therapeutic MB and cisplatin into the cytosol for more effective therapeutic effect *via*

Table 2 Representative examples of RBCs membrane coating

Functions	Diseases	Therapeutic agent	Nanoparticles	Cell/animal models
Antitumor	Melanoma	Merocyanine 540	Upconversion nanoparticles	Mouse[53]
	Colorectal cancer	Gambogic acid	PLGA nanoparticles	Mouse[89]
	Glioma	Dox	PLGA nanoparticles	Mouse[61]
Autoimmune diseases	Antibody-induced anemia disease	—	PLGA nanoparticles	Cell, Mouse[90]
Neuroprotection	Ischemic stroke	NR2B9C	ROS-responsive nanoparticles	Mouse[60]
Active liver failure treatment	Liver failure	Stem cell content	PLGA nanoparticles	Mouse[87]
Thrombus ablation	Thrombus	Heparin and chitosan	Au coating chitosan Janus	Cell[91]

a combination of hyperthermia, photodynamic therapy, and chemotherapy. The as-synthesized artificial cells achieved 97% inhibition of pulmonary metastasis without significant toxicity.[50] The high flexibility of the cell derived membrane in co-assembly has been demonstrated by simultaneously imbedding Prussian blue (PB) nanoparticles (NPs) with Chlorin e6 (Ce6), using RBC vesicles. Obviously boosted necrosis and late apoptosis of tumor cells was observed, favourable for the synergistic therapeutic effect of PTT and PDT.[106] Cross-talking in drug delivery for chemotherapy and PDT has been reported using an erythrocyte membrane-based system. A PTX dimer was constructed *via* a ROS-responsive bond, which was utilized as the inner core. Under laser irradiation, the ROS generated from the loaded photosensitizer was not only employed for PDT, but also triggered the release of PTX for the synergistic killing of cancer cells. Enhanced anticancer therapeutic activity and reduced systematic toxicity was achieved.[48]

In recent years, cancer immunotherapy has received rapidly mounting attention. Membrane camouflaging science has also established its great potential in this emerging area. Targeted delivery of antigens towards dendritic cells represents a key bottleneck in the development of an effective cancer vaccine. As a solution to address this issue, RBC membrane was exploited to coat ovalbumin antigen-carrying nanoparticles, which were anchored with mannose, *via* a lipid tethering technique, a specific ligand for DC recognition, helpful to increase antigen uptake by DC.[107] Rational design of the nanovaccine was able to promote transport to draining lymph nodes and effectively inhibit tumor growth, and suppress tumor metastasis in prophylactic, therapeutic, and metastatic melanoma models.

4.2.2 Platelet membrane. Due to its inherent hallmarks such as vascular damage response and recognition of their interaction with CTCs, platelet cell membrane-based systems have found application in treating tumor metastasis, an intractable clinical challenge. The specific receptor P-Selectin on the surface of platelets can bind specifically to CD44 overexpressed on tumor cells, a recently discovered mechanism for its crucial contribution in tumor metastasis.[66] This specific recognition between platelets and CTCs favors the aggregation of platelets around CTCs and promotes their circulation in the bloodstream and eventual tumor metastasis. With this in mind, Gu *et al.* developed a platelet membrane-coated core–shell nanovehicle for targeting primary tumor sites and CTCs. In their design, Dox containing nanoparticles were loaded inside the platelet membrane and the outside of the membrane was decorated with the protein drug TRAIL, which can activate the apoptosis signalling pathway. The tailored dual-drug loaded system achieved synergistic antitumor efficacy as well as the capacity to eliminate tumor cells that have metastasis potentiality.[108] The same research group tackled multiple myeloma (MM), by showing that the role of thrombus should be considered, since it promotes tumor growth *via* a tumor-specific clot-promoting mechanism. By capitalizing on the crucial role of platelets in thrombus formation, platelet membrane-coated nanoparticles were developed for the targeted delivery of proteasome inhibitor bortezomib at the tumor site based on the bone microenvironment. The platelet membrane here can be used to carry the tissue plasminogen activator (tPA) for dissolving the thrombus. Alendronate, with the capability to chelate calcium ions in the bone microenvironment, was introduced into the system to realize first targeting, while the subsequent targeting of myeloma cells was driven by P-selectin and the CD44 receptor. The therapy successfully decreased blood viscosity and upregulated the level of procoagulant and fibrinolytic activities.[109] This programmed targeting strategy showed promising anti-MM treatment efficacy compared to a traditional active targeting nanoparticle system. In order to tackle multidrug resistance cancer, RGD peptide-modified platelet vesicles were used to encapsulate melanin nanoparticles and Dox to efficiently inhibit the growth and metastasis of drug-resistant tumors *via* the dual-targeting of cancer cells and tumor vasculature. Platelet cell membrane was used here mainly for its immune-evading and tumor-targeting capacity. The RGD decorated nanosystem efficiently inhibited resistant cells *via* a cancer-cell and tumor-vasculature dual-targeting strategy.[42] Taking advantage of platelet biology, other platelet cell membrane biomimetic systems were also proposed, such as gold and magnetic based nanoparticles, making platelet camouflaging highly versatile for cancer therapy.[110,111]

4.2.3 Immune cell membrane

4.2.3.1 Macrophage membrane. As an important cell subset of the innate immune system, macrophages can specifically bind to the VCAM-1 receptor of cancer cells *via* alpah-4 integrins. This mechanism is also acitively involved in conditioning the metastasis of CTCs. A straightforward and simple approach was developed by integrating macrophage membrane with liposome structure for improved delivery to metastatic sites. It was found that this strategy facilitated 4T1 cell uptake of emtansine-carrying liposomes and inhibited the viability of 4T1 cells. *In vivo* studies revealed that the hybrid system was able to target metastatic cells resulting in a notable inhibitory effect on tumor metastasis.[25] Researchers found that the macrophage membrane offered more advantages than RBC membrane functionalization due to the active targeting ability of macrophage surface proteins towards tumor endothelium.[112] An example was demonstrated by macrophage membrane-camouflaged gold nanoshells (AuNSs) with enhanced photothermal cancer therapy.[112] Using a similar approach, the same group further camouflaged macrophage membrane onto mesoporous silica nanocapsules through top-down assembly (Fig. 4a).[44] They demonstrated that the camouflaging system showed 36% and 32% retention even after 24 and 48 h, respectively, while the non-camouflaging system was almost eliminated within 24 h (Fig. 4b). In addition, by virtue of some chemokines like CCR2 expressed on macrophages, the macrophage membrane mimetic system showed active binding to cancer cells that secrete the CCL2 ligand (*e.g.* breast cancer) (Fig. 4c). Transwell assay revealed a 5-fold greater migration capacity of camouflaged photothermal nanoparticles towards the CCL2 positive cancer than that of the control. In order to sensitize cancer cells to PTT, quercetin

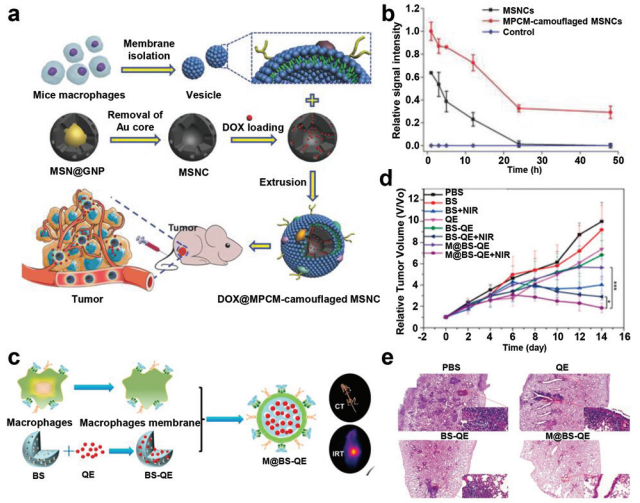


Fig. 4 (a) Schematics of the preparation process of macrophage cell membrane (MPCM)-camouflaged mesoporous silica nanocapsules (MSNCs) and their subsequent *in vivo* cancer therapy. (b) Relative fluorescence intensity of rhodamine B (Rhd B)-labelled nanoparticles in blood after injection. At different time points, 40 μL of blood was collected from the eye socket of mice. (c) Illustration of the preparation of membrane camouflaged and QE loaded photothermal nanoparticles (M@BS-QE) with tumor proactive recruitment/targeting ability (CCL2/CCR2 chemokine axis and α4/VCAM-1 interaction). (d) Tumor volume growth curves of 4T1 tumor-bearing mice in different groups. (e) Histological examination of metastatic lesions in lung tissue after H&E staining (scale bar = 500 μm). Reproduced from ref. 44 and 70. Copyright 2015 John Wiley & Sons and 2018 American Chemical Society, respectively.

(QE), a HSP70 inhibitor, was included in their design for strengthening PTT efficiency. As expected, the therapeutic efficiency, in both primary and lung metastasis, were improved along with minimal side effects (Fig. 4d and e).[70] There have also been developments in intelligent nanoplatforms. As an example, multi-tasking macrophage-membrane-coated nanoparticles were developed. After tumor targeting accumulation, the system functioned to penetrate into the tumor by discharging from the outer membrane. Upon internalization by tumor cells, the loaded drug PTX was quickly released from the nanoparticles in response to the endosome pH for chemotherapy.[27]

4.2.3.2 T cell membrane. T cell membrane contains proteins to sense inflammation and diseased sites. Local low-dose irradiation can upregulate adhesion molecules of tumor vasculature and release chemoattractants, by which $CD8^+$ T cells can be recruited to the tumor site. In order to harness this phenomenon to promote the targeting efficiency of camouflaging nanomedicine, PLGA carrying paclitaxel nanoparticles coated with human cytotoxic T-lymphocyte membranes was developed and administrated into mice with gastric cancer. Aided by low-dose irradiation, it was reported that this strategy could dramatically inhibit tumor growth by up to 88.50%.[71]

4.2.3.3 NK cell membrane. Due to the characteristics of NK cell membrane receptors, an NK cell membrane camouflaged liposome delivery system, named NKsome, was developed for targeting tumors. NKsome exhibited excellent biocompatibility, higher affinity to tumors with enhanced tumor homing efficiency and an extended circulation of 18 h *in vivo*. After loading with Dox, the NKsome showed potent antitumor activity against MCF-7 tumor bearing mice.[32] Deng *et al.* developed a NK cell-membrane biomimetic system for PDT and thus induced anticancer immunotherapy. Photosensitizer-loaded nanoparticles cloaked with NK cell membrane were confirmed to selectively accumulate in the tumor, and PDT induced cancer cell death subsequently strengthened their antitumor immunity efficiency. The system showed the capability to eliminate primary tumors as well as inhibit distant tumors due to an abscopal effect.[33]

4.2.4 Stem cell membrane. Stem cells also possess tumoritropic properties with a great number of molecular recognition moieties, which offers possibilities in constructing biomimetic systems for chemotherapy, PDT and gene therapy. Gao *et al.* developed a highly efficient tumor-targeting drug delivery platform based on bone marrow derived mesenchymal stem cell membrane-coated gelatin nanogels (SCMGs) with a Dox payload. The SCMGs presented excellent mesenchymal stem cell-mimicking cancer targeting capacity and their accumulation in the tumor site was enhanced *in vivo* compared with uncoated nanogels. It was demonstrated that the SCMGs could preserve these tumoritropic properties and decrease clearance *via* the reticuloendothelial system, therefore resulting in enhanced antitumor efficacy.[113] Yang *et al.* found that human umbilical cord-derived mesenchymal stem cell membrane coated Dox-carrying PLGA nanoparticles could be taken up by tumor cells and accumulated in acidic organelles for drug release, thereby inducing obvious apoptosis within tumor lesions.[46] Additionally, mesoporous-silica-encapsulated near-infrared photoactivated upconversion nanoarchitecture was fused with the stem cell membrane for PDT therapy.[114] Furman *et al.* reported a selective and safe universal nonviral gene-therapy platform based on nanoghosts (NGs) originating from the membranes of mesenchymal stem cells (MSCs). They demonstrated 80% inhibition of human prostate cancer was achieved when drug loaded MSCs-NGs were administrated.[115] Moreover, they found that nanoghosts carrying pDNA encoded for a cancer-toxic gene inhibited the growth of metastatic orthotopic lung cancer and subcutaneous prostate cancer models notably and dramatically prolonged the animals' survival.[116]

4.2.5 Cancer cell membrane. Cancer cell membrane inherits the functionality of homologous targeting and antigen pool from source cells, and has been applied in the fields of tumor targeted therapy and immunotherapy. The first study in this subfield revealed that cancer cell membrane coated PLGA nanoparticles showed 40- and 20-fold increases of uptake by homologous cancer cells compared with RBC coated and bare nanoparticles, respectively.[117] After assistance with an FDA approved adjuvant monophosphoryl lipid A, the DCs significantly upregulated the maturation markers CD40, CD80, and CD86. Starting from this initial work, using cancer cell membrane to coat nanoparticles has been a burgeoning topic in the areas of antitumor therapy and immunotherapy.

In cancer therapy, cancer cell membrane was coated onto various nanoparticles and further integrated with different therapeutics to achieve purposeful targeting in the tumor region. In one case, FDA-approved PLGA was employed to load chemotherapeutics like PTX (Fig. 5a). Aided by a 4T1 cell membrane coating, the tumor targeting efficacy and half-life in the blood of PTX showed 4.3-fold (Fig. 5b) and 2-fold (Fig. 5c) increases compared with those of bare nanoparticles after administration, respectively. Remarkable antitumor and antimetastatic efficacy can be achieved in orthotopic transplantation tumor models and advanced metastasis mice models.[37]

Nevertheless, a whole cell membrane on the nanoparticle surface may prevent the release of drug. In order to overcome this issue, some strategies have been developed, including photothermal acceleration. In this respect, photosensitizer indocyanine green (ICG) and Dox nanoparticles were co-encapsulated with cell membrane. *In vitro* experiments proved that the release could be promoted by about 4 times with laser irradiation within 72 h (Fig. 5d), which achieved a synergistic therapeutic effect against tumors *in vivo* (Fig. 5e).[118] Similar to this system, Dox-carrying hyperthermia-responsive gold nanocages were incorporated as an inner core with 4T1 cancer cell membrane as the outer shell (CDAuNs). Upon laser irradiation, approximately 75% of the Dox in the CDAuNs exhibited a burst release within the first 8 h. In contrast, the Dox release was obviously maintained with a cumulative release of 38% over 8 h without laser irradiation (Fig. 5f). The synergistic combination of chemo/photothermal therapy showed extremely high inhibition of tumor growth and metastasis.[39]

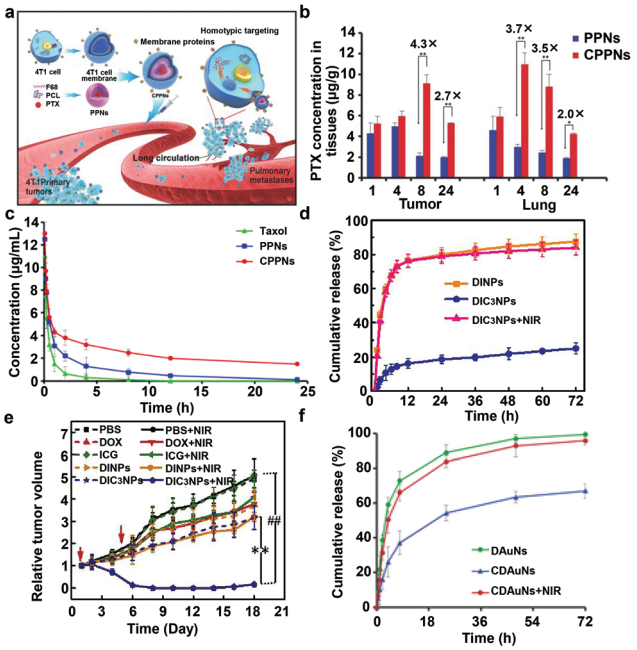


Fig. 5 (a) Schematic illustration of cancer-cell-biomimetic nanoparticles for the treatment of metastatic cancer by targeting homotypic cancer cells located in both the primary tumor and metastatic lesions. (b) Quantitative analysis of the tumor and lung distribution of PTX delivered with nanoparticles (PPNs) or coated nanoparticles (CPPNs). (c) Plasma concentration-time profiles of PTX in rats after administration of various drug formulations at a PTX dose of 10 mg kg^{-1}. (d) *In vitro* release profiles of Dox from a photothermal nanosystem with/without NIR irradiation at pH 7.4. (e) Relative tumor volume of mice treated with different photothermal nanosystems with or without NIR irradiation at 808 nm, 3 W cm^{-2}, 5 (min). (**p < 0.01 *versus* the DIC_3NPs group without NIR irradiation and $^{\#\#}p$ < 0.01 *versus* the PBS group treated using a NIR laser). (f) *In vitro* release profiles of Dox from DAuNs, CDAuNs, and CDAuNs with NIR irradiation in PBS at 37 °C. Reproduced from ref. 37 and 118. Copyright 2016 John Wiley & Sons and 2018 Elsevier, respectively.

PEGylation of the cell membrane was developed using a lipid insertion strategy, so as to further reduce the non-specific interaction between cancer cell membrane and serum.[34] This interaction is reported to mediate undesired aggregation, opsonization, and phagocytosis of nanoparticles *in vivo*. Specifically, PLGA encapsulated ICG was found to show 3.1-fold higher accumulation in the tumor than that without cell membrane coating. Meanwhile, the accumulation in the liver and kidney reduced by as much as 51% and 34%, respectively. The encapsulation of ICG provides the system with fluorescence/photoacoustic imaging properties and photothermal efficacy. In therapy experiments, the multifunctional system completely ablated the MCF-7 tumor with only one single dose.

The improved cancer therapy efficiency by cancer cell membrane coated nanoparticles is also aided by regulating the tumor microenvironment. In order to address the challenges of drug resistance and poor chemotherapy outcome, a PLGA polymeric core encapsulating both haemoglobin (Hb) and Dox camouflaged with cancer cell membrane was developed. The oxygen-carrying capacity of Hb facilitated O_2-interference chemotherapy to overcome hypoxia-induced chemoresistance *via* suppressing the expressions of hypoxia-inducible factor-1α, multidrug resistance gene 1, and P-glycoprotein, therefore resulting in increased DOX accumulation and enhanced cancer therapy effect.[36] In another example, 4T1 tumor cell membrane-coated MnO_2 nanoparticles neutralized excess glutathione (GSH) in the tumor environment, meanwhile the anti-angiogenic drug (Apatinib) was loaded to weaken proangiogenic tumor response. This multifunctional system provides an integrated solution to address the two challenges, including excess GSH and proangiogenic effect during the PDT process.[119]

Apart from tumor targeting therapy, immunotherapy using cancer cell membrane as the antigen pool represents another mainstream technique. In principle, cell membrane alone as a whole could be used as an antigen, which would be captured by APCs. As illustrated in Fig. 6a, a representative nanovaccine was developed, which comprises cancer cell membrane-coated PLGA NPs loaded with an immunostimulatory adjuvant.[81] The nanovaccine hosting both antigen and adjuvant is capable of promoting effective antigen presentation and activating the downstream immune response. In order to exploit the potent antitumor immune response, checkpoint blockades (anti-CTLA4 and anti-PD1) were introduced to relieve the immunosuppressive tumor microenvironment. By this rational design, the tumor growth was successfully controlled (Fig. 6b–d), highlighting the immune potential of a cancer cell membrane

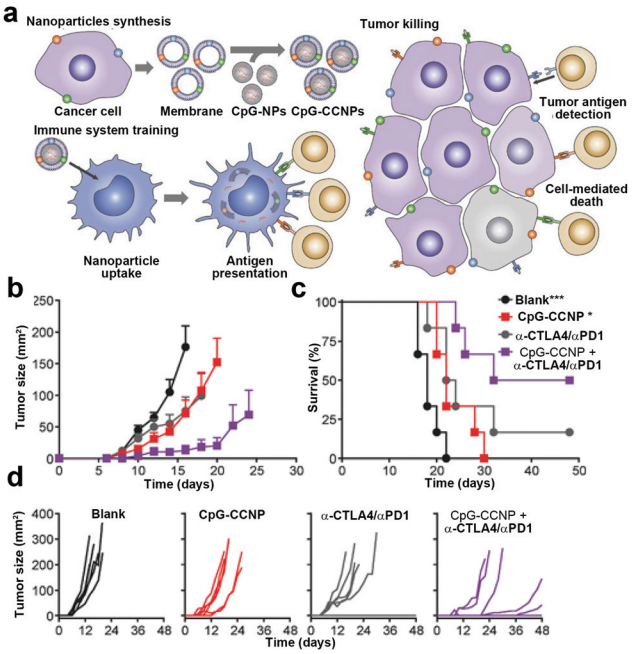


Fig. 6 (a) Schematic of adjuvant (CpG) loaded and membrane coated nanoparticles (CpG-CCNPs) for an anticancer vaccine. Therapeutic efficacy. (b–d) After challenge with B16-F10 cells on day 0, mice were treated using CpG-CCNPs combined with a checkpoint blockade cocktail of anti-CTLA4 plus anti-PD1 (αCTLA4/αPD1), CpG-CCNPs alone, or the checkpoint blockade cocktail alone on days 1, 2, 4, and 7. (b) Average tumor sizes, (c) survival, and (d) individual tumor growth kinetics were plotted over time (n = 6; mean ± SEM). Reporting of average tumor sizes was halted after the first mouse died in each respective group. *p < 0.05, ***p < 0.001 (compared to CpG-CCNP + αCTLA4/αPD1 in the survival plot); log-rank test. Reproduced from ref. 81. Copyright 2017 John Wiley & Sons.

coating strategy.[81] In another case, the antigenicity of cancer cell membrane was also utilized to engineer a personal nanovaccine.[120] To achieve specific targeting to APCs, a mannose ligand was decorated onto a tumor cell-membrane-coated nanovaccine for specific interaction with APCs. In this fashion, the lymph retention showed roughly double the improvement, favourable for eliciting the following immune response.[121]

Another interesting example simultaneously integrates the multiple advantages of immune evasion, homophilic targeting, and immunogenicity of cancer cell membrane. In this design, a core laden with glucose oxidase was coated with a cancer cell membrane to result in a multifunctional system. After accumulation in a tumor, GOx cuts off the glucose source for tumor starvation. The antigen released as a result of starvation mediates tumor cell apoptosis, which, together with the membrane-bound protein coating on the nanoparticle surface, could be captured by APCs to activate an antitumor immune response and effectively inhibit tumor growth in combination with PD-1.[80]

5 Prospects and challenges

In contrast to a synthetic approach such as PEGylation, the cell membrane biomimetic approach has been widely utilized for many purposes beyond prolonged circulation. Active targeting, including homophilic targeting and tumortrophic migration, has been exploited for enhanced drug delivery. Moreover, this development has encouraged researchers to add more functions to the original cell membrane of the source cells. In pioneering work, HEK 293T cells were transfected to express the PD-1 receptor on cell membrane to enhance the membrane's capability to disrupt immune tolerance, opening up a promising opportunity for cancer immunotherapy.[82] Epidermal growth factor receptor (EGFR), highly expressed in many malignant tumors, was engineered onto HEK 293 cell membrane in order to coat magnetic nanoparticles for drug screening.[122] Bacteria pretreatment can be used to modulate a membrane profile of macrophages and, in turn, improve the antibacterial ability of the camouflaged system.[102]

A hybrid cell membrane is a promising way to endow biomimetic nanoparticles with multiple functionalities such as long circulation time and active targeting. The reported hybrid systems include cancer cell and RBC membranes, platelet and RBC membranes, platelet and cancer cell membranes, erythrocytes and platelets, as well as platelets and leukocytes. As an outlook, the field of the hybrid system is likely to grow. However, attention should be paid to the hybridization process, which may further reduce the orientation of membrane molecules and thereby compromise the membrane performance.

The application of camouflaging nanomedicine in treating inflammation is rapidly evolving. In contrast to the immunosuppressive microenvironment of cancer, inflammation usually releases strong immune signals. For example, it will release multiple cytokines that induce a variety of immune cells, including neutrophils, macrophages, and lymphocytes. Immune cell membrane-coated nanoparticles are, therefore, particularly helpful in facilitating the precise treatment of the infection. Cancer immunotherapy represents another emerging pillar that shows the impact of camouflaging nanomedicine. In addition to its targeting capacity, the cancer cell membrane, the host antigen pool, makes the camouflaging of nanoparticles applicable for use in nanovaccines in cancer immunotherapy. This approach overcomes the challenges of specific antigen screening and the complicated process of vaccine fabrication. These developments will definitely further stimulate more advances in 'camouflaging' immunotherapy. To achieve a therapeutic purpose, the recent progress in immunotherapy, such as the anti-PD-1 checkpoint blockade, can be integrated as a cocktail therapy. Also, a promising trend in camouflaging nanomedicine in the applications of infection and cancer is to provide the system with adaptability to the disease microenvironment, such as structural transformation to trigger cargo release.

Despite considerable success, unresolved issues remain that need particular attention for future development in this field. The retainment of cell membrane integrity represents the foremost target, as the cell membrane function is largely dictated by the cell integrity.[123] The degree of integrity (composition and orientation) after the camouflaging process has an

important role in determining how natural behavior can be translated to nanoparticles. During the camouflaging process, the cell membrane structure and protein sequence are likely to change when treated with a lysis buffer or a hypotonic solution *in vitro*. Some membrane fragments tends to be lost upon extrusion and fusion. Characterization of the level of integrity loss remains as a question. Any advance in maintaining the loss of integrity of the cell membrane will significantly improve the impact of this biomimetic approach.

Regarding clinical translation, there are several aspects to consider. The first aspect is safety concerns in using cancer cell or bacterial membranes. Unsuitable explosure of the immunogenicity may induce a harmful immune response. Even for normal cell types, their long-term safety should be considered during clinical translation as there can be a biological discrepancy between the native cell membrane and their extracted formulation. The high heterogeneity of cell membranes and the difficulty in nanoparticle synthesis may present additional challenges to large-scale production.

6 Conclusions

The cell membrane biomimetic strategy has made a significant step in the field of nanomedicine. One of the main advantages of this strategy is the biointerface, which has the inherent character of the native cells. In this review, we gave an overview on the progress in using cell membrane biomimetic nanoparticles for drug delivery by focusing on their applications in infection and cancer therapy. Because of the highly versatile functions of cell membranes in nature, we will undoubtedly envision a broader range of applications of the cell membrane biomimetic approach.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was financially supported by research grants from the National Natural Science Foundation of China (NSFC 51773154, 31771090, 51473124 and 81571801), the Shanghai Natural Science Foundation (17ZR1432100), the Fundamental Research Funds for the Central Universities (22120180062) and the Young Hundred-Talent Program of Tongji University.

Notes and references

1 V. Guillemard and H. U. Saragovi, *Cancer Res.*, 2001, **61**, 694–699.
2 Y. J. Cao, Y. J. Zhou, Q. F. Zhuang, L. Cui, X. L. Xu, R. F. Xu and X. Z. He, *Int. J. Clin. Exp. Med.*, 2015, **8**, 12182–12191.
3 M. B. Zheng, C. X. Yue, Y. F. Ma, P. Gong, P. F. Zhao, C. F. Zheng, Z. H. Sheng, P. F. Zhang, Z. H. Wang and L. T. Cai, *ACS Nano*, 2013, **7**, 2056–2067.
4 X. Q. Yang, J. J. Grailer, I. J. Rowland, A. Javadi, S. A. Hurley, D. A. Steeber and S. Q. Gong, *Biomaterials*, 2010, **31**, 9065–9073.
5 G. Kaul and M. Amiji, *Pharm. Res.*, 2002, **19**, 1061–1067.
6 E. Kajiwara, K. Kawano, Y. Hattori, M. Fukushima, K. Hayashi and Y. Maitani, *J. Controlled Release*, 2007, **120**, 104–110.
7 P. N. Durfee, Y. S. Lin, D. R. Dunphy, A. J. Muniz, K. S. Butler, K. R. Humphrey, A. J. Lokke, J. O. Agola, S. S. Chou, I. M. Chen, W. Wharton, J. L. Townson, C. L. Willman and C. J. Brinker, *ACS Nano*, 2016, **10**, 8325–8345.
8 Z. Yang, J. H. Lee, H. M. Jeon, J. H. Han, N. Park, Y. He, H. Lee, K. S. Hong, C. Kang and J. S. Kim, *J. Am. Chem. Soc.*, 2013, **135**, 11657–11662.
9 E. Vlashi, L. E. Kelderhouse, J. E. Sturgis and P. S. Low, *ACS Nano*, 2013, **7**, 8573–8582.
10 D. Du, K. Wang, Y. Wen, Y. Li and Y. Y. Li, *ACS Appl. Mater. Interfaces*, 2016, **8**, 3287–3294.
11 X. Pang, Y. Jiang, Q. Xiao, A. W. Leung, H. Hua and C. Xu, *J. Controlled Release*, 2016, **222**, 116–129.
12 Y. Yang, D. Y. Pan, K. Luo, L. Li and Z. W. Gu, *Biomaterials*, 2013, **34**, 8430–8443.
13 Y. J. Cheng, G. F. Luo, J. Y. Zhu, X. D. Xu, X. Zeng, D. B. Cheng, Y. M. Li, Y. Wu, X. Z. Zhang, R. X. Zhuo and F. He, *ACS Appl. Mater. Interfaces*, 2015, **7**, 9078–9087.
14 W. J. M. Lokerse, A. M. M. Eggermont, H. Grull and G. A. Koning, *J. Controlled Release*, 2018, **270**, 282–289.
15 D. Bamberger, D. Hobernik, M. Konhauser, M. Bros and P. R. Wich, *Mol. Pharm.*, 2017, **14**, 4403–4416.
16 C. Corbo, R. Molinaro, F. Taraballi, N. E. T. Furman, K. A. Hartman, M. B. Sherman, E. De Rosa, D. K. Kirui, F. Salvatore and E. Tasciotti, *ACS Nano*, 2017, **11**, 3262–3273.
17 F. F. Chen, G. K. Wang, J. I. Griffin, B. Brenneman, N. K. Banda, V. M. Holers, D. S. Backos, L. P. Wu, S. M. Moghimi and D. Simberg, *Nat. Nanotechnol.*, 2017, **12**, 387–393.
18 C. M. J. Hu, L. Zhang, S. Aryal, C. Cheung, R. H. Fang and L. Zhang, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, **108**, 10980–10985.
19 G. K. Wang, J. I. Griffin, S. Inturi, B. Brenneman, N. K. Banda, V. M. Holers, S. M. Moghimi and D. Simberg, *Front. Immunol.*, 2017, **8**, 151.
20 C. A. Simpson, A. C. Agrawal, A. Balinski, K. M. Harkness and D. E. Cliffel, *ACS Nano*, 2011, **5**, 3577–3584.
21 Q. Yang and S. K. Lai, *Wiley Interdiscip. Rev.: Nanomed. Nanobiotechnol.*, 2015, **7**, 655–677.
22 H. Ando, A. S. Abu Lila, M. Kawanishi, T. Shimizu, K. Okuhira, Y. Ishima and T. Ishida, *J. Controlled Release*, 2018, **270**, 114–119.
23 K. Bourzac, *Proc. Natl. Acad. Sci. U. S. A.*, 2016, **113**, 12600–12603.

24 D. Dehaini, X. Wei, R. H. Fang, S. Masson, P. Angsantikul, B. T. Luk, Y. Zhang, M. Ying, Y. Jiang, A. V. Kroll, W. Gao and L. Zhang, *Adv. Mater.*, 2017, **29**, 1606209.
25 K. Zhang, X. Meng, Z. Yang, Y. Cao, Y. Cheng, D. Wang, H. Lu, Z. Shi, H. Dong and X. Zhang, *Adv. Mater.*, 2019, **31**, 1807888.
26 L. Rao, L. L. Bu, B. Cai, J. H. Xu, A. Li, W. F. Zhang, Z. J. Sun, S. S. Guo, W. Liu, T. H. Wang and X. Z. Zhao, *Adv. Mater.*, 2016, **28**, 3460–3466.
27 Y. Zhang, K. Cai, C. Li, Q. Guo, Q. Chen, X. He, L. Liu, Y. Zhang, Y. Lu, X. Chen, T. Sun, Y. Huang, J. Cheng and C. Jiang, *Nano Lett.*, 2018, **18**, 1908–1915.
28 Z. Chai, D. Ran, L. Lu, C. Zhan, H. Ruan, X. Hu, C. Xie, K. Jiang, J. Li, J. Zhou, J. Wang, Y. Zhang, R. H. Fang, L. Zhang and W. Lu, *ACS Nano*, 2019, **13**, 5591–5601.
29 J. Dupire, M. Socol and A. Viallat, *Proc. Natl. Acad. Sci. U. S. A.*, 2012, **109**, 20808–20813.
30 R. S. Franco, *Transfus. Med. Hemoth.*, 2012, **39**, 302–307.
31 J. Palis, *Front. Physiol.*, 2014, **5**, 3.
32 A. Pitchaimani, T. D. T. Nguyen and S. Aryal, *Biomaterials*, 2018, **160**, 124–137.
33 G. Deng, Z. Sun, S. Li, X. Peng, W. Li, L. Zhou, Y. Ma, P. Gong and L. Cai, *ACS Nano*, 2018, **12**, 12096–12108.
34 Z. Chen, P. Zhao, Z. Luo, M. Zheng, H. Tian, P. Gong, G. Gao, H. Pan, L. Liu, A. Ma and L. Cai, *ACS Nano*, 2016, **10**(11), 10049–10057.
35 D. Shao, M. Li, Z. Wang, X. Zheng, Y. H. Lao, Z. Chang, F. Zhang, M. Lu, J. Yue, H. Hu, H. Yan, L. Chen, W. F. Dong and K. W. Leong, *Adv. Mater.*, 2018, **30**, 1801198.
36 H. Tian, Z. Luo, L. Liu, M. Zheng, Z. Chen, A. Ma, R. Liang, Z. Han, C. Lu and L. Cai, *Adv. Funct. Mater.*, 2017, **27**, 1703197.
37 H. Sun, J. Su, Q. Meng, Q. Yin, L. Chen, W. Gu, P. Zhang, Z. Zhang, H. Yu, S. Wang and Y. Li, *Adv. Mater.*, 2016, **28**, 9581–9588.
38 L. Zhang, X. Zhang, G. Lu, F. Li, W. Bao, C. Song, W. Wei and G. Ma, *Small*, 2019, **15**, 1805544.
39 H. Sun, J. Su, Q. Meng, Q. Yin, L. Chen, W. Gu, Z. Zhang, H. Yu, P. Zhang, S. Wang and Y. Li, *Adv. Funct. Mater.*, 2016, **27**, 1604300.
40 C. Gao, Z. Wu, Z. Lin, X. Lin and Q. He, *Nanoscale*, 2016, **8**, 3548–3554.
41 T. Kang, Q. Zhu, D. Wei, J. Feng, J. Yao, T. Jiang, Q. Song, X. Wei, H. Chen, X. Gao and J. Chen, *ACS Nano*, 2017, **11**(2), 1397–1411.
42 L. Jing, H. Qu, D. Wu, C. Zhu, Y. Yang, X. Jin, J. Zheng, X. Shi, X. Yan and Y. Wang, *Theranostics*, 2018, **8**, 2683–2695.
43 Q. Hu, W. Sun, C. Qian, C. Wang, H. N. Bomba and Z. Gu, *Adv. Mater.*, 2015, **27**, 7043–7050.
44 M. Xuan, J. Shao, L. Dai, Q. He and J. Li, *Adv. Healthcare Mater.*, 2015, **4**, 1645–1652.
45 Y. Li, T. Yan, W. Chang, C. Cao and D. Deng, *Biomater. Sci.*, 2019, **7**, 3652–3661.
46 N. Yang, Y. Ding, Y. Zhang, B. Wang, X. Zhao, K. Cheng, Y. Huang, M. Taleb, J. Zhao, W. F. Dong, L. Zhang and G. Nie, *ACS Appl. Mater. Interfaces*, 2018, **10**, 22963–22973.
47 J. Peng, Q. Yang, W. Li, L. Tan, Y. Xiao, L. Chen, Y. Hao and Z. Qian, *ACS Appl. Mater. Interfaces*, 2017, **9**, 44410–44422.
48 Q. Pei, X. Hu, X. Zheng, S. Liu, Y. Li, X. Jing and Z. Xie, *ACS Nano*, 2018, **12**, 1630–1641.
49 L. Zhang, Z. Wang, Y. Zhang, F. Cao, K. Dong, J. Ren and X. Qu, *ACS Nano*, 2018, **12**, 10201–10211.
50 Y. Zhai, W. Ran, J. Su, T. Lang, J. Meng, G. Wang, P. Zhang and Y. Li, *Adv. Mater.*, 2018, **30**, 1802378.
51 Y. Zou, Y. Liu, Z. Yang, D. Zhang, Y. Lu, M. Zheng, X. Xue, J. Geng, R. Chung and B. Shi, *Adv. Mater.*, 2018, **30**, 1803717.
52 Q. Fu, P. Lv, Z. Chen, D. Ni, L. Zhang, H. Yue, Z. Yue, W. Wei and G. Ma, *Nanoscale*, 2015, **7**, 4020–4030.
53 H. Ding, Y. Lv, D. Ni, J. Wang, Z. Tian, W. Wei and G. Ma, *Nanoscale*, 2015, **7**, 9806–9815.
54 D. Wang, H. Dong, M. Li, Y. Cao, F. Yang, K. Zhang, W. Dai, C. Wang and X. Zhang, *ACS Nano*, 2018, **12**, 5241–5252.
55 Q. Jiang, Y. Liu, R. Guo, X. Yao, S. Sung, Z. Pang and W. Yang, *Biomaterials*, 2019, **192**, 292–308.
56 H. He, C. Guo, J. Wang, W. J. Korzun, X. Y. Wang, S. Ghosh and H. Yang, *Nano Lett.*, 2018, **18**, 6164–6174.
57 C.-M. J. Hu, R. H. Fang, K.-C. Wang, B. T. Luk, S. Thamphiwatana, D. Dehaini, P. Nguyen, P. Angsantikul, C. H. Wen and A. V. Kroll, *Nature*, 2015, **526**, 118–121.
58 A. Parodi, N. Quattrocchi, A. L. van de Ven, C. Chiappini, M. Evangelopoulos, J. O. Martinez, B. S. Brown, S. Z. Khaled, I. K. Yazdi, M. Vittoria Enzo, L. Isenhart, M. Ferrari and E. Tasciotti, *Nat. Nanotechnol.*, 2013, **8**, 61–68.
59 C. Menaa, M. Fan, H. C. Lu, A. Alexandrou, S. Juma, J. Perks and J. J. Li, *Cancer Res.*, 2013, **73**, 4963.
60 W. Lv, J. Xu, X. Wang, X. Li, Q. Xu and H. Xin, *ACS Nano*, 2018, **12**, 5417–5426.
61 Z. Chai, X. Hu, X. Wei, C. Zhan, L. Lu, K. Jiang, B. Su, H. Ruan, D. Ran, R. H. Fang, L. Zhang and W. Lu, *J. Controlled Release*, 2017, **264**, 102–111.
62 W. Liu, M. Ruan, Y. Wang, R. Song, X. Ji, J. Xu, J. Dai and W. Xue, *Small*, 2018, **14**, 1801754.
63 H. Liu, W. Jiang, Q. Wang, L. Hang, Y. Wang and Y. Wang, *Biomater. Sci.*, 2019, **7**, 3706–3716.
64 C. Wang, W. Sun, Y. Ye, Q. Hu, H. N. Bomba and Z. Gu, *Nat. Biomed. Eng.*, 2017, **1**, 0011.
65 L. Erpenbeck and M. P. Schon, *Blood*, 2010, **115**, 3427–3436.
66 L. Borsig, R. Wong, J. Feramisco, D. R. Nadeau, N. M. Varki and A. Varki, *Proc. Natl. Acad. Sci. U. S. A.*, 2001, **98**, 3352–3357.
67 D. L. Sprague, J. M. Sowa, B. D. Elzey and T. L. Ratliff, *Immunol. Res.*, 2007, **39**, 185–193.
68 J. Tang, T. Su, K. Huang, P. U. Dinh, Z. Wang, A. Vandergriff, M. T. Hensley, J. Cores, T. Allen, T. Li, E. Sproul, E. Mihalko, L. J. Lobo, L. Ruterbories, A. Lynch, A. Brown, T. G. Caranasos, D. Shen, G. A. Stouffer, Z. Gu, J. Zhang and K. Cheng, *Nat. Biomed. Eng.*, 2018, **2**, 17–26.

69 L. Yang, R. M. Froio, T. E. Sciuto, A. M. Dvorak, R. Alon and F. W. Luscinskas, *Blood*, 2005, **106**, 584–592.
70 H. Zhao, L. Li, J. Zhang, C. Zheng, K. Ding, H. Xiao, L. Wang and Z. Zhang, *ACS Appl. Mater. Interfaces*, 2018, **10**, 31124–31135.
71 L. Zhang, R. Li, H. Chen, J. Wei, H. Qian, S. Su, J. Shao, L. Wang, X. Qian and B. Liu, *Int. J. Nanomed.*, 2017, **12**, 2129–2142.
72 B. Ruster, S. Gottig, R. J. Ludwig, R. Bistrian, S. Muller, E. Seifried, J. Gille and R. Henschler, *Blood*, 2006, **108**, 3938–3944.
73 D. D. Wang, H. F. Dong, M. Li, Y. Cao, F. Yang, K. Zhang, W. H. Dai, C. T. Wang and X. J. Zhang, *ACS Nano*, 2018, **12**, 5241–5252.
74 D. Dehaini, X. Wei, R. H. Fang, S. Masson, P. Angsantikul, B. T. Luk, Y. Zhang, M. Ying, Y. Jiang, A. V. Kroll, W. Gao and L. Zhang, *Adv. Mater.*, 2017, **29**, 1606209.
75 Y. Liu, X. Wang, B. Ouyang, X. Liu, Y. Du, X. Cai, H. Guo, Z. Pang, W. Yang and S. Shen, *J. Mater. Chem. B*, 2018, **6**, 7033–7041.
76 L. L. Bu, L. Rao, G. T. Yu, L. Chen, W. W. Deng, J. F. Liu, H. Wu, Q. F. Meng, S. S. Guo, X. Z. Zhao, W. F. Zhang, G. J. Chen, Z. Gu, W. Liu and Z. J. Sun, *Adv. Funct. Mater.*, 2019, **29**, 1807733.
77 L. Rao, Q.-F. Meng, Q. Huang, Z. Wang, G.-T. Yu, A. Li, W. Ma, N. Zhang, S.-S. Guo, X.-Z. Zhao, K. Liu, Y. Yuan and W. Liu, *Adv. Funct. Mater.*, 2018, **28**, 1803531.
78 G.-T. Yu, L. Rao, H. Wu, L.-L. Yang, L.-L. Bu, W.-W. Deng, L. Wu, X. Nan, W.-F. Zhang, X.-Z. Zhao, W. Liu and Z.-J. Sun, *Adv. Funct. Mater.*, 2018, **28**, 1801389.
79 J. Li, X. Zhen, Y. Lyu, Y. Jiang, J. Huang and K. Pu, *ACS Nano*, 2018, **12**, 8520–8530.
80 W. Xie, W. W. Deng, M. Zan, L. Rao, G. T. Yu, D. M. Zhu, W. T. Wu, B. Chen, L. W. Ji, L. Chen, K. Liu, S. S. Guo, H. M. Huang, W. F. Zhang, X. Zhao, Y. Yuan, W. Dong, Z. J. Sun and W. Liu, *ACS Nano*, 2019, **13**, 2849–2857.
81 A. V. Kroll, R. H. Fang, Y. Jiang, J. Zhou, X. Wei, C. L. Yu, J. Gao, B. T. Luk, D. Dehaini, W. Gao and L. Zhang, *Adv. Mater.*, 2017, **29**, 1703969.
82 X. Zhang, C. Wang, J. Wang, Q. Hu, B. Langworthy, Y. Ye, W. Sun, J. Lin, T. Wang, J. Fine, H. Cheng, G. Dotti, P. Huang and Z. Gu, *Adv. Mater.*, 2018, **30**, 1707112.
83 W. Gao, R. H. Fang, S. Thamphiwatana, B. T. Luk, J. Li, P. Angsantikul, Q. Zhang, C.-M. J. Hu and L. Zhang, *Nano Lett.*, 2015, **15**, 1403–1409.
84 Y. Zhang, Y. Chen, C. Lo, J. Zhuang, P. Angsantikul, Q. Zhang, X. Wei, Z. Zhou, M. Obonyo, R. H. Fang, W. Gao and L. Zhang, *Angew. Chem., Int. Ed.*, 2019, **58**, 11404–11408.
85 S. I. Grivennikov, F. R. Greten and M. Karin, *Cell*, 2010, **140**, 883–899.
86 Y. Wang, K. Zhang, X. Qin, T. Li, J. Qiu, T. Yin, J. Huang, S. McGinty, G. Pontrelli, J. Ren, Q. Wang, W. Wu and G. Wang, *Adv. Sci.*, 2019, **6**, 1900172.
87 H. Liang, K. Huang, T. Su, Z. Li, S. Hu, P. U. Dinh, E. A. Wrona, C. Shao, L. Qiao, A. C. Vandergriff, M. T. Hensley, J. Cores, T. Allen, H. Zhang, Q. Zeng, J. Xing, D. O. Freytes, D. Shen, Z. Yu and K. Cheng, *ACS Nano*, 2018, **12**, 6536–6544.
88 X. Hao, Q. Li, H. Wang, K. Muhammad, J. Guo, X. Ren, C. Shi, S. Xia, W. Zhang and Y. Feng, *J. Mater. Chem. B*, 2018, **6**, 5975–5985.
89 Z. Zhang, H. Qian, M. Yang, R. Li, J. Hu, L. Li, L. Yu, B. Liu and X. Qian, *Int. J. Nanomed.*, 2017, **12**, 1593–1605.
90 J. A. Copp, R. H. Fang, B. T. Luk, C.-M. J. Hu, W. Gao, K. Zhang and L. Zhang, *Proc. Natl. Acad. Sci. U. S. A.*, 2014, **111**, 13481–13486.
91 J. Shao, M. Abdelghani, G. Shen, S. Cao, D. S. Williams and J. C. M. van Hest, *ACS Nano*, 2018, **12**, 4877–4885.
92 Y. Song, Z. Huang, X. Liu, Z. Pang, J. Chen, H. Yang, N. Zhang, Z. Cao, M. Liu, J. Cao, C. Li, X. Yang, H. Gong, J. Qian and J. Ge, *Nanomedicine*, 2019, **15**, 13–24.
93 Y. He, R. Li, J. Liang, Y. Zhu, S. Zhang, Z. Zheng, J. Qin, Z. Pang and J. Wang, *Nano Res.*, 2018, **11**, 6086–6101.
94 N. Doshi, J. N. Orje, B. Molins, J. W. Smith, S. Mitragotri and Z. M. Ruggeri, *Adv. Mater.*, 2012, **24**, 3864–3869.
95 X. Zhou, X. Cao, H. Tu, Z. R. Zhang and L. Deng, *Mol. Pharm.*, 2019, **16**, 1397–1405.
96 Y. Z. Zhao, D. L. ZhuGe, M. Q. Tong, M. T. Lin, Y. W. Zheng, X. Jiang, W. G. Yang, Q. Yao, Q. Xiang, X. K. Li and H. L. Xu, *J. Controlled Release*, 2019, **299**, 90–106.
97 C. Corbo, W. E. Cromer, R. Molinaro, N. E. T. Furman, K. A. Hartman, E. De Rosa, C. Boada, X. Wang, D. C. Zawieja, M. Agostini, F. Salvatore, B. P. Abraham and E. Tasciotti, *Nanoscale*, 2017, **9**, 14581–14591.
98 L. L. Bu, L. Rao, G. T. Yu, L. Chen, W. W. Deng, J. F. Liu, H. Wu, Q. F. Meng, S. S. Guo, X. Z. Zhao, W. F. Zhang, G. J. Chen, Z. Gu, W. Liu and Z. J. Sun, *Adv. Funct. Mater.*, 2019, **29**, 1807733.
99 S. Thamphiwatana, P. Angsantikul, T. Escajadillo, Q. Zhang, J. Olson, B. T. Luk, S. Zhang, R. H. Fang, W. Gao and V. Nizet, *Proc. Natl. Acad. Sci. U. S. A.*, 2017, **114**, 201714267.
100 Q. Zhang, D. Dehaini, Y. Zhang, J. Zhou, X. Chen, L. Zhang, R. H. Fang, W. Gao and L. Zhang, *Nat. Nanotechnol.*, 2018, **13**, 1182–1190.
101 R. Li, Y. He, Y. Zhu, L. Jiang, S. Zhang, J. Qin, Q. Wu, W. Dai, S. Shen, Z. Pang and J. Wang, *Nano Lett.*, 2019, **19**, 124–134.
102 C. Wang, Y. Wang, L. Zhang, R. J. Miron, J. Liang, M. Shi, W. Mo, S. Zheng, Y. Zhao and Y. Zhang, *Adv. Mater.*, 2018, **30**, 1804023.
103 X. Dong, J. Gao, C. Y. Zhang, C. Hayworth, M. Frank and Z. Wang, *ACS Nano*, 2019, **13**, 1272–1283.
104 P. Angsantikul, S. Thamphiwatana, Q. Zhang, K. Spiekermann, J. Zhuang, R. H. Fang, W. Gao, M. Obonyo and L. Zhang, *Adv. Ther.*, 2018, **1**, 1800016.
105 J. Tang, D. Shen, T. G. Caranasos, Z. Wang, A. C. Vandergriff, T. A. Allen, M. T. Hensley, P.-U. Dinh, J. Cores, T.-S. Li, J. Zhang, Q. Kan and K. Cheng, *Nat. Commun.*, 2017, **8**, 13724.

106 L. Sun, Q. Li, M. Hou, Y. Gao, R. Yang, L. Zhang, Z. Xu, Y. Kang and P. Xue, *Biomater. Sci.*, 2018, **6**, 2881–2895.
107 Y. Guo, D. Wang, Q. Song, T. Wu, X. Zhuang, Y. Bao, M. Kong, Y. Qi, S. Tan and Z. Zhang, *ACS Nano*, 2015, **9**, 6918–6933.
108 Q. Hu, W. Sun, C. Qian, C. Wang, H. N. Bomba and Z. Gu, *Adv. Mater.*, 2015, **27**, 7043–7050.
109 Q. Hu, C. Qian, W. Sun, J. Wang, Z. Chen, H. N. Bomba, H. Xin, Q. Shen and Z. Gu, *Adv. Mater.*, 2016, **28**, 9573–9580.
110 L. Rao, L.-L. Bu, Q.-F. Meng, B. Cai, W.-W. Deng, A. Li, K. Li, S.-S. Guo, W.-F. Zhang, W. Liu, Z.-J. Sun and X.-Z. Zhao, *Adv. Funct. Mater.*, 2017, **57**, 986–991.
111 L. Rao, L. L. Bu, L. Ma, W. Wang, H. Liu, D. Wan, J. F. Liu, A. Li, S. S. Guo, L. Zhang, W. F. Zhang, X. Z. Zhao, Z. J. Sun and W. Liu, *Angew. Chem., Int. Ed.*, 2018, **57**, 986–991.
112 M. Xuan, J. Shao, L. Dai, J. Li and Q. He, *ACS Appl. Mater. Interfaces*, 2016, **8**, 9610–9618.
113 C. Gao, Z. Lin, B. Jurado-Sanchez, X. Lin, Z. Wu and Q. He, *Small*, 2016, **12**, 4056–4062.
114 C. Gao, Z. Lin, Z. Wu, X. Lin and Q. He, *ACS Appl. Mater. Interfaces*, 2016, **8**, 34252–34260.
115 N. E. T. Furman, Y. Lupu-Haber, T. Bronshtein, L. Kaneti, N. Letko, E. Weinstein, L. Baruch and M. Machluf, *Nano Lett.*, 2013, **13**, 3248–3255.
116 L. Kaneti, T. Bronshtein, N. M. Dayan, I. Kovregina, N. L. Khait, Y. Lupu-Haber, M. Fliman, B. W. Schoen, G. Kaneti and M. Machluf, *Nano Lett.*, 2016, **16**, 1574–1582.
117 R. H. Fang, C.-M. J. Hu, B. T. Luk, W. Gao, J. A. Copp, Y. Tai, D. E. O'Connor and L. Zhang, *Nano Lett.*, 2014, **14**, 2181–2188.
118 N. Zhang, M. Li, X. Sun, H. Jia and W. Liu, *Biomaterials*, 2018, **159**, 25–36.
119 H. Min, J. Wang, Y. Qi, Y. Zhang, X. Han, Y. Xu, J. Xu, Y. Li, L. Chen, K. Cheng, G. Liu, N. Yang, Y. Li and G. Nie, *Adv. Mater.*, 2019, **31**, 1808200.
120 F. Fontana, M. A. Shahbazi, D. Liu, H. Zhang, E. Makila, J. Salonen, J. T. Hirvonen and H. A. Santos, *Adv. Mater.*, 2016, **29**, 1603239.
121 R. Yang, J. Xu, L. Xu, X. Sun, Q. Chen, Y. Zhao, R. Peng and Z. Liu, *ACS Nano*, 2018, **12**, 5121–5129.
122 Y. Bu, Q. Hu, R. Ke, Y. Sui, X. Xie and S. Wang, *Chem. Commun.*, 2018, **54**, 13427–13430.
123 X. Zhen, P. Cheng and K. Pu, *Small*, 2019, **15**, 1804105.

