Materials Today Bio 24 (2024) 100913

Contents lists available at ScienceDirect

Materials Today Bio

journal homepage: www.journals.elsevier.com/materials-today-bio

Red blood cell-derived materials for cancer therapy: Construction, distribution, and applications

Jianghua Ding [a,b,1], Xinjing Ding [c,1], Weifang Liao [b,d,*], Zhihui Lu [c]

[a] Department of Hematology & Oncology, Clinical Medical College/Affiliated Hospital of Jiujiang University, Jiujiang, Jiangxi, 332005, China
[b] Jiujiang Clinical Precision Medicine Research Center, Jiujiang, Jiangxi, 332005, China
[c] Oncology of Department, First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, 332000, China
[d] Department of Medical Laboratory, Clinical Medical College/Affiliated Hospital of Jiujiang University, Jiujiang, Jiangxi, 332005, China

ARTICLE INFO

Keywords:
Red blood cell (RBC)
RBC hitchhiking
Extracellular vesicles
Nanometer materials
Cancer
Drug delivery system (DDS)

ABSTRACT

Cancer has become an increasingly important public health issue owing to its high morbidity and mortality rates. Although traditional treatment methods are relatively effective, they have limitations such as highly toxic side effects, easy drug resistance, and high individual variability. Meanwhile, emerging therapies remain limited, and their actual anti-tumor effects need to be improved. Nanotechnology has received considerable attention for its development and application. In particular, artificial nanocarriers have emerged as a crucial approach for tumor therapy. However, certain deficiencies persist, including immunogenicity, permeability, targeting, and biocompatibility. The application of erythrocyte-derived materials will help overcome the above problems and enhance therapeutic effects. Erythrocyte-derived materials can be acquired via the application of physical and chemical techniques from natural erythrocyte membranes, or through the integration of these membranes with synthetic inner core materials using cell membrane biomimetic technology. Their natural properties such as biocompatibility and long circulation time make them an ideal choice for drug delivery or nanoparticle biocoating. Thus, red blood cell-derived materials are widely used in the field of biomedicine. However, further studies are required to evaluate their efficacy, in vivo metabolism, preparation, design, and clinical translation. Based on the latest research reports, this review summarizes the biology, synthesis, characteristics, and distribution of red blood cell-derived materials. Furthermore, we provide a reference for further research and clinical transformation by comprehensively discussing the applications and technical challenges faced by red blood cell-derived materials in the treatment of malignant tumors.

1. Introduction

Owing to its high morbidity and mortality rates, cancer is a leading cause of death worldwide, posing a significant threat to human health and socioeconomic development [1]. Advancements in scientific research and technology have led to major breakthroughs in cancer treatment strategies such as targeted therapy and immunotherapy [2]. Currently, surgery, chemotherapy, and radiotherapy (RT) are the most commonly used treatment methods [3]. However, due to the complex pathogenesis of tumors, traditional treatment methods have failed to achieve satisfactory results [4,5]. The growth of malignant tumors is commonly accompanied by invasion and metastasis to other tissues. Moreover, there is a high rate of local recurrence after tumor surgery due to the difficulty of removing the entire tumor tissue [6,7]. Despite the widespread use of chemotherapy, chemotherapeutic agents continue to encounter formidable obstacles, such as inadequate targeting capabilities and pronounced adverse effects. Moreover, a significant proportion of patients inevitably acquire drug resistance over time, leading to constrained therapeutic efficacy [8]. The clinical application of RT is limited by the sensitivity of various tissues and organs as well as the oxygenation function of tumor cells [9,10]. Moreover, immunotherapeutic medications exhibit apparent variation among individuals and are expensive. The rapid development of drug resistance is a major obstacle in the implementation of targeted therapies [11–14].

To overcome barriers to the application of traditional therapies, various emerging strategies for cancer treatment are being developed

* Corresponding author. Department of Medical Laboratory, Clinical Medical College/Affiliated Hospital of Jiujiang University, Jiujiang, Jiangxi, 332005, China.
E-mail address: 15070285697@163.com (W. Liao).
[1] J.D. and X.D. contributed equally to this paper.

https://doi.org/10.1016/j.mtbio.2023.100913
Received 30 September 2023; Received in revised form 2 December 2023; Accepted 11 December 2023
Available online 15 December 2023

and studied. However, each of these emerging technologies has limitations. For example, gene therapy has low transfection efficiency, low tumor targeting, and high technical difficulty, whereas anti-angiogenic therapy is limited in its effectiveness and requires long-term use, which is very challenging for patients [15,16]. Phototherapy also proves challenging for the accurate treatment of tumors owing to the distribution and localization of photosensitizers in the human body, as well as uneven laser exposure [17]. Therefore, further improvement in the efficacy of the above treatments, reduction of adverse reactions during the treatment process, and optimization of the control over the treatment strategy have become urgent problems that need to be addressed.

In light of these challenges, the targeted design and development of biomaterials emerged as a promising approach to explore. These biomaterials would be combined with anti-tumor treatments to meet diverse biomedical requirements. It is noteworthy that biomaterials derived from natural cells have emerged as a compelling avenue of exploration [18]. Due to their resemblance to human cells in terms of structure, these biomaterials exhibit favorable biological effects and possess targeting specificity, thereby aligning with the requirements of personalized medicine, as outlined subsequently (Table 1). Among them , red blood cells (RBC) and their derivatives have emerged as biomaterials with wide application prospects in the biomedical field owing to their high loading capacity, long circulation time, good biocompatibility, and low immunogenicity [19–21]. With these desirable characteristics, RBCs can be used in various processes, including loading therapeutic agents, modifying cell membranes, expressing specific antibodies, and carrying specific antigens while conserving their circulation and immune function [22]. Recently, various RBC-based delivery strategies have been developed, including whole cells, extracellular vesicles (EVs), and cell membrane-coated particles; these have been gradually applied to major chronic diseases including malignant tumors. This makes them ideal choices for drug delivery, photothermal imaging, RT sensitization, and immune regulation [22–26].

This review summarizes the fundamental principles and recent advancements of different RBC-derived materials in the anti-tumor field and focuses on the four main aspects of overview and characteristics, construction and preparation, metabolism and distribution, and specific applications. Additionally, it discusses the key challenges associated with future oncology therapeutic applications and their clinical potential. Especially, a systematic analysis of the unintended effects and safety associated with these materials, with the aim of assisting researchers in enhancing and refining RBC-derived materials to propel the discipline forward and enhance the practicality of clinical implementation.

Table 1
Comparison of different cell-derived materials.

Biomaterial source	Advantages	Limits
Red blood cell [20,27–32]	Lack of nucleus, high safety, diversity of modifications and cargo-loading, rich sources, and easy access	Lack of an intrinsic targeting component, difficulty of mass production
Platelet [33–36]	Lack of nucleus, natural tendency of damaged endothelial cells or tumor tissue, and easy access	Low levels in the blood, difficulty of mass production
White blood cell [35,37–42]	High recognition of inflammatory and diseased areas, diversity of surface receptors, ease of self-clearance and activation of immune response	Great variety, small number, high requirement of purification technology, and possible disease progression caused by phenotypic transformation
Mesenchymal stem cell [43,44]	Multipotent, self-renewing, wide range of organizational sources, and easy to access	Limited homing ability of tumor targets, poor survival after implantation
Cancer cell [45–48]	Expression of neoantigens and induction of tumor immune response	Difficulty of obtaining sufficient autologous patient-specific cells, potential or long-term cytotoxicity

2. Overview and characteristics

RBCs are the most common cell type in the blood with a biconcave discoid shape [17,26,49]. Unlike other blood cells, RBCs gradually lose their nuclei and organelles during maturation, leaving only the hemoglobin (Hb) solution encapsulated by the plasma membrane. As an integral component of gas exchange between the lungs and tissues in the human body, Hb is responsible for transporting oxygen in the circulatory system [50,51]. Red blood cell membranes (RBCM or RBCm) have unique structures consisting of lipids (phospholipids and cholesterol), proteins, and sugars in different ratios [52]. Phospholipids are essential components of membranes and are involved in regulating membrane integrity, fluidity and dynamics [53]. The most abundant proteins on the surface of RBCs are band 3 protein and glycoprotein A [54]. Band 3, a protein that constitutes approximately 25 % of the erythrocyte membrane, serves as a prominent component and primary facilitator of anion transportation within the human RBCM. The glycoprotein A present on the membrane possesses a substantial negative charge attributed to its sialic acid content. This negative charge serves to impede the aggregation of RBCs among themselves and their adhesion to blood vessels [55]. Additionally, RBCs also have a subplasma cytoskeleton formed by the cross-linking of many unique proteins such as actin, spectrin, ankyrin, and band 4.1 protein [56]. The cytoskeleton exhibits a planar network structure in its entirety. The formation of complexes resulting from the binding of spectrin to actin is of utmost importance in establishing the structural framework of the cytoskeleton, as these complexes confer both strength and elasticity, thereby guaranteeing the preservation of cellular morphology. Numerous binding proteins, such as band 4.1 protein, tropomyosin and adducin, establish interconnections among individual shadow protein fibers in order to enhance the stability of the mesh structure and govern its functionality. Ankyrins simultaneously interact with both shadow proteins and transmembrane proteins, thereby creating a linkage between shadow proteins and the plasma membrane [57–59].

The circulating half-life of RBCs is 120 days, during which time RBCs circulate multiple times throughout the human body. The long circulation time can significantly improve the duration and bioavailability of associated drugs [60,61]. Aged or damaged RBCs are mostly removed and recycled by the reticuloendothelial system (RES) located in the liver, spleen, and bone marrow, and there is no harm to normal tissue from the degradation process or its products [62]. As natural, long-circulating carriers, RBCs are abundant and biocompatible. They can be obtained through autologous blood transfusion or blood donation, with fewer associated immune rejections and other adverse reactions [20,29].

An important property of RBCs is their high deformability which enables them to pass through capillaries and spleen in a bullet-like or parachute-like shape while maintaining a viable state [63,64]. However, when external forces exceed the resistance range of RBCs, they shrink, expand, or even rupture [65]. Furthermore, RBCs are osmotically fragile, which means that they can expand and rupture in hypotonic solutions, allowing Hb to escape, a process called hemolysis. After hemolysis, RBCs can maintain their normal form, which can isolate and help prevent their contents from being degraded under external conditions [30,66]. Hence, the shell of RBCM can be obtained and modified in vitro by disrupting the isotonic state within and outside RBCs, thereby coupling or inserting various peptides, proteins, antibodies, nucleic acids, or even nanoparticles (NPs) onto the RBCM, which prevents them from being cleared by the RES [31,67–69]. The concept of “carrier RBCs” was first proposed in 1979, and since then RBCs and their membranes have received increasing attention in the biomedical field as biologically inspired materials [70].

Based on different preparation methods and functional characteristics, RBC and their derivatives can be grouped roughly into three categories: whole RBC (including RBC hitchhiking), RBC membrane-

camouflaged nanoparticles (RBCNPs), and RBC-derived extracellular vesicles (RBCEVs). Their preparation, characteristics, and applications are systematically summarized in the following section.

Currently, many related scientific studies and clinical trials are underway; however, some limitations prevent their full application in clinical practice. First, given the increasing clinical demand for blood and blood products, it is difficult to obtain additional and stable blood from animals or humans for the innovative development and large-scale production of related materials [71]. Second, proper preservation and processing of extracted RBCs and their membranes in vitro are challenging, and the related materials cannot be universally used at the current level of technological advancement [31]. Finally, the high costs of related research and development remain an unaddressed problem. Therefore, further studies are required to overcome these limitations.

3. Construction and preparation

3.1. RBCs

In recent years, various cell types including immune cells, stem cells, and RBCs have received extensive attention as potential biomaterials. Among these, RBCs have become a research hotspot owing to their unique structure and function [18]. Currently, RBCs can be processed in a variety of ways, enabling the encapsulation of small-molecule drugs, proteins, and other substances within the cells or coupling to the surfaces, mainly as follows (Table 2).

3.1.1. Methods for encapsulation in the cell interior

3.1.1.1. Osmosis-based method. The rationale for this approach is hypotonic hemolysis. Under hypotonic conditions, RBCs absorb water from the solution and expand to 1.25-fold of their original size. At this time, pores within the RBCM, with sizes ranging from 10 to 500 nm, open to allow the exchange of macromolecular substances so that the required cargo could be passively diffused into the RBCs along the concentration gradient [70,72,73]. After this expansion, applying a hypertonic or isotonic solution to the RBCs can restore the volume, and the transiently opened reversible pores are closed, which preserves the cargo within the cytosol [74]. Notably, the tension of the RBC expansion during preparation must be strictly controlled; otherwise, it may result in irreversible rupture of the RBCM. As a result of cell lysis, the contents of the cells are released and removed, leaving RBC ghosts behind [75,76].

By adopting the specific details of this method, researchers have developed similar methods based on the above principles, including hypotonic dilution, hypotonic dialysis, and hypotonic pre-swelling [18]. The majority of samples obtained by hypotonic dilution were RBC ghosts, which are easily swallowed by macrophages in the RES and can successfully deliver embedded substances to RES-rich organs [76,77]. However, the vector "ghost" has low embedding efficiency and a significantly shortened life span. The two methods of hypotonic dialysis and hypotonic pre-swelling have overcome the above limitations and led to industrial production. Constructed cells exhibited similar longevity to that of normal cells, but greater entrapment efficiency [70].

A suspension of RBCs can also be created in an isotonic solution containing substances that can freely flow through the RBCM, such as dimethyl sulfoxide (DMSO), and is balanced between the pressures inside and outside the RBCs. By gradually adding an isotonic drug solution without DMSO, the suspension was diluted to produce a concentration gradient of intracellular hyperosmotic and extracellular hypoosmotic compounds. When water is being absorbed to balance osmotic pressure, temporary channels on the RBCs surface are opened, allowing drugs to pass through. Subsequently, substances such as DMSO diffused freely, and the isotonic state of the suspension was restored. Consequently, the channels of the RBCs are closed, and drugs are successfully entrapped within the RBCs. This method, known as osmotic pulse, is rarely used in practice [70].

Among these, hypotonic dialysis is the most used method. The reaction conditions are relatively mild, and the obtained RBCs maintain some activity and show a long natural life after reinjection. These characteristics make this method capable of achieving a higher capture efficiency (30–50 %) and cell recovery (70–80 %) [70]. Recently, using surface-modified RBCs as drug carriers, Wang et al. successfully

Table 2
Summary of engineering methods for vector RBCs.

Location of cargo	Engineering method	Engineering principle	Advantages	Limits
Interior	Osmosis-based method	Transient pore opening on the membrane occurs when the isotonic environment of the RBCs is disrupted, allowing cargo to enter the cells [70,78].	They can prolong the circulation time and evade immune clearance [116].	They may disrupt cell viability or membrane structure [117].
	Electroporation	Transient pore opening on the membrane occurs when electric field is applied to RBCM, allowing cargo to enter the cells [80,86,87].		
	Drug-endocytosis	As a result of the drug's action, the RBCM and cytoskeleton are permanently altered, the RBCs swell and form vesicles internally, allowing cargo to enter through endocytosis [88–90].		
	Lipid fusion	As the cargo is wrapped in the outer shell of the liposome, the lipid bilayers are fused with the plasma membrane of the RBC, allowing cargo to enter the cells [88,91].		
	CCP mediation	Through disulfide bonds, cargo such as proteins are covalently bound to CCP, allowing them to enter through endocytosis without altering the structure or function of RBCs [96,97].		
Surface	Chemical conjugation	The cargo is coupled to the RBCM by the biotin-avidin reaction system or ester reaction [99,100].	They can modulate pharmacokinetic features and target cargo to non-RES regions [116].	Excessive surface modification may affect biocompatibility [116].
	Affinity interactions	The cargo is coupled to the RBCM by an antibody-protein interaction system [96,104,105].		
	Enzymatic ligation	Covalent attachment of protein substrates to RBCM proteins is mediated by protein ligases such as OaAEP1 and Sortase A [110–112].		
Interior or surface	Genetic engineering	The genetic material of progenitor RBCs is directly modified to express specific proteins in the cytoplasm or membrane. Cells then expand and differentiate into mature RBCs [107,108].	They can introduce proteins with specific conformations and functions at specific locations [117].	The procedure is cumbersome and costly, and it is difficult to ensure the stable expression of target genes [117].

Abbreviations: RBCs, red blood cell; RBCM, red blood cell membrane; CCP, cell-penetrating peptide; RES, reticuloendothelial system.

encapsulated doxorubicin (DOX) into mouse RBCs via a modified hypotonic dialysis method. Therefore, a novel RBC-based drug delivery system (DDS) was constructed [78].

3.1.1.2. Electroporation. A seminal study by Teissie et al. reported that a pulsed electric field (PEF) could reversibly break the cell membrane structure. When an electric field of 30 kV/cm is applied to the phospholipid bilayer, the vesicular structures exhibit a transient increase in electrical conductivity and permeability, and small molecules, such as sucrose, can pass through the formed transient pores. Damage to the vesicular structure was reversible during this procedure [79]. Subsequently, research has focused on the application of reversible electroporation in clinical settings. In 1998, Lizano et al. encapsulated alcohol dehydrogenase and acetaldehyde dehydrogenase in human RBCs by electroporation (3000V/1 m s) and resealing (37 °C). High encapsulation efficiency was achieved, and carrier RBCs were recovered [80].

The key to this method is transient pore opening. When RBCs are exposed to an external electric field exceeding a critical value or threshold, there is an imbalance in the osmotic pressure inside and outside the RBCs, as well as in the pores formed on its surface. Target agents can then diffuse into the cell via the pores [81,82]. Electroporation is currently used to encapsulate small-molecule drugs and enzymes [83–85]. However, if the PEF created by electrical stimulation is sufficiently large, rupture of the RBC and cell death may occur. Owing to the irreversibility of this process, it is important to control the parameters that affect the electric field during synthesis [86,87].

3.1.1.3. Other methods. Although less common, there are other methods of loading drugs into the cytosol, such as drug endocytosis (primaquine, chlorpromazine, etc.) and lipid fusion [88–91]. However, these methods exhibit several disadvantages. For most existing techniques, RBCM must be physically or chemically disrupted in order to create "channels" for cargo to enter the cell. On the one hand, important components such as Hb and cytoskeleton can leak outside through these "channels." The loss of Hb not only affects the function of RBCs in storing and transporting oxygen but also reduces the resistance of RBCs to oxidative stress [92,93]. In contrast, loss of the cytoskeleton within RBCs can weaken their structural and functional integrity to varying degrees [94]. These changes may result in processed RBCs being recognized and eliminated by the body's immune system as "foreign bodies" [95].

To overcome these difficulties, researchers have explored and developed new encapsulation techniques that do not change the structure and function of RBCs, such as cell-penetrating peptide (CCP) mediation [96,97]. Notably, CCPs possess a universal and efficient membrane-penetrating activity that enables the internalization of CCP protein conjugates while maintaining RBCs integrity.

Leukemic cells are incapable of producing asparagine (ASN), an amino acid essential for survival. ASN deficiency results in leukemic cell death. As a clinically approved protein drug, asparaginase (ASNase) can therefore be used for the treatment of acute lymphoblastic leukemia (ALL). Given the therapeutic efficacy of ASNase and the penetrating nature of CCP, He et al. developed an effective and nontoxic CCP-low molecular weight protamine (LMWP) and prepared a model of encapsulating ASNase in RBCs using CCP as a mediator. Specifically, ASNase was coupled to LMWP by disulfide bonds, and the conjugate was delivered into the cell via the transmembrane ability of the LMWP. Due to the high glutathione (GSH) and GSH reductase activities in RBCs, disulfide bonds were oxidized, allowing ASNase to remain in the RBCs interior for a long period. Using ASNase-loaded RBCs as bioreactors, circulating ASN was continuously consumed and converted into aspartic acid, thus achieving therapeutic effects in ALL [97].

3.1.2. Methods for coupling to the cell surface

3.1.2.1. Chemical conjugation. Chemical conjugation mainly refers to the surface modification of RBCs through biotin-avidin reactions or ester reaction systems. Among these, biotin-avidin coupling is the most commonly used method. Biotin has two distinct rings in its molecular structure. The first is the imidazolone ring, which is the main avidin-binding site. The second is the thiophene ring, and its terminal carboxyl group can bind to antibodies and other biological macromolecules. After chemical modification, a variety of active groups can attach to the biotin. Avidin, also known as streptavidin, is a basic glycoprotein composed of four identical subunits, each of which can bind to a single biotin molecule. The biotin-avidin system is highly sensitive, specific, and stable [98]. Avidin molecules can bind to biotinylated macromolecular derivatives in the multivalent form, and the affinity of the two is much higher than that of antigen-antibody reactions. In addition, it is not affected by acid–base reactions, or substances such as proteolytic enzymes and organic solvents [88–90].

The specific preparation process is as follows: the carboxyl group of biotin reacts with the amino group of RBCM to form biotin-modified RBCs. Bioactive substances, such as proteins and NPs, can be conjugated with avidin and incubated with biotinylated RBCs, which can be coupled to the surface of RBCs using a biotin-avidin bridge [99]. Within 24 h, RBCs obtained using this method can survive stably in blood circulation with a recovery rate of 90 % [100]. In this process, avidin can activate the complement system and induce the formation of a membrane attack complex (MAC), which leads to RBCs lysis [101,102]. Controlling the copy number of biotin or avidin molecules per cell has been demonstrated to be effective [103].

3.1.2.2. Affinity interaction. The nature of the affinity interaction is an antibody-protein reaction, including the fusion of two specific antibodies and the binding of Fab fragments on specific antibodies to specific proteins on the RBCM [104,105]. Zaitsev et al. combined a tissue-type plasminogen activator (tPA) with the monoclonal antibody 7G9 directed against the complement receptor 1 (CR1) expressed on human RBCs to form an anti-CR1/tPA conjugate. They tested the hypothesis that the injection of anti-CR1/tPA conjugates would produce RBCs with fibrinolytic activity in mice. Pulmonary embolisms in mice resolve rapidly without affecting RBC survival [106]. In addition to new ideas for the prophylactic use of CR1-directed immune targeting of tPA to circulating RBCs, this study provides insights into thrombosis, expansion, and recurrence treatment. The antibody-protein binding complex is much smaller than the biotin-avidin system, and it is easy to dissociate, thus reducing the cycling half-life and cargo loading. However, its biocompatibility, safety, and encapsulation efficiency are superior [96,106–108]. Additionally, even in the complex environment of blood and vasculature, antibody-protein fusion maintains high levels of specificity [96].

3.1.2.3. Enzymatic ligation. Under the catalysis of protein ligases such as OaAEP1 and Sortase A, enzyme ligation refers to the covalent attachment of specially designed protein substrates to proteins on the RBCM to produce protein polymers [109–111]. Using OaAEP1, peptides or proteins can be covalently linked to form peptide bonds through the two ends within a short period. Catalysis mediated by OaAEP1 is relatively simple and productive, and no additional chemical modifications are required to achieve the coupling of monomeric proteins. Even under harsh conditions such as acidic and metal ion-rich solutions, it can maintain the stability of its function. As OaAEP1 is not responsible for cysteine catalysis, it cannot efficiently polymerize multiple mixed forms of proteins, such as metalloproteins. Therefore, additional purification is required to obtain monomeric proteins for conjugation. Furthermore, it is difficult to construct long protein oligomers or polymers using OaAEP1 [111]. In *Staphylococcus aureus*, Sortase A is responsible for the

attachment of cell surface proteins to the cell wall and is capable of achieving ligation between peptides or proteins [110,112]. However, Sortase A is mainly used to catalyze large peptide sequences. For peptide sequences shorter than 16 amino acids, the main products of the catalytic reaction are oligomers, which cannot achieve an effective linkage between proteins. Furthermore, this enzyme performs catalysis with low efficiency, so a large amount of catalyst and long reaction time are required [110].

Jayasinghe et al. demonstrated that protein ligases, including OaAEP1, can be useful in covalent ligation in engineering RBCs, especially RBCEVs, which not only efficiently functionalize their surface but also show strong antigen-specific targeting abilities [113]. Pishesha et al. successfully achieved surface modification of engineered RBCs through the utilization of Sortase A-mediated catalytic reactions. This reaction exhibits mild characteristics, thereby preserving the biological attributes of RBCs to the minimum extent required for modification. Furthermore, the process is repeatable, controllable, and does not hasten the clearance of engineered RBCs [66].

3.1.3. Methods of loading in interior or on surface of cells

3.1.3.1. Genetic engineering. Genetic engineering or DNA recombination technology refers to the integration of complete genes or fragments with the host's genetic material through in vitro biotechnology, which is then introduced into microorganisms or eukaryotic cells for amplification to induce the expression of recombinant genes [114]. As mature RBCs lack nuclei, they cannot be genetically modified. Therefore, genetic engineering of RBCs mainly involves the genetic modification of hematopoietic stem cells or progenitor RBCs. Thus, specific proteins or peptides can be expressed in the cytoplasm or membranes of mature RBCs [115]. Shi et al. engineered progenitor RBCs to express proteins, such as Kell and glycoprotein A, which can be modified by bacterial sortases on plasma membrane surfaces after maturation. After testing, they found that the engineered RBCs had unique advantages. First, the integrity of the RBC plasma membrane could be maintained during the preparation process, and damage to the RBCs was minimal. Second, RBCs of this type can survive in circulation for up to 28 days. Third, RBCs can be modified and labeled through the catalytic action of sortases with a variety of substituents, including those that cannot be genetically encoded. The results of these experiments confirm the feasibility of the precursor RBCs genetic engineering method and provide a reference for its use in clinical practice [107]. Rubius Therapeutics, an RBC-based commercial technology platform, has successfully constructed multiple drug-loaded RBCs for treating a wide range of diseases, including cancer. This provides further evidence for the potential clinical value of genetic engineering [108].

Modified RBCs do not develop into tumors because they have no nuclei after differentiation and maturation; therefore, this method is completely safe and controllable [115]. However, genetic engineering methods require not only complex procedures, expensive reagents, and long preparation times but also strict control of the expansion and differentiation of progenitor cells [108]. Compared to other RBC processing methods, this method is expensive and has limited practical applications.

3.2. RBC hitchhiking

NPs have been widely used in the biomedical field owing to their malleability, good bioavailability, and highly controlled and sustained-release properties [118–120]. In addition to the complexity and cost of preparation, limited loading capacity, low targeting ability and low stability of ordinary NPs make them unsuitable for anti-tumor applications [121,122]. NPs are quickly recognized as a foreign body and cleared by the mononuclear phagocyte system (MPS) [123]. Additionally, NP size also affects its accumulation and penetration into tumor tissues. NPs with larger particle diameters are mostly distributed around the tumor blood vessels but have poor penetration ability. However, NPs with smaller particle diameters mostly penetrate tumor tissue but have poor retention ability [124]. Furthermore, the low targeting ability of NPs may result in the premature release of drugs making them ineffective [117].

As a hybrid delivery strategy, RBC hitchhiking combines RBCs and NPs to fully leverage their advantages and overcome the aforementioned limitations (Fig. 1A) [125,126]. The RBC hitchhiking involves the adsorption of NPs onto the RBCs surface through noncovalent interactions, including electrostatic interactions, van der Waals interactions, and hydrophobic effects [61]. The specific procedure is as follows (Fig. 1B–C): NPs are mixed with washed RBCs and incubated for approximately 30 min, after which the unadsorbed NPs are removed by centrifugation [125]. Owing to the strong shear stress between RBCs and capillaries, it is difficult for NPs injected intravenously into the body to pass through the alveolar/capillary barrier and be removed from the RBC surfaces [127]. After desorption, NPs mainly accumulate in lung endothelial cells but can also accumulate in the heart, brain, and other organs (Fig. 1D–E) [61,125,128]. This improves the pharmacokinetics of NPs and increases their lifetime in blood circulation, especially for NPs with positive charges. It also significantly enhances the targeting of the lung for drug delivery while avoiding uptake and clearance by the liver and spleen, thus providing a new strategy for the treatment of lung tumors [126,129]. However, this combination may have adverse effects on RBCs, including hemolysis, agglutination, small vessel embolism, oxidative stress response [129]. RBC hitchhiking has been used to deliver a variety of drugs, including DOX, camptothecin (CPT), dexamethasone, paclitaxel, and methylprednisolone [128–131]. RBC hitchhiking in a mouse model of melanoma lung metastasis is effective [129,130]. Zelepukin et al. created a lung metastasis model of B16–F1 melanoma cells in which RBC hitchhiking was used to load DOX. According to their findings, the RBC-bound NPs group showed significantly slowed growth of lung metastases in melanoma mice compared to the negative control and free NPs group [129]. This is also the first demonstration of the therapeutic potential of RBC hitchhiking in lung tumors. Zhao et al. reported a highly efficient erythrocyte-leveraged chemotherapy (ELeCt) platform consisting of degradable drug NPs assembled on the surface of RBCs (Fig. 2). They confirmed that ELeCt loaded with DOX was able to slow the progression of lung metastases and improve survival in mice in both early and advanced melanoma lung metastasis models (B16F10-Luc) [130].

The abovementioned preclinical studies have fully demonstrated the anti-tumor potential of RBC hitchhiking. However, further research and evaluation are required to assess its efficacy in organs other than the lungs. Human studies also need to be conducted.

3.3. RBCNPs

Nanomaterials exhibit anticancer activity due to their antioxidant properties [132]. Nanomaterials can be roughly divided into three categories: organic nanomaterials (including polymeric NPs, liposomes, dendrimers, and micelles), inorganic nanomaterials (including carbon, noble metals, metal oxides, and nonmetals), and nanozymes. Many of these nanomaterials have unique optical, electrical, and antibacterial properties that make them suitable for various applications [133]. In the field of drug delivery, many types of nanocarriers have been developed, each with its own pros and cons, which are discussed in part below (Table 3). However, the implementation of NPs in cancer therapy is limited by various factors, such as low mechanical strength, limited cellular internalization, and difficulty in selective localization [134,135]. With technological advancements, the size of the prepared NPs has decreased dramatically, increasing the number of highly reactive particles and the effective surface areas [136]. As a result, the friction between NPs, as well as between NPs and biomolecules, increases leading to the production of reactive oxygen species (ROS) and resulting in

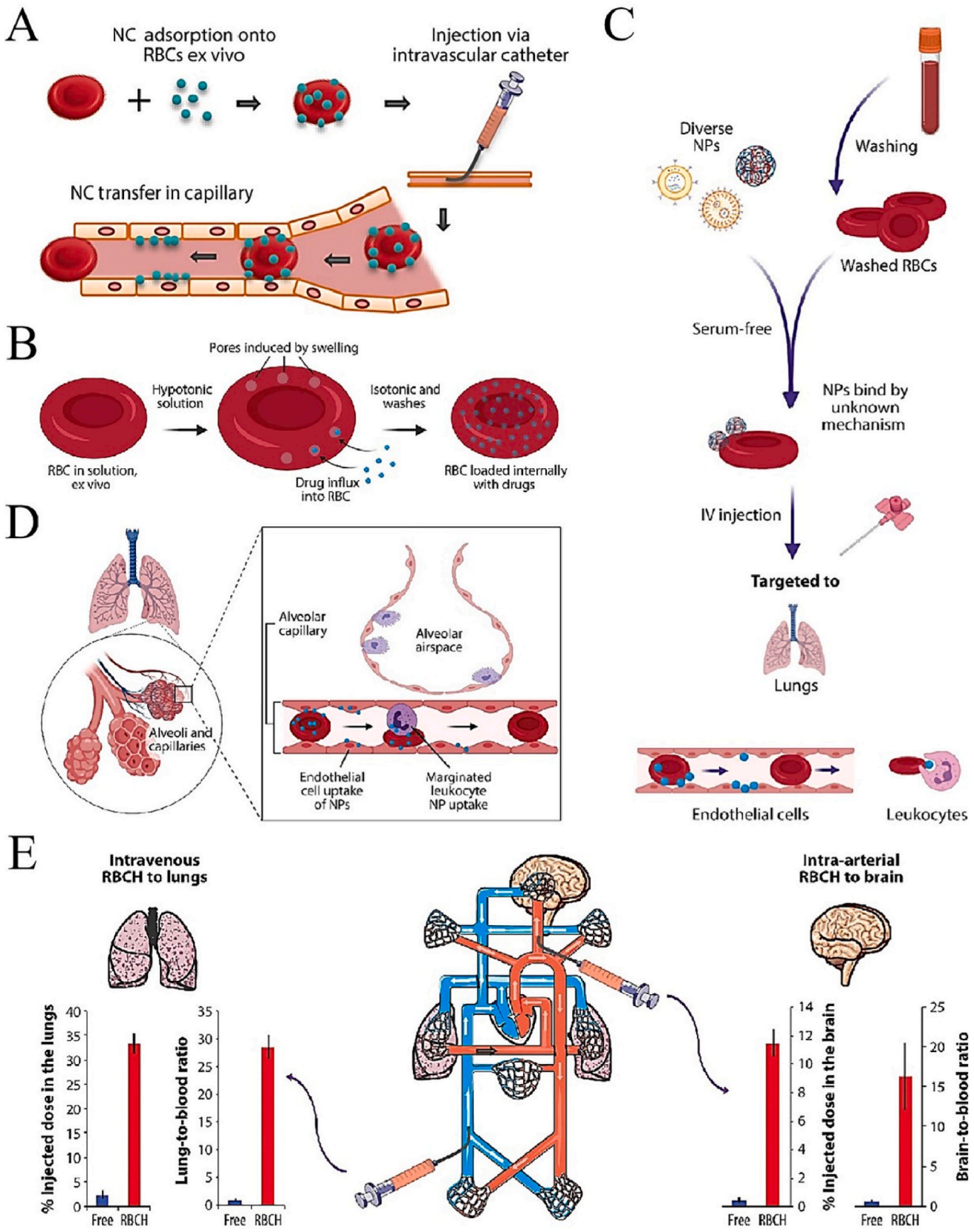


Fig. 1. Schematic illustration of RBC hitchhiking for vascular delivery of nano-carriers. A) Schematic representation of the originally proposed mechanism of RBC hitchhiking. B) Schematic of the mechanism of loading small molecule drugs and therapeutic proteins inside RBCs by hypotonic dialysis method. C) Schematic of the design engineering and action mechanism of RBC hitchhiking. D) Uptake of NPs via RBC hitchhiking. E) The prepared RBC hitchhiking can be targeted to any organ by selecting the catheter injection site. In the circulatory system, it is mainly targeted to the lungs and brain. (Reproduced with permission from Ref. [125]. Copyright 2021, Annual Reviews).

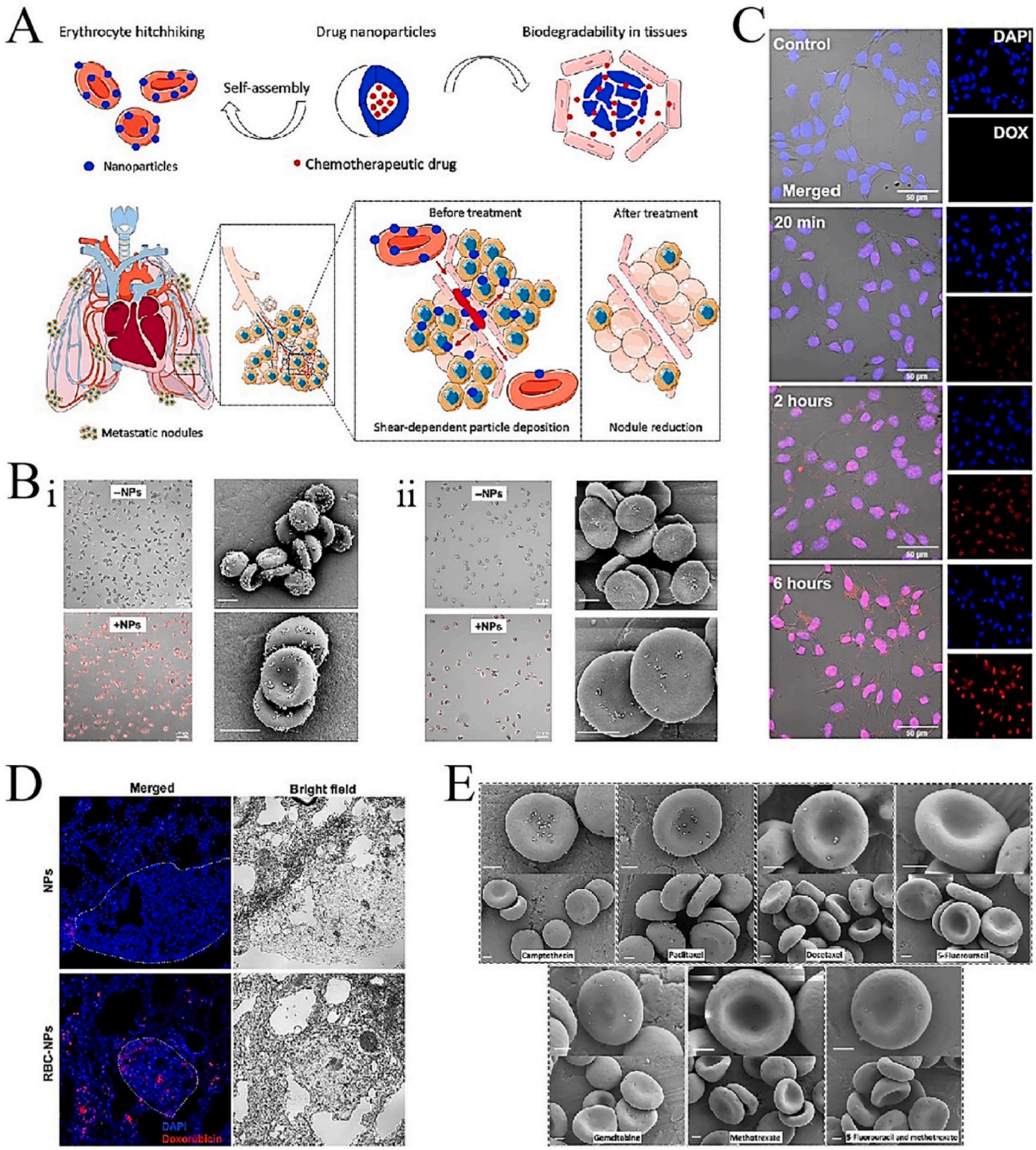


Fig. 2. Schematic illustration of the ELeCt platform. A) Schematic representation of the preparation and mechanism of biodegradable drugs-loaded NPs assembling on RBCs platform (ELeCt) to treat lung metastases. B) Confocal laser scanning microscopy (CLSM) (*left panel*) and scanning electron microscope (SEM) (*right panel*) images of mouse (i) and human (ii) RBCs assembled with drug-loaded NPs. Scale bars (in *left panel*) = 20 μm. Scale bars (in *right panel*) = 2 μm. C) CLSM images showing the interaction of drug-loaded NPs with B16F10-Luc melanoma cells. Scale bars = 50 μm. D) Drug distribution in the diseased lungs 20 min after intravenous administration of DOX formulations. Dashed lines indicate the edge of metastasis nodules. Original scale bars not mentioned. E) Chemotherapeutic agent–loaded biodegradable NPs can efficiently bind to erythrocytes. Scale bars = 1 μm. (Reproduced with permission from Ref. [130]. Copyright 2019, American Association for the Advancement of Science).

Table 3
Application, advantages, and disadvantages of various nanocarriers.

Nanomaterials	Advantages	Limits	Applications
Micelle [143–147]	Delivery of low-soluble drugs, and low cytotoxicity	Uncontrolled drug leakage, and easily diluted by blood flow	Antiviral therapy, tumor therapy
Liposome [148–150]	High structural flexibility, easy surface modification, good biocompatibility, and high permeability to deep skin	Low stability, leakage of hydrophilic drugs, high production cost, and limited drug load	Tumor therapy, gene delivery, signal enhancers, treatment of neurodegenerative diseases
Polymeric nanoparticle [151–155]	High encapsulation efficiency, wide variety, strong designability, and enhanced circulation characteristics	Complex synthesis process, poor structural stability, and rapid degradation	Tumor therapy, gene delivery, tissue engineering
Dendrimer [156–159]	Controllable molecular size, large number of functional groups, and simplicity of functionalization	High molecular weight, and low solubility	Antitumor therapy, antiviral therapy, anti-inflammatory therapy, cardiovascular disease treatment, imaging diagnosis
Carbon-based nanoparticle [160–162]	High light absorption and utilization efficiency, high surface area to volume ratio	Cytotoxic and inflammatory reactions, difficult to biodegrade	Optical imaging, phototherapy, drug delivery
Metal-based nanoparticle [163–167]	High biocompatibility and stability, adjustable size, good optical properties, easy surface functionalization, and long activity cycle	Difficult to biodegrade and potentially toxic	Phototherapy and biosensor
Metal oxide-based nanoparticle [168–170]	High light stability, large emission quantum yield, and easy surface modification	Poor biocompatibility and potential adverse reactions	Fluorescent labeling, and drug delivery
Silica nanoparticle [171–173]	Mesoporous structure, high surface area, biocompatibility, and degradability	Poor biological distribution	Photoacoustic imaging, drug delivery and release
Nanozyme [174–176]	Catalytic stability, low production costs, high tolerance to environmental changes, and adjustable biological function	Low reproducibility, less specificity toward substrate, and plausible catalytic mechanism	Biosensing, immunoassays, disease diagnosis, and drug delivery

adverse effects on cells or organisms, such as oxidative stress, inflammation, and DNA and protein damage [137,138]. Recently, drug encapsulation and cell membrane coating technologies have created new therapeutic modalities in the field of nanomedicine, including cancer [139,140]. In contrast to encapsulating the cargo in the cytoplasm of RBCs or attaching it to the surface of RBCs, RBCM-camouflaged polymeric NPs are prepared by extracting RBCMs from blood and coating them on NPs, thereby combining the advantages of RBCs and NPs, such as strong circulation characteristics, low immunogenicity, biocompatibility and degradability, easy modification and other characteristics. This will also expand its scope of application [141,142].

The preparation process of RBCNPs includes three phases: preparation of RBCM, preparation of NPs, and coating of NPs with RBCM. First, the two key steps in the preparation of RBCM are hypotonic treatment and sequential extrusion. Fresh whole blood is collected and stored at 4 °C, repeatedly washed with phosphate-buffered saline, and subjected to centrifugal resting and hypotonic dialysis to obtain RBC "ghosts". The collected residual cell pellets are subjected to centrifugation, sonication, and other dispositions to remove impurities. Finally, an extrusion process is carried out, i.e., an appropriately sized RBCM is prepared using polycarbonate membranes with different pore sizes [177]. Second, the preparation of NPs mainly follows the subsequent two routes [178]. The top-down approach involves breaking down bulk raw materials into nanoscale particles through wear, grinding, and etching. Hyperoxides and strong acids can be used to produce smaller particles. The bottom-up approach involves employing chemical and physical techniques to utilize atoms and molecules in a solid, liquid, or gas as starting materials that are aggregated to form nanoscale particles through non-covalent bonds [134,179–183]. In addition, natural biological systems can be applied to nanomaterials production. This synthetic method has the advantages of low cost, low toxicity, and safety due to the renewable raw materials; bacteria, fungi, yeast, algae, and other microorganisms and plants have been used as substrates for the green synthesis of NPs [182,184]. The selection of specific preparation routes and methods for NPs mainly depends on the physicochemical properties of cargo molecules, types of raw materials, and sizes and loading requirements of the NPs [185]. Third, the assembly of RBCM and NPs can be achieved by different methods, such as co-extrusion, sonication, in situ polymerization, and microfluidic electroporation. By mechanically disrupting the structure of RBCM, coextrusion allows RBCM to surround and cover the NP cores with minimal cell loss [117,186]. When using this method, it is important to maintain the integrity and stability of the phospholipid bilayer structure in the RBCM. In contrast, disruption by ultrasonic energy causes less loss of NPs and enables production to be scaled up [117]. The latter two methods must be further explored because of their difficulty and high cost [31,187].

Through the above methods, the core, shell, and surface of RBCNPs are processed and designed to maximize the application range and functional state while realizing cargo loading. For example, Ghasemzadeh encapsulated sulfur hexafluoride 6 (SF6) in a hydrophilic core and packaged hydrophobic CPT in lipophilic bilayers. In addition, mucin 1 (MUC1) aptamers were modified on the surface to obtain RBCM-based core-shell vesicular NPs. Studies have also confirmed that the nanotherapeutic system demonstrates not only safety and stability but also high targeting capacity, imaging ability, and treatment performance [188]. However, NPs can cross a variety of human barriers, including the blood–brain barrier (BBB); therefore, the potentially toxic and harmful effects of nanomaterials on humans should be further investigated before their application in clinical settings [189,190].

In recent years, a novel approach has been introduced for the design of biomimetic nanomaterials, involving the generation of nanovesicles composed of membrane proteins through the extraction and subsequent integration of these proteins into synthetic phospholipid bilayers. The methodology comprises of two primary stages. The initial step involves the extraction of the membrane protein from intricate cellular components through the utilization of detergent buffer and centrifugation procedures. Subsequently, the second step entails the integration of said membrane proteins into the cell. Phospholipids and cholesterol are dissolved in solutions such as chloroform or ethanol, resulting in the formation of lipid layers. These lipid layers are subsequently assembled into nanovesicles with the assistance of aqueous hydration, which contains the membrane proteins, or through the utilization of microfluid platforms [34,191,192]. Martinez et al. have successfully demonstrated the viability of the aforementioned methodology and developed nanovesicles derived from phospholipids and cholesterol, referred to as white blood cell nanovesicles [191]. Additionally, there exist studies that provide additional evidence supporting the effective integration of

albumen membrane protein onto the surface of these particles [193]. This methodology is applicable to a wide range of cell types and facilitates rapid and scalable production of biomimetic nanoformulations. It not only streamlines the preparation of nanocarriers while maintaining the function of cell membranes, but also enhances the consistency of product quality [34,192]. However, additional investigation is required to further explore the implementation of this method in RBCs.

3.4. RBCEVs

EVs are bilayer membrane structures that are released from the cell into the extracellular environment either by direct outward budding or via the endosome-lysosome pathway [18,128,194,195]. EVs are primarily released into blood circulation during the activation, injury, or apoptosis of endothelial cells and a variety of blood cells [196,197]. In addition to being diagnostic and prognostic biomarkers, EVs have been confirmed to play a role in a variety of biological activities, such as inflammation, extracellular matrix (ECM) degradation, vascular remodeling and generation, and coagulation processes [195,198–201]. Unlike RBCs, which are limited by vascular space and have weak barrier penetration and low extravasation capacity, EVs, especially small-sized EVs, demonstrate considerable potential in traversing anatomical barriers. Hence, EVs theoretically have the ability to disseminate to remote sites via the bloodstream. Nevertheless, this capability may be impeded by factors such as the ECM. This characteristic endows EVs with the capacity to facilitate communication between effector cells and target cells [54,201,202]. Therefore, EVs can serve as drug carriers or bioreactors in clinical settings [69,203]. Among them, RBCEVs have attracted widespread attention owing to their strong ductility and low risk of tumorigenesis [204]. In addition, RBCEVs can maintain relative stability, and their structure and function will not be adversely affected even after repeated freeze-thaw cycles [109].

Before preparing RBCEVs, it is often necessary to add antibodies, antigen-binding fragments, or ligands to the RBCs to enhance their targeting [108]. The preparation of the RBCEVs involves three steps. First, the collected blood is processed under hypo-osmolar conditions by high-speed centrifugation, sonication, and other methods to remove the contents of blood cells and obtain a mixture of blood cell membranes [177]. Second, the residual cell pellet mixture is isolated and purified. Pure RBCEVs can be obtained by ultracentrifugation, filtration, size-exclusion chromatography, polymer-based precipitation, and immunological separation techniques, among which ultracentrifugation gives EVs with the highest purity [109,205]. Third, RBCEVs of target sizes are fabricated using a microextruder by repeated extrusion of polycarbonate membranes with different pore sizes [177]. Finally, the cargo is loaded inside or coupled to the surface of the RBCEVs by physical or chemical means, as discussed before [203]. Based on the above steps, Jayasinghe et al. designed a drug delivery platform based on RBCEVs and successfully functionalized the surface of RBCEVs by a biotin-streptavidin reaction and the enzyme OaAEP1. After evaluation, the number of targeted molecules after copying the engineered EVs was far higher than that of other surface modification methods, reflecting a high targeting ability [113].

In addition to EVs, blood contains substances such as lipoproteins (LPP) and a variety of proteins. A certain overlap exists between EVs from different sources, and between EVs and LPPs in terms of size and density [206]. This makes it challenging to isolate and purify RBCEVs from blood due to complicated operations and high costs. Furthermore, it is impossible to remove all the impurities from an isolate [207].

4. Metabolism and distribution

With the advent of various cargo-loading methods and biofilm-coating technologies, RBC-based biomaterials have been rapidly developed as carriers of drugs and other active ingredients. The most prominent advantage of RBC/RBC-derived materials over other technologies is that they are recognized as “self” in the biological environment, which can reduce the host immune response and prolong drug circulation half-life. Multiple studies on the circulation characteristics of RBCs and their biomimetic coatings have been conducted, and the following conclusions have been drawn. A variety of surface proteins expressed on the RBCM, such as CD47, CR1, and decay accelerating factor (DAF), are the main reasons why the RBCM can evade the uptake and clearance by the immune system [31]. The long circulation time of RBCs and their derivatives significantly improves the pharmacokinetic and pharmacodynamic characteristics in vivo [208]. Although RBC-related materials have been successful in clinical studies, several factors have limited their effectiveness, including the obstruction of biological barriers, rate of degradation in circulation, ability to target specific cells and tissues, route of internalization to target cells, and efficiency of escape from endocytic organelles [209]. In addition, RBCs and their derivatives lack sufficient targeting activity [210].

Therefore, current important research directions are to adjust and improve the pharmacokinetics and to deliver RBC-derived materials and their loaded cargo efficiently and safely to the cytoplasm of target cells to exert their therapeutic potential.

4.1. Biological barrier

Solid tumors, particularly desmoplastic tumors, have a complex tumor microenvironment (TME). The TME includes but is not limited to, components such as the ECM, multiple cell types (immune cells, endothelial cells, and supporting stromal cells, such as cancer-associated fibroblasts), multiple signaling molecules, blood vessels, and lymphatic vessels. The TME forms a natural biological barrier around solid tumors, limiting the application of RBC-derived materials in tumor therapy (Fig. 3A) [211–214]. Effective targeting of solid tumors requires RBC-derived materials to pass through the rich blood vessel walls, dense tissue matrices, and tumor cell membranes.

4.1.1. Blood barrier

Unlike other RBC-derived materials, NPs have unique blood barriers. Once NPs are exposed to blood circulation, they rapidly form a protein corona (PC) composed of various biomolecules, such as the serum proteins around them [216]. The formation of a PC tends to shield or cover the functional groups on the NP surface. This endows NPs with new biological characteristics and further affects the interactions between NPs and their surrounding environment, such as their targeting ability, cell receptor type, and internalization pathway [217,218]. Notably, after the formation of the PC, functional molecules on the surface of the NPs may fail, leading to the reduction or even elimination of its targeting ability. Macrophages rapidly take up and clear NPs, thereby significantly reducing their circulation time.

To overcome these obstacles, PC barrier layers, such as polymers, proteins, and cell-derived biomimetic coatings, can be applied to block the adhesion to serum proteins and improve the cycling state of NPs [218,219]. One of the most common surface modification methods is the addition of polyethylene glycol (PEG) polymers and the use of the RBCM as a biologically invisible coating. In a study by Hu CM, a comparative analysis was conducted to examine the circulation half-life and blood retention rate of NPs coated with PEG invisible and RBCM biomimetic coatings. The findings provided additional evidence that the utilization of both PEG and RBCM coatings resulted in a significant reduction in the uptake and clearance of NPs by macrophages. Furthermore, the RBCM coating exhibited superior effectiveness [220]. It is also possible to incorporate a pH-sensitive material with switchable surface charges in order to disrupt the positive charge environment formed by PC, thus alleviating its adverse effects [209].

Additionally, after entering the blood circulation, RBCs and their derivatives need to escape filtration and clearance by the kidney, as well as the uptake and degradation by RES, especially Kupffer cells in the liver and macrophages in the spleen [221].

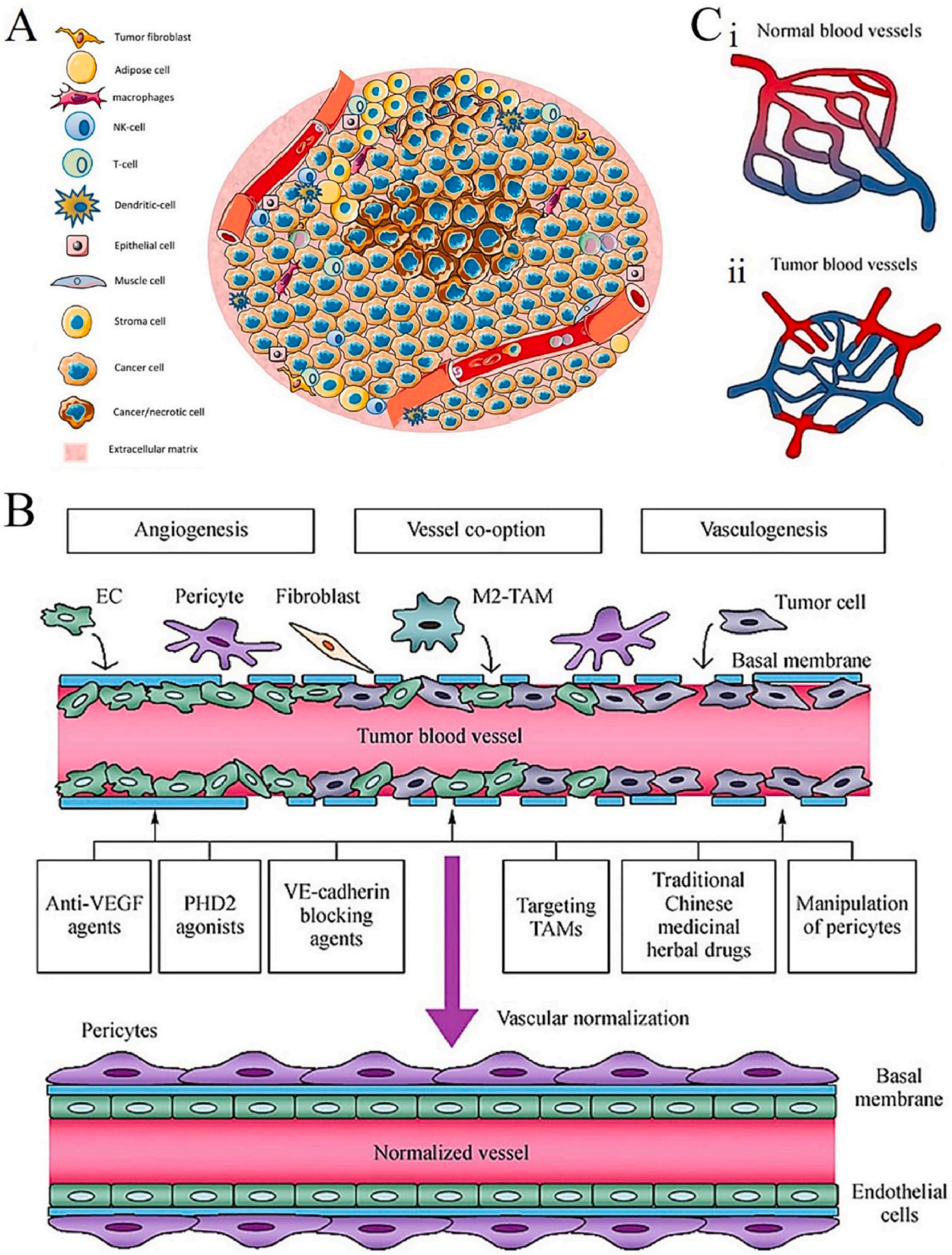


Fig. 3. Metabolic and distributional characteristics of RBC and its derived materials. A) An overview of the TME. (Reproduced with permission from Ref. [214]. Copyright 2019, MDPI, Basel, Switzerland). B) Normalization of disorganized tumor blood vessels for anticancer therapy. C) Comparison of normal vascular structure (i) and tumor vascular structure (ii). (Reproduced with permission from Ref. [215]. Copyright 2012, Springer Nature).

4.1.2. Vascular/matrix barrier

After entering the blood circulation via various routes of administration, RBC-derived materials first reach the vicinity of the tumor tissue through the blood supply and penetrate the microvascular wall to leak into extravascular tissues. They then pass through the desmoplastic stroma of solid tumors to reach target cells [211,222].

There are several specific pore sizes and distributions in microvessels, and the pore parameters differ among different tissues. For example, the intercept sizes of the pores in the brain and breast tissues are 1 nm and 5 nm, respectively. The size of these pores determines the diameter and permeation rate of molecules entering the tissue from blood. The vascular system of tumor tissue is derived from normal microvessels, and its related parameters are affected by tissue origin and tumor location, among other factors. For example, the permeation size of brain tumors is 7 nm, whereas that of pancreatic tumors can reach 50–60 nm. Therefore, if the cutoff size of the pore is small or the particle diameter of the molecule is large, it may result in a slow, small number, and uneven distribution of particles that penetrate the microvascular wall and tumor vascular tissue [222]. In contrast, smaller particles have a stronger ability to penetrate the vessel wall; however, particles smaller than 10 nm in diameter are rapidly removed by the kidneys, liver, and gallbladder. Larger particles can be targeted to tumor blood vessels under the action of MPS, but it is difficult for them to enter the tumor tissue [124].

Therefore, for different tumor models, it is necessary to design and select an appropriate particle size to maximize vascular permeability and reduce the clearance in blood circulation [223]. Anti-angiogenic and vascular normalization therapies can also be used to repair abnormal tumor vessels, reduce interstitial fluid pressure, and increase blood circulation perfusion (Fig. 3B) [215]. Currently, anti-vascular endothelial growth factor receptor (VEGFR) 2 antibody, transforming growth factor-β inhibitor, and drugs such as captopril have been proven to improve the delivery of nanomedicine for cancer therapy [224,225]. To investigate the effect of vascular normalization on nano-drug delivery in vivo, Chauhan et al. used DC101, a VEGFR blocker, to reduce the diameter of blood vessels in breast tumors in situ and repair abnormal blood vessels. They selected two orthotopic breast tumor models, E0711 and 4T1, and infused them with DC101 at doses of 5 mg/kg and 10 mg/kg, respectively, to calculate the permeability of NPs in the tumor tissue of the two groups. Results from the two groups led to the conclusion that the vascular permeability of 12 nm-sized NPs was significantly increased (approximately 2.7- or 3.1-fold) after the application of DC101, whereas the penetration of 60 or 125 nm-sized NPs did not improve. Thus, the above results confirm that vascular-related therapy can reduce the dependence of tumor therapeutic drug delivery on material size and enhance the effective penetration of smaller particles [224]. Jiang et al. further found that NPs of medium size (20–40 nm) can also benefit from tumor vascular remodeling; however, once they enter the tumor matrix, their diffusion is limited to a greater extent [226]. Considering this prior research, it was proposed that NPs with "size variability" could take full advantage of "enhanced permeability and retention" (EPR) in solid tumors. One specific strategy involves loading goods into a large NP. After passing through the vascular lumen and reaching the tumor stroma, it can be degraded by tumor-specific enzymes (proteases, hyaluronidase, etc.) into smaller particles, allowing it to penetrate deeply, distribute evenly in the tumor area, and release therapeutic drugs. Liu et al. demonstrated the feasibility of this strategy. They prepared thermosensitive NPs that reduce in size and release drugs under the induction of tumor-specific hyaluronidase. By applying this to photothermal therapy (PTT) for breast cancer, they found that their NPs possess a significant anti-tumor effect [227].

The ECM is composed of multiple interacting protein complexes, including structural proteins (collagen and elastin), specialized proteins (fibronectin and laminin), and proteoglycans [228]. During the dynamic process of protein formation and degradation, the ECM can maintain a highly balanced state through enzymatic degradation (including matrix metalloproteinase (MMP), collagenase, and hyaluronidas) and cellular secretion (such as fibroblasts and myofibroblasts), providing mechanical support and signal regulation for cellular components [229,230]. In malignant tumors, ECM is produced and consumed in unbalanced proportions, and its dynamic state is disrupted. Excessive ECM degradation is one of the hallmarks of tumor invasion and metastasis, whereas excessive ECM accumulation leads to fibrosis and hinders the effective penetration and uniform distribution of molecules [211,231]. The dense ECM acts as a barrier to drug delivery through several mechanisms. First, it leads to an increase in interstitial fluid pressure and mechanical stress in the tumor, compressing the tumor blood vessels and impairing tumor perfusion. This can affect the delivery and penetration of therapeutic agents [232]. Second, its complex network structure acts as a physical barrier to the further diffusion of therapeutic agents. Third, the charges carried by ECM components may affect the delivery of therapeutic agents to the mesenchyme [211].

Therefore, certain measures can be taken to weaken the barrier effect of ECM. The first measure is the reduction in ECM production. The main targets of this method are collagen, hyaluronic acid (HA), and cancer-associated fibroblasts, and an inhibitory effect can be achieved by restricting the formation and impairing the function of these components. For example, collagen prolyl 4-hydroxylase inhibitors can block the hydroxylation of collagen prolyl and reduce the production of collagen, thereby inhibiting tumor proliferation, invasion, and metastasis and enhancing the delivery of anti-tumor drugs to tumor cells. Similarly, 4-methylumbelliferone inhibits HA synthesis by depleting HA components and decreasing HA synthetases. The second measure is the induction of ECM remodeling. Strategies such as ultrasound therapy, sonodynamic therapy, and phototherapy can reduce the density of the ECM and induce ECM remodeling, thereby regulating the permeability of therapeutic agents in the mesenchyme [211,219]. Lysine oxidase (LOX) is secreted by cells to mediate the covalent cross-linking of collagen with other ECM components, such as elastin. It is also a key factor for the deposition of matrix-insoluble components and the increase in ECM stiffness; it also plays an important role in ECM remodeling [233]. Therefore, chemical methods or LOX antibodies can inhibit LOX's action to reduce ECM cross-linking, prevent collagen remodeling, and increase vascularization, thereby achieving anticancer effects [234]. The third measure is the promotion of ECM degradation. The aforementioned degrading enzymes can be directly injected into the organism or combined with NPs (modified on their surface or embedded in their interior) to reduce ECM density through indirect effects [211,219]. They can also disrupt the network structure of the ECM by promoting the expression of degrading enzymes. MMP expression is regulated by relaxins (RLX). It has been confirmed that RLX enhances the expression of MMPs and efficiently degrades dense ECM. Mardhian et al. chemically coupled RLX with superparamagnetic iron oxide nanoparticles (SPION) to prepare RLX-SPIONs. They found that the carrier reduced the density of the ECM and inhibited tumor growth and that the effect of this NP was better than that of free RLX [235].

4.1.3. Blood–brain/blood–brain tumor barrier

Unlike tumors of other tissue origins, central nervous system (CNS) tumors have unique resident cell types and vasculature. In addition to universal TME components, specialized cell types such as neurons, microglia, and astrocytes are included in the TME of brain tumors to ensure the normal functional status of all regions of the brain [236]. Moreover, there is a special physiological blood-brain interface between systemic blood circulation and the CNS, which is used to separate other organs from the brain and maintain stability and functional properties within the brain. Depending on their positional distribution and structural composition, these physiological interfaces can be classified into the following categories: the BBB, blood–cerebrospinal fluid barrier, arachnoid barrier, brain–retinal barrier, and spinal cord barrier [237]. The BBB is considered the most important barrier for exogenous substances to penetrate the brain [224]. It is a physical and functional

barrier comprising a high density of microvascular endothelial cells [238]. The BBB, as a physiologic anatomical barrier, limits the passage of substances from the circulatory system into the brain parenchymal tissue and protects the brain from toxins, infection, inflammation, and injury. Studies show that more than 98 % of small-molecule drugs and almost all large-molecule drugs cannot cross the BBB [239]. The BBB, as an active tissue, also expresses a variety of proteins such as receptors and enzymes, and participates in various biological processes, such as the clearance of toxic substances and exchange of substances between the blood and brain [236,237]. Hence, the utilization of an effective brain-targeted carrier system is imperative for facilitating substance delivery.

In order to overcome the barriers mentioned above and enhance the effectiveness of CNS tumor treatment, the RBCNPs can be modified in the following ways: incorporating therapeutic agents and implementing targeted modifications. The sensitivity of NPs to specific stimulus responses (including pH, ROS, enzymes, light, and heat) can also be exploited to achieve high targeting and penetration as well as maximum accumulation of NPs and loaded cargo in the delivery process [239]. Fu et al. designed new RBC biomimetic nano-carriers modified with T7 and NGR peptides and loaded them with vincristine (VCR). They demonstrated that RBCNP could cross the BBB and target the tumor site not only by increasing the concentration of VCR in glioma but also by further reducing the toxic side effects of VCR [240]. This discovery provides substantial evidence for the extensive utilization of membrane coating technology and nanotechnology in the treatment of CNS tumors.

4.2. Targeting effect

Cell targeting can achieve precise treatment of affected cells, avoid collateral damage in non-targeted areas, and prevent the development of a variety of drug resistance mechanisms [241]. It is mainly divided into two categories: passive and active targeting [242].

4.2.1. Passive targeting

Passive targeting mainly depends on the physiological characteristics of the tumors. Compared to normal vascular endothelial architecture, the tumor vasculature (blood and lymphatic vessels) is inherently highly leaky (Fig. 3C) [215,243]. In most solid tumors, unique features of the vasculature are observed, such as discontinuous epithelium, impaired lymphatic drainage, slow venous return rate, and elevated interstitial fluid pressure. Based on the high permeability of tumor blood vessels and the low functionality of lymphatic drainage, macromolecules, and NPs ranging from 100 to 200 nm in diameter can penetrate tumor tissues and play different roles in vivo. This phenomenon is referred to as the EPR effect [221,244,245].

The EPR effect, as a passive targeting strategy, is widely used to control the differential accumulation of drugs in the tumor region [246]. However, the effectiveness of the EPR is limited by several factors. First, the EPR phenomenon is highly specific, with distinct differences in EPR sensitivity among patients, tumors, and delivery agents with different physical and chemical properties [247]. The size, shape, surface characteristics, and other physicochemical properties of the delivered substance may affect the passive targeting efficiency. For example, compounds with high molecular weights (above 50 kD) and small NPs (below 200 nm) are more likely to accumulate at specific target sites, mediated by the EPR effect [242]. Second, not all tumor environments exhibit the EPR effect. Limited by the hypoxic microenvironment, only a small amount of drug accumulates in the central area of metastatic tumors and some tumors with low permeability (pancreatic cancer) [248]. The third limitation is the difficulty of achieving efficient drug transport through the EPR effect alone. Infected or inflamed sites have been reported to exhibit the EPR effect by producing large amounts of bradykinin, inducing an increase in vascular permeability [249]. Therefore, passive targeting via the EPR effect can result in small, inadequate, and uneven accumulation of anticancer drugs in the target cancer tissues [246]. It is difficult to fully achieve the therapeutic goal if drug targeting is insufficient, and residual cancer cells may lead to treatment failure or drug resistance [250]. To overcome the limitations of passive targeting, active targeting strategies based on biological ligands have been developed and are discussed in detail in the following paragraphs.

4.2.2. Active targeting

Active targeting involves the systematic delivery of cargo to the tumor area using specific homing ligands. The specific mechanism is as follows: Target-specific functionalization of RBC and their derivatives can be achieved by attaching targeting ligands to the surface. These ligands can bind to the corresponding receptors overexpressed on tumor cells to achieve the retention and accumulation of cargo at tumor sites through receptor-mediated endocytosis [246,251]. Typically, active targeting also depends on the EPR effect, but the delivery efficiency is significantly higher than that of passive targeting mediated by the EPR effect alone [252]. Various tumor-targeting agents have been used and validated in previous studies, including monoclonal antibodies, aptamers, nucleic acids, and functional ligands based on small molecules, peptides, proteins, and even carbohydrates [246].

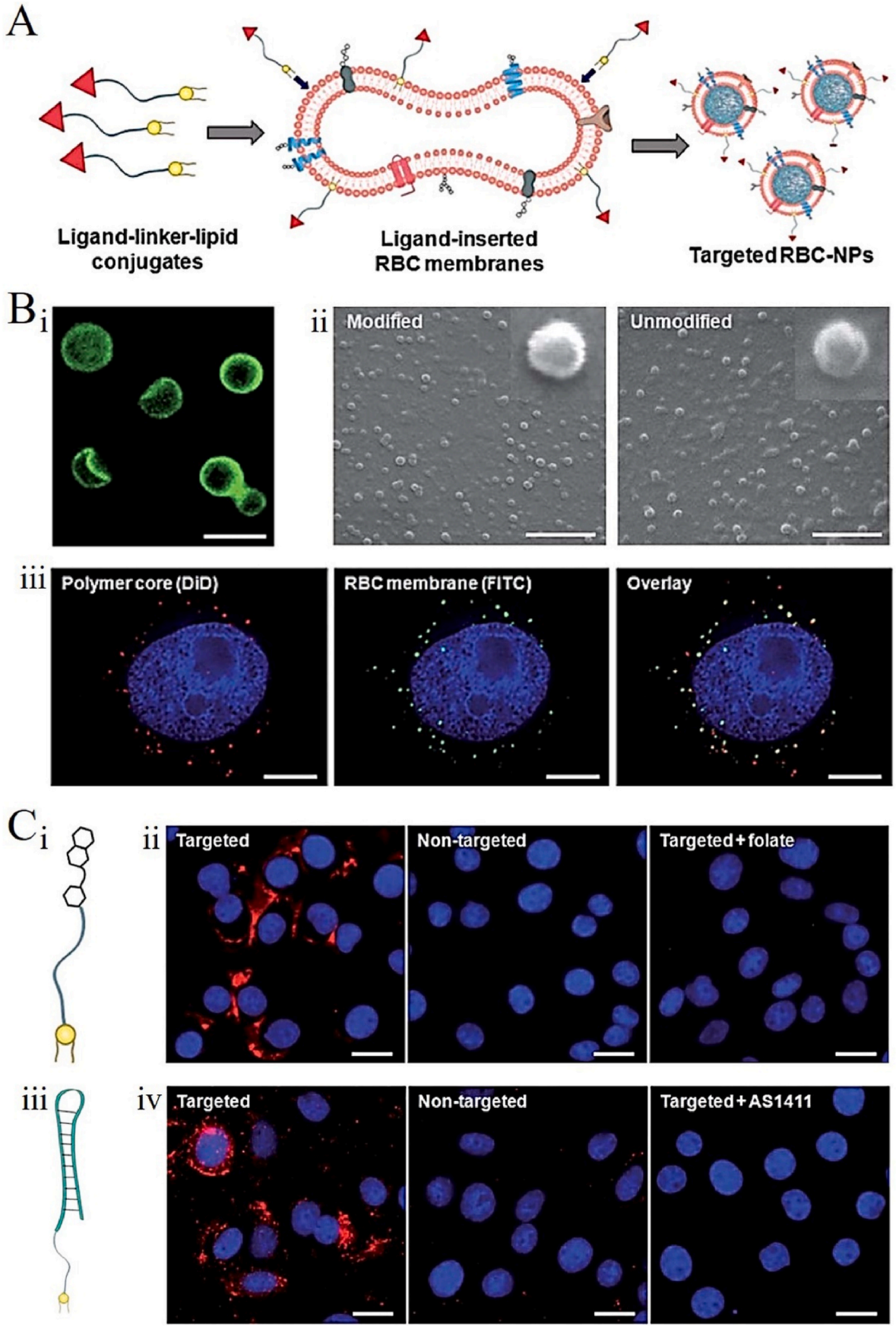
Fang et al. successfully prepared a functionalized RBCNP by inserting targeting ligands such as folate and nucleolin targeting aptamer AS1411 into the RBCM in the form of a lipid insertion form of "ligand-linker-lipid conjugate" (Fig. 4). This process did not destroy the original surface proteins. These RBC biomimetic NPs have been shown to target tumor cells overexpressing the corresponding receptors with greatly improved targeting ability [253]. Similarly, Zhang et al. used folate as an active targeting agent and observed a significant enhancement in the prepared NPs during cell internalization [244]. In addition, the efficacy of substances such as arginine-glycine-aspartic acid (RGD) and epidermal growth factor (EGFR) antibody in enhancing cellular uptake has also been well validated [254,255].

4.2.3. Stimulation of responsive targeting

Several factors limit the practical efficacy of the EPR effect, and active targeting strategies depend on overexpressing receptors on tumor cells, without which receptor-ligand interactions are difficult to achieve. Considering these limitations, recent research focused on investigating and applying targeting strategies that utilize irritant-sensitive NPs [256].

The stimulus-responsive targeting strategy consists of two phases. In the first phase, the NPs and their cargo are passively delivered to the tumor tissue via the EPR effect. In the second phase, when NPs reach the target sites, the precise release of cargo in the target tissue is achieved through changes in the endogenous (including pH, temperature, and redox state) or exogenous (including light, electric field, and ultrasound) stimulation conditions [246,256,257]. For example, changes in pH, especially under acidic conditions, can destroy covalent crosslinks and biological coatings in NP carriers, enabling the rapid release of the payload [257]. In addition, the pH can be used as an external stimulus to regulate surface charge conversion and initiate biological reactions [258]. Changes in the magnetic field can stimulate NPs transfer to tumors, and the heat induced by near-infrared light can stimulate thermosensitive elements to change the leakage characteristics of tumor blood vessels, such as the pore size, to achieve efficient accumulation of NPs [258,259].

Although still in the early stages of concept research and design, specific targeting strategies based on stimulus responses can improve targeting efficiency. Liu et al. developed a novel bionic nanotherapy platform by incorporating 1, 2-diaminocyclohexane-platinum and indocyanine green (ICG) into targeted peptide-modified RBCM. This platform demonstrated tumor targeting capability, facilitating enhanced tumor internalization, and enabled the simultaneous application of chemotherapy and phototherapy. Upon exposure to light, the nanotherapeutic system disassembled, leading to efficient drug release and resulting in substantial tumor ablation and suppression of lung



(caption on next page)

Fig. 4. Lipid-insertion enables targeting functionalization of RBCNPs. A) Schematic representation of the preparation of targeted RBCNPs by the form of "ligand-linker-lipid conjugate". B) As verified by fluorescein isothiocyanate (FITC), the lipid insertion method could achieve ligand binding to RBCM. i) Fluorescence microscopy visualization of RBC ghosts modified with FITC. Scale bar = 8 μm. ii) SEM images of FITC-modified and unmodified RBCNPs. Scale bars = 500 nm. iii) Colocalization of the polymeric core (red) and the FITC-modified RBCM shell (green) upon intracellular uptake by tumor cells. Scale bars = 8 μm. C) Folate/AS1411-targeted functionalization of RBCNPs. Schematic representation of folate (i)/AS1411 (iii)–linker–lipid. Fluorescence microscopy images of tumor cells incubated with different RBCNP preparations and free folate (ii)/AS1411 (iv). Scale bars = 25 μm. (Reproduced with permission from Ref. [253]. Copyright 2013, Royal Society of Chemistry). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

metastasis through the synergistic effects of photothermal and chemotherapy [260].

4.3. Endocytosis and endosomal escape

Upon reaching the tumor tissue, RBC-derived materials must be effectively internalized by the tumor cells to exert their effects. Currently, the internalization of extracellular delivery agents is mainly achieved through the endocytic pathway without cell destruction [242,261]. Endocytosis is composed of various pathways, including phagocytosis (uptake of large particles) and pinocytosis (uptake of fluids and solutes) [262]. The mechanisms of pinocytosis are classified as macropinocytosis, receptor-dependent (also known as clathrin-dependent) endocytosis, caveolin-dependent endocytosis, as well as clathrin- and/or caveolin-independent endocytosis [263]. However, the specific mode of endocytic uptake depends on factors such as the modification of RBC-derived materials and the type of recipient cells [264].

In general, various types of cargos enter the cell and are transported to early endosomes, which are sorting sites located at the cell periphery. Materials to be degraded are transported through late endosomes to lysosomes for degradation, whereas materials to be recycled are transported back through recycling endosomes to the plasma membrane or further transported to the Golgi for reuse [265,266]. Pham et al. have demonstrated that RBCEVs and their cargo enter recipient cells via various endocytic pathways. They used specific markers to label and localize the various stages of transportation after the internalization of RBCEVs, further verifying that endocytosed RBCEVs and their cargo eventually accumulate in late endosomes and lysosomes [264].

However, materials delivered to endocytic organelles (endosomes or lysosomes) are mostly stored inside or quickly destroyed without being released into the cytoplasm, thus limiting their biological effect [267]. It has been reported that anti-tumor drugs loaded by NPs are limited by internal barriers in endocytic vesicles, affecting their release efficiency and therapeutic effect [264]. For macromolecules to penetrate effectively, they must be transferred from endocytic vesicles to the cytosolic space. Usually, the escape of materials from endosomes to the cytoplasm is promoted by four mechanisms: rupture of the endosomal membrane and formation of pores, fusion of liposomes with endosomal membranes, pH buffering (or proton sponge effect), and photochemical decomposition of endosomes. However, these mechanisms lack optimal efficiency [268,269]. Therefore, enhancing endosomal escape could effectively solve the problem of endosomal interception and improve the efficiency of cargo delivery [270]. Several strategies were confirmed to improve endosomal escape efficiency, such as surface functionalization, use of membrane osmotic agents, and utilization of CCP [264]. CCP is a short peptide rich in positive charges, usually composed of natural amino acid (lysine and arginine) residues, which can mediate the process of active or passive shuttling to the plasma membrane [209].

4.4. Degradation process

In aging or abnormal RBCs, metabolic pathways are inactivated, and surface viscosity is increased, resulting in the destruction of cell membrane integrity and function. Finally, RBC constructs with reduced deformability cannot pass through the splenic venous sinuses and are thus removed by macrophages. However, most of the remaining RBCs that pass through the spleen are recognized and recovered by the RES located in the bone marrow [70].

5. Application

5.1. Drug delivery system

Despite their wide use in clinical practice, conventional drugs have many disadvantages and limitations, such as low water solubility, rapid metabolism, high clearance rates, off-target side effects, and the need for large or repeated doses to achieve therapeutic effect [271,272]. Compared with traditional drugs, DDSs offer significant benefits in terms of optimizing pharmacokinetics and spatiotemporal specificity. These advantages encompass the extension of circulation lifespan, limitation of premature clearance, enhancement of targeting ability, augmentation of biological utilization and drug load, and mitigation of adverse effects [208,273,274]. In addition, it can overcome biological barriers and deliver poorly soluble and toxic drugs, among others [275,276]. There has been significant progress in the role of DDSs in cancer treatment recently; however, there are still many challenges to overcome in terms of selectivity, efficacy, and safety. The design and development of DDS based on the biological, physical, and chemical properties of cancer cells can enhance cellular uptake and achieve efficient delivery, thus providing promising advancements to solve important problems in drug research [277]. Research has shown that DDSs derived from RBCs and their derivatives have great potential for prolonging circulation time, reducing immune responses, and achieving sustained release [31,277].

5.1.1. Chemotherapy

Yao et al. designed a novel platinum-based anticancer prodrug (ERY1-Pt IV) that hitchhikes to RBCs. In their design, the RBC-binding peptide ERY1 enabled platinum complexes to attach to RBCs to improve circulation time and tumor accumulation. Subsequently, the conjugate was proven to be effective in inhibiting tumor growth in vivo compared to the original platinum drug, and its circulating half-life and tumor accumulation were also proven to increase [278]. Ghasemzadeh et al. successfully developed novel RBCM-based vesicular nanobubbles (NBs) (Fig. 5). The specific preparation process was as follows: SF6 gas was added to the core as an ultrasound contrast agent, CPT was packaged into the shell as a chemotherapeutic drug, and the MUC1 aptamer (referred to as Apt) was covalently modified onto the surface of the NBs. The MUC1 aptamer was modified to enhance the cellular uptake and cytotoxicity of CPT in MUC1-positive tumor cells. The higher echogenicity was verified using in vitro and in vivo ultrasound imaging. Preclinical evaluation in the C26 intestinal adenocarcinoma model of BALB/c mice showed that NBs exhibited higher tumor suppression and mouse survival than free CPT treatment [188].

In addition to targeting limitations, poor drug penetration also decreases the effectiveness of drug delivery [279]. The BBB and blood-brain tumor barrier (BBTB) are particularly problematic for the CNS because they vastly hinder the effective accumulation of therapeutic drugs in the tumor area [280]. To solve this problem, Fu et al. prepared a novel bionic nano-carrier (T7/NGR-RBCSLNs) with dual targeting and barrier-crossing abilities (Fig. 6). Specifically, using lipid insertion technology, an active-targeting RBCNP with T7 and NGR peptides was developed, and VCR was encapsulated within it as a therapeutic agent. With the capability of T7 to bypass the BBB and target gliomas and the ability of NGR to target gliomas, the two peptide-combination can be synergistically effective in targeting brain tumors, so that the nano-carrier can cross the BBB and BBTB to

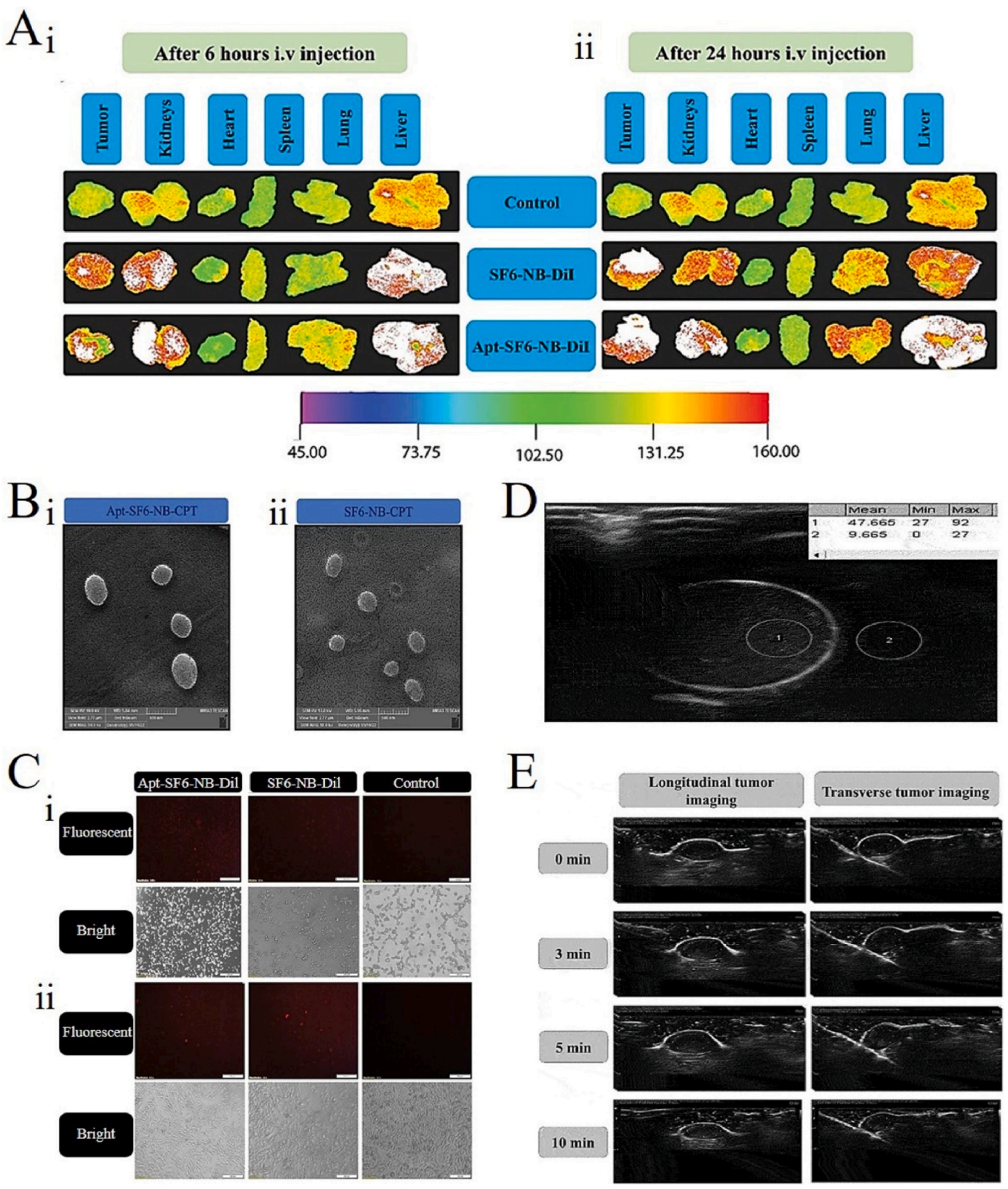


Fig. 5. Schematic illustration of the biomimetic NBs for treatment of colon adenocarcinoma. A) Ex vivo fluorescence imaging of tumor tissues and major organs in mice after 6 h (i) and 24 h (ii) of intravenous injection of different NBs. B) Field emission scanning electron microscopy images of prepared targeted (designated Apt-SF6-NB-CPT) (i) and non-targeted (designated SF6-NB-CPT) (ii) nanovesicles. Scale bars = 500 nm. C) Fluorescence microscopy images of the uptake situation of different NB preparations by colon cancer cells (i) and normal cells (ii). Scale bars = 200 μm. D) Assessment of echogenicity of SF6-filled biological NB using ex vivo ultrasound imaging. E) Assessment of echogenicity of SF6-filled biological NB using in vivo ultrasound imaging. (Reproduced with permission from Ref. [188]. Copyright 2023, Informa UK Limited).

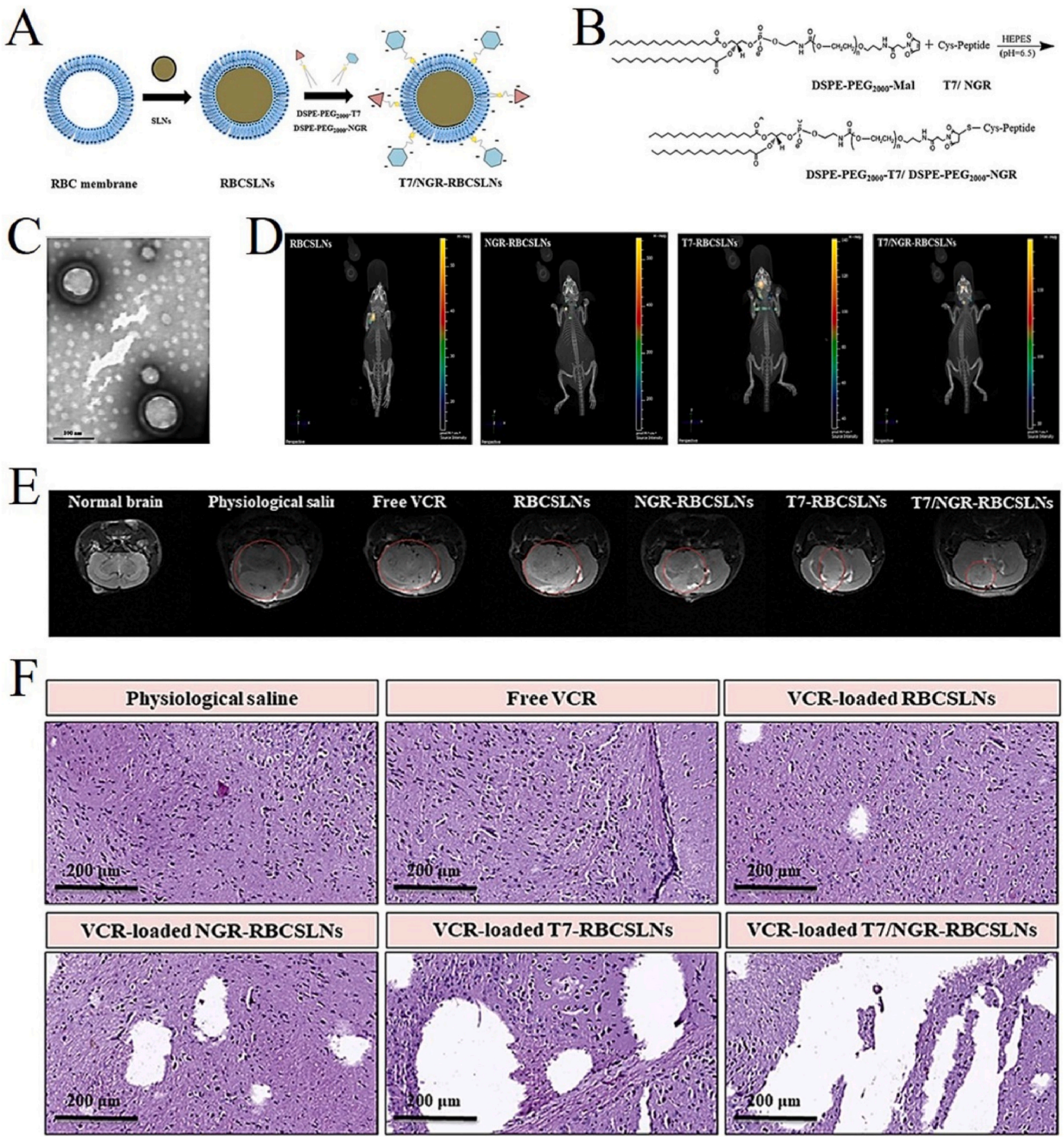


Fig. 6. Schematic of the RBC-based biomimetic nano-carriers with T7 and NGR peptide (T7/NGR-RBCSLN) for glioma treatment. A) Schematic of preparation of T7/NGR-RBCSLN. B) Preparation principle of DSPE-PEG_{2000}-T7/NGR. C) Morphological appearance of VCR-loaded T7/NGR-RBCSLNs based on transmission electron microscope (TEM). Scale bar = 100 nm. D) In vivo targeting ability of different RBCSLN preparations. E) Magnetic resonance imaging images of normal brain and the brain of cases 16 days after inoculation with different RBCSLN preparations in the C6 glioma mouse model. F) Hematoxylin and eosin staining analysis of brain tumors with various formulations. Scale bars = 200 μm. (Reproduced with permission from Ref. [240]. Copyright 2018, American Chemical Society).

accumulate at the tumor site. Through in vivo and in vitro experiments in the C6 glioma mouse model, not only was NP found to have high targeting potential, but it also significantly inhibited tumor growth and reduced the systemic toxicity of VCR [240]. This will provide a new research direction for the treatment of CNS tumors such as glioma.

5.1.2. *Immunotherapy*

Generally, immunotherapy generates or enhances an immune response against tumor cells to achieve anti-tumor goals [14,281]. Various mechanisms have been developed to enhance the ability of the immune system to detect and eliminate malignant cells, including

immune cell-targeted monoclonal antibody therapy, adoptive cell therapy, and the use of nonspecific cytokines [282]. In recent years, the emergence of immune checkpoint blockade therapies and cancer vaccines has established an important role for immunotherapy in cancer treatment. However, owing to the low immune response rate and development of drug resistance, the number of patients who benefit from this treatment remains small [283,284]. Therefore, further development of more effective immunotherapeutic strategies is necessary.

Some specific chemotherapeutic drugs, such as DOX and oxaliplatin (OXA), have been shown to initiate anti-tumor immune responses by inducing immunogenic cell death (ICD), causing the release of tumor-associated antigens (TAAs) and damage-associated molecular patterns (DAMPs) and synergistically improving the efficacy of immunotherapy. Su et al. have reported a novel therapeutic RBC vaccine that improved the response rate to cancer immunotherapy. CT-26 cells were treated with irinotecan in vitro to induce the production of tumor antigens (cAgs), which were then anchored to the RBC surface by covalent modification. In this study, subcutaneously injected RBC vaccines were primarily phagocytosed by dendritic cells, thereby establishing a long-term anti-tumor immune response by promoting T-cell infiltration and expansion inside the tumor. As observed in the CT-26 syngeneic mouse model, conjugating cAgs to RBCs produced satisfactory tumor suppression and significantly prolonged mouse survival. Furthermore, compared to the direct combination of chemotherapy and immunotherapy, RBC vaccines may encompass less chemotherapy-induced cytotoxicity and adverse effects [285].

Immune response against cancer can be activated by 5′-phosphorylated RNA via the RIG-I pathway. However, these molecules are usually degraded before reaching tumor cells in vivo. Peng et al. used EVs from RBC for RIG-I agonist delivery, such as microRNA (miRNA) or 3p-125 b-antisense oligonucleotide (ASO). Subsequently, they observed that tumor cell growth was significantly inhibited, and immune cell infiltration mediated by RIG-I cascade activation increased in the breast cancer model after multiple injections of RBCEVs. They also added an EGFR antibody to RBCM to enhance intrapulmonary targeted delivery, promoting the accumulation of RBCEVs in the metastatic tumor region of the lung, which would help inhibit tumor migration and invasion to the lung [254].

5.1.3. Gene therapy

As genetics is closely related to tumorigenesis, therapies based on genetic modifications such as gene knockdown and gene silencing (RNA interference, or called RNAi) have been investigated as emerging options for cancer treatment [286]. Gene knockout refers to the disruption of the expression of a specific gene by the introduction of exogenous DNA fragments. However, this method is technically difficult and expensive, and its success rate is not ideal. RNAi is a post-transcriptional regulatory process that inhibits gene expression by blocking the translation of a specific messenger RNA by non-coding double-stranded RNA of endogenous (miRNA) or exogenous (small interfering RNA or called siRNA) origin. RNAi is easy to perform and requires a short cycle time. However, owing to the existence of intracellular and extracellular barriers, endosomal escape and cellular uptake of oligonucleotides are suboptimal, making it difficult to effectively deliver siRNA and other molecules to tumor cells [287,288]. Further exploration and development of safe and effective siRNA vectors are required to overcome these obstacles.

Wu et al. constructed a new fluorinated coordination polymer (FEGCG/Zn) delivery system and verified a high drug loading, release efficiency, and stability of the platform with chemotherapeutic drugs such as sorafenib, gemcitabine, and DOX, as well as other substances such as peptides and proteins. They also integrated the platform with the construction of hitchhiking in live cells. In the case of RBCs, Cy5-tagged siPD-L1 was loaded to alleviate T-cell exhaustion by modulating the expression of programmed death ligand 1 (PD-L1) in tumor cells, enabling enhanced *anti*-PD-L1 immunotherapy based on gene therapy [289]. In recent years, nanotechnology has shown great application prospects for overcoming the limitations of traditional gene therapy and providing better therapeutic effects; this includes meeting the stringent requirements in the delivery stage of CNS tumor therapy. To improve RNAi-based glioblastoma (GBM) treatment, Liu et al. synthesized a charge-converted biomimetic nanoplatform with a three-layer core-shell structure (Ang-RBCm-CA/siRNA) (Fig. 7). Upon stimulation of charge conversion, this nanocomposite rapidly disintegrated and fully exposed its siPLK1 core which quickly downregulated the expression of the GBM oncogene PLK1, thereby inhibiting tumor survival and proliferation. After several in vitro tests, the RBCM biomimetic nanocomposites were found to have excellent and unique properties such as a long plasma half-life and excellent BBB penetration. During subsequent testing of the GBM mouse model, significant early and late apoptoses of tumor cells were observed, and the mice showed few systemic adverse reactions. This confirms that this biomimetic nanobody has high safety, gene transfection efficiency, and gene silencing ability [290]. This study provides an effective reference for the delivery and release of other biological agents.

Multiple drug resistance (MDR) is the main cause of chemotherapy failure and disease progression in malignant tumors [291]. An important mechanism involves the *P*-glycoprotein (*P*-gp) gene-mediated anti--cancer drug outflow [292]. To solve this problem, Xu et al. designed a novel gene/chemotherapeutic drug nanodelivery system to deliver siRNA/chemotherapeutic drugs as follows: chemotherapeutic drugs with positive charges and *anti-P*-gp siRNA (siPgp) with negative charges were selected, and self-assembled into spherical NPs with uniform particle size through electrostatic interactions. Then, the RBCM were coated onto the surface of the NPs to enhance their physiological stability and prolong their life cycle. Taking DOX as an example, after in vitro and in vivo evaluations, this NP model can specifically downregulate the expression of the *P*-gp gene and restore the sensitivity of tumor cells to DOX, effectively reversing tumor drug resistance [293]. This strategy provides a safe and effective method for combining functional oligonucleotides/chemotherapeutic drugs in patients with MDR tumors.

Previous studies have confirmed that anti-apoptotic protein BCL2 can regulate apoptosis through a variety of stimuli and that its overexpression is related to the progression of tumors. Pham et al. developed a platform for RBCEVs loaded with a fragment consisting of anti-apoptotic protein gene (*BCL2*) and ASOs. The authors further validated the in vivo therapeutic efficacy of this fragment in a mouse xenograft model of acute myeloid leukemia. After the application of this platform, the accumulation and growth of leukemia cells in the bone marrow, liver, and spleen were significantly inhibited without weight loss or toxicity being noticed in the mouse model. These results indicated that ASOs loaded inside RBCEVs can escape the restriction of endosomes and lysosomes, enter the cytoplasm, and down-regulate the expression of gene *BCL2*, thereby effectively inhibiting the progression of leukemia [264].

5.1.4. Other therapies

Albertsen et al. studied patients with ALL who had hypersensitivity to PEGylated ASNase and designed a preparation of eryaspase, a synthetic ASNase, encapsulated in RBCs. The results showed that most patients had a good tolerance to eryaspase, which reached therapeutic levels of ASNase after the first infusion. Although the validity of this study has been questioned, it provides a feasible strategy for continuing enzyme therapy despite hypersensitivity reactions [294].

Anti-tumor compounds in herbal preparations have received increasing attention because of their efficacy, affordability, and low toxicity [295]. One of these traditional drugs is ursolic acid (UA), which regulates multiple signaling pathways to induce apoptosis and autophagy in tumor cells. Its potential anti-tumor activity and mechanism of action have been studied and verified in malignant tumors such as colorectal and breast cancers. To overcome obstacles such as poor water solubility, low bioavailability, and systemic toxicity of UA in practical

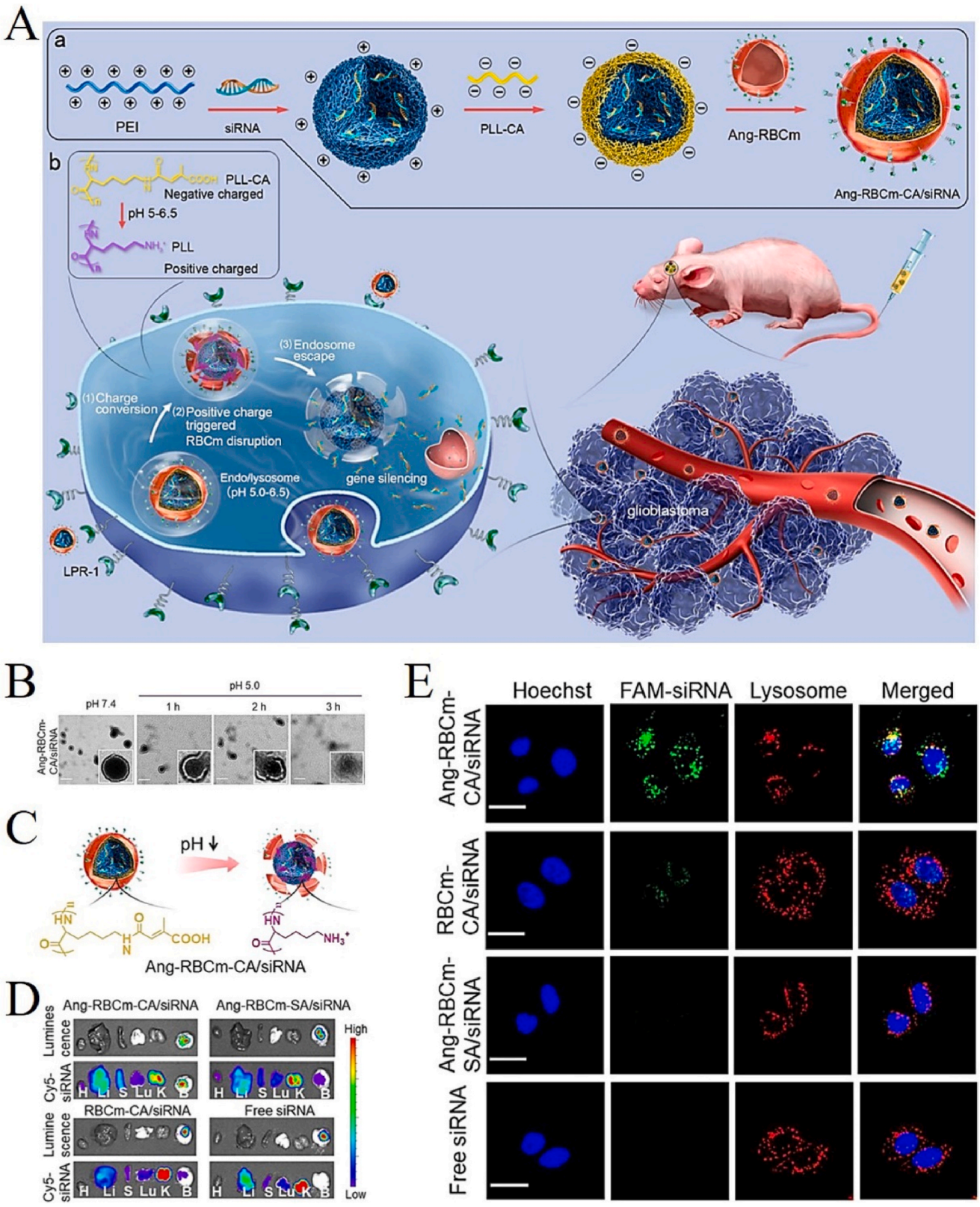


Fig. 7. The charge-conversion biomimetic nanocomposite (Ang-RBCm-CA/siRNA) can facilitate RNAi therapy for GBM in situ. A) Schematic of the preparation process and mechanism of action of Ang-RBCm-CA/siRNA. B) TEM images of Ang-RBCm-CA/siRNA incubated at pH 7.4 or 5.0 for 1, 2, or 3 h. Scale bars = 200 nm. C) Illustration of Ang-RBCm-CA/siRNA membrane disruption triggered by low pH. D) Bioluminescence and Cy5-siRNA fluorescence images of major organs from nude mice bearing human GBM tumor after intravenous injection of different siRNA-loaded nanoformulations or free siRNA. E) CLSM images of orthotopic U87MG human GBM cells following transfection with Ang-RBCm-CA/siRNA for 4 h. Scale bars = 200 μm. The scale bars of FAM-labeled siRNA concentration were 200 nm. (Reproduced with permission from Ref. [290]. Copyright 2020, American Chemical Society).

applications, Wu et al. designed a UA-loaded RBCM-coated biomimetic nanoplatform (UMNPs). The platform exhibited improved water solubility, stability, biosafety, immune escape, and tumor accumulation ability. Primarily, results from in vitro and in vivo models showed that UMNPs significantly inhibited the migration and invasion of non-small cell lung cancer (NSCLC) cells and promoted their apoptosis and autophagy through the caspase cascade pathway and intracellular ROS activation, among other pathways, with superior anti-tumor activity to UA [296]. Ji et al. prepared a novel icariin (ICA) biomimetic targeting nanoformulation and reported similar findings, showing enhanced anticancer efficacy against NSCLC and reduced ICA side effects [297]. These studies indicate that bionic nano-carriers can overcome the limitations of traditional Chinese medicine preparations in cancer precision treatment and provide a promising platform for their applications. In addition, other natural compounds with anti-tumor activity have been similarly studied and reported by Juglone et al. [298]. A plethora of traditional Chinese medicine constituents possessing anti-cancer attributes have been largely overlooked, such as ginsenoside. Numerous studies have substantiated the capacity of ginsenosides and their metabolites to elicit anti-tumor effects via intricate mechanisms, encompassing the inhibition of tumor proliferation, invasion, and metastasis, facilitation of tumor apoptosis, induction of tumor autophagy, and augmentation of immune regulation [299,300]. Although pertinent bionic NP immune evasion tactics have been devised and implemented to stimulate anti-tumor immunity, their implementation in the realm of RBCs necessitates additional experimentation [300].

PD-L1 is mainly located in the plasma membrane and binds to programmed death 1 (PD-1) to regulate immune responses. However, the role of non-plasma membrane (NPM)-localized PD-L1, which is highly expressed in osteosarcoma, is not limited to immune regulation. Wu et al. previously demonstrated that NPM PD-L1 interacts with insulin-like growth factor-binding protein-3 (IGFBP3) to promote osteosarcoma growth by activating the mammalian target of rapamycin (mTOR) signaling. This interaction is enhanced by the phosphorylation of PD-L1 terminal, mediated by phosphoglycerate kinase 1. Based on these findings, they designed and synthesized a PD-L1 phosphomimetic peptide embedded in RBCM-coated cyclic RGD (cRGD)-modified nanocapsules. These data suggest that this mimetic peptide can significantly inhibit osteosarcoma tumor growth after intratumoral injection by disrupting the formation of the PD-L1/IGFBP3 complex [301]. This approach not only combines RBCM and peptide therapies but also facilitates the use of RBCM for drug delivery.

5.2. Phototherapeutic media

5.2.1. Background

ROS, including oxygen radicals and their derivatives, are inevitable byproducts of oxidative metabolism in all aerobic organisms [302]. ROS are particularly unstable and react rapidly with almost all biomolecules including proteins, lipids, and nucleic acids [303]. ROS play both pro-tumor and anti-tumor roles in tissue damage. Moderate levels of ROS can induce DNA damage, leading to mutations in oncogenes or tumor suppressor genes. If these injuries are not properly repaired, they might affect cell cycle genes, leading to abnormal proliferation, that is carcinogenesis [304]. In contrast, high levels of ROS are cytotoxic and can damage the integrity of the cell membrane and cause lipid peroxidation [305]. Moreover, excessive ROS can enhance the permeability of mitochondria, leading to the release of cytochrome *c* and other apoptosis inducers that activate the intrinsic apoptotic pathway [306]. These processes ultimately lead to cell senescence, death and apoptosis. Hence, numerous anticancer therapies elicit their therapeutic outcomes through the generation of ROS and the induction of apoptosis [307].

Given the role of ROS in cancer progression, non-surgical ROS-mediated therapies, including chemodynamic therapy (CDT), phototherapy, and RT, have become new options for cancer treatment due to their noninvasive, intrinsic tumor selectivity [308]. CDT refers to altering the TME by weak acidity, H_2O_2, hypoxia, or high GSH levels to produce abundant ROS at the tumor site through Fenton- or Fenton-like reactions to kill cancer cells [272,309]. However, the amount of ROS produced during this process is limited by the concentration of endogenous H_2O_2 in tumor cells, which may reduce its anticancer efficacy [310]. Phototherapy effectively eliminates tumor cells via a photosensitizer-mediated photothermal effect. It has been widely used as a minimally invasive adjuvant treatment for superficial tumors, mainly in photodynamic therapy (PDT) and PTT [311]. PDT converts the absorbed light into ROS in different ways, leading to oxidative stress and cell death. However, PTT converts absorbed light into thermal energy through a non-radiative transition, which causes the temperature of tumor cells to rise, inducing cell death [312,313]. Phototherapy has the advantages of being noninvasive, precise, safe, and effective. However, its effectiveness, as opposed to CDT, is largely limited by the penetration of external laser irradiation and the hypoxic nature of the tumor environment [314–316].

Several studies have been conducted to enhance the supply of ROS to achieve profound anti-tumor effects. Some nanomaterials can be used as catalysts for CDT or photosensitizers in phototherapy to enhance ROS production [186,317]. Wang et al. incorporated in situ lactate oxidase and the anti-glycolytic drug Mito-LND into $CaCO_3$-coated Fe_3O_4/g-C_3N_4 NPs. They successfully developed a multifunctional nanomaterial platform (FGLMC) based on an increase in ROS generation at multiple levels. They also verified that the nanoplatform has excellent ROS generation ability and can exert powerful anticancer effect in combination with CDT, PDT, and other treatments [318].

5.2.2. Application

Wang et al. constructed an innovative RBC-derived DDS by surface modification and internal loading of RBCs extracted from the whole blood of mice. Specifically, cRGD and ICG were conjugated to the RBC surface via biotin-avidin interactions. DOX was loaded into RBCs via hypotonic dialysis. The physicochemical properties, drug release, cellular uptake, targeting ability, and therapeutic effects of the RBC constructs were tested. The morphology and physical and chemical states of the cells remained stable before and after drug loading as well as within 7 days of storage, and cells showed higher DOX release efficiency, targeting ability, and cellular uptake [78]. This study found that a combination of chemotherapy and PTT could better control tumor growth and provide a new niche for the clinical treatment of cancer. In addition to targeted peptide modification, folate, HA, and low-density lipoprotein antibodies can be added to the RBCM to enhance the targeting performance and improve therapeutic efficacy [319–321].

Iron-porphyrin-based metal-organic frameworks (MOFs) exhibit excellent performance in PDT owing to their porosity and highly specific surface area, which lead to good adsorption and catalytic effects. Zhao et al. successfully designed and constructed a novel MOF-based iron oxide (FeTCPP/Fe_2O_3) nanocrystal carrier using liquid diffusion (Fig. 8). This was then chemically modified by RBCM coating and an AS1411 aptamer, in which TCPP was used as an organic ligand to coordinate with ferric chloride. After coating with RBCM, the nano-bulk structure maintained integrity, and the residence time in circulation and in tissues increased. Both cellular assays and animal models showed that the nanocapsules catalyzed the decomposition of H_2O_2 via Fenton or Fenton-like reactions, thereby exerting significant synergistic effects on CDT and PDT in tumor inhibition [322]. This study provides a reference for the use of MOF materials in combined anti-tumor therapy of CDT and PDT. Similarly, Li et al. prepared an RBC-mimetic nanocatalyst constructed using a mixture of iron-porphyrin-based MOFs and RBCM and confirmed that this catalyst could induce systemic immune responses and ICD by promoting the release of TAAs and DAMPs [323]. This suggests that the free radical “storm” induced by nanocatalysts has a synergistic effect with immunotherapy.

Moreover, other types of nanomaterials have been applied to phototherapy and demonstrated improved photothermal conversion

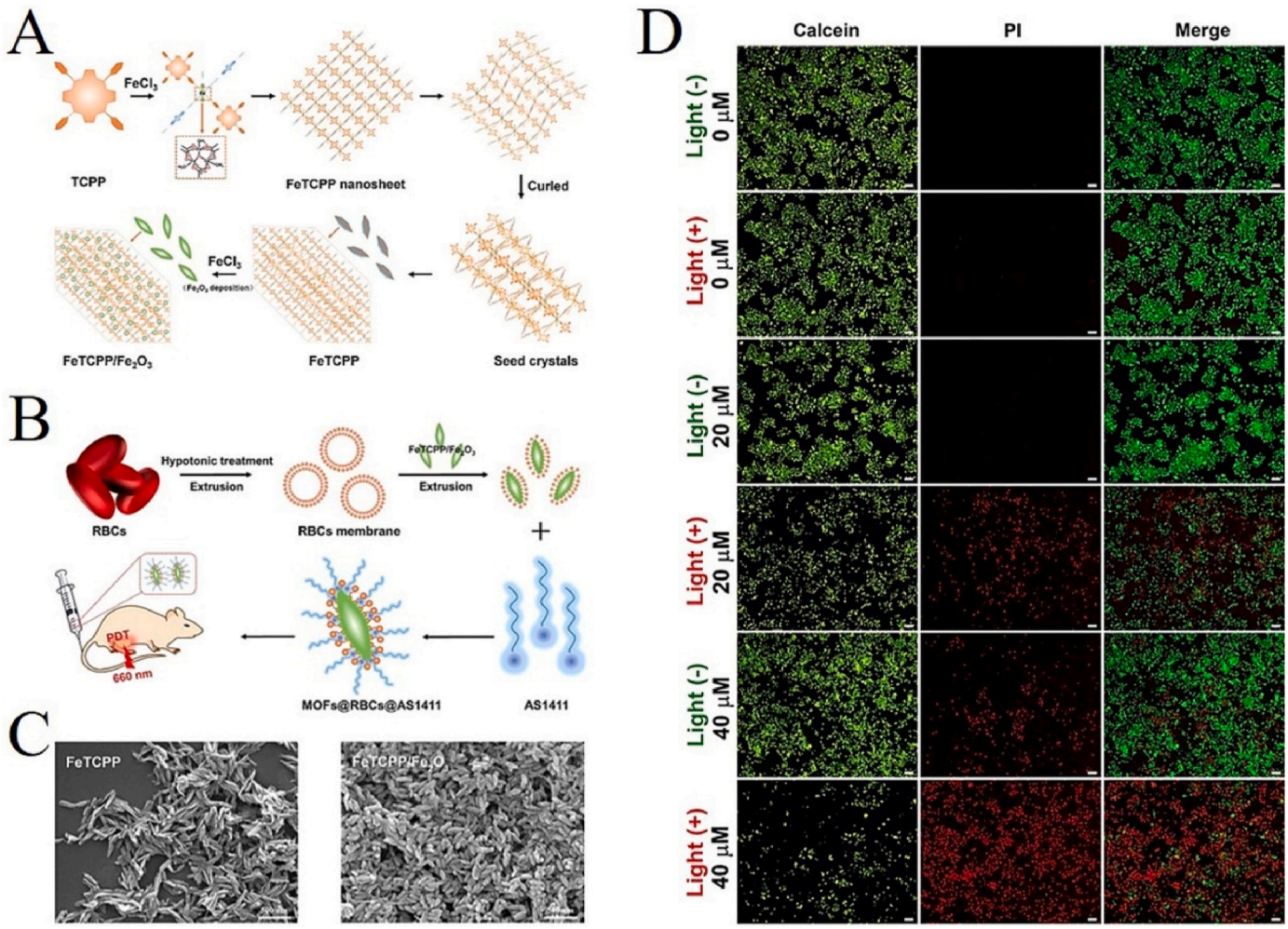


Fig. 8. Schematic of the ferric oxide loaded metal-organic frameworks (FeTCPP/Fe_2O_3 MOFs) nanopore for PDT. A) Formation mechanism of FeTCPP and FeTCPP/Fe_2O_3 nanopores based on MOFs. B) Schematic diagram of MOFs@RBCs@AS1411 nanopore for tumor targeted PDT. C) SEM images of FeTCPP and FeTCPP/Fe_2O_3 nanopores based on MOFs. Scale bars = 500 nm. D) Fluorescence images of cancer cells after co-incubation of different concentrations of FeTCPP/Fe_2O_3 nanoparticles based on MOFs with dyes (green/red, live/dead). Scale bars = 100 μm. (Reproduced with permission from Ref. [322]. Copyright 2020, American Chemical Society). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

efficiency. These include mesoporous silica NPs, Prussian blue (PB) NPs, graphene oxide quantum dots, zeolite imidazole salt frameworks, and polydopamine NPs [244,255,324–326]. Chen et al. combined PB NPs with high catalase activity and MnO_2 NPs with a GSH-depleting function to prepare MnO_2-coated PB nanocomposites which were subjected to photosensitizer loading, tumor-targeting peptide (RGD) modification and RBCM vesicle camouflage (Fig. 9). The in vitro data showed that the NPs effectively alleviated tumor hypoxia by converting endogenous H_2O_2 to O_2 and depleting GSH. In a mouse model, the tumor inhibition rate of the PDT/PTT group using these NPs was 92.9 %. An in vivo study demonstrated their excellent photothermal properties and anti-tumor effects. At the same time, tumor-targeting peptide modification and RBCM coating significantly improved the active targeting and immune evasion capabilities of nanobodies [255].

5.3. Radiotherapeutic sensibilization

Because of its ability to deliver a sufficient radiation dose that kills tumor cells but falls within healthy tissue tolerance limits, RT has become the primary treatment for patients with local malignant tumors. However, RT therapeutic efficacy is decreased by a hypoxic environment. Various strategies aiming at improving oxygen supply in the hypoxic regions of tumors to enhance the efficacy of RT have been investigated. These include RBCs and NPs with oxygen-carrying characteristics [246,327].

For example, Zhou et al. found in a previous study that internalized RGD (iRGD) can enhance radiation efficacy by remodeling the penetration of tumor tissues while free iRGD was rapidly consumed by metabolism in the body (Fig. 10). Accordingly, their group designed and manufactured an RBC-iRGD to target the tumors and enhance RT. They subsequently evaluated its safety and efficacy in a mouse model of subcutaneous gastric tumors and found that mice treated with RBC-iRGD and RT had a significantly increased reduction in tumor volume compared with the control group, without showing adverse effects on body weight or major organs during the preparation and treatment procedures [327].

6. Ongoing clinical trials

Rubius Therapeutics has successfully engineered RBCs to serve as cellular drugs capable of eliciting an anti-tumor immune response through the activation of pathways such as 4-1BB and IL-12/15, exemplified by RTX-224/240. Initial clinical trials have demonstrated tumor response in select patients; nevertheless, both investigations were prematurely terminated.

In addition, there are also multiple ongoing clinical trials to evaluate

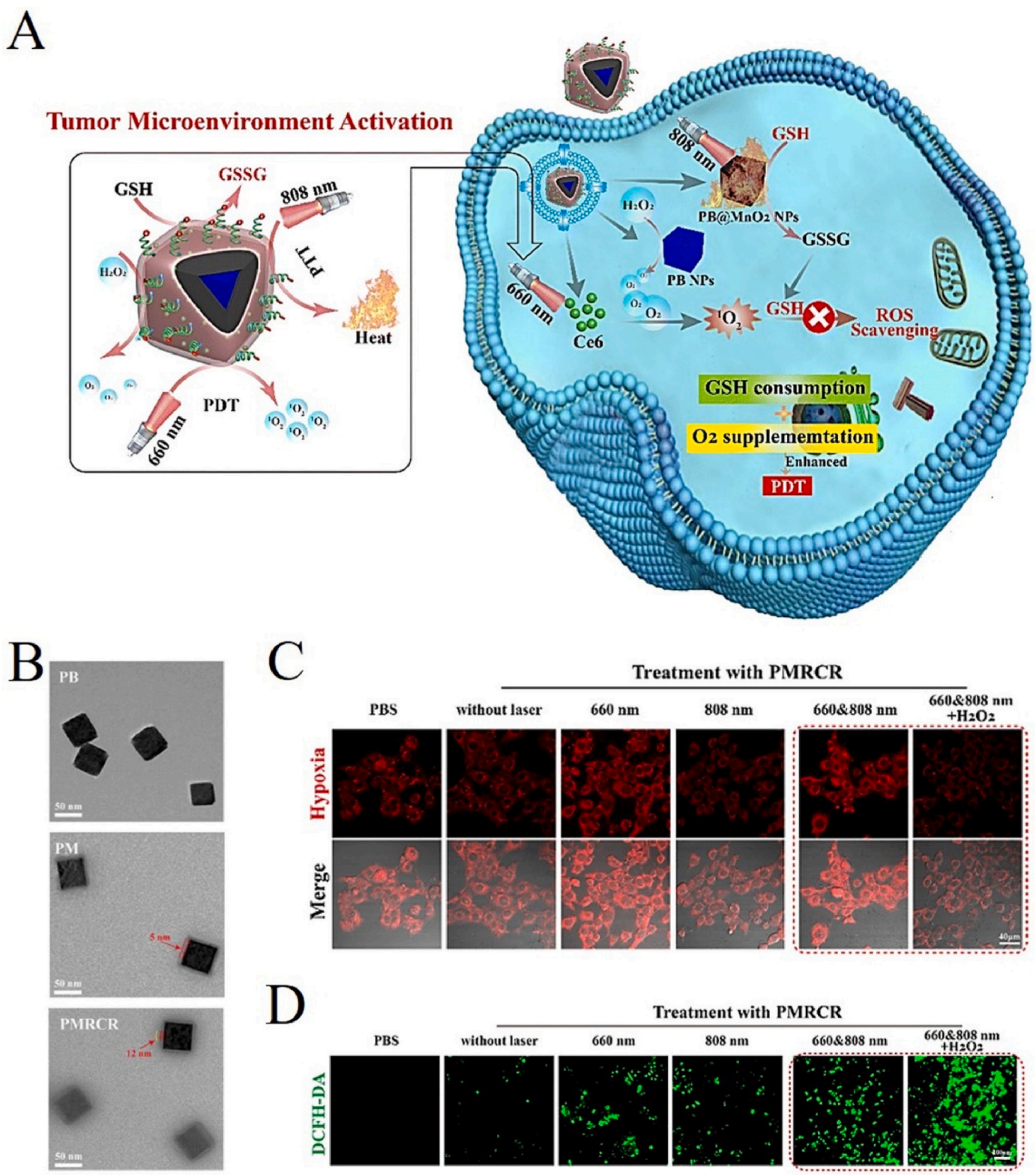
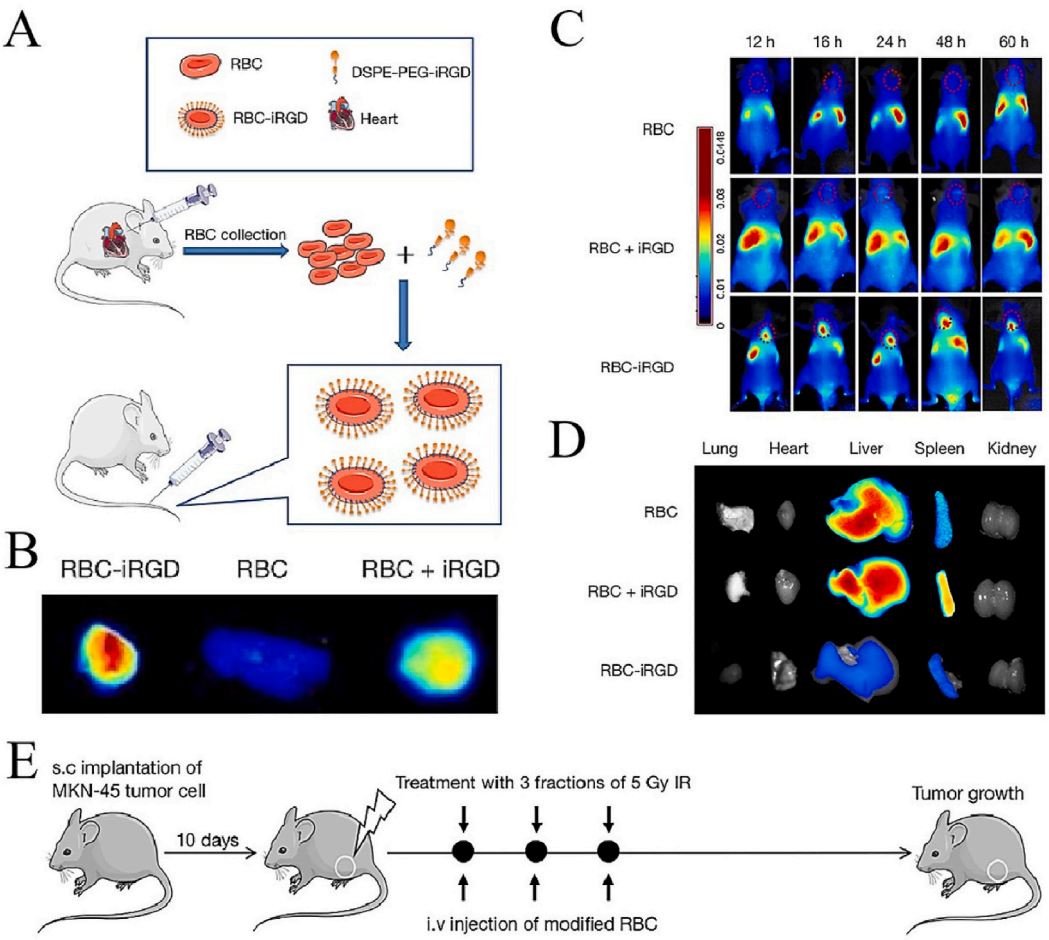


Fig. 9. Based on MnO_2-coated Prussian blue (PM) NPs, TME-reprogrammed multifunctional nanocomposites containing the PB NPs core, MnO_2 shell and Ce6-embedded erythrocyte membrane (designated PMRCR NPs) can enhance the anti-tumor effect of PDT/PTT. A) Schematic illustration of the preparation of PMRCR NPs and the mechanism against cancer cells through enhanced PDT/PTT. B) TEM images of PB NPs, PM NPs and PMRCR NPs. Scale bars = 50 nm. C) Fluorescence images of intracellular hypoxia levels with different treatments under hypoxic conditions. D) ROS imaging. (Reproduced with permission from Ref. [255]. Copyright 2023, Royal Society of Chemistry). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)



(caption on next page)

Fig. 10. Schematic representation of the iRGD-modified RBCs for tumor targeting and RT enhancement. A) Illustration of the preparation of RBC-iRGD and its therapeutic application in a mouse model. B) Evaluation of fluorescence intensity of increased tumors from mice injected with different RBC preparations. C) Subcutaneous tumor-bearing nude mice were established, followed by injection of different RBC preparations and tumor tracking. The red dashed line indicates the subcutaneous tumor. D) Evaluation of organ fluorescence intensity for safety purpose. E) Schematic representation of the generation of a mouse model of gastric subcutaneous tumors, RT (5 Gy, 3 fractions), and injection of RBC preparations to monitor tumor growth. F) HE-stained sections of major organs from mice different treatments. Scale bars = 200 μm. (Reproduced with permission from Ref. [327]. Copyright 2022, Journal of Gastrointestinal Oncology). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

the effectiveness of engineered RBCs in the treatment of malignant tumors and an even larger number are under development. Several clinical trials (including NCT06026605 and NCT06106152) are underway to investigate the safety, tolerability, and efficacy of the erythrocyte-*anti*-PD-1 antibody conjugate (WTX212) in patients with advanced malignant tumors. Among them, a single-arm, open-label, dose-escalation/expansion phase I trial (NCT05707325) is currently being conducted at multiple centers. The study is expected to address PD-1 treatment failure by engineering RBCs to specifically target the PD-1 inhibitor pembrolizumab to spleen tissue and activate T cells. Also, a single-arm, multicenter, open-label, phase I trial (NCT04292743) is evaluating the effects of eryaspase encapsulated in donor RBCs (an engineered L-ASNase) in combination with FOLFRINOX regimens (5-fluorouracil, leucovorin, irinotecan, and OXA) on efficacy and prognosis in patients with advanced and metastatic pancreatic cancer. The results of these ongoing clinical trials are highly awaited.

7. Challenges and limitations

These successful preclinical trials have provided evidence that RBC-derived biomaterials can address the many challenges faced by traditional delivery systems in cancer therapy. However, studies on RBC-derived materials are mostly in the conceptual design stage and have only been validated through cellular or animal experiments. There remain many obstacles and challenges to overcome before the transition from preclinical research in laboratories to clinical trials.

7.1. Unintended effects and safety

It is worth noting that RBC-derived materials may cause potential toxicity and harmful effects in humans, which need to be further explored and evaluated.

7.1.1. Possible storage lesion

RBC storage lesions might occur. RBCs are readily available in the blood and can be stored for long periods after processing [29]. However, with the extended storage time, loss of endogenous antioxidants inevitably occurs. Therefore, RBCs may undergo changes in their physical and chemical properties, as well as in cell morphology, and potentially toxic bioactive substances may be released [328,329].

7.1.2. Possible immune response

Although RBCs, their membranes, and EVs exhibit good biocompatibility, a comprehensive understanding of their intricate characteristics remains incomplete. Different blood groups may lead to immune rejection, such as hemolytic reactions triggered by mismatched blood groups [330]. Therefore, when extracting the RBCM, it is necessary to determine whether the blood group is compatible with that of the recipient and whether cellular components of the blood and other components of erythrocytes are completely removed. Furthermore, empirical evidence has substantiated that the alteration of PEG polymers on the exterior of RBCMs can effectively impede alloimmunity within the framework of the RBC transfusion [331].

7.1.3. Harmful over-embellishment

During the processing of RBCs and their associated membrane structures (RBCM and RBCEVs), excessive modification has the potential to disturb the asymmetry of the cell membrane and cytoskeleton, thereby exerting detrimental impacts on biocompatibility, as discussed below. This is also one of the potential risks of RBC-based DDSs in clinical application [42,94].

First, when RBCs undergo mechanical damage, their deformability and plasticity are reduced, leading to hemolysis and the subsequent release of a significant amount of cell-free Hb and heme into the bloodstream. The pro-oxidative characteristics of cell-free Hb, along with the active interaction between heme and peroxides, can induce the liberation of cholesterol, the synthesis of lipid peroxidation, and the conglomeration of protein and iron, which results in the release of ROS and inflammatory mediators in substantial quantities. This exacerbates the manifestation of oxidative stress, inflammatory reaction, and a cytokine storm. Ultimately, the integrity of vascular endothelial cells becomes compromised, leading to the subsequent deterioration and destruction of tissues and organs [332–335].

Secondly, the deformability of RBCs results in abnormal shape, hindering their regular circulation within the bloodstream and elevating blood viscosity [336,337]. This phenomenon can result in the impeded passage of RBCs within constricted areas of circulation, consequently diminishing the velocity of blood flow. Subsequent to vascular impairment, lipids and other compounds may accumulate on the intimal layer of blood vessels, culminating in plaque formation and ultimately contributing to the occlusion of small arteries and disruption of microcirculation. Moreover, this process significantly augments the prevalence of atherosclerosis and thrombotic microangiopathy [338,339].

Thirdly, the destruction of the RBC structure leads to the exposure of its internal phosphatidylserine (PS) on the outer surface of the plasma membrane. The exposed PS will serve as the primary location for prothrombin assembly and activation of the clotting cascade, thereby initiating blood clotting and facilitating thrombosis [335,340–343]. Furthermore, the ROS and powerful oxidants produced by the above processes have the potential to trigger platelet activation, and subsequently form platelet-white blood cell aggregates. These aggregates can further intensify the clotting mechanism, and potentially culminate in thrombosis [42,105,334,344].

Lastly, the abnormal activation of complement cannot be disregarded due to its crucial role in defense against infection and maintenance of immune homeostasis. The initiation of the protease cascade of complement can occur through three distinct pathways, namely the classical, alternative, and lectin pathways. Each of these pathways ultimately results in the activation of a shared terminal pathway, known as C3 and C5 invertase, which subsequently catalyzes the cleavage of C3 and C5 molecules. This cleavage result serves to activate downstream inflammatory responses and amplify the complement cascade. The culmination of these processes results in the generation of MAC and the chemotactic response of allergenic toxins towards leukocytes. Hence, dysregulation of the complement system can engender deleterious responses within the host, potentially giving rise to pathological conditions, including autoimmune disorders and transfusion reaction-mediated diseases [345,346].

Within the context of homeostasis, a diverse array of complement regulatory proteins can be found in both plasma and erythrocyte membrane. These proteins can be categorized as either soluble proteins or membrane binding proteins, with the purpose of preventing aberrant complement activation and subsequent self-lysis of cells [347]. Unlike nucleated cells, RBCs do not express CD46, also known as membrane cofactor protein. Their membrane binding components primarily consist of CD55 (also referred to as DAF) and CD59. CD55 functions to expedite

the degradation of C3 and C5 invertase, whereas CD59 disrupts the formation of MAC, thereby impeding complement activation [345,348]. CR1 (also referred to as CD35) can be anchored in the plasma membrane, while is also present in soluble form in plasma [349]. CR1 plays a crucial role in regulating the activation of complement by accelerating the decay of C3 convertases in the aforementioned three pathways. Additionally, it actively contributes to the elimination of immune complexes and pathogens [345]. Among soluble regulatory proteins, C1 esterase inhibitor and C4B-binding protein are responsible for regulating the classical pathway, while H factor (FH) and factor H-like protein 1 serve as the primary regulators of the alternative pathway [350]. It is worth mentioning that FH has the ability to regulate complement activation through its interaction with sialic acid present on the surface of host cells, thereby exerting a protective influence on host cells and tissues [351,352].

In view of this, the interaction between complement and RBC carriers needs further study and discussion. During the biotin-avidin modification process on RBC surfaces, Muzykantov et al. discovered that the binding of avidin triggers the activation of the complement alternative pathway, leading to the lysis of the modified RBCs. Additionally, the clearance of RBCs is intricately linked to the density of biotin present on the membrane surface and the manner in which biotin binds to these RBCs [103,353,354]. Zaltzman et al. demonstrated that RBCs subjected to biotin-avidin treatment exhibit a heightened susceptibility to complement activation, potentially attributed to the presence of CD59 and DAF [355]. Further investigation is warranted to explore the potential adverse effects of alternative methods of modifying RBCs in conjunction with the involvement of the complement system.

7.1.4. Unclear toxicological reaction

In addition, the magnitude of the risk of human exposure to NPs cannot be determined because of the lack of toxicological data on NPs [137]. NPs exhibit distinct behaviors within the human body compared to their behavior in external environments, and typically undergo complex biodegradation, metabolism, and excretion processes [335,356]. For example, it has been proven that NPs such as precious metals and metal oxides can penetrate important biological barriers, including the BBB, intestinal barrier, and placental barrier, enriching the circulatory, digestive, respiratory, urinary, and other systems and causing damage to target organs. The involved mechanisms are complex and include the production of ROS and induction of oxidative stress, causing DNA damage and altering protein structure and function [54,178,301].

Conducting experimental assessments using appropriate animal models is imperative in order to effectively address the aforementioned concerns and ascertain the equilibrium between the advantages and potential hazards associated with the proposed intervention.

7.2. Difficulties in preparation and production

Primarily, the optimal RBC source is the use of autologous blood to prepare RBC-derived materials. However, because of the high clinical demand for blood and blood products, ensuring a stable source of blood is difficult [71]. In addition, the collected blood requires additional processing, which might involve mechanical changes and biochemical fluctuations, and carry a risk of contamination. All of these factors may affect the regular supply of blood products [357].

Additionally, it is difficult to achieve large-scale and efficient production of RBC-derived materials. On the one hand, the preparation methods for different types of RBC-derived materials are complex and diverse, and there is a lack of precise production standards and operating guidelines for these constructs. This reduces the reproducibility of the process and makes it challenging to achieve mass production on an industrial scale [358]. On the other hand, specialized technologies such as the extraction and purification of RBCs and RBCM and the modification of NP materials need further optimization and control. If necessary, RBC characteristics, NP characteristics, and conventional parameters such as loading efficiency, cargo content, and cargo release behavior should be monitored [359]. It is also noteworthy that the variances in RBCEV size and population heterogeneity resulting from diverse separation methods are nearly unavoidable. Research has demonstrated that the fusion and aggregation of EVs can potentially hinder their yield and purity in plasma. Consequently, the implementation of supplementary quality control measures is imperative to mitigate the limitations arising from the inherent variability within EVs, especially RBCEVs [109,360,361]. In addition, most of the existing material-related data come from cellular assays or animal models such as mice, but the complexity of the actual clinical environment may hinder clinical translation. Further experiments with larger animals and human trials are required [362,363].

Finally, storage and stability issues must be addressed after successful preparation. RBC-derived materials contain a variety of bioactive compounds such as proteins, lipids, and sugars. During long-term storage, their structure and function can be damaged by changes in the external environment [364]. Therefore, it is necessary to further develop and use cryoprotectants to ensure the integrity of the structure and function of RBC-derived materials and to extend their storage life.

In conclusion, the utilization of RBC-based biomaterials encounters intricate regulatory obstacles. In contrast to entirely synthetic and clinically sanctioned nanomaterials such as liposomes and protein-based NPs, the incorporation of RBC components introduces supplementary management protocols primarily related to the equipment, technology, and processes for blood and cell collection, processing, and return [54]. Furthermore, the exorbitant expenses associated with engineering design utilizing RBCs as carriers pose a significant challenge in achieving immediate economic impact. Consequently, the clinical application of drug delivery vectors derived from RBCs for targeted tumor therapy remains elusive.

8. Conclusions and prospects

Both traditional and emerging cancer treatments have limitations, and their efficacy needs to be further improved. RBCs and their derived materials have a variety of excellent properties such as long circulation half-life and strong immune evasion ability. Research has proven their safety and efficacy as carriers for cancer treatment, in addition to their potential for a wide range of applications. This article systematically discusses the engineering design, pharmacokinetics, specific applications, and obstacles to the application of RBCs and their derivatives in clinical settings, with the aim of contributing to the progress of this field in clinical trials.

As a new “hot spot” in the field of biomedicine, RBCs and their derivatives have a large potential for progress in research and technology. As membrane modification technology develops based on a single RBCM coating, it can be further hybridized or fused with other biofilms and liposomes to obtain different desired characteristics and expand its application range. Future studies should focus on different types of biofilms and sources of NPs to expand the field and solve urgent medical problems.

Funding

This work was supported by the Science and Technology Program of Health Commission of Jiangxi Province [NO.SKJP220210528]; the Education Science and Technology Research Project of Jiangxi Province of China [NO.GJJ2201921]; and the National Natural Science Foundation of China [NO.82360704].

CRediT authorship contribution statement

Jianghua Ding: Investigation, Writing - original draft, Writing - review & editing. **Xinjing Ding:** Investigation, Writing - original draft, Writing - review & editing. **Weifang Liao:** Conceptualization, Funding

acquisition, Writing - review & editing. **Zhihui Lu:** Investigation, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Weifang Liao reports article publishing charges and writing assistance were provided by the Science and Technology Program of Health Commission of Jiangxi Province. Weifang Liao reports article publishing charges and writing assistance were provided by the Education Science and Technology Research Project of Jiangxi Province of China. Weifang Liao reports article publishing charges and writing assistance were provided by the National Natural Science Foundation of China.

Data availability

No data was used for the research described in the article.

References

[1] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, Ca-Cancer J. Clin. 71 (3) (2021) 209–249, https://doi.org/10.3322/caac.21660.

[2] M.L. Espinosa, C. Abad, Y. Kurtzman, F.R. Abdulla, Dermatologic toxicities of targeted therapy and immunotherapy in head and neck cancers, Front. Oncol. 11 (2021), 605941, https://doi.org/10.3389/fonc.2021.605941.

[3] R. Li, Y. Wang, J. Du, X. Wang, A. Duan, R. Gao, J. Liu, B. Li, Graphene oxide loaded with tumor-targeted peptide and anti-cancer drugs for cancer target therapy, Sci Rep-Uk 11 (1) (2021) 1725, https://doi.org/10.1038/s41598-021-81218-3.

[4] R. Chen, S. Wang, J. Zhang, M. Chen, Y. Wang, Aloe-emodin loaded solid lipid nanoparticles: formulation design and in vitro anti-cancer study, Drug Deliv. 22 (5) (2015) 666–674, https://doi.org/10.3109/10717544.2014.882446.

[5] Y. Wang, Y. Zhang, M. Jin, Y. Lv, Z. Pei, Y. Pei, A hypericin delivery system based on polydopamine coated cerium oxide nanorods for targeted photodynamic therapy, Polym. Bull. (Heidelberg, Ger.) 11 (6) (2019), https://doi.org/10.3390/polym11061025.

[6] R. Vikram, W.C. Chou, S.C. Hung, C.Y. Shen, Tumorigenic and metastatic role of CD44(-/low)/CD24(-/low) cells in luminal breast cancer, Cancers 12 (5) (2020), https://doi.org/10.3390/cancers12051239.

[7] S. Zheng, Z. Zhang, Y. Qu, X. Zhang, H. Guo, X. Shi, M. Cai, C. Cao, Z. Hu, H. Liu, J. Tian, Radiopharmaceuticals and fluorescein sodium mediated triple-modality molecular imaging allows precise image-guided tumor surgery, Adv. Sci. 6 (13) (2019), 1900159, https://doi.org/10.1002/advs.201900159.

[8] C. Woodman, G. Vundu, A. George, C.M. Wilson, Applications and strategies in nanodiagnosis and nanotherapy in lung cancer, Semin. Cancer Biol. 69 (2021) 349–364, https://doi.org/10.1016/j.semcancer.2020.02.009.

[9] F. Lin, Y.W. Bao, F.G. Wu, Improving the phototherapeutic efficiencies of molecular and nanoscale materials by targeting mitochondria, Molecules 23 (11) (2018), https://doi.org/10.3390/molecules23113016.

[10] W. Jiang, X. Han, J. Wang, L. Wang, Z. Xu, Q. Wei, W. Zhang, H. Wang, miR-22 enhances the radiosensitivity of small-cell lung cancer by targeting the WRNIP1, J. Cell. Biochem. 120 (10) (2019) 17650–17661, https://doi.org/10.1002/jcb.29032.

[11] Q. Xie, C. Sun, Z. Fei, X. Yang, Accepting immunotherapy after multiline treatment failure: an exploration of the anxiety and depression in patients with advanced cancer experience, Patient Prefer. Adherence 16 (2022) 1–9, https://doi.org/10.2147/PPA.S346171.

[12] L. Huang, S. Zhao, F. Fang, T. Xu, M. Lan, J. Zhang, Advances and perspectives in carrier-free nanodrugs for cancer chemo-monotherapy and combination therapy, Biomaterials 268 (2021), 120557, https://doi.org/10.1016/j.biomaterials.2020.120557.

[13] S. Ellebaek, S. Brix, M. Grandal, J. Lantto, I.D. Horak, M. Kragh, T.T. Poulsen, Pan-HER-An antibody mixture targeting EGFR, HER2 and HER3 abrogates preformed and ligand-induced EGFR homo- and heterodimers, Int. J. Cancer 139 (9) (2016) 2095–2105, https://doi.org/10.1002/ijc.30242.

[14] M. Xiao, Q. Tang, S. Zeng, Q. Yang, X. Yang, X. Tong, G. Zhu, L. Lei, S. Li, Emerging biomaterials for tumor immunotherapy, Biomater. Res. 27 (1) (2023) 47, https://doi.org/10.1186/s40824-023-00369-8.

[15] H. Wang, L. Qin, X. Zhang, J. Guan, S. Mao, Mechanisms and challenges of nanocarriers as non-viral vectors of therapeutic genes for enhanced pulmonary delivery, J. Contr. Release 352 (2022) 970–993, https://doi.org/10.1016/j.jconrel.2022.10.061.

[16] P. Nasarre, M. Thomas, K. Kruse, I. Helfrich, V. Wolter, C. Deppermann, D. Schadendorf, G. Thurston, U. Fiedler, H.G. Augustin, Host-derived angiopoietin-2 affects early stages of tumor development and vessel maturation but is dispensable for later stages of tumor growth, Cancer Res. 69 (4) (2009) 1324–1333, https://doi.org/10.1158/0008-5472.CAN-08-3030.

[17] M. Khafaji, M. Vossoughi, M.R. Hormozi-Nezhad, R. Dinarvand, F. Borrnert, A. Irajizad, A new bifunctional hybrid nanostructure as an active platform for photothermal therapy and MR imaging, Sci Rep-Uk 6 (2016), 27847, https://doi.org/10.1038/srep27847.

[18] S. Tan, T. Wu, D. Zhang, Z. Zhang, Cell or cell membrane-based drug delivery systems, Theranostics 5 (8) (2015) 863–881, https://doi.org/10.7150/thno.11852.

[19] E. Koren, V.P. Torchilin, Drug carriers for vascular drug delivery, IUBMB Life 63 (8) (2011) 586–595, https://doi.org/10.1002/iub.496.

[20] P.D. Patel, N. Dand, R.S. Hirlekar, V.J. Kadam, Drug loaded erythrocytes: as novel drug delivery system, Curr. Pharmaceut. Des. 14 (1) (2008) 63–70, https://doi.org/10.2174/138161208783330772.

[21] X. Du, A.R. Khan, M. Fu, J. Ji, A. Yu, G. Zhai, Current development in the formulations of non-injection administration of paclitaxel, Int. J. Pharm. (Amst.) 542 (1–2) (2018) 242–252, https://doi.org/10.1016/j.ijpharm.2018.03.030.

[22] J. Du, X. Wang, X. Dong, C. Zhang, L. Mei, Y. Zang, L. Yan, H. Zhang, Z. Gu, Enhanced radiosensitization of ternary Cu(3)BiSe(3) nanoparticles by photo-induced hyperthermia in the second near-infrared biological window, Nanoscale 11 (15) (2019) 7157–7165, https://doi.org/10.1039/c8nr09618j.

[23] Y. Liu, Y. Yi, C. Zhong, Z. Ma, H. Wang, X. Dong, F. Yu, J. Li, Q. Chen, C. Lin, X. Li, Advanced bioactive nanomaterials for diagnosis and treatment of major chronic diseases, Front. Mol. Biosci. 10 (2023), 1121429, https://doi.org/10.3389/fmolb.2023.1121429.

[24] J.K. Patra, G. Das, L.F. Fraceto, E. Campos, M. Rodriguez-Torres, L.S. Acosta-Torres, L.A. Diaz-Torres, R. Grillo, M.K. Swamy, S. Sharma, S. Habtemariam, H. S. Shin, Nano based drug delivery systems: recent developments and future prospects, J. Nanobiotechnol. 16 (1) (2018) 71, https://doi.org/10.1186/s12951-018-0392-8.

[25] H. Xu, W. Nie, L. Dai, R. Luo, D. Lin, M. Zhang, J. Zhang, F. Gao, Recent advances in natural polysaccharides-based controlled release nanosystems for anti-cancer phototherapy, Carbohydr. Polym. 301 (Pt A) (2023), 120311, https://doi.org/10.1016/j.carbpol.2022.120311.

[26] H. Yang, S.Y. Fung, S. Xu, D.P. Sutherland, T.R. Kollmann, M. Liu, S.E. Turvey, Amino acid-dependent attenuation of toll-like receptor signaling by peptide-gold nanoparticle hybrids, ACS Nano 9 (7) (2015) 6774–6784, https://doi.org/10.1021/nn505634h.

[27] J. Zhang, P.A. Ney, NIX induces mitochondrial autophagy in reticulocytes, Autophagy 4 (3) (2008) 354–356, https://doi.org/10.4161/auto.5552.

[28] S. Wang, H. Zhao, H. Zhang, C. Gao, X. Guo, L. Chen, C. Lobo, K. Yazdanbakhsh, S. Zhang, X. An, Analyses of erythropoiesis from embryonic stem cell-CD34(+) and cord blood-CD34(+) cells reveal mechanisms for defective expansion and enucleation of embryomic stem cell-erythroid cells, J. Cell Mol. Med. 26 (8) (2022) 2404–2416, https://doi.org/10.1111/jcmm.17263.

[29] O.R. Busch, W.C. Hop, V.P.M. Hoynck, R.L. Marquet, J. Jeekel, Blood transfusions and prognosis in colorectal cancer, N. Engl. J. Med. 328 (19) (1993) 1372–1376, https://doi.org/10.1056/NEJM199305133281902.

[30] O.Y. Selyutina, N.E. Polyakov, D.V. Korneev, B.N. Zaitsev, Influence of glycyrrhizin on permeability and elasticity of cell membrane: perspectives for drugs delivery, Drug Deliv. 23 (3) (2016) 858–865, https://doi.org/10.3109/10717544.2014.919544.

[31] A. Vincy, S. Mazumder, Amrita, I. Banerjee, K.C. Hwang, R. Vankayala, Recent progress in red blood cells-derived particles as novel bioinspired drug delivery systems: challenges and strategies for clinical translation, Front. Chem. 10 (2022), 905256, https://doi.org/10.3389/fchem.2022.905256.

[32] L.E. Rustom, T. Boudou, S. Lou, I. Pignot-Paintrand, B.W. Nemke, Y. Lu, M. D. Markel, C. Picart, J.A. Wagoner, Micropore-induced capillarity enhances bone distribution in vivo in biphasic calcium phosphate scaffolds, Acta Biomater. 44 (2016) 144–154, https://doi.org/10.1016/j.actbio.2016.08.025.

[33] E.C. Lowenberg, J.C. Meijers, M. Levi, Platelet-vessel wall interaction in health and disease, Neth. J. Med. 68 (6) (2010) 242–251.

[34] R. Rampado, P. Caliceti, M. Agostini, Latest advances in biomimetic cell membrane-coated and membrane-derived nanovectors for biomedical applications, Nanomaterials-Basel 12 (9) (2022), https://doi.org/10.3390/nano12091543.

[35] H. Ye, K. Wang, M. Wang, R. Liu, H. Song, N. Li, Q. Lu, W. Zhang, Y. Du, W. Yang, L. Zhong, Y. Wang, B. Yu, H. Wang, Q. Kan, H. Zhang, Y. Wang, Z. He, J. Sun, Bioinspired nanoplatelets for chemo-photothermal therapy of breast cancer metastasis inhibition, Biomaterials 206 (2019) 1–12, https://doi.org/10.1016/j.biomaterials.2019.03.024.

[36] B. Bahmani, H. Gong, B.T. Luk, K.J. Haushalter, E. DeTeresa, M. Previti, J. Zhou, W. Gao, J.D. Bui, L. Zhang, R.H. Fang, J. Zhang, Intratumoral immunotherapy using platelet-cloaked nanoparticles enhances antitumor immunity in solid tumors, Nat. Commun. 12 (1) (2021) 1999, https://doi.org/10.1038/s41467-021-22311-z.

[37] K. Ley, C. Laudanna, M.I. Cybulsky, S. Nourshargh, Getting to the site of inflammation: the leukocyte adhesion cascade updated, Nat. Rev. Immunol. 7 (9) (2007) 678–689, https://doi.org/10.1038/nri2156.

[38] A. Rossin, G. Miloro, A.O. Hueber, TRAIL and FasL functions in cancer and autoimmune diseases: towards an increasing complexity, Cancers 11 (5) (2019), https://doi.org/10.3390/cancers11050639.

[39] M. Wieczorek, E.T. Abualrous, J. Sticht, M. Alvaro-Benito, S. Stolzenberg, F. Noe, C. Freund, Major histocompatibility complex (MHC) class I and MHC class II proteins: conformational plasticity in antigen presentation, Front. Immunol. 8 (2017) 292, https://doi.org/10.3389/fimmu.2017.00292.

[40] R.J. Meesters, G.P. Hooff, State-of-the-art dried blood spot analysis: an overview of recent advances and future trends, Bioanalysis 5 (17) (2013) 2187–2208, https://doi.org/10.4155/bio.13.175.
[41] J.J. Hulmi, T. Myllymaki, M. Tenhumaki, N. Mutanen, R. Puurtinen, G. Paulsen, A.A. Mero, Effects of resistance exercise and protein ingestion on blood leukocytes and platelets in young and older men, Eur. J. Appl. Physiol. 109 (2) (2010) 343–353, https://doi.org/10.1007/s00421-010-1360-7.
[42] P.M. Glassman, C.H. Villa, A. Ukidve, Z. Zhao, P. Smith, S. Mitragotri, A. J. Russell, J.S. Brenner, V.R. Muzykantov, Vascular drug delivery using carrier red blood cells: focus on RBC surface loading and pharmacokinetics, Pharmaceutics 12 (5) (2020), https://doi.org/10.3390/pharmaceutics12050440.
[43] S. Aravindhan, S.S. Ejam, M.H. Lafta, A. Markov, A.V. Yumashev, M. Ahmadi, Mesenchymal stem cells and cancer therapy: insights into targeting the tumour vasculature, Cancer Cell Int. 21 (1) (2021) 158, https://doi.org/10.1186/s12935-021-01836-9.
[44] P. Kadam, D. Van Saen, E. Goossens, Can mesenchymal stem cells improve spermatogonial stem cell transplantation efficiency? Andrology-Us 5 (1) (2017) 2–9, https://doi.org/10.1111/andr.12304.
[45] J. Jin, B. Krishnamachary, J.D. Barnett, S. Chatterjee, D. Chang, Y. Mironchik, F. Wildes, E.M. Jaffee, S. Nimmagadda, Z.M. Bhujwalla, Human cancer cell membrane-coated biomimetic nanoparticles reduce fibroblast-mediated invasion and metastasis and induce T-cells, Acs Appl. Mater. Inter. 11 (8) (2019) 7850–7861, https://doi.org/10.1021/acsami.8b22309.
[46] H.C. Pal, S.K. Katiyar, Cryptolepine, a plant alkaloid, inhibits the growth of non-melanoma skin cancer cells through inhibition of topoisomerase and induction of DNA damage, Molecules 21 (12) (2016), https://doi.org/10.3390/molecules21121758.
[47] 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, W. Liu, Platelet-facilitated photothermal therapy of head and neck squamous cell carcinoma, Angew. Chem., Int. Ed. 57 (4) (2018) 986–991, https://doi.org/10.1002/anie.201709457.
[48] A.V. Kroll, R.H. Fang, Y. Jiang, J. Zhou, X. Wei, C.L. Yu, J. Gao, B.T. Luk, D. Dehaini, W. Gao, L. Zhang, Nanoparticulate delivery of cancer cell membrane elicits multiantigenic antitumor immunity, Adv. Mater. 29 (47) (2017), https://doi.org/10.1002/adma.201703969.
[49] V.R. Muzykantov, Drug delivery carriers on the fringes: natural red blood cells versus synthetic multilayered capsules, Expet Opin. Drug Deliv. 10 (1) (2013) 1–4, https://doi.org/10.1517/17425247.2013.750292.
[50] Z. Liu, A. Ciocea, L. Devireddy, Endogenous siderophore 2,5-dihydroxybenzoic acid deficiency promotes anemia and splenic iron overload in mice, Mol. Cell Biol. 34 (13) (2014) 2533–2546, https://doi.org/10.1128/MCB.00231-14.
[51] L. Mesarec, W. Gozdz, A. Iglic, V. Kralj-Iglic, E.G. Virga, S. Kralj, Normal red blood cells' shape stabilized by membrane's in-plane ordering, Sci Rep-Uk 9 (1) (2019), 19742, https://doi.org/10.1038/s41598-019-56128-0.
[52] L. Chen, Y. Sun, Y. Liu, Y. Zou, J. Huang, Y. Zheng, G. Liu, The N-terminal region of soybean PM1 protein protects liposomes during freeze-thaw, Int. J. Mol. Sci. 21 (15) (2020), https://doi.org/10.3390/ijms21155552.
[53] Y. Tong, Q. Zhang, W. Shi, J. Wang, Mechanisms of oral absorption improvement for insoluble drugs by the combination of phospholipid complex and SNEDDS, Drug Deliv. 26 (1) (2019) 1155–1166, https://doi.org/10.1080/10717544.2019.1686086.
[54] C.H. Villa, A.C. Anselmo, S. Mitragotri, V. Muzykantov, Red blood cells: supercarriers for drugs, biologicals, and nanoparticles and inspiration for advanced delivery systems, Adv. Drug Deliv. Rev. 106 (Pt A) (2016) 88–103, https://doi.org/10.1016/j.addr.2016.02.007.
[55] G. Cutillo, A.H. Saariaho, S. Meri, Physiology of gangliosides and the role of antiganglioside antibodies in human diseases, Cell. Mol. Immunol. 17 (4) (2020) 313–322, https://doi.org/10.1038/s41423-020-0388-9.
[56] M.J. Greenberg, C.L. Wang, W. Lehman, J.R. Moore, Modulation of actin mechanics by caldesmon and tropomyosin, Cell Motil Cytoskeleton 65 (2) (2008) 156–164, https://doi.org/10.1002/cm.20251.
[57] Y.L. Clarkson, E.M. Perkins, C.J. Cairncross, A.R. Lyndon, P.A. Skehel, M. Jackson, beta-III spectrin underpins ankyrin R function in Purkinje cell dendritic trees: protein complex critical for sodium channel activity is impaired by SCA5-associated mutations, Hum. Mol. Genet. 23 (14) (2014) 3875–3882, https://doi.org/10.1093/hmg/ddu103.
[58] L. Lai, X. Xu, C.T. Lim, J. Cao, Stiffening of red blood cells induced by cytoskeleton disorders: a joint theory-experiment study, Biophys. J. 109 (11) (2015) 2287–2294, https://doi.org/10.1016/j.bpj.2015.10.036.
[59] M.N. Starodubtseva, Mechanical properties of cells and ageing, Ageing Res. Rev. 10 (1) (2011) 16–25, https://doi.org/10.1016/j.arr.2009.10.005.
[60] A. Chorzalska, A. Lach, T. Borowik, M. Wolny, A. Hryniewicz-Jankowska, A. Kolondra, M. Langner, A.F. Sikorski, The effect of the lipid-binding site of the ankyrin-binding domain of erythroid beta-spectrin on the properties of natural membranes and skeletal structures, Cell. Mol. Biol. Lett. 15 (3) (2010) 406–423, https://doi.org/10.2478/s11658-010-0012-6.
[61] J. Zheng, C. Lu, Y. Ding, J. Zhang, F. Tan, J. Liu, G. Yang, Y. Wang, Z. Li, M. Yang, Y. Yang, W. Gong, C. Gao, Red blood cell-hitchhiking mediated pulmonary delivery of ivermectin: effects of nanoparticle properties, Int. J. Pharm. (Amst.) 619 (2022), 121719, https://doi.org/10.1016/j.ijpharm.2022.121719.
[62] S.W. Ng, S.G. Norwitz, E.R. Norwitz, The impact of iron overload and ferroptosis on reproductive disorders in humans: implications for preeclampsia, Int. J. Mol. Sci. 20 (13) (2019), https://doi.org/10.3390/ijms20133283.
[63] I. Mustafa, M.A. Al, N.K. Mamdouh, K.N. Abdulla, T. Hadwan, Time dependent assessment of morphological changes: leukodepleted packed red blood cells stored in SAGM, BioMed Res. Int. 2016 (2016), 4529434, https://doi.org/10.1155/2016/4529434.
[64] R. Liu, G. Spicer, S. Chen, H.F. Zhang, J. Yi, V. Backman, Theoretical model for optical oximetry at the capillary level: exploring hemoglobin oxygen saturation through backscattering of single red blood cells, J. Biomed. Opt. 22 (2) (2017), 25002, https://doi.org/10.1117/1.JBO.22.2.025002.
[65] S.N. Somasundaram, S. Shanmugam, B. Subramanian, R. Jaganathan, Cytotoxic effect of fucoidan extracted from Sargassum cinereum on colon cancer cell line HCT-15, Int. J. Biol. Macromol. 91 (2016) 1215–1223, https://doi.org/10.1016/j.ijbiomac.2016.06.084.
[66] N. Pishesha, A.M. Bilate, M.C. Wibowo, N.J. Huang, Z. Li, R. Deshycka, D. Bousbaine, H. Li, H.C. Patterson, S.K. Dougan, T. Maruyama, H.F. Lodish, H. L. Ploegh, Engineered erythrocytes covalently linked to antigenic peptides can protect against autoimmune disease, P. Natl Acad. Sci. USA 114 (12) (2017) 3157–3162, https://doi.org/10.1073/pnas.1701746114.
[67] P.Y. Mantel, D. Hjelmqvist, M. Walch, S. Kharoubi-Hess, S. Nilsson, D. Ravel, M. Ribeiro, C. Gruring, S. Ma, P. Padmanabhan, A. Trachtenberg, J. Ankarklev, N. M. Brancucci, C. Huttenhower, M.T. Duraisingh, I. Ghiran, W.P. Kuo, L. Filgueira, R. Martinelli, M. Marti, Infected erythrocyte-derived extracellular vesicles alter vascular function via regulatory Ago2-miRNA complexes in malaria, Nat. Commun. 7 (2016), 12727, https://doi.org/10.1038/ncomms12727.
[68] Q. Jiang, Z. Luo, Y. Men, P. Yang, H. Peng, R. Guo, Y. Tian, Z. Pang, W. Yang, Red blood cell membrane-camouflaged melanin nanoparticles for enhanced photothermal therapy, Biomaterials 143 (2017) 29–45, https://doi.org/10.1016/j.biomaterials.2017.07.027.
[69] S.R. Croy, G.S. Kwon, Polymeric micelles for drug delivery, Curr. Pharmaceut. Des. 12 (36) (2006) 4669–4684, https://doi.org/10.2174/138161206779026245.
[70] M. Hamidi, H. Tajerzadeh, Carrier erythrocytes: an overview, Drug Deliv. 10 (1) (2003) 9–20, https://doi.org/10.1080/713840329.
[71] T. Volken, A. Buser, D. Castelli, S. Fontana, B.M. Frey, I. Rusges-Wolter, A. Sarraj, J. Sigle, J. Thierbach, T. Weingand, B.M. Taleghani, Red blood cell use in Switzerland: trends and demographic challenges, Blood Transfus-Italy 16 (1) (2018) 73–82, https://doi.org/10.2450/2016.0079-16.
[72] M. Magnani, Engineered red blood cells as therapeutic agents, Am. J. Hematol. 92 (10) (2017) 979–980, https://doi.org/10.1002/ajh.24874.
[73] P. Seeman, Transient holes in the erythrocyte membrane during hypotonic hemolysis and stable holes in the membrane after lysis by saponin and lysolecithin, J. Cell Biol. 32 (1) (1967) 55–70, https://doi.org/10.1083/jcb.32.1.55.
[74] C.M. Hu, R.H. Fang, L. Zhang, Erythrocyte-inspired delivery systems, Adv. Healthcare Mater. 1 (5) (2012) 537–547, https://doi.org/10.1002/adhm.201200138.
[75] J. Lindmark, A. Lagerkvist, E. Nilsson, M. Carlsson, E. Thorin, E. Dahlquist, Evaluating the effects of electroporation pre-treatment on the biogas yield from ley crop silage, Appl. Biochem. Biotechnol. 174 (7) (2014) 2616–2625, https://doi.org/10.1007/s12010-014-1213-7.
[76] F. Zhang, J. Zhuang, F.D.A.B. Esteban, S. Tang, Q. Zhang, R.H. Fang, L. Zhang, J. Wang, A nanomotor-based active delivery system for intracellular oxygen transport, ACS Nano 13 (10) (2019) 11996–12005, https://doi.org/10.1021/acsnano.9b06127.
[77] S. Nagata, Apoptosis and clearance of apoptotic cells, Annu. Rev. Immunol. 36 (2018) 489–517, https://doi.org/10.1146/annurev-immunol-042617-053010.
[78] C. Wang, J. Huang, Y. Zhang, H. Jia, B. Chen, Construction and evaluation of red blood cells-based drug delivery system for chemo-photothermal therapy, Colloids Surf., B 204 (2021), 111789, https://doi.org/10.1016/j.colsurfb.2021.111789.
[79] J. Teissie, T.Y. Tsong, Electric field induced transient pores in phospholipid bilayer vesicles, Biochemistry-Us 20 (6) (1981) 1548–1554, https://doi.org/10.1021/bi00509a022.
[80] C. Lizano, S. Sanz, J. Luque, M. Pinilla, In vitro study of alcohol dehydrogenase and acetaldehyde dehydrogenase encapsulated into human erythrocytes by an electroporation procedure, Biochim. Biophys. Acta 1425 (2) (1998) 328–336, https://doi.org/10.1016/s0304-4165(98)00085-3.
[81] J. Mosqueda-Melgar, P. Elez-Martinez, R.M. Raybaudi-Massilia, O. Martin-Belloso, Effects of pulsed electric fields on pathogenic microorganisms of major concern in fluid foods: a review, Crit. Rev. Food Sci. 48 (8) (2008) 747–759, https://doi.org/10.1080/10408390701691000.
[82] P. Manas, R. Pagan, Microbial inactivation by new technologies of food preservation, J. Appl. Microbiol. 98 (6) (2005) 1387–1399, https://doi.org/10.1111/j.1365-2672.2005.02561.x.
[83] K.K. Phua, D. Boczkowski, J. Dannull, S. Pruitt, K.W. Leong, S.K. Nair, Whole blood cells loaded with messenger RNA as an anti-tumor vaccine, Adv. Healthcare Mater. 3 (6) (2014) 837–842, https://doi.org/10.1002/adhm.201300512.
[84] Q. Dong, W. Jin, Monitoring diclofenac sodium in single human erythrocytes introduced by electroporation using capillary zone electrophoresis with electrochemical detection, Electrophoresis 22 (13) (2001) 2786–2792, https://doi.org/10.1002/1522-2683(200108)22:13<2786::AID-ELPS2786>3.0.CO;2-V.
[85] A. De Virgilio, M. Ralli, L. Longo, P. Mancini, G. Attanasio, F. Atturo, M. De Vincentiis, A. Greco, Electrochemotherapy in head and neck cancer: a review of an emerging cancer treatment, Oncol. Lett. 16 (3) (2018) 3415–3423, https://doi.org/10.3892/ol.2018.9140.
[86] J. Oblak, D. Krizaj, S. Amon, A. Macek-Lebar, D. Miklavcic, Feasibility study for cell electroporation detection and separation by means of dielectrophoresis, Bioelectrochemistry 71 (2) (2007) 164–171, https://doi.org/10.1016/j.bioelechem.2007.04.001.

[87] S. Wang, X. Sun, W. Cheng, J. Zhang, J. Wang, Pilot in vitro and in vivo study on a mouse model to evaluate the safety of transcutaneous low-frequency electrical nerve stimulation on cervical cancer patients, Int. Urogynecol. J. 30 (1) (2019) 71–80, https://doi.org/10.1007/s00192-018-3625-3.
[88] M.E. Favretto, J.C. Cluitmans, G.J. Bosman, R. Brock, Human erythrocytes as drug carriers: loading efficiency and side effects of hypotonic dialysis, chlorpromazine treatment and fusion with liposomes, J. Contr. Release 170 (3) (2013) 343–351, https://doi.org/10.1016/j.jconrel.2013.05.032.
[89] A. Villares, C. Moreau, B. Cathala, Star-like supramolecular complexes of reducing-end-functionalized cellulose nanocrystals, ACS Omega 3 (11) (2018) 16203–16211, https://doi.org/10.1021/acsomega.8b02559.
[90] H. Wang, M. Xing, W. Deng, M. Qian, F. Wang, K. Wang, A.C. Midgley, Q. Zhao, Anti-Sca-1 antibody-functionalized vascular grafts improve vascular regeneration via selective capture of endogenous vascular stem/progenitor cells, Bioact. Mater. 16 (2022) 433–450, https://doi.org/10.1016/j.bioactmat.2022.03.007.
[91] N.D. Donahue, H. Acar, S. Wilhelm, Concepts of nanoparticle cellular uptake, intracellular trafficking, and kinetics in nanomedicine, Adv. Drug Deliv. Rev. 143 (2019) 68–96, https://doi.org/10.1016/j.addr.2019.04.008.
[92] L. Tao, N. Sedkova, H. Yao, R.W. Ye, P.L. Sharpe, Q. Cheng, Expression of bacterial hemoglobin genes to improve astaxanthin production in a methanotrophic bacterium Methylomonas sp, Appl. Microbiol. Biotechnol. 74 (3) (2007) 625–633, https://doi.org/10.1007/s00253-006-0708-8.
[93] H.B. Xiao, X.Y. Lu, Y.J. Li, J.P. Xu, Z.L. Sun, Effect of 3,4,5,6-tetrahydroxyxanthone on erythrocyte deformability in apolipoprotein E-deficient mice, J. Asian Nat. Prod. Res. 11 (7) (2009) 643–651, https://doi.org/10.1080/10286020902953753.
[94] J.M. Softeland, A. Casselbrant, A.R. Biglarnia, J. Linders, M. Hellstrom, A. Pesce, A.M. Padma, L.P. Jiga, B. Hoinoiu, M. Ionac, M. Oltean, Intestinal preservation injury: a comparison between rat, porcine and human intestines, Int. J. Mol. Sci. 20 (13) (2019), https://doi.org/10.3390/ijms20133135.
[95] T.M. Ferrisse, A.B. de Oliveira, A.K. Surur, H.S. Buzo, F.L. Brighenti, C.R. Fontana, Photodynamic therapy associated with nanomedicine strategies for treatment of human squamous cell carcinoma: a systematic review and meta-analysis, Nanomedicine-Uk 40 (2022), 102505, https://doi.org/10.1016/j.nano.2021.102505.
[96] S. Kontos, I.C. Kourtis, K.Y. Dane, J.A. Hubbell, Engineering antigens for in situ erythrocyte binding induces T-cell deletion, P. Natl Acad. Sci. USA 110 (1) (2013) E60–E68, https://doi.org/10.1073/pnas.1216353110.
[97] H. He, J. Ye, Y. Wang, Q. Liu, H.S. Chung, Y.M. Kwon, M.C. Shin, K. Lee, V. C. Yang, Cell-penetrating peptides meditated encapsulation of protein therapeutics into intact red blood cells and its application, J. Contr. Release 176 (2014) 123–132, https://doi.org/10.1016/j.jconrel.2013.12.019.
[98] Y. Zhang, L. Yong, Y. Luo, X. Ding, D. Xu, X. Gao, S. Yan, Q. Wang, J. Luo, D. Pu, J. Zou, Enhancement of HIFU ablation by sonosensitizer-loading liquid fluorocarbon nanoparticles with pre-targeting in a mouse model, Sci Rep-Uk 9 (1) (2019) 6982, https://doi.org/10.1038/s41598-019-43416-y.
[99] V.R. Muzykantov, R.P. Taylor, Attachment of biotinylated antibody to red blood cells: antigen-binding capacity of immunoerythrocytes and their susceptibility to lysis by complement, Anal. Biochem. 223 (1) (1994) 142–148, https://doi.org/10.1006/abio.1994.1559.
[100] M. Magnani, L. Chiarantini, U. Mancini, Preparation and characterization of biotinylated red blood cells, Biotechnol. Appl. Biochem. 20 (3) (1994) 335–345, https://doi.org/10.1111/j.1470-8744.1994.tb00321.x.
[101] L. Rossi, A. Fraternale, M. Bianchi, M. Magnani, Red blood cell membrane processing for biomedical applications, Front. Physiol. 10 (2019) 1070, https://doi.org/10.3389/fphys.2019.01070.
[102] J.R. Tan, Y.X. Koo, P. Kaur, F. Liu, A. Armugam, P.T. Wong, K. Jeyaseelan, microRNAs in stroke pathogenesis, Curr. Mol. Med. 11 (2) (2011) 76–92, https://doi.org/10.2174/156652411794859232.
[103] V.R. Muzykantov, J.C. Murciano, R.P. Taylor, E.N. Atochina, A. Herraez, Regulation of the complement-mediated elimination of red blood cells modified with biotin and streptavidin, Anal. Biochem. 241 (1) (1996) 109–119, https://doi.org/10.1006/abio.1996.0384.
[104] S. Hirose, K. Yokota, Y. Kuroda, H. Wako, S. Endo, S. Kanai, T. Noguchi, Prediction of protein motions from amino acid sequence and its application to protein-protein interaction, BMC Struct. Biol. 10 (2010) 20, https://doi.org/10.1186/1472-6807-10-20.
[105] C.H. Villa, D.C. Pan, I.H. Johnston, C.F. Greineder, L.R. Walsh, E.D. Hood, D. B. Cines, M. Poncz, D.L. Siegel, V.R. Muzykantov, Biocompatible coupling of therapeutic fusion proteins to human erythrocytes, Blood Adv. 2 (3) (2018) 165–176, https://doi.org/10.1182/bloodadvances.2017011734.
[106] S. Zaitsev, K. Danielyan, J.C. Murciano, K. Ganguly, T. Krasik, R.P. Taylor, S. Pincus, S. Jones, D.B. Cines, V.R. Muzykantov, Human complement receptor type 1-directed loading of tissue plasminogen activator on circulating erythrocytes for prophylactic fibrinolysis, Blood 108 (6) (2006) 1895–1902, https://doi.org/10.1182/blood-2005-11-012336.
[107] J. Shi, L. Kundrat, N. Pishesha, A. Bilate, C. Theile, T. Maruyama, S.K. Dougan, H. L. Ploegh, H.F. Lodish, Engineered red blood cells as carriers for systemic delivery of a wide array of functional probes, P. Natl Acad. Sci. USA 111 (28) (2014) 10131–10136, https://doi.org/10.1073/pnas.1409861111.
[108] P. Nguyen, M.K. Jayasinghe, A.H. Le, B. Peng, M.T.N. Le, Advances in drug delivery systems based on red blood cells and their membrane-derived nanoparticles, ACS Nano 17 (6) (2023) 5187–5210, https://doi.org/10.1021/acsnano.2c11965.
[109] W. Chiangjong, P. Netsirisawan, S. Hongeng, S. Chutipongtanate, Red blood cell extracellular vesicle-based drug delivery: challenges and opportunities, Front Med-Lausanne 8 (2021), 761362, https://doi.org/10.3389/fmed.2021.761362.
[110] H.Y. Chow, Y. Zhang, E. Matheson, X. Li, Ligation technologies for the synthesis of cyclic peptides, Chem. Rev. 119 (17) (2019) 9971–10001, https://doi.org/10.1021/acs.chemrev.8b00657.
[111] Y. Deng, T. Wu, M. Wang, S. Shi, G. Yuan, X. Li, H. Chong, B. Wu, P. Zheng, Enzymatic biosynthesis and immobilization of polyprotein verified at the single-molecule level, Nat. Commun. 10 (1) (2019) 2775, https://doi.org/10.1038/s41467-019-10696-x.
[112] D. Mu, Y. Luan, L. Wang, Z. Gao, P. Yang, S. Jing, Y. Wang, H. Xiang, T. Wang, D. Wang, The combination of salvianolic acid A with latamoxef completely protects mice against lethal pneumonia caused by methicillin-resistant Staphylococcus aureus, Emerg. Microb. Infect. 9 (1) (2020) 169–179, https://doi.org/10.1080/22221751.2020.1711817.
[113] M.K. Jayasinghe, M. Pirisinu, Y. Yang, B. Peng, T.T. Pham, C.Y. Lee, M. Tan, L. T. Vu, X.T. Dang, T.C. Pham, H. Chen, A. Leung, W.C. Cho, J. Shi, M.T. Le, Surface-engineered extracellular vesicles for targeted delivery of therapeutic RNAs and peptides for cancer therapy, Theranostics 12 (7) (2022) 3288–3315, https://doi.org/10.7150/thno.68667.
[114] M. Kan, T. Huang, P. Zhao, Artificial chromosome technology and its potential application in plants, Front. Plant Sci. 13 (2022), 970943, https://doi.org/10.3389/fpls.2022.970943.
[115] X. Han, C. Wang, Z. Liu, Red blood cells as smart delivery systems, Bioconjugate Chem. 29 (4) (2018) 852–860, https://doi.org/10.1021/acs.bioconjchem.7b00758.
[116] Y. Li, F. Raza, Y. Liu, Y. Wei, R. Rong, M. Zheng, W. Yuan, J. Su, M. Qiu, Y. Li, F. Raza, Y. Liu, Y. Wei, R. Rong, M. Zheng, W. Yuan, J. Su, M. Qiu, Clinical progress and advanced research of red blood cells based drug delivery system, Biomaterials 279 (2021), 121202, https://doi.org/10.1016/j.biomaterials.2021.121202.
[117] Z. Wu, H. Zhang, J. Yan, Y. Wei, J. Su, Engineered biomembrane-derived nanoparticles for nanoscale theranostics, Theranostics 13 (1) (2023) 20–39, https://doi.org/10.7150/thno.76894.
[118] S. Shi, L. Zhang, M. Zhu, G. Wan, C. Li, J. Zhang, Y. Wang, Y. Wang, Reactive oxygen species-responsive nanoparticles based on PEGlated prodrug for targeted treatment of oral tongue squamous cell carcinoma by combining photodynamic therapy and chemotherapy, Acs Appl. Mater. Inter. 10 (35) (2018) 29260–29272, https://doi.org/10.1021/acsami.8b08269.
[119] J. Llop, T. Lammers, Nanoparticles for cancer diagnosis, radionuclide therapy and theranostics, ACS Nano 15 (11) (2021) 16974–16981, https://doi.org/10.1021/acsnano.1c09139.
[120] S. Zeng, Q. Tang, M. Xiao, X. Tong, T. Yang, D. Yin, L. Lei, S. Li, Cell membrane-coated nanomaterials for cancer therapy, Mater. Today Bio. 20 (2023), 100633, https://doi.org/10.1016/j.mtbio.2023.100633.
[121] T. Zhang, H. Cui, C.Y. Fang, K. Cheng, X. Yang, H.C. Chang, M.L. Forrest, Targeted nanodiamonds as phenotype-specific photoacoustic contrast agents for breast cancer, Nanomedicine-Uk 10 (4) (2015) 573–587, https://doi.org/10.2217/nnm.14.141.
[122] A. Zhu, K. Miao, Y. Deng, H. Ke, H. He, T. Yang, M. Guo, Y. Li, Z. Guo, Y. Wang, X. Yang, Y. Zhao, H. Chen, Dually pH/reduction-responsive vesicles for ultrahigh-contrast fluorescence imaging and thermo-chemotherapy-synergized tumor ablation, ACS Nano 9 (8) (2015) 7874–7885, https://doi.org/10.1021/acsnano.5b02843.
[123] H. Li, Y. Li, H. Ao, D. Bi, M. Han, Y. Guo, X. Wang, Folate-targeting annonaceous acetogenins nanosuspensions: significantly enhanced antitumor efficacy in HeLa tumor-bearing mice, Drug Deliv. 25 (1) (2018) 880–887, https://doi.org/10.1080/10717544.2018.1455761.
[124] G. Hu, H. Zhang, L. Zhang, S. Ruan, Q. He, H. Gao, Integrin-mediated active tumor targeting and tumor microenvironment response dendrimer-gelatin nanoparticles for drug delivery and tumor treatment, Int. J. Pharm. (Amst.) 496 (2) (2015) 1057–1068, https://doi.org/10.1016/j.ijpharm.2015.11.025.
[125] J.S. Brenner, S. Mitragotri, V.R. Muzykantov, Red blood cell hitchhiking: a novel approach for vascular delivery of nanocarriers, Annu. Rev. Biomed. Eng. 23 (2021) 225–248, https://doi.org/10.1146/annurev-bioeng-121219-024239.
[126] A.C. Anselmo, V. Gupta, B.J. Zern, D. Pan, M. Zakrewsky, V. Muzykantov, S. Mitragotri, Delivering nanoparticles to lungs while avoiding liver and spleen through adsorption on red blood cells, ACS Nano 7 (12) (2013) 11129–11137, https://doi.org/10.1021/nn404853z.
[127] J. Zheng, C. Lu, M. Yang, J. Sun, J. Zhang, Y. Meng, Y. Wang, Z. Li, Y. Yang, W. Gong, C. Gao, Lung-targeted delivery of cepharanthine by an erythrocyte-anchoring strategy for the treatment of acute lung injury, Pharmaceutics 14 (9) (2022), https://doi.org/10.3390/pharmaceutics14091820.
[128] V. Lenders, R. Escudero, X. Koutsoumpou, A.L. Armengol, J. Rozenski, S. J. Soenen, Z. Zhao, S. Mitragotri, P. Baatsen, K. Allegaert, J. Toelen, B. B. Manshian, Modularity of RBC hitchhiking with polymeric nanoparticles: testing the limits of non-covalent adsorption, J. Nanobiotechnol. 20 (1) (2022) 333, https://doi.org/10.1186/s12951-022-01544-0.
[129] I.V. Zelepukin, A.V. Yaremenko, V.O. Shipunova, A.V. Babenyshev, I. V. Balalaeva, P.I. Nikitin, S.M. Deyev, M.P. Nikitin, Nanoparticle-based drug delivery via RBC-hitchhiking for the inhibition of lung metastases growth, Nanoscale 11 (4) (2019) 1636–1646, https://doi.org/10.1039/c8nr07730d.
[130] Z. Zhao, A. Ukidve, Y. Gao, J. Kim, S. Mitragotri, Erythrocyte leveraged chemotherapy (ELeCt): nanoparticle assembly on erythrocyte surface to combat lung metastasis, Sci. Adv. 5 (11) (2019), eaax9250, https://doi.org/10.1126/sciadv.aax9250.

[131] Y. Ding, B. Lv, J. Zheng, C. Lu, J. Liu, Y. Lei, M. Yang, Y. Wang, Z. Li, Y. Yang, W. Gong, J. Han, C. Gao, RBC-hitchhiking chitosan nanoparticles loading methylprednisolone for lung-targeting delivery, J. Contr. Release 341 (2022) 702–715, https://doi.org/10.1016/j.jconrel.2021.12.018.
[132] N. Alrushaid, F.A. Khan, E.A. Al-Suhaimi, A. Elaissari, Nanotechnology in cancer diagnosis and treatment, Pharmaceutics 15 (3) (2023), https://doi.org/10.3390/pharmaceutics15031025.
[133] W.S. Lee, E. Kim, H.J. Cho, T. Kang, B. Kim, M.Y. Kim, Y.S. Kim, N.W. Song, J. S. Lee, J. Jeong, The relationship between dissolution behavior and the toxicity of silver nanoparticles on zebrafish embryos in different ionic environments, Nanomaterials-Basel 8 (9) (2018), https://doi.org/10.3390/nano8090652.
[134] J.L. Mejia-Mendez, E.R. Lopez-Mena, E. Sanchez-Arreola, Activities against lung cancer of biosynthesized silver nanoparticles: a review, Biomedicines 11 (2) (2023), https://doi.org/10.3390/biomedicines11020389.
[135] C. Gao, Y. Jin, G. Jia, X. Suo, H. Liu, D. Liu, X. Yang, K. Ge, X.J. Liang, S. Wang, J. Zhang, Y(2)O(3) nanoparticles caused bone tissue damage by breaking the intracellular phosphate balance in bone marrow stromal cells, ACS Nano 13 (1) (2019) 313–323, https://doi.org/10.1021/acsnano.8b06211.
[136] G. Kratosova, V. Holisova, Z. Konvickova, A.P. Ingle, S. Gaikwad, K. Skrlova, A. Prokop, M. Rai, D. Placha, From biotechnology principles to functional and low-cost metallic bionanocatalysts, Biotechnol. Adv. 37 (1) (2019) 154–176, https://doi.org/10.1016/j.biotechadv.2018.11.012.
[137] K.S. El-Said, E.M. Ali, K. Kanehira, A. Taniguchi, Molecular mechanism of DNA damage induced by titanium dioxide nanoparticles in toll-like receptor 3 or 4 expressing human hepatocarcinoma cell lines, J. Nanobiotechnol. 12 (2014) 48, https://doi.org/10.1186/s12951-014-0048-2.
[138] S.W. Shin, I.H. Song, S.H. Um, Role of physicochemical properties in nanoparticle toxicity, Nanomaterials-Basel 5 (3) (2015) 1351–1365, https://doi.org/10.3390/nano5031351.
[139] X. Fang, X. Wu, Z. Li, L. Jiang, W.S. Lo, G. Chen, Y. Gu, W.T. Wong, Biomimetic anti-PD-1 peptide-loaded 2D FePSe(3) nanosheets for efficient photothermal and enhanced immune therapy with multimodal MR/PA/Thermal Imaging, Adv. Sci. 8 (2) (2021), 2003041, https://doi.org/10.1002/advs.202003041.
[140] G.F. Luo, W.H. Chen, X. Zeng, X.Z. Zhang, Cell primitive-based biomimetic functional materials for enhanced cancer therapy, Chem. Soc. Rev. 50 (2) (2021) 945–985, https://doi.org/10.1039/d0cs00152j.
[141] E. Ben-Akiva, R.A. Meyer, H. Yu, J.T. Smith, D.M. Pardoll, J.J. Green, Biomimetic anisotropic polymeric nanoparticles coated with red blood cell membranes for enhanced circulation and toxin removal, Sci. Adv. 6 (16) (2020), eaay9035, https://doi.org/10.1126/sciadv.aay9035.
[142] N.J. Huang, N. Pishesha, J. Mukherjee, S. Zhang, R. Deshycka, V. Sudaryo, M. Dong, C.B. Shoemaker, H.F. Lodish, Genetically engineered red cells expressing single domain camelid antibodies confer long-term protection against botulinum neurotoxin, Nat. Commun. 8 (1) (2017) 423, https://doi.org/10.1038/s41467-017-00448-0.
[143] S.M. Simoes, A.R. Figueiras, F. Veiga, A. Concheiro, C. Alvarez-Lorenzo, Polymeric micelles for oral drug administration enabling locoregional and systemic treatments, Expet Opin. Drug Deliv. 12 (2) (2015) 297–318, https://doi.org/10.1517/17425247.2015.960841.
[144] Y. Zeng, W.G. Pitt, Poly(ethylene oxide)-b-poly(N-isopropylacrylamide) nanoparticles with cross-linked cores as drug carriers, J. Biomater. Sci. Polym. Ed. 16 (3) (2005) 371–380, https://doi.org/10.1163/1568562053654121.
[145] N.U. Nguyen, B.D. Stamper, A template-based approach for guiding and refining the development of cinnamon-based phenylpropanoids as drugs, Molecules 25 (20) (2020), https://doi.org/10.3390/molecules25204629.
[146] I. Jimenez-Pardo, R. Gonzalez-Pastor, A. Lancelot, R. Claveria-Gimeno, A. Velazquez-Campoy, O. Abian, M.B. Ros, T. Sierra, Shell cross-linked polymeric micelles as camptothecin nanocarriers for anti-HCV therapy, Macromol. Biosci. 15 (10) (2015) 1381–1391, https://doi.org/10.1002/mabi.201500094.
[147] M. Moussa, S.N. Goldberg, G. Kumar, R.R. Sawant, T. Levchenko, V.P. Torchilin, M. Ahmed, Nanodrug-enhanced radiofrequency tumor ablation: effect of micellar or liposomal carrier on drug delivery and treatment efficacy, PLoS One 9 (8) (2014), e102727, https://doi.org/10.1371/journal.pone.0102727.
[148] V.P. Torchilin, Recent advances with liposomes as pharmaceutical carriers, Nat. Rev. Drug Discov. 4 (2) (2005) 145–160, https://doi.org/10.1038/nrd1632.
[149] K.C. Weng, C.O. Noble, B. Papahadjopoulos-Sternberg, F.F. Chen, D. C. Drummond, D.B. Kirpotin, D. Wang, Y.K. Hom, B. Hann, J.W. Park, Targeted tumor cell internalization and imaging of multifunctional quantum dot-conjugated immunoliposomes in vitro and in vivo, Nano Lett. 8 (9) (2008) 2851–2857, https://doi.org/10.1021/nl801488u.
[150] M.W. Seo, T.E. Park, Recent advances with liposomes as drug carriers for treatment of neurodegenerative diseases, Biomed. Eng. Lett. 11 (3) (2021) 211–216, https://doi.org/10.1007/s13534-021-00198-5.
[151] F. Alexis, E. Pridgen, L.K. Molnar, O.C. Farokhzad, Factors affecting the clearance and biodistribution of polymeric nanoparticles, Mol. Pharm. 5 (4) (2008) 505–515, https://doi.org/10.1021/mp800051m.
[152] C.P. Reis, R.J. Neufeld, A.J. Ribeiro, F. Veiga, I. Nanoencapsulation, Methods for preparation of drug-loaded polymeric nanoparticles, Nanomedicine-Uk 2 (1) (2006) 8–21, https://doi.org/10.1016/j.nano.2005.12.003.
[153] A. Kumari, S.K. Yadav, S.C. Yadav, Biodegradable polymeric nanoparticles based drug delivery systems, Colloids Surf., B 75 (1) (2010) 1–18, https://doi.org/10.1016/j.colsurfb.2009.09.001.
[154] T. Hong, X. Shen, M.Z. Syeda, Y. Zhang, H. Sheng, Y. Zhou, J. Xu, C. Zhu, H. Li, Z. Gu, L. Tang, Recent advances of bioresponsive polymeric nanomedicine for cancer therapy, Nano Res. 16 (2) (2023) 2660–2671, https://doi.org/10.1007/s12274-022-5002-2.
[155] S.K. Nitta, K. Numata, Biopolymer-based nanoparticles for drug/gene delivery and tissue engineering, Int. J. Mol. Sci. 14 (1) (2013) 1629–1654, https://doi.org/10.3390/ijms14011629.
[156] A.A. Chis, C. Dobrea, C. Morgovan, A.M. Arseniu, L.L. Rus, A. Butuca, A. M. Juncan, M. Totan, A.L. Vonica-Tincu, G. Cormos, A.C. Muntean, M.L. Muresan, F.G. Gligor, A. Frum, Applications and limitations of dendrimers in biomedicine, Molecules 25 (17) (2020), https://doi.org/10.3390/molecules25173982.
[157] E.R. Gillies, J.M. Frechet, Dendrimers and dendritic polymers in drug delivery, Drug Discov. Today 10 (1) (2005) 35–43, https://doi.org/10.1016/S1359-6446(04)03276-3.
[158] S. Svenson, D.A. Tomalia, Dendrimers in biomedical applications–reflections on the field, Adv. Drug Deliv. Rev. 57 (15) (2005) 2106–2129, https://doi.org/10.1016/j.addr.2005.09.018.
[159] C.C. Lee, J.A. MacKay, J.M. Frechet, F.C. Szoka, Designing dendrimers for biological applications, Nat. Biotechnol. 23 (12) (2005) 1517–1526, https://doi.org/10.1038/nbt1171.
[160] K. Kostarelos, L. Lacerda, G. Pastorin, W. Wu, S. Wieckowski, J. Luangsivilay, S. Godefroy, D. Pantarotto, J.P. Briand, S. Muller, M. Prato, A. Bianco, Cellular uptake of functionalized carbon nanotubes is independent of functional group and cell type, Nat. Nanotechnol. 2 (2) (2007) 108–113, https://doi.org/10.1038/nnano.2006.209.
[161] Z. Liu, S. Tabakman, K. Welsher, H. Dai, Carbon nanotubes in biology and medicine: in vitro and in vivo detection, imaging and drug delivery, Nano Res. 2 (2) (2009) 85–120, https://doi.org/10.1007/s12274-009-9009-8.
[162] L. Chen, J. Huang, X. Li, M. Huang, S. Zeng, J. Zheng, S. Peng, S. Li, Progress of nanomaterials in photodynamic therapy against tumor, Front. Bioeng. Biotechnol. 10 (2022), 920162, https://doi.org/10.3389/fbioe.2022.920162.
[163] M. Hu, J. Chen, Z.Y. Li, L. Au, G.V. Hartland, X. Li, M. Marquez, Y. Xia, Gold nanostructures: engineering their plasmonic properties for biomedical applications, Chem. Soc. Rev. 35 (11) (2006) 1084–1094, https://doi.org/10.1039/b517615h.
[164] P. Ghosh, G. Han, M. De, C.K. Kim, V.M. Rotello, Gold nanoparticles in delivery applications, Adv. Drug Deliv. Rev. 60 (11) (2008) 1307–1315, https://doi.org/10.1016/j.addr.2008.03.016.
[165] M.C. Daniel, D. Astruc, Gold nanoparticles: assembly, supramolecular chemistry, quantum-size-related properties, and applications toward biology, catalysis, and nanotechnology, Chem. Rev. 104 (1) (2004) 293–346, https://doi.org/10.1021/cr030698+.
[166] K.J. Stine, Nanoporous gold and other related materials, Nanomaterials-Basel 9 (8) (2019), https://doi.org/10.3390/nano9081080.
[167] M.R. Younis, G. He, J. Qu, J. Lin, P. Huang, X.H. Xia, Inorganic nanomaterials with intrinsic singlet oxygen generation for photodynamic therapy, Adv. Sci. 8 (21) (2021), e2102587, https://doi.org/10.1002/advs.202102587.
[168] J.W. Rasmussen, E. Martinez, P. Louka, D.G. Wingett, Zinc oxide nanoparticles for selective destruction of tumor cells and potential for drug delivery applications, Expet Opin. Drug Deliv. 7 (9) (2010) 1063–1077, https://doi.org/10.1517/17425247.2010.502560.
[169] Z. Dai, X. Xu, Z. Guo, K. Zheng, X.Z. Song, X. Qi, Z. Tan, Effect of ROS generation on highly dispersed 4-layer O-Ti(7)O(13) nanosheets toward tumor synergistic therapy, Mat. Sci. Eng. C-Mater. 120 (2021), 111666, https://doi.org/10.1016/j.msec.2020.111666.
[170] Z. Zhen, J. Xie, Development of manganese-based nanoparticles as contrast probes for magnetic resonance imaging, Theranostics 2 (1) (2012) 45–54, https://doi.org/10.7150/thno.3448.
[171] Z. Li, J.C. Barnes, A. Bosoy, J.F. Stoddart, J.I. Zink, Mesoporous silica nanoparticles in biomedical applications, Chem. Soc. Rev. 41 (7) (2012) 2590–2605, https://doi.org/10.1039/c1cs15246g.
[172] I.I. Slowing, J.L. Vivero-Escoto, C.W. Wu, V.S. Lin, Mesoporous silica nanoparticles as controlled release drug delivery and gene transfection carriers, Adv. Drug Deliv. Rev. 60 (11) (2008) 1278–1288, https://doi.org/10.1016/j.addr.2008.03.012.
[173] J. Wang, F. Chen, S.J. Arconada-Alvarez, J. Hartanto, L.P. Yap, R. Park, F. Wang, I. Vorobyova, G. Dagliyan, P.S. Conti, J.V. Jokerst, A nanoscale tool for photoacoustic-based measurements of clotting time and therapeutic drug monitoring of heparin, Nano Lett. 16 (10) (2016) 6265–6271, https://doi.org/10.1021/acs.nanolett.6b02557.
[174] Y. Feng, G. Liu, C. Zhang, J. Li, Y. Li, L. Liu, Fluorescent immunoassay with a copper polymer as the signal label for catalytic oxidation of O-phenylenediamine, Molecules 27 (12) (2022), https://doi.org/10.3390/molecules27123675.
[175] H. Yu, K. Tang, Z. Cai, X. Lin, Y. Huang, T. Yu, Q. Zhang, Q. Wang, L. Wu, L. Yang, H. Shan, H. Luo, Carbon dots-based nanozyme for drug-resistant lung cancer therapy by encapsulated doxorubicin/siRNA cocktail, Int. J. Nanomed. 18 (2023) 933–948, https://doi.org/10.2147/IJN.S390984.
[176] S. Singh, Nanomaterials exhibiting enzyme-like properties (nanozymes): current advances and future perspectives, Front. Chem. 7 (2019) 46, https://doi.org/10.3389/fchem.2019.00046.
[177] Q. Xia, Y. Zhang, Z. Li, X. Hou, N. Feng, Red blood cell membrane-camouflaged nanoparticles: a novel drug delivery system for antitumor application, Acta Pharm. Sin. B 9 (4) (2019) 675–689, https://doi.org/10.1016/j.apsb.2019.01.011.
[178] S. Chen, X. Huang, Nanomaterials in scaffolds for periodontal tissue engineering: frontiers and prospects, Bioengineering-Basel 9 (9) (2022), https://doi.org/10.3390/bioengineering9090431.
[179] A. Taufiq, A. Nikmah, A. Hidayat, S. Sunaryono, N. Mufti, N. Hidayat, H. Susanto, Synthesis of magnetite/silica nanocomposites from natural sand to create a drug

delivery vehicle, Heliyon 6 (4) (2020), e3784, https://doi.org/10.1016/j.heliyon.2020.e03784.
[180] W. Wu, X. Xiao, S. Zhang, H. Li, X. Zhou, C. Jiang, One-pot reaction and subsequent annealing to synthesis hollow spherical magnetite and maghemite nanocages, Nanoscale Res. Lett. 4 (8) (2009) 926–931, https://doi.org/10.1007/s11671-009-9342-6.
[181] V. Harish, M.M. Ansari, D. Tewari, M. Gaur, A.B. Yadav, M.L. Garcia-Betancourt, F.M. Abdel-Haleem, M. Bechelany, A. Barhoum, Nanoparticle and nanostructure synthesis and controlled growth methods, Nanomaterials-Basel 12 (18) (2022), https://doi.org/10.3390/nano12183226.
[182] M.A. Ahmad, Y.Y. Aung, A.A. Widati, S. Sakti, S. Sumarsih, I. Irzaman, B. Yuliarto, J.Y. Chang, M.Z. Fahmi, A perspective on using organic molecules composing carbon dots for cancer treatment, Nanotheranostics 7 (2) (2023) 187–201, https://doi.org/10.7150/ntno.80076.
[183] Z. Ji, W. Guo, S. Sakkiah, J. Liu, T.A. Patterson, H. Hong, Nanomaterial databases: data sources for promoting design and risk assessment of nanomaterials, Nanomaterials-Basel 11 (6) (2021), https://doi.org/10.3390/nano11061599.
[184] A. Rahman, S. Kumar, A. Bafana, J. Lin, S.A. Dahoumane, C. Jeffryes, A mechanistic view of the light-induced synthesis of silver nanoparticles using extracellular polymeric substances of chlamydomonas reinhardtii, Molecules 24 (19) (2019), https://doi.org/10.3390/molecules24193506.
[185] N. Kamaly, B. Yameen, J. Wu, O.C. Farokhzad, Degradable controlled-release polymers and polymeric nanoparticles: mechanisms of controlling drug release, Chem. Rev. 116 (4) (2016) 2602–2663, https://doi.org/10.1021/acs.chemrev.5b00346.
[186] N. Gupta, B. Patel, F. Ahsan, Nano-engineered erythrocyte ghosts as inhalational carriers for delivery of fasudil: preparation and characterization, Pharm. Res.-Dordr 31 (6) (2014) 1553–1565, https://doi.org/10.1007/s11095-013-1261-7.
[187] Y. Chen, M. Zhu, B. Huang, Y. Jiang, J. Su, Advances in cell membrane-coated nanoparticles and their applications for bone therapy, Biomater. Adv. 144 (2023), 213232, https://doi.org/10.1016/j.bioadv.2022.213232.
[188] T. Ghasemzadeh, M. Hasannia, K. Abnous, S.M. Taghdisi, S. Nekooei, N. Nekooei, M. Ramezani, M. Alibolandi, Preparation of targeted theranostic red blood cell membranes-based nanobubbles for treatment of colon adenocarcinoma, Expet Opin. Drug Deliv. 20 (1) (2023) 131–143, https://doi.org/10.1080/17425247.2022.2152792.
[189] D.M. Teleanu, C. Chircov, A.M. Grumezescu, R.I. Teleanu, Neurotoxicity of nanomaterials: an up-to-date overview, Nanomaterials-Basel 9 (1) (2019), https://doi.org/10.3390/nano9010096.
[190] J. Wan, J.H. Wang, T. Liu, Z. Xie, X.F. Yu, W. Li, Surface chemistry but not aspect ratio mediates the biological toxicity of gold nanorods in vitro and in vivo, Sci Rep-Uk 5 (2015), 11398, https://doi.org/10.1038/srep11398.
[191] J.O. Martinez, R. Molinaro, K.A. Hartman, C. Boada, R. Sukhovershin, E. De Rosa, D. Kirui, S. Zhang, M. Evangelopoulos, A.M. Carter, J.A. Bibb, J.P. Cooke, E. Tasciotti, Biomimetic nanoparticles with enhanced affinity towards activated endothelium as versatile tools for theranostic drug delivery, Theranostics 8 (4) (2018) 1131–1145, https://doi.org/10.7150/thno.22078.
[192] R. Molinaro, C. Corbo, J.O. Martinez, F. Taraballi, M. Evangelopoulos, S. Minardi, I.K. Yazdi, P. Zhao, E. De Rosa, M.B. Sherman, A. De Vita, F.N. Toledano, X. Wang, A. Parodi, E. Tasciotti, Biomimetic proteolipid vesicles for targeting inflamed tissues, Nat. Mater. 15 (9) (2016) 1037–1046, https://doi.org/10.1038/nmat4644.
[193] R. Molinaro, M. Evangelopoulos, J.R. Hoffman, C. Corbo, F. Taraballi, J. O. Martinez, K.A. Hartman, D. Cosco, G. Costa, I. Romeo, M. Sherman, D. Paolino, S. Alcaro, E. Tasciotti, Design and development of biomimetic nanovesicles using a microfluidic approach, Adv. Mater. 30 (15) (2018), e1702749, https://doi.org/10.1002/adma.201702749.
[194] A. Arakelyan, O. Ivanova, E. Vasilieva, J.C. Grivel, L. Margolis, Antigenic composition of single nano-sized extracellular blood vesicles, Nanomedicine-Uk 11 (3) (2015) 489–498, https://doi.org/10.1016/j.nano.2014.09.020.
[195] Y. Ju, Y. Hu, P. Yang, X. Xie, B. Fang, Extracellular vesicle-loaded hydrogels for tissue repair and regeneration, Mater. Today Bio. 18 (2023), 100522, https://doi.org/10.1016/j.mtbio.2022.100522.
[196] P. Horn, M.M. Cortese-Krott, N. Amabile, C. Hundsdorfer, K.D. Kroncke, M. Kelm, C. Heiss, Circulating microparticles carry a functional endothelial nitric oxide synthase that is decreased in patients with endothelial dysfunction, J. Am. Heart Assoc. 2 (1) (2012), e3764, https://doi.org/10.1161/JAHA.112.003764.
[197] Y.N. Zhang, F. Vernooij, I. Ibrahim, S. Ooi, C.M. Gijsberts, A.H. Schoneveld, K. W. Sen, H.M. den Ruijter, L. Timmers, A.M. Richards, C.T. Jong, I. Mazlan, J. W. Wang, C.S. Lam, D.P. de Kleijn, Extracellular vesicle proteins associated with systemic vascular events correlate with heart failure: an observational study in a dyspnoea cohort, PLoS One 11 (1) (2016), e148073, https://doi.org/10.1371/journal.pone.0148073.
[198] S.Y. Lin, W.H. Hsu, C.C. Lin, C.L. Lin, H.C. Yeh, C.H. Kao, Association of transfusion with risks of dementia or alzheimer's disease: a population-based cohort study, Front. Psychiatr. 10 (2019) 571, https://doi.org/10.3389/fpsyt.2019.00571.
[199] G. Taraboletti, S. D'Ascenzo, P. Borsotti, R. Giavazzi, A. Pavan, V. Dolo, Shedding of the matrix metalloproteinases MMP-2, MMP-9, and MT1-MMP as membrane vesicle-associated components by endothelial cells, Am. J. Pathol. 160 (2) (2002) 673–680, https://doi.org/10.1016/S0002-9440(10)64887-0.
[200] T. Neri, C. Cordazzo, Y. Carmazzi, S. Petrini, C. Balia, F. Stefanelli, A. Amoruso, S. Brunelleschi, M.C. Breschi, R. Pedrinelli, P. Paggiaro, A. Celi, Effects of peroxisome proliferator-activated receptor-gamma agonists on the generation of microparticles by monocytes/macrophages, Cardiovasc. Res. 94 (3) (2012) 537–544, https://doi.org/10.1093/cvr/cvs125.
[201] W. Bao, H. Xing, S. Cao, X. Long, H. Liu, J. Ma, F. Guo, Z. Deng, X. Liu, Neutrophils restrain sepsis associated coagulopathy via extracellular vesicles carrying superoxide dismutase 2 in a murine model of lipopolysaccharide induced sepsis, Nat. Commun. 13 (1) (2022) 4583, https://doi.org/10.1038/s41467-022-32325-w.
[202] H.A. Al, S.M. Mithieux, G.C. Yeo, E. Hosseini-Beheshti, A.S. Weiss, Extracellular vesicles: interplay with the extracellular matrix and modulated cell responses, Int. J. Mol. Sci. 23 (6) (2022), https://doi.org/10.3390/ijms23063389.
[203] O. Wiklander, M.A. Brennan, J. Lotvall, X.O. Breakefield, A.S. El, Advances in therapeutic applications of extracellular vesicles, Sci. Transl. Med. 11 (492) (2019), https://doi.org/10.1126/scitranslmed.aav8521.
[204] L. Balaj, R. Lessard, L. Dai, Y.J. Cho, S.L. Pomeroy, X.O. Breakefield, J. Skog, Tumour microvesicles contain retrotransposon elements and amplified oncogene sequences, Nat. Commun. 2 (2011) 180, https://doi.org/10.1038/ncomms1180.
[205] W. Mao, Y. Wen, H. Lei, R. Lu, S. Wang, Y. Wang, R. Chen, Y. Gu, L. Zhu, K. K. Abhange, Z.J. Quinn, Y. Chen, F. Xue, M. Zheng, Y. Wan, Isolation and retrieval of extracellular vesicles for liquid biopsy of malignant ground-glass opacity, Anal. Chem. 91 (21) (2019) 13729–13736, https://doi.org/10.1021/acs.analchem.9b03064.
[206] G. Vergauwen, J. Tulkens, C. Pinheiro, C.F. Avila, S. Dedeyne, M.A. De Scheerder, L. Vandekerckhove, F. Impens, I. Miinalainen, G. Braems, K. Gevaert, P. Mestdagh, J. Vandesompele, H. Denys, O. De Wever, A. Hendrix, Robust sequential biophysical fractionation of blood plasma to study variations in the biomolecular landscape of systemically circulating extracellular vesicles across clinical conditions, J. Extracell. Vesicles 10 (10) (2021), e12122, https://doi.org/10.1002/jev2.12122.
[207] X. Dang, J.M. Kavishka, D.X. Zhang, M. Pirisinu, M.T.N. Le, Extracellular vesicles as an efficient and versatile system for drug delivery, Cells-Basel 9 (10) (2020), https://doi.org/10.3390/cells9102191.
[208] A. Anitha, S. Maya, N. Deepa, K.P. Chennazhi, S.V. Nair, R. Jayakumar, Curcumin-loaded N,O-carboxymethyl chitosan nanoparticles for cancer drug delivery, J. Biomater. Sci. Polym. Ed. 23 (11) (2012) 1381–1400, https://doi.org/10.1163/092050611X581534.
[209] P.H. Kuo, Y.H. Teng, A.L. Cin, W. Han, P.W. Huang, L.H. Wang, Y.T. Chou, J. L. Yang, Y.L. Tseng, M. Kao, M.D. Chang, Heparan sulfate targeting strategy for enhancing liposomal drug accumulation and facilitating deep distribution in tumors, Drug Deliv. 27 (1) (2020) 542–555, https://doi.org/10.1080/10717544.2020.1745326.
[210] J. Li, J. Liu, S. Li, Y. Hao, L. Chen, X. Zhang, Antibody h-R3-dendrimer mediated siRNA has excellent endosomal escape and tumor targeted delivery ability, and represents efficient siPLK1 silencing and inhibition of cell proliferation, migration and invasion, Oncotarget 7 (12) (2016) 13782–13796, https://doi.org/10.18632/oncotarget.7368.
[211] X. Han, Y. Xu, M. Geranpayehvaghei, G.J. Anderson, Y. Li, G. Nie, Emerging nanomedicines for anti-stromal therapy against desmoplastic tumors, Biomaterials 232 (2020), 119745, https://doi.org/10.1016/j.biomaterials.2019.119745.
[212] N. van Bree, M. Wilhelm, The tumor microenvironment of medulloblastoma: an intricate multicellular network with therapeutic potential, Cancers 14 (20) (2022), https://doi.org/10.3390/cancers14205009.
[213] I. Gaurav, X. Wang, A. Thakur, A. Iyaswamy, S. Thakur, X. Chen, G. Kumar, M. Li, Z. Yang, Peptide-conjugated nano delivery systems for therapy and diagnosis of cancer, Pharmaceutics 13 (9) (2021), https://doi.org/10.3390/pharmaceutics13091433.
[214] J. Frisch, A. Angenendt, M. Hoth, R.L. Prates, A. Lis, STIM-orai channels and reactive oxygen species in the tumor microenvironment, Cancers 11 (4) (2019), https://doi.org/10.3390/cancers11040457.
[215] B. Shang, Z. Cao, Q. Zhou, Progress in tumor vascular normalization for anticancer therapy: challenges and perspectives, Front Med-Prc 6 (1) (2012) 67–78, https://doi.org/10.1007/s11684-012-0176-8.
[216] M. Amin, M. Bagheri, M. Mansourian, M.R. Jaafari, H.T. Ten, Regulation of in vivo behavior of TAT-modified liposome by associated protein corona and avidity to tumor cells, Int. J. Nanomed. 13 (2018) 7441–7455, https://doi.org/10.2147/IJN.S170274.
[217] C.C. Fleischer, U. Kumar, C.K. Payne, Cellular binding of anionic nanoparticles is inhibited by serum proteins independent of nanoparticle composition, Biomater. Sci. -Uk 1 (9) (2013) 975–982, https://doi.org/10.1039/C3BM60121H.
[218] S. Ma, C. Gu, J. Xu, J. He, S. Li, H. Zheng, B. Pang, Y. Wen, Q. Fang, W. Liu, J. Tian, Strategy for avoiding protein corona inhibition of targeted drug delivery by linking recombinant affibody scaffold to magnetosomes, Int. J. Nanomed. 17 (2022) 665–680, https://doi.org/10.2147/IJN.S338349.
[219] H. Mahmudi, M.A. Adili-Aghdam, M. Shahpouri, M. Jaymand, Z. Amoozgar, R. Jahanban-Esfahlan, Tumor microenvironment penetrating chitosan nanoparticles for elimination of cancer relapse and minimal residual disease, Front. Oncol. 12 (2022), 1054029, https://doi.org/10.3389/fonc.2022.1054029.
[220] C.M. Hu, L. Zhang, S. Aryal, C. Cheung, R.H. Fang, L. Zhang, Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform, P. Natl Acad. Sci. USA 108 (27) (2011) 10980–10985, https://doi.org/10.1073/pnas.1106634108.
[221] W. Chen, H. Li, Z. Liu, W. Yuan, Lipopolyplex for therapeutic gene delivery and its application for the treatment of Parkinson's Disease, Front. Aging Neurosci. 8 (2016) 68, https://doi.org/10.3389/fnagi.2016.00068.
[222] V.P. Chauhan, R.K. Jain, Strategies for advancing cancer nanomedicine, Nat. Mater. 12 (11) (2013) 958–962, https://doi.org/10.1038/nmat3792.

[223] G. Jalani, V. Tam, F. Vetrone, M. Cerruti, Seeing, targeting and delivering with upconverting nanoparticles, J. Am. Chem. Soc. 140 (35) (2018) 10923–10931, https://doi.org/10.1021/jacs.8b03977.
[224] V.P. Chauhan, T. Stylianopoulos, J.D. Martin, Z. Popovic, O. Chen, W.S. Kamoun, M.G. Bawendi, D. Fukumura, R.K. Jain, Normalization of tumour blood vessels improves the delivery of nanomedicines in a size-dependent manner, Nat. Nanotechnol. 7 (6) (2012) 383–388, https://doi.org/10.1038/nnano.2012.45.
[225] B. Zhang, T. Jiang, Y. Tuo, K. Jin, Z. Luo, W. Shi, H. Mei, Y. Hu, Z. Pang, X. Jiang, Captopril improves tumor nanomedicine delivery by increasing tumor blood perfusion and enlarging endothelial gaps in tumor blood vessels, Cancer Lett. 410 (2017) 12–19, https://doi.org/10.1016/j.canlet.2017.09.007.
[226] W. Jiang, Y. Huang, Y. An, B.Y. Kim, Remodeling tumor vasculature to enhance delivery of intermediate-sized nanoparticles, ACS Nano 9 (9) (2015) 8689–8696, https://doi.org/10.1021/acsnano.5b02028.
[227] R. Liu, C. Hu, Y. Yang, J. Zhang, H. Gao, Theranostic nanoparticles with tumor-specific enzyme-triggered size reduction and drug release to perform photothermal therapy for breast cancer treatment, Acta Pharm. Sin. B 9 (2) (2019) 410–420, https://doi.org/10.1016/j.apsb.2018.09.001.
[228] J. Cheng, H. Sauthoff, J.G. Hay, How do changes in tumor matrix affect the outcome of virotherapy? Cancer Biol. Ther. 6 (2) (2007) 290–292, https://doi.org/10.4161/cbt.6.2.4023.
[229] G. Ruiz-Gomez, S. Vogel, S. Moller, M.T. Pisabarro, U. Hempel, Glycosaminoglycans influence enzyme activity of MMP2 and MMP2/TIMP3 complex formation - insights at cellular and molecular level, Sci Rep-Uk 9 (1) (2019) 4905, https://doi.org/10.1038/s41598-019-41355-2.
[230] D. Walma, K.M. Yamada, The extracellular matrix in development, Development 147 (10) (2020), https://doi.org/10.1242/dev.175596.
[231] Y.T. Deng, J.K. Lin, EGCG inhibits the invasion of highly invasive CL1-5 lung cancer cells through suppressing MMP-2 expression via JNK signaling and induces G2/M arrest, J. Agric. Food Chem. 59 (24) (2011) 13318–13327, https://doi.org/10.1021/jf204149c.
[232] M. Diab, A. Azmi, R. Mohammad, P.A. Philip, Pharmacotherapeutic strategies for treating pancreatic cancer: advances and challenges, Expet Opin. Pharmacother. 20 (5) (2019) 535–546, https://doi.org/10.1080/14656566.2018.1561869.
[233] J.T. Erler, A.J. Giaccia, Lysyl oxidase mediates hypoxic control of metastasis, Cancer Res. 66 (21) (2006) 10238–10241, https://doi.org/10.1158/0008-5472.CAN-06-3197.
[234] M. Kanapathipillai, A. Mammoto, T. Mammoto, J.H. Kang, E. Jiang, K. Ghosh, N. Korin, A. Gibbs, R. Mannix, D.E. Ingber, Inhibition of mammary tumor growth using lysyl oxidase-targeting nanoparticles to modify extracellular matrix, Nano Lett. 12 (6) (2012) 3213–3217, https://doi.org/10.1021/nl301206p.
[235] D.F. Mardhian, G. Storm, R. Bansal, J. Prakash, Nano-targeted relaxin impairs fibrosis and tumor growth in pancreatic cancer and improves the efficacy of gemcitabine in vivo, J. Contr. Release 290 (2018) 1–10, https://doi.org/10.1016/j.jconrel.2018.09.031.
[236] D.F. Quail, J.A. Joyce, The microenvironmental landscape of brain tumors, Cancer Cell 31 (3) (2017) 326–341, https://doi.org/10.1016/j.ccell.2017.02.009.
[237] A. Zaghmi, J. Drouin-Ouellet, D. Brambilla, M.A. Gauthier, Treating brain diseases using systemic parenterally-administered protein therapeutics: dysfunction of the brain barriers and potential strategies, Biomaterials 269 (2021), 120461, https://doi.org/10.1016/j.biomaterials.2020.120461.
[238] L. Marchetti, D. Francisco, S. Soldati, J.N. Haghayegh, S. Barcos, I. Gruber, J. R. Pareja, A. Thiriot, U. von Andrian, U. Deutsch, R. Lyck, R. Bruggmann, B. Engelhardt, ACKR1 favors transcellular over paracellular T-cell diapedesis across the blood-brain barrier in neuroinflammation in vitro, Eur. J. Immunol. 52 (1) (2022) 161–177, https://doi.org/10.1002/eji.202149238.
[239] J. Yang, Z. Shi, R. Liu, Y. Wu, X. Zhang, Combined-therapeutic strategies synergistically potentiate glioblastoma multiforme treatment via nanotechnology, Theranostics 10 (7) (2020) 3223–3239, https://doi.org/10.7150/thno.40298.
[240] S. Fu, M. Liang, Y. Wang, L. Cui, C. Gao, X. Chu, Q. Liu, Y. Feng, W. Gong, M. Yang, Z. Li, C. Yang, X. Xie, Y. Yang, C. Gao, Dual-modified novel biomimetic nanocarriers improve targeting and therapeutic efficacy in glioma, Acs Appl. Mater. Inter. 11 (2) (2019) 1841–1854, https://doi.org/10.1021/acsami.8b18664.
[241] P.M. Gonzalez, P.N. Durfee, A.M. Gregory, G.C. Sieck, C.J. Brinker, C.B. Mantilla, A novel approach for targeted delivery to motoneurons using cholera toxin-B modified protocells, J. Neurosci. Methods 273 (2016) 160–174, https://doi.org/10.1016/j.jneumeth.2016.09.003.
[242] S. Raj, S. Khurana, R. Choudhari, K.K. Kesari, M.A. Kamal, N. Garg, J. Ruokolainen, B.C. Das, D. Kumar, Specific targeting cancer cells with nanoparticles and drug delivery in cancer therapy, Semin. Cancer Biol. 69 (2021) 166–177, https://doi.org/10.1016/j.semcancer.2019.11.002.
[243] A.K. Jain, M. Das, N.K. Swarnakar, S. Jain, Engineered PLGA nanoparticles: an emerging delivery tool in cancer therapeutics, Crit. Rev. Ther. Drug 28 (1) (2011) 1–45, https://doi.org/10.1615/critrevtherdrugcarriersyst.v28.i1.10.
[244] L. Zhang, P. Huang, S. Huang, T. Wang, S. Chen, Z. Chen, Y. Zhou, L. Qin, Development of ligand modified erythrocyte coated polydopamine nanomedicine to codeliver chemotherapeutic agent and oxygen for chemo-photothermal synergistic cancer therapy, Int. J. Pharm. (Amst.) 626 (2022), 122156, https://doi.org/10.1016/j.ijpharm.2022.122156.
[245] N.O. Keely, M.J. Meegan, Targeting tumors using estrogen receptor ligand conjugates, Curr. Cancer Drug Targets 9 (3) (2009) 370–380, https://doi.org/10.2174/156800909788166628.
[246] E. Piktel, K. Niemirowicz, M. Watek, T. Wollny, P. Deptula, R. Bucki, Recent insights in nanotechnology-based drugs and formulations designed for effective anti-cancer therapy, J. Nanobiotechnol. 14 (1) (2016) 39, https://doi.org/10.1186/s12951-016-0193-x.
[247] H. Yamada, Y. Hasegawa, Y. Suzuki, H. Imai, T. Matsuda, Y. Kimura, A. Toshimitsu, Y. Aoyama, T. Kondo, Magnetic resonance imaging of tumor with a self-traceable polymer conjugated with an antibody fragment, Bioorg. Med. Chem. Lett. 25 (13) (2015) 2675–2678, https://doi.org/10.1016/j.bmcl.2015.04.072.
[248] H. Khan, H.R. Mirzaei, A. Amiri, A.E. Kupeli, H.S. Ashhad, H. Mirzaei, Glyco-nanoparticles: new drug delivery systems in cancer therapy, Semin. Cancer Biol. 69 (2021) 24–42, https://doi.org/10.1016/j.semcancer.2019.12.004.
[249] D. Chenthamara, S. Subramaniam, S.G. Ramakrishnan, S. Krishnaswamy, M. M. Essa, F.H. Lin, M.W. Qoronfleh, Therapeutic efficacy of nanoparticles and routes of administration, Biomater. Res. 23 (2019) 20, https://doi.org/10.1186/s40824-019-0166-x.
[250] N. Dwivedi, J. Shah, V. Mishra, A.M. Mohd, A.K. Iyer, R.K. Tekade, P. Kesharwani, Dendrimer-mediated approaches for the treatment of brain tumor, J. Biomater. Sci. Polym. Ed. 27 (7) (2016) 557–580, https://doi.org/10.1080/09205063.2015.1133155.
[251] 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, C.J. Brinker, Mesoporous silica nanoparticle-supported lipid bilayers (protocells) for active targeting and delivery to individual leukemia cells, ACS Nano 10 (9) (2016) 8325–8345, https://doi.org/10.1021/acsnano.6b02819.
[252] H. Song, R. He, K. Wang, J. Ruan, C. Bao, N. Li, J. Ji, D. Cui, Anti-HIF-1alpha antibody-conjugated pluronic triblock copolymers encapsulated with Paclitaxel for tumor targeting therapy, Biomaterials 31 (8) (2010) 2302–2312, https://doi.org/10.1016/j.biomaterials.2009.11.067.
[253] R.H. Fang, C.M. Hu, K.N. Chen, B.T. Luk, C.W. Carpenter, W. Gao, S. Li, D. E. Zhang, W. Lu, L. Zhang, Lipid-insertion enables targeting functionalization of erythrocyte membrane-cloaked nanoparticles, Nanoscale 5 (19) (2013) 8884–8888, https://doi.org/10.1039/c3nr03064d.
[254] B. Peng, T.M. Nguyen, M.K. Jayasinghe, C. Gao, T.T. Pham, L.T. Vu, E. Yeo, G. Yap, L. Wang, B.C. Goh, W.L. Tam, D. Luo, M.T. Le, Robust delivery of RIG-I agonists using extracellular vesicles for anti-cancer immunotherapy, J. Extracell. Vesicles 11 (4) (2022), e12187, https://doi.org/10.1002/jev2.12187.
[255] S. Chen, J. Fan, F. Xiao, Y. Qin, Y. Long, L. Yuan, B. Liu, Erythrocyte membrane-camouflaged Prussian blue nanocomplexes for combinational therapy of triple-negative breast cancer, J. Mater. Chem. B 11 (10) (2023) 2219–2233, https://doi.org/10.1039/d2tb02289c.
[256] Y. Sun, E. Davis, Nanoplatforms for targeted stimuli-responsive drug delivery: a review of platform materials and stimuli-responsive release and targeting mechanisms, Nanomaterials-Basel 11 (3) (2021), https://doi.org/10.3390/nano11030746.
[257] E. Jager, S. Petrova, R. Konefal, Novel poly(ethylene oxide monomethyl ether)-b-poly(ε-caprolactone) dibtock copolymers containing a pH-acid labile ketal group as a block linkage, Polym Chem-Uk 5 (2014) 3884–3893, https://doi.org/10.1039/c4py00114a.
[258] Q. Ban, T. Bai, X. Duan, J. Kong, Noninvasive photothermal cancer therapy nanoplatforms via integrating nanomaterials and functional polymers, Biomater. Sci. -Uk 5 (2) (2017) 190–210, https://doi.org/10.1039/c6bm00600k.
[259] A. Singh, S.K. Sahoo, Magnetic nanoparticles: a novel platform for cancer theranostics, Drug Discov, Today Off. 19 (4) (2014) 474–481, https://doi.org/10.1016/j.drudis.2013.10.005.
[260] W. Liu, M. Ruan, Y. Wang, R. Song, X. Ji, J. Xu, J. Dai, W. Xue, Light-triggered biomimetic nanoerythrocyte for tumor-targeted lung metastatic combination therapy of malignant melanoma, Small 14 (38) (2018), e1801754, https://doi.org/10.1002/smll.201801754.
[261] A. Erazo-Oliveras, K. Najjar, D. Truong, T.Y. Wang, D.J. Brock, A.R. Prater, J. P. Pellois, The late endosome and its lipid BMP act as gateways for efficient cytosolic access of the delivery agent dfTAT and its macromolecular cargos, Cell Chem. Biol. 23 (5) (2016) 598–607, https://doi.org/10.1016/j.chembiol.2016.03.016.
[262] A.J. Kim, J. Hanes, The emergence of multiple particle tracking in intracellular trafficking of nanomedicines, Biophys. Rev. 4 (2) (2012) 83–92, https://doi.org/10.1007/s12551-012-0066-y.
[263] T. Tashima, Delivery of orally administered digestible antibodies using nanoparticles, Int. J. Mol. Sci. 22 (7) (2021), https://doi.org/10.3390/ijms22073349.
[264] T.T. Pham, H. Chen, P. Nguyen, M.K. Jayasinghe, A.H. Le, M.T. Le, Endosomal escape of nucleic acids from extracellular vesicles mediates functional therapeutic delivery, Pharmacol. Res. 188 (2023), 106665, https://doi.org/10.1016/j.phrs.2023.106665.
[265] J. Rahajeng, S. Caplan, N. Naslavsky, Common and distinct roles for the binding partners Rabenosyn-5 and Vps45 in the regulation of endocytic trafficking in mammalian cells, Exp. Cell Res. 316 (5) (2010) 859–874, https://doi.org/10.1016/j.yexcr.2009.11.007.
[266] I. Pilecka, L. Sadowski, Y. Kalaidzidis, M. Miaczynska, Recruitment of APPL1 to ubiquitin-rich aggresomes in response to proteasomal impairment, Exp. Cell Res. 317 (8) (2011) 1093–1107, https://doi.org/10.1016/j.yexcr.2011.02.002.
[267] W. He, Z. Jin, Y. Lv, H. Cao, J. Yao, J. Zhou, L. Yin, Shell-crosslinked hybrid nanoparticles for direct cytosolic delivery for tumor therapy, Int. J. Pharm. (Amst.) 478 (2) (2015) 762–772, https://doi.org/10.1016/j.ijpharm.2014.12.039.
[268] J. Gou, K. Zhang, X. Tang, Self-assembling nanoparticles for the release of bisphosphonates in the treatment of human cancers [WO2012042024], Expert

Opin. Ther. Pat. 22 (11) (2012) 1367–1375, https://doi.org/10.1517/13543776.2012.714371.
[269] M.M. Yang, S.B. Yarragudi, S. Jamieson, M. Tang, W.R. Wilson, Z. Wu, Calcium enabled remote loading of a weak acid into pH-sensitive liposomes and augmented cytosolic delivery to cancer cells via the proton sponge effect, Pharm. Res.-Dordr 39 (6) (2022) 1181–1195, https://doi.org/10.1007/s11095-022-03206-0.
[270] J. Allen, K. Najjar, A. Erazo-Oliveras, H.M. Kondow-McConaghy, D.J. Brock, K. Graham, E.C. Hager, A. Marschall, S. Dubel, R.L. Juliano, J.P. Pellois, Cytosolic delivery of macromolecules in live human cells using the combined endosomal escape activities of a small molecule and cell penetrating peptides, ACS Chem. Biol. 14 (12) (2019) 2641–2651, https://doi.org/10.1021/acschembio.9b00585.
[271] P. Shi, J.A. Gustafson, J.A. MacKay, Genetically engineered nanocarriers for drug delivery, Int. J. Nanomed. 9 (2014) 1617–1626, https://doi.org/10.2147/IJN.S53886.
[272] Y. Chen, B. Wang, W. Chen, T. Wang, M. Li, Z. Shen, F. Wang, J. Jia, F. Li, X. Huang, J. Zhuang, N. Li, Co-delivery of dihydroartemisinin and indocyanine green by metal-organic framework-based vehicles for combination treatment of hepatic carcinoma, Pharmaceutics 14 (10) (2022), https://doi.org/10.3390/pharmaceutics14102047.
[273] W. Wang, L. Zhang, T. Chen, W. Guo, X. Bao, D. Wang, B. Ren, H. Wang, Y. Li, Y. Wang, S. Chen, B. Tang, Q. Yang, C. Chen, Anticancer effects of resveratrol-loaded solid lipid nanoparticles on human breast cancer cells, Molecules 22 (11) (2017), https://doi.org/10.3390/molecules22111814.
[274] P. Utreja, S. Jain, A.K. Tiwary, Novel drug delivery systems for sustained and targeted delivery of anti- cancer drugs: current status and future prospects, Curr. Drug Deliv. 7 (2) (2010) 152–161, https://doi.org/10.2174/156720110791011783.
[275] I. Biancacci, Q. Sun, D. Mockel, F. Gremse, S. Rosenhain, F. Kiessling, M. Bartneck, Q. Hu, M. Thewissen, G. Storm, W.E. Hennink, Y. Shi, C. Rijcken, T. Lammers, A.M. Sofias, Optical imaging of the whole-body to cellular biodistribution of clinical-stage PEG-b-pHPMA-based core-crosslinked polymeric micelles, J. Contr. Release 328 (2020) 805–816, https://doi.org/10.1016/j.jconrel.2020.09.046.
[276] J. German-Cortes, M. Vilar-Hernandez, D. Rafael, I. Abasolo, F. Andrade, Solid lipid nanoparticles: multitasking nano-carriers for cancer treatment, Pharmaceutics 15 (3) (2023), https://doi.org/10.3390/pharmaceutics15030831.
[277] Y. Liang, W. Huang, D. Zeng, X. Huang, L. Chan, C. Mei, P. Feng, C.H. Tan, T. Chen, Cancer-targeted design of bioresponsive prodrug with enhanced cellular uptake to achieve precise cancer therapy, Drug Deliv. 25 (1) (2018) 1350–1361, https://doi.org/10.1080/10717544.2018.1477862.
[278] H. Yao, Z. Wang, N. Wang, Z. Deng, G. Liu, J. Zhou, S. Chen, J. Shi, G. Zhu, Enhancing circulation and tumor accumulation of carboplatin via an erythrocyte-anchored prodrug strategy, Angew. Chem., Int. Ed. 61 (25) (2022), e202203838, https://doi.org/10.1002/anie.202203838.
[279] M. Zhai, Y. Wang, L. Zhang, M. Liang, S. Fu, L. Cui, M. Yang, W. Gong, Z. Li, L. Yu, X. Xie, C. Yang, Y. Yang, C. Gao, Glioma targeting peptide modified apoferritin nanocage, Drug Deliv. 25 (1) (2018) 1013–1024, https://doi.org/10.1080/10717544.2018.1464082.
[280] C. Ruan, L. Liu, Y. Lu, Y. Zhang, X. He, X. Chen, Y. Zhang, Q. Chen, Q. Guo, T. Sun, C. Jiang, Substance P-modified human serum albumin nanoparticles loaded with paclitaxel for targeted therapy of glioma, Acta Pharm. Sin. B 8 (1) (2018) 85–96, https://doi.org/10.1016/j.apsb.2017.09.008.
[281] J.S. McCune, Rapid advances in immunotherapy to treat cancer, Clin. Pharmacol. Ther. 103 (4) (2018) 540–544, https://doi.org/10.1002/cpt.985.
[282] J.R. Hu, R. Florido, E.J. Lipson, J. Naidoo, R. Ardehali, C.G. Tocchetti, A.R. Lyon, R.F. Padera, D.B. Johnson, J. Moslehi, Cardiovascular toxicities associated with immune checkpoint inhibitors, Cardiovasc. Res. 115 (5) (2019) 854–868, https://doi.org/10.1093/cvr/cvz026.
[283] L. Zhang, J. Yu, M. Zheng, H. Zhen, Q. Xie, C. Zhang, Z. Zhou, G. Jin, Raga prevents tumor immune evasion of LUAD by promoting CD47 lysosome degradation, Commun. Biol. 6 (1) (2023) 211, https://doi.org/10.1038/s42003-023-04581-z.
[284] K. Kodar, M.J. McConnell, J.L. Harper, M.S. Timmer, B.L. Stocker, The coadministration of trehalose dibehenate and monosodium urate crystals promotes an antitumor phenotype in human-derived myeloid cells, Immunol. Cell Biol. 98 (5) (2020) 411–422, https://doi.org/10.1111/imcb.12329.
[285] L. Su, Y. Hao, R. Li, W. Pan, X. Ma, J. Weng, Y. Min, Red blood cell-based vaccines for ameliorating cancer chemoimmunotherapy, Acta Biomater. 154 (2022) 401–411, https://doi.org/10.1016/j.actbio.2022.10.001.
[286] Y. Yu, Y. Gao, L. He, B. Fang, W. Ge, P. Yang, Y. Ju, X. Xie, L. Lei, Biomaterial-based gene therapy, Medcomm 4 (3) (2023) e259, https://doi.org/10.1002/mco2.259.
[287] N. Khelghati, M.J. Soleimanpour, M. Mir, F. Alemi, Z. Asemi, A. Sadeghpour, M. Maleki, K.H. Samadi, F. Jadidi-Niaragh, M. Majidinia, B. Yousefi, The importance of co-delivery of nanoparticle-siRNA and anticancer agents in cancer therapy, Chem. Biol. Drug Des. 97 (4) (2021) 997–1015, https://doi.org/10.1111/cbdd.13824.
[288] G. Li, X. Zhang, C. Zhong, J. Mo, R. Quan, J. Yang, D. Liu, Z. Li, H. Yang, Z. Wu, Small molecules enhance CRISPR/Cas9-mediated homology-directed genome editing in primary cells, Sci Rep-Uk 7 (1) (2017) 8943, https://doi.org/10.1038/s41598-017-09306-x.
[289] P. Wu, H. Zhang, Y. Yin, M. Sun, S. Mao, H. Chen, Y. Deng, S. Chen, S. Li, B. Sun, Engineered EGCG-containing biomimetic nanoassemblies as effective delivery platform for enhanced cancer therapy, Adv. Sci. 9 (15) (2022), e2105894, https://doi.org/10.1002/advs.202105894.
[290] Y. Liu, Y. Zou, C. Feng, A. Lee, J. Yin, R. Chung, J.B. Park, H. Rizos, W. Tao, M. Zheng, O.C. Farokhzad, B. Shi, Charge conversional biomimetic nanocomplexes as a multifunctional platform for boosting orthotopic glioblastoma RNAi therapy, Nano Lett. 20 (3) (2020) 1637–1646, https://doi.org/10.1021/acs.nanolett.9b04683.
[291] Y. Tao, M. Li, D.T. Auguste, Pattern-based sensing of triple negative breast cancer cells with dual-ligand cofunctionalized gold nanoclusters, Biomaterials 116 (2017) 21–33, https://doi.org/10.1016/j.biomaterials.2016.11.050.
[292] Z.G. Liao, T. Tang, X.J. Guan, W. Dong, J. Zhang, G.W. Zhao, M. Yang, X.L. Liang, Improvement of transmembrane transport mechanism study of imperatorin on P-Glycoprotein-mediated drug transport, Molecules 21 (12) (2016), https://doi.org/10.3390/molecules21121606.
[293] J. Xu, T. Chen, T. Sun, C. Yu, D. Yan, L. Zhu, Erythrocyte membrane camouflaged siRNA/chemodrug nanoassemblies for cancer combination therapy, Biomater. Sci. -Uk 10 (22) (2022) 6601–6613, https://doi.org/10.1039/d2bm01478e.
[294] I.M. van der Sluis, Y. Bertrand, A. Baruchel, R. Pieters, Is asparaginase encapsulated in erythrocytes effective as second-line treatment in acute lymphoblastic leukaemia? Brit, J. Haematol. 198 (6) (2022) e82–e83, https://doi.org/10.1111/bjh.18372.
[295] Y. Fan, Y. Jiang, J. Liu, Y. Kang, R. Li, J. Wang, The anti-tumor activity and mechanism of alkaloids from Aconitum szechenyianum Gay, Bioorg. Med. Chem. Lett. 26 (2) (2016) 380–387, https://doi.org/10.1016/j.bmcl.2015.12.006.
[296] T. Wu, D. Yan, W. Hou, H. Jiang, M. Wu, Y. Wang, G. Chen, C. Tang, Y. Wang, H. Xu, Biomimetic red blood cell membrane-mediated nanodrugs loading ursolic acid for targeting NSCLC therapy, Cancers 14 (18) (2022), https://doi.org/10.3390/cancers14184520.
[297] Y. Ji, Z. Zhang, W. Hou, M. Wu, H. Wu, N. Hu, M. Ni, C. Tang, F. Wu, H. Xu, Enhanced antitumor effect of icariin nanoparticles coated with iRGD functionalized erythrocyte membrane, Eur. J. Pharmacol. 931 (2022), 175225, https://doi.org/10.1016/j.ejphar.2022.175225.
[298] J. Mao, Y. Bian, Q. Zhang, L. Kong, X. Shi, J. Hu, M. Yang, L. Li, H. Qian, B. Liu, X. Qian, Antitumor activity of iRGD-modified red blood cell membrane nanoparticles loaded with Juglone and Oxaliplatin against colorectal cancer, J. Biomater. Appl. 36 (7) (2022) 1301–1316, https://doi.org/10.1177/08853282211052386.
[299] H. Wang, Y. Zheng, Q. Sun, Z. Zhang, M. Zhao, C. Peng, S. Shi, Ginsenosides emerging as both bifunctional drugs and nanocarriers for enhanced antitumor therapies, J. Nanobiotechnol. 19 (1) (2021) 322, https://doi.org/10.1186/s12951-021-01062-5.
[300] A.S. Wong, C.M. Che, K.W. Leung, Recent advances in ginseng as cancer therapeutics: a functional and mechanistic overview, Nat. Prod. Rep. 32 (2) (2015) 256–272, https://doi.org/10.1039/c4np00080c.
[301] W. Wu, H. Guo, D. Jing, Z. Zhang, Z. Zhang, F. Pu, W. Yang, X. Jin, X. Huang, Z. Shao, Targeted delivery of PD-L1-derived phosphorylation-mimicking peptides by engineered biomimetic nanovesicles to enhance osteosarcoma treatment, Adv. Healthcare Mater. 11 (23) (2022), e2200955, https://doi.org/10.1002/adhm.202200955.
[302] J. Zhou, Q. Yang, X. Zhu, T. Lin, D. Hao, J. Xu, Antioxidant activities of Clerodendrum cyrtophyllum Turcz leaf extracts and their major components, PLoS One 15 (6) (2020), e234435, https://doi.org/10.1371/journal.pone.0234435.
[303] O.A. Khomich, S.N. Kochetkov, B. Bartosch, A.V. Ivanov, Redox biology of respiratory viral infections, Viruses-Basel 10 (8) (2018), https://doi.org/10.3390/v10080392.
[304] X. Mao, C. Gu, D. Chen, B. Yu, J. He, Oxidative stress-induced diseases and tea polyphenols, Oncotarget 8 (46) (2017) 81649–81661, https://doi.org/10.18632/oncotarget.20887.
[305] C. Tan, V. Reddy, J. Dannull, E. Ding, S.K. Nair, D.S. Tyler, S.K. Pruitt, W.T. Lee, Impact of anti-CD25 monoclonal antibody on dendritic cell-tumor fusion vaccine efficacy in a murine melanoma model, J. Transl. Med. 11 (2013) 148, https://doi.org/10.1186/1479-5876-11-148.
[306] H. Yang, N. Bushue, P. Bu, Y.J. Wan, Induction and intracellular localization of Nur77 dictate fenretinide-induced apoptosis of human liver cancer cells, Biochem. Pharmacol. 79 (7) (2010) 948–954, https://doi.org/10.1016/j.bcp.2009.11.004.
[307] F.H. Gao, F. Liu, W. Wei, L.B. Liu, M.H. Xu, Z.Y. Guo, W. Li, B. Jiang, Y.L. Wu, Oridonin induces apoptosis and senescence by increasing hydrogen peroxide and glutathione depletion in colorectal cancer cells, Int. J. Mol. Med. 29 (4) (2012) 649–655, https://doi.org/10.3892/ijmm.2012.895.
[308] P. He, J.C. Ahn, J.I. Shin, P.S. Chung, Photoactivation of 9-hydroxypheophorbide alpha triggers apoptosis through the reactive oxygen species-mediated mitochondrial pathway and endoplasmic reticulum stress in AMC-HN-3 laryngeal cancer cells, Int. J. Oncol. 36 (4) (2010) 801–808, https://doi.org/10.3892/ijo_00000556.
[309] Q. Xu, G. Zhan, Z. Zhang, T. Yong, X. Yang, L. Gan, Manganese porphyrin-based metal-organic framework for synergistic sonodynamic therapy and ferroptosis in hypoxic tumors, Theranostics 11 (4) (2021) 1937–1952, https://doi.org/10.7150/thno.45511.
[310] Y. Hao, Z. Dong, M. Chen, Y. Chao, Z. Liu, L. Feng, Y. Hao, Z.L. Dong, M.C. Chen, Y. Chao, Z. Liu, L.Z. Feng, Near-infrared light and glucose dual-responsive cascading hydroxyl radical generation for in situ gelation and effective breast cancer treatment, Biomaterials 228 (2020), 119568, https://doi.org/10.1016/j.biomaterials.2019.119568.
[311] D. Meng, S. Yang, Y. Yang, L. Zhang, L. Cui, Synergistic chemotherapy and phototherapy based on red blood cell biomimetic nanomaterials, J. Contr. Release 352 (2022) 146–162, https://doi.org/10.1016/j.jconrel.2022.10.019.

[312] H. Liang, Z. Zhou, R. Luo, M. Sang, B. Liu, M. Sun, W. Qu, F. Feng, W. Liu, Tumor-specific activated photodynamic therapy with an oxidation-regulated strategy for enhancing anti-tumor efficacy, Theranostics 8 (18) (2018) 5059–5071, https://doi.org/10.7150/thno.28344.
[313] V.K. Chaturvedi, A. Singh, V.K. Singh, M.P. Singh, Cancer nanotechnology: a new revolution for cancer diagnosis and therapy, Curr. Drug Metabol. 20 (6) (2019) 416–429, https://doi.org/10.2174/1389200219666180918111528.
[314] G. Yang, J. Tian, C. Chen, D. Jiang, Y. Xue, C. Wang, Y. Gao, W. Zhang, An oxygen self-sufficient NIR-responsive nanosystem for enhanced PDT and chemotherapy against hypoxic tumors, Chem. Sci. 10 (22) (2019) 5766–5772, https://doi.org/10.1039/c9sc00985j.
[315] Y. Liu, P. Bhattarai, Z. Dai, X. Chen, Photothermal therapy and photoacoustic imaging via nanotheranostics in fighting cancer, Chem. Soc. Rev. 48 (7) (2019) 2053–2108, https://doi.org/10.1039/c8cs00618k.
[316] S. Zhang, C. Cao, X. Lv, H. Dai, Z. Zhong, C. Liang, W. Wang, W. Huang, X. Song, X. Dong, A H(2)O(2) self-sufficient nanoplatform with domino effects for thermal-responsive enhanced chemodynamic therapy, Chem. Sci. 11 (7) (2020) 1926–1934, https://doi.org/10.1039/c9sc05506a.
[317] S. Zhuang, H. Xiang, Y. Chen, L. Wang, Y. Chen, J. Zhang, Engineering 2D Cu-composed metal-organic framework nanosheets for augmented nanocatalytic tumor therapy, J. Nanobiotechnol. 20 (1) (2022) 66, https://doi.org/10.1186/s12951-022-01250-x.
[318] H. Wang, M. Cui, Y. Xu, T. Liu, Y. Gu, P. Wang, H. Tang, Multifaceted elevation of ROS generation for effective cancer suppression, Nanomaterials-Basel 12 (18) (2022), https://doi.org/10.3390/nano12183150.
[319] J.T. Mac, R. Vankayala, C.H. Lee, B. Anvari, Erythrocyte-derived nanoparticles with folate functionalization for near infrared pulsed laser-mediated photochemotherapy of tumors, Int. J. Mol. Sci. 23 (18) (2022), https://doi.org/10.3390/ijms231810295.
[320] Y. Zhang, Q. Xia, T. Wu, Z. He, Y. Li, Z. Li, X. Hou, Y. He, S. Ruan, Z. Wang, J. Sun, N. Feng, A novel multi-functionalized multicellular nanodelivery system for non-small cell lung cancer photochemotherapy, J. Nanobiotechnol. 19 (1) (2021) 245, https://doi.org/10.1186/s12951-021-00977-3.
[321] Y. Pan, Y. He, X. Zhao, Y. Pan, X. Meng, Z. Lv, Z. Hu, X. Mou, Y. Cai, Engineered red blood cell membrane-coating salidroside/indocyanine green nanovesicles for high-efficiency hypoxic targeting phototherapy of triple-negative breast cancer, Adv. Healthcare Mater. 11 (17) (2022), e2200962, https://doi.org/10.1002/adhm.202200962.
[322] Y. Zhao, J. Wang, X. Cai, P. Ding, H. Lv, R. Pei, Metal-organic frameworks with enhanced photodynamic therapy: synthesis, erythrocyte membrane camouflage, and aptamer-targeted aggregation, Acs Appl. Mater. Inter. 12 (21) (2020) 23697–23706, https://doi.org/10.1021/acsami.0c04363.
[323] J. Li, S. Wang, X. Lin, Y. Cao, Z. Cai, J. Wang, Z. Zhang, X. Liu, M. Wu, C. Yao, Red blood cell-mimic nanocatalyst triggering radical storm to augment cancer immunotherapy, Nano-Micro Lett. 14 (1) (2022) 57, https://doi.org/10.1007/s40820-022-00801-z.
[324] S. Zong, C. Cao, K. Chen, Y. Cui, J. Li, Z. Wang, Red blood cell membrane camouflaged mesoporous silica nanorods as nanocarriers for synergistic chemo-photothermal therapy, IEEE T. Nanobiosci. (2022), https://doi.org/10.1109/TNB.2022.3233378.
[325] Z. Lei, J. Fan, X. Li, Y. Chen, D. Shi, H. Xie, B. Liu, Biomimetic graphene oxide quantum dots nanoparticles targeted photothermal-chemotherapy for gastric cancer, J. Drug Target. 31 (3) (2023) 320–333, https://doi.org/10.1080/1061186X.2022.2162060.
[326] Y. Wang, Y. Cao, Z. Jiang, Y. Li, B. Yuan, J. Xing, M. Li, Q. Gao, K. Xu, O. U. Akakuru, A. Wu, J. Li, The neuropeptide Y(1) receptor ligand-modified cell membrane promotes targeted photodynamic therapy of zeolitic imidazolate frameworks for breast cancer, J. Phys. Chem. Lett. 12 (46) (2021) 11280–11287, https://doi.org/10.1021/acs.jpclett.1c03562.
[327] C. Zhou, Q. Liu, F. Meng, N. Ding, J. Yan, B. Liu, Modification of erythrocytes by internalizing Arg-Gly-Asp (iRGD) in boosting the curative effect of radiotherapy for gastric carcinoma, J. Gastrointest. Oncol. 13 (5) (2022) 2249–2258, https://doi.org/10.21037/jgo-22-951.
[328] N.S. Mangalmurti, Z. Xiong, M. Hulver, M. Ranganathan, X.H. Liu, T. Oriss, M. Fitzpatrick, M. Rubin, D. Triulzi, A. Choi, J.S. Lee, Loss of red cell chemokine scavenging promotes transfusion-related lung inflammation, Blood 113 (5) (2009) 1158–1166, https://doi.org/10.1182/blood-2008-07-166264.
[329] K. Yazdanbakhsh, W. Bao, H. Zhong, Immunoregulatory effects of stored red blood cells, Hematol. -Am. Soc. Hematol. 2011 (2011) 466–469, https://doi.org/10.1182/asheducation-2011.1.466.
[330] B. Rudlof, B. Just, R. Deitenbeck, T. Ehmann, Mismatched transfusion of 8 AB0-incompatible units of packed red blood cells in a patient with acute intermittent porphyria, Saudi J. Anaesth. 5 (1) (2011) 101–104, https://doi.org/10.4103/1658-354X.76497.
[331] D.P. Blackall, J.K. Armstrong, H.J. Meiselman, T.C. Fisher, Polyethylene glycol-coated red blood cells fail to bind glycophorin A-specific antibodies and are impervious to invasion by the Plasmodium falciparum malaria parasite, Blood 97 (2) (2001) 551–556, https://doi.org/10.1182/blood.v97.2.551.
[332] J.D. Belcher, C. Chen, J. Nguyen, F. Abdulla, P. Zhang, H. Nguyen, P. Nguyen, T. Killeen, S.M. Miescher, N. Brinkman, K.A. Nath, C.J. Steer, G.M. Vercellotti, Haptoglobin and hemopexin inhibit vaso-occlusion and inflammation in murine sickle cell disease: role of heme oxygenase-1 induction, PLoS One 13 (4) (2018), e196455, https://doi.org/10.1371/journal.pone.0196455.
[333] F.L. Willekens, J.M. Werre, Y.A. Groenen-Dopp, B. Roerdinkholder-Stoelwinder, B. de Pauw, G.J. Bosman, Erythrocyte vesiculation: a self-protective mechanism? Br. J. Haematol. 141 (4) (2008) 549–556, https://doi.org/10.1111/j.1365-2141.2008.07055.x.
[334] M. Minetti, L. Agati, W. Malorni, The microenvironment can shift erythrocytes from a friendly to a harmful behavior: pathogenetic implications for vascular diseases, Cardiovasc. Res. 75 (1) (2007) 21–28, https://doi.org/10.1016/j.cardiores.2007.03.007.
[335] L. Luo, D. Zhu, Z. Zhang, H. Zeng, M. Huang, S. Zhou, 11beta-Hydroxysteroid dehydrogenase type 1 amplifies inflammation in LPS-induced THP-1 cells, Iran J, Basic Med. Sci. 26 (3) (2023) 374–379, https://doi.org/10.22038/IJBMS.2023.67927.14852.
[336] M. Firdaus, F. Muh, J.H. Park, S.K. Lee, S.H. Na, W.S. Park, K.S. Ha, J.H. Han, E. T. Han, In-depth biological analysis of alteration in Plasmodium knowlesi-infected red blood cells using a noninvasive optical imaging technique, Parasites Vectors 15 (1) (2022) 68, https://doi.org/10.1186/s13071-022-05182-1.
[337] M. Arkuszewski, E.R. Melhem, J. Krejza, Neuroimaging in assessment of risk of stroke in children with sickle cell disease, Adv. Med. Sci. -Poland 55 (2) (2010) 115–129, https://doi.org/10.2478/v10039-010-0045-0.
[338] P. Du, R. Guo, K. Gao, S. Yang, B. Yao, H. Cui, M. Zhao, S. Jia, Identification of differentially expressed genes and the role of PDK4 in CD14+ monocytes of coronary artery disease, Biosci. Rep. 41 (4) (2021), https://doi.org/10.1042/BSR20204124.
[339] J. Huo, Z. Wu, H. Jiang, H. Zhang, Multislice computed tomography angiography imaging diagnosis of lower extremity arteriosclerosis in patients with hypertension and its correlation with the level of high-sensitivity C-reactive protein, Comput. Math. Methods Med. 2022 (2022), 1768208, https://doi.org/10.1155/2022/1768208.
[340] A. Malik, R. Bissinger, K. Jilani, F. Lang, Stimulation of erythrocyte cell membrane scrambling by nystatin, Basic Clin. Pharmacol. 116 (1) (2015) 47–52, https://doi.org/10.1111/bcpt.12279.
[341] M.D. Cappellini, E. Poggiali, A.T. Taher, K.M. Musallam, Hypercoagulability in beta-thalassemia: a status quo, Expert Rev. Hematol. 5 (5) (2012) 505–511, https://doi.org/10.1586/ehm.12.42, 512.
[342] S.M. Chung, O.N. Bae, K.M. Lim, J.Y. Noh, M.Y. Lee, Y.S. Jung, J.H. Chung, Lysophosphatidic acid induces thrombogenic activity through phosphatidylserine exposure and procoagulant microvesicle generation in human erythrocytes, Arterioscl. Throm. Vas. 27 (2) (2007) 414–421, https://doi.org/10.1161/01.ATV.0000252898.48084.6a.
[343] D.C. Pan, J.W. Myerson, J.S. Brenner, P.N. Patel, A.C. Anselmo, S. Mitragotri, V. Muzykantov, Nanoparticle properties modulate their attachment and effect on carrier red blood cells, Sci Rep-Uk 8 (1) (2018) 1615, https://doi.org/10.1038/s41598-018-19897-8.
[344] S. Wu, X. Shi, Q. Zhou, X. Duan, X. Zhang, H. Guo, The association between systemic immune-inflammation index and all-cause mortality in acute ischemic stroke patients: analysis from the MIMIC-IV database, Emerg. Med. Int. 2022 (2022), 4156489, https://doi.org/10.1155/2022/4156489.
[345] A. Thielen, S. Zeerleder, D. Wouters, Consequences of dysregulated complement regulators on red blood cells, Blood Rev. 32 (4) (2018) 280–288, https://doi.org/10.1016/j.blre.2018.01.003.
[346] A.R. Shih, M.R. Murali, Laboratory tests for disorders of complement and complement regulatory proteins, Am. J. Hematol. 90 (12) (2015) 1180–1186, https://doi.org/10.1002/ajh.24209.
[347] Y. Shang, N. Chai, Y. Gu, L. Ding, Y. Yang, J. Zhou, G. Ren, X. Hao, D. Fan, K. Wu, Y. Nie, Systematic immunohistochemical analysis of the expression of CD46, CD55, and CD59 in colon cancer, Arch. Pathol. Lab Med. 138 (7) (2014) 910–919, https://doi.org/10.5858/arpa.2013-0064-OA.
[348] J. Przezdziecka-Dolyk, A. Brzecka, M. Ejma, M. Misiuk-Hojlo, S.L. Torres, H. A. Solis, S.G. Somasundaram, C.E. Kirkland, G. Aliev, Ocular paraneoplastic syndromes, Biomedicines 8 (11) (2020), https://doi.org/10.3390/biomedicines8110490.
[349] I. Hamer, J.P. Paccaud, D. Belin, C. Maeder, J.L. Carpentier, Soluble form of complement C3b/C4b receptor (CR1) results from a proteolytic cleavage in the C-terminal region of CR1 transmembrane domain, Biochem. J. 329 (Pt 1) (1998) 183–190, https://doi.org/10.1042/bj3290183 (Pt 1).
[350] J.J. Muhleip, Y.P. Lin, P. Kraiczy, Further insights into the interaction of human and animal complement regulator factor H with viable lyme disease spirochetes, Front. Vet. Sci. 5 (2018) 346, https://doi.org/10.3389/fvets.2018.00346.
[351] A. Kopp, M. Hebecker, E. Svobodova, M. Jozsi, Factor h: a complement regulator in health and disease, and a mediator of cellular interactions, Biomolecules 2 (1) (2012) 46–75, https://doi.org/10.3390/biom2010046.
[352] S.J. Moons, G.J. Adema, M.T. Derks, T.J. Boltje, C. Bull, Sialic acid glycoengineering using N-acetylmannosamine and sialic acid analogs, Glycobiology 29 (6) (2019) 433–445, https://doi.org/10.1093/glycob/cwz026.
[353] V.R. Muzykantov, M.D. Smirnov, A.L. Klibanov, Avidin attachment to red blood cells via a phospholipid derivative of biotin provides complement-resistant immunoerythrocytes, J. Immunol. Methods 158 (2) (1993) 183–190, https://doi.org/10.1016/0022-1759(93)90212-p.
[354] V.R. Muzykantov, M.D. Smirnov, A.L. Klibanov, Avidin attachment to biotinylated amino groups of the erythrocyte membrane eliminates homologous restriction of both classical and alternative pathways of the complement, FEBS Lett. 318 (2) (1993) 108–112, https://doi.org/10.1016/0014-5793(93)80002-c.
[355] A.B. Zaltzman, C.W. Van den Berg, V.R. Muzykantov, B.P. Morgan, Enhanced complement susceptibility of avidin-biotin-treated human erythrocytes is a consequence of neutralization of the complement regulators CD59 and decay accelerating factor, Biochem. J. 307 (Pt 3) (1995) 651–656, https://doi.org/10.1042/bj3070651 (Pt 3).

[356] M. Howard, B.J. Zern, A.C. Anselmo, V.V. Shuvaev, S. Mitragotri, V. Muzykantov, Vascular targeting of nanocarriers: perplexing aspects of the seemingly straightforward paradigm, ACS Nano 8 (5) (2014) 4100–4132, https://doi.org/10.1021/nn500136z.

[357] H. Baieth, I.S. Elashmawi, Influence of ozone on the rheological and electrical properties of stored human blood, J. Biomed Res 26 (3) (2012) 185–192, https://doi.org/10.7555/JBR.26.20110070.

[358] G. Pyrgiotakis, W. Luu, Z. Zhang, N. Vaze, G. DeLoid, L. Rubio, W. Graham, D. C. Bell, D. Bousfield, P. Demokritou, Development of high throughput, high precision synthesis platforms and characterization methodologies for toxicological studies of nanocellulose, Cellulose 25 (2018) 2303–2319.

[359] G. Singh, R.S. Pai, Optimization (central composite design) and validation of HPLC method for investigation of emtricitabine loaded poly(lactic-co-glycolic acid) nanoparticles: in vitro drug release and in vivo pharmacokinetic studies, Sci. World J. 2014 (2014), 583090, https://doi.org/10.1155/2014/583090.

[360] Y. Tian, M. Gong, Y. Hu, H. Liu, W. Zhang, M. Zhang, X. Hu, D. Aubert, S. Zhu, L. Wu, X. Yan, Quality and efficiency assessment of six extracellular vesicle isolation methods by nano-flow cytometry, J. Extracell. Vesicles 9 (1) (2020), 1697028, https://doi.org/10.1080/20013078.2019.1697028.

[361] E. Reategui, K.E. van der Vos, C.P. Lai, M. Zeinali, N.A. Atai, B. Aldikacti, F. J. Floyd, K.A. H, V. Thapar, F.H. Hochberg, L.V. Sequist, B.V. Nahed, C.B. S, M. Toner, L. Balaj, T.D. T, X.O. Breakefield, S.L. Stott, Engineered nanointerfaces for microfluidic isolation and molecular profiling of tumor-specific extracellular vesicles, Nat. Commun. 9 (1) (2018) 175, https://doi.org/10.1038/s41467-017-02261-1.

[362] N.C. Sarker, P. Ray, C. Pfau, V. Kalavacharla, K. Hossain, M. Quadir, Development of functional nanomaterials from wheat bran derived arabinoxylan for nucleic acid delivery, J. Agric. Food Chem. 68 (15) (2020) 4367–4373, https://doi.org/10.1021/acs.jafc.0c00029.

[363] A.M. Alkilany, C.J. Murphy, Toxicity and cellular uptake of gold nanoparticles: what we have learned so far? J. Nanoparticle Res. 12 (7) (2010) 2313–2333, https://doi.org/10.1007/s11051-010-9911-8.

[364] H. Li, J. Zheng, H. Wang, M.L. Becker, N.D. Leipzig, Neural stem cell encapsulation and differentiation in strain promoted crosslinked polyethylene glycol-based hydrogels, J. Biomater. Appl. 32 (9) (2018) 1222–1230, https://doi.org/10.1177/0885328218755711.