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Tailoring cell-inspired biomaterials to fuel cancer therapy

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ABSTRACT

Cancer stands as a predominant cause of mortality across the globe. Traditional cancer treatments, including surgery, radiotherapy, and chemotherapy, are effective yet face challenges like normal tissue damage, complications, and drug resistance. Biomaterials, with their advantages of high efficacy, targeting, and spatiotemporal controllability, have been widely used in cancer treatment. However, the biocompatibility limitations of traditional synthetic materials have restricted their clinical translation and application. Natural cell-inspired biomaterials inherently possess the targeting abilities of cells, biocompatibility, and immune evasion capabilities. Therefore, cell-inspired biomaterials can be used alone or in combination with other drugs or treatment strategies for cancer therapy. In this review, we first introduce the timeline of key milestones in cell-inspired biomaterials for cancer therapy. Then, we describe the abnormalities in cancer including biophysics, cellular biology, and molecular biology aspects. Afterwards, we summarize the design strategies of cell-inspired antitumor biomaterials. Subsequently, we elaborate on the application of antitumor biomaterials inspired by various cell types. Finally, we explore the current challenges and prospects of cell-inspired antitumor materials. This review aims to provide new opportunities and references for the development of antitumor cell-inspired biomaterials.

1. Introduction

Despite considerable progress in medical science and technology, cancer persists as a condition with a constrained array of treatment options [1]. The metastasis and recurrence of cancer significantly enhance the risk of disability and mortality, and the precise mechanisms underlying these phenomena remain to be fully elucidated [2,3]. Traditional cancer treatment methods, including surgery, radiotherapy, and chemotherapy, are effective, but they face challenges such as damage to normal tissues, complications, and drug resistance [4–8]. Compared to traditional treatments, targeted therapy and immunotherapy based on advanced biomaterials have fewer side effects and more precise therapeutic outcomes [9,10]. Synthetic biomaterials such as metal materials, inorganic non-metal materials, and polymer materials have shown promising antitumor properties in recent years, thanks to their advantages such as targeting, personalization, and controllability [10–12]. However, synthetic biomaterials of non-biological origin inevitably face inherent issues such as biocompatibility and biodegradability, which limit their further translational application [11,13–15]. Therefore, researchers have focused on the development of cell-inspired biomaterials, which possess inherent advantages such as excellent biocompatibility, biodegradability, targeting, and stealth properties (Fig. 1). In addition, cell-inspired biomaterials are abundant in sources and do not require complex construction and synthesis, making them convenient for large-scale preparation and clinical application [16,17]. Researchers can harness the inherent cytotoxicity of immune cells against tumor cells and the prolonged circulation properties of blood cells, among other characteristics, to develop biomaterials with diverse functionalities [18,19]. Cell-inspired biomaterials can be used alone for antitumor purposes and, thanks to their drug-loading capacity, can be combined with other antitumor strategies or formulations to enhance the antitumor efficacy [20–22]. To date,

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researchers have developed various strategies for constructing cell-inspired biomaterials, including living cell-based drug delivery system, engineered cells, biomimetic cellular materials and cell-derived vesicle delivery system (Fig. 2). From the perspective of cell types, cell-inspired biomaterials primarily involve blood cells (erythrocytes and platelets (PLTs)), immune cells (T cells, macrophages, DC cells, Natural killer (NK) cells, and neutrophils), and tumor cells [23]. In this review, we commence by delineating the various abnormalities in cancer such as biophysics, cellular biology, and molecular biology. Then, we introduce the design strategies of cell-inspired antitumor biomaterials. After that, we proceed to expound upon the advances of these biomaterials, which are anchored in a diversity of cell types. Concluding our discourse, we assess cell-inspired antitumor biomaterials' prevailing impediments and prospective horizons. The objective of this review is to furnish a novel paradigm and a referential framework for the advancement of antitumor cell-inspired biomaterials.

2. Cancer abnormalities

The tumor microenvironment (TME) encompasses tumor cells, surrounding blood vessels, lymphatics, immune cells, fibroblasts, signaling molecules, and the tumor interstitium [24,25]. Components of the TME interact dynamically and continuously with tumor cells, regulating tumor growth, development, invasion, and metastasis. Abnormalities in the TME primarily manifest in three aspects: biophysics, cellular biology, and molecular biology (Fig. 3) [26]. Tumors exhibit several biophysical abnormalities, such as increased mechanical stiffness, elevated osmotic pressure, hypoxia, and reduced pH, which may facilitate tumor initiation, progression, metastasis, and resistance to therapy [24].

The solid and liquid stresses within tumors pose significant barriers to the penetration of various biomaterials into tumor tissue. Alleviating intratumoral stress may facilitate the deeper penetration of biomaterials and enhance therapeutic efficacy. These anomalies constrain the efficacy of both traditional and emerging cancer therapies. Hypoxia is a hallmark of locally advanced solid tumors, with the prevalence of hypoxic regions observed in many malignant neoplasms [27]. Local hypoxia also leads to reduced vascular density and irregular blood flow, further restricting the transport of oxygen and nutrients. Since normal tissues typically lack hypoxic areas, targeting the hypoxic microenvironment of tumors has proven to be a promising strategy for enhancing the efficacy of cancer treatments. Numerous hypoxia-targeting/activating biomaterial platforms, such as quinones, nitro/azo, and metal-based therapies, have been developed. Even in the presence of oxygen, cancer cells exhibit a preference for increased glucose uptake and lactate production, a phenomenon known as the Warburg effect. This characteristic leads to an acidic extracellular pH (pH 6.5–6.9) in malignant tumors due to the accumulation of lactate and other metabolic byproducts, in contrast to the physiological pH of normal tissues (pH 7.2–7.4). Researchers have developed numerous smart biomaterials using low pH-responsive groups such as hydrazone bonds, imine bonds, keto-enol tautomer, and cis-aconitic anhydride, among others, for TME-responsive delivery [28–30]. These biomaterials are engineered to respond to the acidic conditions prevalent in tumor tissues, enabling them to release therapeutic agents in a controlled and targeted manner, thereby enhancing the effectiveness of cancer treatments [31].

Various cells within the TME play significant roles. Endothelial cells lining the blood vessel lumens are the front-line cells in contact with the blood. Tumor endothelial cells regulate tumor proliferation, invasion, and metastasis. Although not part of the tumor tissue, endothelial cells are crucial, and more importantly, they are more susceptible to modulation by external factors than tumor cells. Consequently, targeting endothelial cells holds great promise [32]. Cancer-associated fibroblasts are likely the most abundant stromal cells in the TME, influencing tumor stroma remodeling and interactions with cancer cells and leukocytes. However, cancer-associated fibroblasts (CAFs) exert both pro-tumor and anti-tumor effects, and non-specific depletion of these cells may lead to unintended consequences. Therefore, future therapeutic approaches should aim to regulate these cells rather than simply eliminating them [33]. Cancer cells can transform surrounding normal adipocytes into cancer-associated adipocytes within the TME. These cells can promote tumor growth by producing various metabolites, hormones, and cytokines. However, the lack of specific biomarkers for these cells limits the development of targeted therapies against them, necessitating a focus on inhibiting their interactions with tumor cells instead [34]. Numerous studies have demonstrated the presence of a vast array of immune cells in the tumor environment, including macrophages, neutrophils, regulatory T cells, T cells, B cells, DC cells, and NK cells. Immunosuppressive cells create a favorable environment for tumor growth and help tumors evade immune surveillance, while the abilities of immunostimulatory cells are usually suppressed within the tumor environment, preventing them from exerting their antitumor effects [35]. Therefore, modulating immune cell activation to enhance the antitumor immune response through biomaterials represents an effective and non-invasive therapeutic approach. The specific functions of these immune cells are detailed further in the following sections, hence will not be elaborated upon here. Tumor stem cells closely regulate various activities of tumors, yet their existence and functions remain controversial due to the

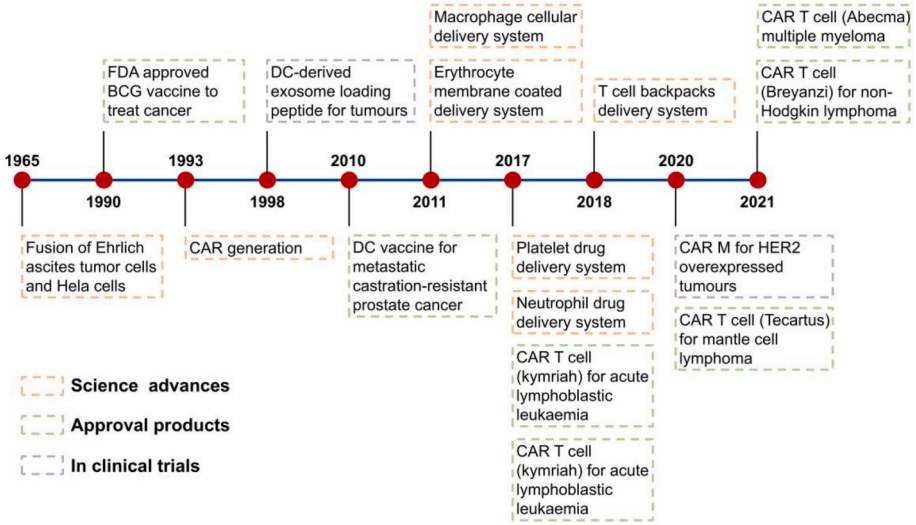

Fig. 1. Timeline of key milestones in cell-inspired biomaterials for cancer therapy, which include science advances, approval products, and clinical trials.

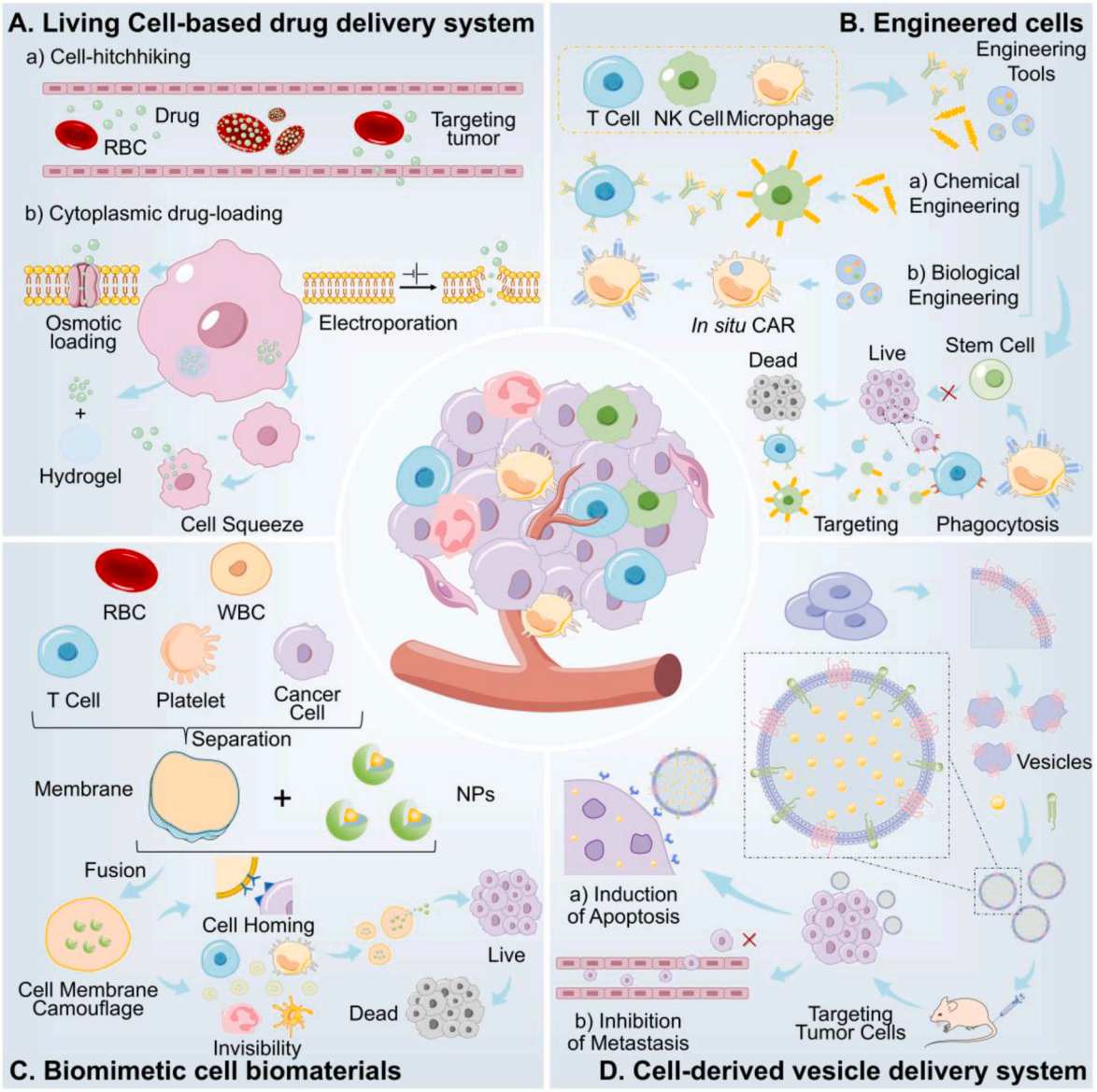

Fig. 2. Illustration of the material design and action mechanism of cell-inspired anti-cancer biomaterials, which include living-cell based drug delivery system, engineered cells, biomimetic cell biomaterials, and cell-derived vesicle delivery system.

lack of specific biomarkers for their identification. Targeting signaling pathways that affect tumor stem cells, such as Hedgehog, Hippo, Notch, and WNT, has proven to be effective in the field of tumor therapy [36].

The biochemical and molecular characteristics of tumor cells significantly differ from those of normal tissue cells, regulating the phenotypes and fates of these cells. Due to the profound metabolic alterations in tumor cells, small molecules such as lactate, glutamine, lipids, and fatty acids are overexpressed in tumor tissues. However, most experimental approaches targeting these small molecule metabolites have not progressed to clinical trials due to the inevitable systemic toxicity they entail [37]. ATP is virtually absent in the extracellular tissue of normal cells, but the opposite is true in tumor tissues. Moreover, ATP can serve as a pro-inflammatory signal, holding promise for tumor therapy. Unfortunately, ATP can be converted into adenosine—a product with immunosuppressive properties—by the overexpressed membrane proteins CD73 and CD39 in tumors. Therefore, targeting the interconversion process between ATP and adenosine may enhance antitumor immunity [38]. Oxidative stress-related products, such as reactive oxygen species (ROS) and glutathione (GSH), play a crucial role in cancer. While the depletion of GSH has been shown to enhance the antitumor effects of ROS, attention should be given to strategies that prevent the continuous production of GSH within tumor cells [39]. Certain gas molecules, such as NO, H_2S, CO, and H_2, can act as molecular messengers, exerting either antitumor or protumor effects depending on their concentrations. Therapeutic approaches targeting these gas molecules or their production are increasingly common. However, a key challenge in this field is how to control the uncontrolled diffusion of these gas molecules [40]. Metal ions, such as copper, zinc, iron, and manganese, have been shown to regulate tumor development and progression through mechanisms such as programmed cell death. However, the therapeutic use of these elemental ions should consider their systemic toxicity [41]. Cancer is characterized by dysfunctional or dysregulated enzyme activity. The aberrant enzyme profiles in tumors can be leveraged to design stimulus-responsive biomaterials or drug delivery systems [42]. Non-coding RNAs, including microRNAs, tRNAs, long non-coding RNAs, and circular RNAs, have been found to influence gene expression levels through chromatin modification, transcription, and post-transcriptional processing, thereby regulating cancer invasion, metastasis, and drug resistance [43]. Last but not least, many immune checkpoints, such as PD-1, have been discovered and have achieved

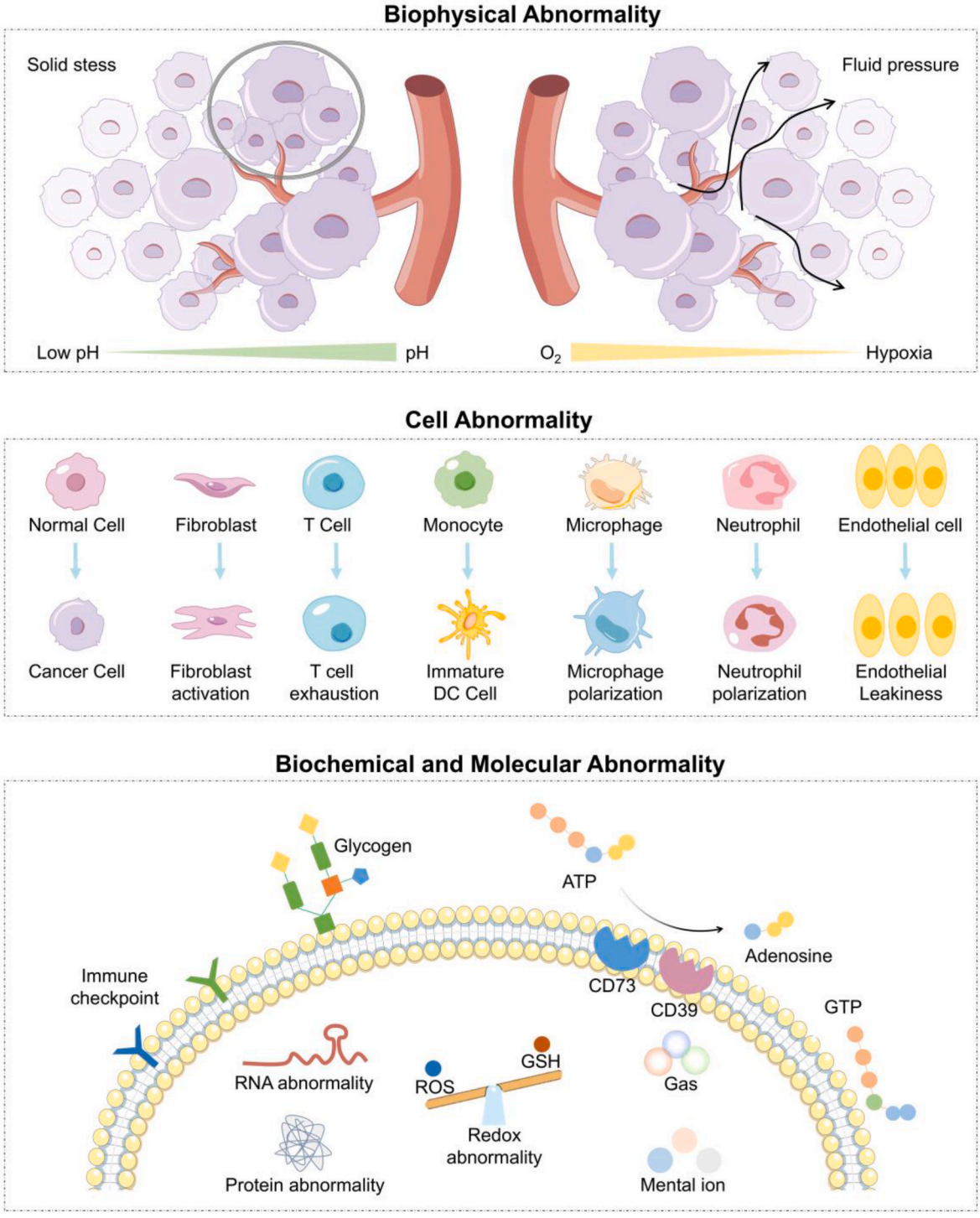

Fig. 3. Tumor abnormalities in biophysics, cell, biochemistry, and molecular biology. Understanding the heterogeneity of the tumor microenvironment is beneficial for improving the design of anti-tumor biomaterials.

significant success, especially in bringing new hope for the treatment of cancer metastasis [44].

In this section, we briefly outline the heterogeneity of tumor tissues, as this not only aids in understanding the complexity of tumors but also relates to the design of antitumor biomaterials. In addition, as vital constituents of the TME, various cells are poised to play a significant role in modulating its heterogeneity. Consequently, cell-inspired biomaterials may synergistically enhance cancer therapy when with or without other treatment modalities, leveraging their multifaceted crosstalk with the TME.

3. Design strategies of cell-inspired biomaterials for cancer therapy

The various design strategies and their advantages, shortcomings, and prospects of cell-inspired biomaterials for cancer therapy have been compiled in Table 1.

3.1. Living cell-based delivery systems

Cell-hitchhiking technology is mainly produced by the adsorption of

Table 1
The design strategies and their advantages, shortcomings, and prospects of cell-inspired biomaterials for cancer therapy.

Design strategies	Advantages	Shortcomings	Prospects
Living cell-based delivery systems	Enhance the targeting of drugs; Reduce immune clearance; Improved drug stability; Prolonged action duration.	Drug loss; Damage to the living cells; High cost; Challenge of long-term storage; Challenge of vitality maintenance.	Biorthogonal and click chemistry-based cell surface piggyback.
Engineered cells	High specificity and Reducing toxic to normal tissues; Potent killing capacity for hematological cancers.	Challenge from solid tumors, Inhibited by the TME; *In vivo* persistence of cells.	Enhance stability of functions; Simplify production processes; Reduce costs; Large-scale manufacturing.
Biomimetic cell biomaterials	High specificity; Reducing toxicity to normal tissues; Potent killing capacity for hematological cancers.	Poor stability *in vivo*; Not standard separation and purification method; Low loading efficiency; Inhibited by TME.	Utilize different cell-derived membranes; Optimize membrane extraction and fusion method.
Cell-derived vesicle delivery systems	Inherent biocompatibility; Immune stealth properties; Blood-brain barrier permeability.	Characterization and standardization are inconsistency; Complex isolation methods; Limited loading capacity; Poor stability *in vivo*.	Standardizing the synthesis process; Artificially modifying natural EVs; Enhance the production efficiency.

biomaterials and cell membrane surfaces. When they pass through the capillary, shearing force makes them desorption. Hence, agents accumulate at disease sites [45,46]. The key advantage of this strategy lies in its ability to promote the targeting of drugs and suppress the recognition and clearance by the immune system. By coating nanoparticles (NPs) with targeting antibodies on their surface, their ability to target specific diseases can be further improved. Additionally, altering the shape of NPs can increase their contact area with cell membranes, thereby enhancing adsorption. The cell-hitchhiking strategy has shown potential in fields such as cancer treatment, as it can increase the accumulation of drugs at tumor sites while reducing damage to healthy tissues. This approach offers new insights for the development of more effective treatments for diseases.

Cytoplasmic drug loading is a strategy for drug delivery that involves loading drug molecules into the internal space of cells, namely the cytoplasm. This strategy can be used with various types of cells, including red blood cells (RBCs), white blood cells, and other cell types. The purpose of cytoplasmic drug loading is typically to protect drugs from degradation by the body's environment, to prolong the half-life of the cargo, to improve their stability and bioavailability, and to enhance their targeting capabilities [47]. During the process of cytoplasmic drug loading, drugs can be introduced into the cells through various methods, including: 1) Osmotic loading: By treating cells in a hypotonic solution, taking advantage of transient nanopores on the cell membrane to load drugs [48,49]; 2) Electroporation: Using an electric field to temporarily increase the permeability of the cell membrane, allowing drugs to enter the cytoplasm [50,51]; 3) Cell squeeze technology: Using physical methods to make cells pass quickly through narrow channels, causing transient rupture of the cell membrane and thus loading drugs [52]; 4) Nanogel loading: Encapsulating drugs in nanogels and then loading these gels into the cells through specific methods [53]. Examples of cytoplasmic drug loading include using RBCs to load L-asparaginase for the treatment of AML and pancreatic cancer [54,55]. This method not only prolongs the half-life of L-ASP but also reduces the risk of allergic reactions. Additionally, by loading chitosan nanogels containing sodium valproate into RBCs, the slow release of the drug can be achieved, enhancing the therapeutic effect. Cytoplasmic drug loading technology provides an innovative method for drug delivery, particularly suitable for treatment strategies that require improved drug stability, prolonged duration of action, and enhanced targeting. However, cytoplasmic drug loading results in drug loss and is difficult to avoid causing damage to the carrier cells. In the future, a biorthogonal and click chemistry-based cell surface piggyback strategy will be a better choice. Besides, the cost and difficulty of long-term storage and vitality maintenance of living cells are relatively high.

3.2. Engineered cells

Engineered cell therapy for cancer is a treatment method that utilizes genetic engineering techniques to modify cells, enabling them to specifically recognize and kill tumor cells [56,57]. This strategy typically involves the following steps: 1) Selection of appropriate cell types: Immunocytes such as T cells, NK cells, or macrophages are commonly used, as they possess natural immune surveillance and killing functions; 2) Genetic modification: Specific genes, such as chimeric antigen receptors (CARs), T cell receptors (TCRs), or NK cell activation receptors, are introduced into the cells using genetic engineering techniques, allowing them to recognize and attack tumor cells; 3) Cell culture: The modified cells are cultured and amplified *in vitro* to ensure there are sufficient numbers for treatment; 4) Safety and efficacy testing: Rigorous safety and efficacy testing is conducted before the engineered cells are infused into animals and patients, to ensure the safety and effectiveness of the treatment; 5) Infusion and treatment: The engineered cells are administered to the animals and patient via intravenous injection, where they migrate to the tumor site, recognize, and kill the tumor cells. The advantages of engineered cell therapy for cancer lie in its high specificity and potent killing capacity against tumor cells, while reducing damage to normal tissues. This method has shown significant therapeutic effects in certain types of hematological cancers, such as acute lymphoblastic leukemia and some types of lymphomas. However, for solid tumor therapy, engineered cell therapy still faces challenges, including the inhibitory effects of the TME and the *in vivo* persistence of the engineered cells [58]. For instance, mitochondria from bone marrow stromal cells can be transplanted into T cells via intercellular nanotubes, effectively "recharging" the T cells. These "supercharged" T cells exhibit enhanced anti-tumor activity and show reduced signs of exhaustion. By penetrating the tumor and overcoming the immunosuppressive state within it, these "boosted" T cells surmount a fundamental barrier in immunotherapy [59]. The future of engineered cell strategies should focus on enhancing the stability of cell functions, simplifying production processes, reducing costs, and exploring methods for large-scale manufacturing.

3.3. Biomimetic cell biomaterials

Cell membrane-modified materials for cancer treatment are a strategy that utilizes biocompatible materials to modify or camouflage cell membranes, enhancing the targeting and therapeutic efficacy of drug delivery systems [19,60]. These biomimetic cells typically possess the following characteristics: 1) Cell membrane camouflage: Biomimetic cells can be coated with a layer of natural cell membrane, such as RBC

membrane, to evade recognition by the immune system, prolong circulation time in the bloodstream, and enhance targeting; 2) Smart drug release: These cells can control drug release in response to environmental stimuli (such as pH, temperature, enzyme activity, etc.), thereby specifically releasing drugs in the TME; 3) Multifunctionality: Biomimetic cells can carry multiple therapeutic molecules simultaneously, such as chemotherapeutic drugs, gene therapeutic agents, immunomodulators, etc., to achieve combination therapy; 4) Biocompatibility and degradability: These particles are usually made from biocompatible materials that can safely degrade in the body, reducing side effects. The advantages of using biomimetic cells for cancer treatment lie in their high specificity and potent cytotoxicity against tumor cells, while minimizing damage to normal tissue [61]. This approach has shown promise in laboratory research and animal models but still faces challenges in translating the technology into clinical applications, including issues related to large-scale production, stability, pharmacokinetics, safety, and validation of efficacy [62]. The advantage of using cell membrane-modified materials for cancer treatment lies in their high specificity against tumor cells while reducing damage to normal tissues. This method has shown significant therapeutic effects in certain types of hematological cancers, such as acute lymphoblastic leukemia and some types of lymphomas. However, for solid tumor therapy, cell membrane-modified materials still face challenges, including the *in vivo* stability, separation and purification method, loading efficiency, and the inhibitory effects of the TME [60]. The future development and improvement of biomaterials coated with cell membranes mainly focus on the following aspects: utilizing cell membranes from different sources to endow biomaterials with various capabilities; optimizing the steps of membrane extraction and fusion to enhance the stability and functionality of NPs in the body [63].

3.4. Cell-derived vesicle delivery systems

Cell-derived vesicles, such as exosomes and microvesicles, are utilized as drug delivery vectors in cancer treatment, leveraging their natural secretion by cells [64]. These vesicles, which can be isolated from various cell types including immune cells, stem cells, and cancer cells, possess inherent blood-brain barrier permeability, biocompatibility, and immune stealth properties. Despite the promising potential of extracellular vesicles (EVs) for cancer treatment, there are several associated challenges, including poor stability issues *in vivo*, limited loading capacity, manufacturing challenges, and the inconsistency characterization and standardization of EVs preparations [65]. The future development and improvement of vesicle-based biomaterials mainly focus on the following aspects: simplifying and standardizing the synthesis process; artificially modifying natural EVs; and developing new technologies to enhance the production efficiency and performance of vesicles. For instance, some research teams have creatively proposed separation strategies based on phospholipid membrane recognition, achieving high-efficiency and high-purity enrichment of EVs from complex clinical samples, which facilitates the discovery of novel EV tumor biomarkers [66,67]. They first established a phospholipid membrane modification strategy based on physical insertion, which efficiently binds to thiol-containing magnetic beads through click chemistry, enabling rapid magnetic enrichment of EVs. To further enhance the efficiency and purity of EV separation and enrichment, they designed choline phosphate-functionalized hydrogel magnetic beads (referred to as MB@CP), which utilize the high-affinity CP-PC multivalent coordination bonds formed between CP and phosphatidyl choline (PC) on the EV membrane to achieve high-efficiency and high-purity separation and enrichment of EVs from various clinical samples.

4. Application of cell-inspired biomaterials for fueling anticancer therapy

The advances in cell-inspired biomaterials for cancer therapy have been compiled in Table 2.

4.1. Blood cells

4.1.1. PLTs

PLTs with large volume and superficial area are conducive to high-performance drug-loaded, the abundant number, speedy replenishment, and specific targeting make PLTs a promising platform for targeted drug delivery [68]. Cancer cells and PLTs hold a tangled two-way crosstalk. Cancer cells alter PLTs' phenotype and RNA spectrum, trigger PLTs' particle and EVs release, induce tumor-PLT aggregation, and augment thrombosis formation. PLTs promote cancer growth by enhancing proliferation signals, helping immune escape, and inducing cancer cells' epithelial-mesenchymal transition [69].

4.1.1.1. Living PLTs-based delivery systems. Efficiently, safely, and precisely constructing drug-loaded therapeutic cells while retaining their inherent biological properties remains a formidable challenge. Gu's group designed a strategy for simultaneously loading multiple drugs into PLTs through a one-step fusion method (Fig. 4A) [70]. Research findings indicate that liposomes encapsulating doxorubicin (DOX) and conjugated with interleukin-15 (IL-15) can fuse with PLTs, thereby achieving cytoplasmic drug loading and surface cytokine modification, with drug loading efficiencies exceeding 70 % within minutes. Experimental results demonstrate that these engineered PLTs, capable of targeting metastatic tumors and postoperative bleeding sites, can exhibit synergistic therapeutic effects against lung metastasis and postoperative recurrence in a mouse B16F10 melanoma model (Fig. 4B). Ultrasound-responsive sonodynamic therapy (SDT) is an effective anticancer tactic strategy due to its unique non-invasive nature, favorable biosafety profile, and ability to penetrate deep into tissues. Zhou *et al.* have developed a biotic son-responsive platelet drug delivery system tailored for precision oncology, capitalizing on tumors' strong dependence on glutamine and the neutralization of GSH and ROS [71]. The PLT bio-nano platform is loaded with the amino acid transporter SLC6A14 blocking agent α-methyl-DL-tryptophan (α-MT) and coated with MnO_2, which collectively enhances the anti-tumor efficacy of SDT through stimuli-responsive glutamine deprivation and blood blockade. The tumor-targeted migration characteristics of PLTs, combined with their stimulus-responsive capabilities in DC coagulation, present an innovative paradigm for biomedical engineering [72,73].

4.1.1.2. Engineered PLTs. Tang *et al.* reported an endogenous enzyme-powered Janus PLT micromotor (JPL-motor) system that effectively targets cancer cells. JPL-motor preparation with combination urease asymmetrically onto PLTs' surface [74]. The Janus distributing urease results in nonuniform urea distribution in biological fluids to produce growing chemophoretic propulsion, which is beneficial in biological applications. JPL-motor harnesses the catalytic power of urease to decompose urea, generating a concentration gradient that propels them through a process known as chemotaxis. This autonomous movement is achieved by the conversion of urea into ammonia and carbon dioxide by urease, which creates a concentration gradient around the JPL-motor. This gradient drives a directional flow of reaction products, resulting in the self-propulsion of the JPL-motor. Factors such as urea concentration, urease distribution, the type of biological fluid, and drug loading can all influence the propulsion performance of JPL-motor. Therefore, further optimization is needed to better control the speed and direction of these nanomotors. In this experiment, researchers verify the therapeutic effect of chemodrug loading DOX JPL-motors on breast cancer cells (MDA-MB-231 cells). Under lower pH conditions (pH = 5.0), the instability and protein denaturation of PLTs cause increased DOX releasing, which is beneficial for JPL-motors to target acidic TME. The efficacious anti-cancer effect was attributed to the efficient self-propulsion of JPL-motors and incremental local DOX concentration.

Table 2
The advances of cell-inspired biomaterials for cancer therapy.

Cell origin	Cell type	Strategies	Characteristics	Refs.
Blood cells	PLTs	Living PLTs-based delivery systems	Efficient drug loading; synergistic therapeutic effect; stimuli-responsive ability; blood blockade.	[70–73]
		Engineered PLTs	pH-responsive ability; incremental local drug concentration; deep penetration.	[74,75]
		Biomimetic PLTs biomaterials	Excellent biocompatibility; low immunogenicity; proactive targeted ability; escape early systemic clearance; vascular disruption and anti-angiogenesis.	[76]
		PLTs-derived vesicle delivery systems	Biocompatibility; less extravascular escape; risk of pro-coagulation and thrombogenicity; excessive pro-inflammatory inducting.	[77–86]
	RBCs	Living RBCs-based drug delivery systems	Less anaphylaxis; tumor cell apoptosis; extended circulation half-life.	[89–97]
		Engineered RBCs biomaterials	Tumor control; cellular immunotherapy.	[98]
		Biomimetic RBCs biomaterials	Enhancing antitumor immune response; specific tropism; lower immunoreaction; circulated durability.	[99–104]
		RBCs-derived vesicle delivery systems	Starvation therapy; altering TME; blocking nutrient supply; repolarize resident macrophages.	[105]
Immune cells	Neutrophils	Living neutrophils-based delivery systems	Reshaping TME; penetrate the tumor blood barrier; nanoscale mimics of pathogens; fewer potential toxicity.	[107–110]
		Engineered neutrophils	Non-drug approach; neutrophil-based cancer immunotherapy; no need complex genetic modification.	[111]
		Biomimetic neutrophils biomaterials	Cancer cells selectivity; overcoming the limitations of cell pyroptosis; reshaping TME; activating systemic antitumor immunity.	[112,113]
		Neutrophil-derived vehicles delivery systems	Innate targeting and penetrating capabilities; chemotactic response to inflammatory stimuli; inhibit proliferation and induce apoptosis of tumors.	[114,115]
	Macrophages	Engineered macrophages-based biomaterials delivery systems	Suppressing the anti-phagocytic signalling; expressing and enhancing the phagocytic efficiency; of higher long-term safety profile; phenotypic antigen presentation.	[119,123]
		Biomimetic macrophage biomaterials	Sustainable oxygen supplier; biocompatibility; inflammatory homing effect.	[122]
		Macrophages-derived vehicle delivery systems	efficient blood-brain barrier penetration capability; good tumor cell targeting; anti-tumor immune memory; alleviating tumor hypoxia.	[123]
	T cells	Engineered T cells	Macrophages recruitment; inhibiting postoperative recurrence; facilitating T cell therapy.	[124–126]
		Biomimetic T-cells biomaterials	Mimic T cells; triggering intracellular signaling cascades; silently cross the BBB.	[127]
		T-cells-derived vehicles delivery systems	Inhibiting T cell exhaustion; maintain antitumor activity in immunosuppressive TME; immunochemotherapy.	[128,129]
	NK cells	Living NK cell-based delivery systems	Improved retention time; Enhanced functionality;	[130]
		Engineered NK Cells	Programmable functionalization; easily modified; enhancing the activation efficiency.	[131–135]
		Biomimetic NK cell biomaterials	Recruiting immune cells; consuming glucose; improving the hypoxic TME.	[136]
	DC cells	Living DC cell delivery systems	Prolonging the survival of DC; promoting continuous migration to lymph nodes; filling tumor defect after surgery; inhibiting tumor growth; prolonging the survival time of mice.	[137]
		Biomimetic DC cell biomaterials	Mimic the surface morphology of natural APCs; inducing potent antigen-specific immune response; migrating to lymph nodes; increasing their tumor delivery efficiency; traversing the BBB.	[138–141]
		DC cells-derived	Inducing ICD; highly specific;	[142,143]

(*continued on next page*)

Table 2 (*continued*)

Cell origin	Cell type	Strategies	Characteristics	Refs.
		vehicle delivery systems	strongly immunogenic antigen targets; long-term preventive tumor immune memory protection; synergistic effect of humoral and cellular immunity.	
Tumor cells		Engineered tumor cells	Identifying and gathering at the lesion site; across BBB; preimmunization; damage-associated molecular patterns; microenvironment underwent reconstruction; prolonged survival in mice.	[144,145]
		Biomimetic tumor cell biomaterials	Awaken the host immune system; BBB penetrating ability; targeting homologous cells; easily absorbed by antigen-presenting cells; effectively draining to the lymph nodes.	[146–149]

The deep penetration of engineered PLTs in cancer sites determines their treatment efficacy [75]. Li *et al.* proposed an engineered PLTs micromotor (PLT@PDA-DOX) to target cancer tissues, prepared by the π-π stacking effect of polydopamine (PDA) and the endocytosis effect of PLTs. PLT@PDA-DOX specifically targets cancer sites and produces derived particles PMP@PDA-DOX under the activation of a neoplasm environment. At the same time, PDA endows PLT@PDA-DOX micromotors and PMP@PDA-DOX nanomotors with photothermal conversion capability, they could realize deep penetration to neoplasm sites owing to the propulsion of near-infrared light, which is significant for the ablation of tumor. Future research should delve into the stability of PDA films within the *in vivo* environment and their long-term impact on platelet activity to ensure safety. Additionally, designing varied PDA film structures or incorporating alternative propulsion mechanisms could enhance the controllability of PLT@PDA-DOX micro/nanomotors, enabling more precise targeting of tumor tissues.

4.1.1.3. Biomimetic PLTs biomaterials. NPs with biocompatibility and short systemic circulation times have disadvantages in targeted cancer treatment. Simple surface modification cannot exactly mimic the biological environment, even decreasing the uptake of NPs by disease sites and causing an immune response. NPs coated with natural cell membranes endow them with excellent biocompatibility, low immunogenicity, and proactive targeted ability. Vascular disrupting agents have the advantage of being able to quickly block nutrient supply and starve tumors. However, although VDAs can be effective in some cases, this treatment often leads to angiogenesis in the later stages, resulting in tumor recurrence and treatment failure. In light of this, the Wei's group utilized mesoporous silica NPs (MSNs) coated with platelet membranes to combine VDAs with anti-angiogenic drugs to achieve targeted aggregation of both in tumors [76]. The camouflage provided by the platelet membrane allows the NPs to escape early systemic clearance and achieve tumor targeting through receptor-ligand interactions between the platelet membrane and the endothelial cells of the tumor vasculature. Because the platelet membrane-coated NPs target and adhere to the ruptured blood vessels, more NPs accumulate in the tumor tissue, leading to significant vascular disruption and effective anti-angiogenesis in animal models.

4.1.1.4. PLTs-derived vesicle delivery systems. PLT EVs (p-EVs) combine PLTM with synthetic nanocarriers and express various glycoproteins/differentiation clusters of PLT, which is significant for targeting and retention at cancer sites [77–79]. P-EVs might transform molecules independent of particular transformer proteins to avoid limited medicine uptake, which is considered a meaningful resistance mechanism [80]. Wu *et al.* extracted P-EVs by sonication and extrusion and then incubated them with DOX to form DOX-P-EVs, demonstrating noticeable anti-breast cancer cells [81]. Compared with free drugs, P-EVs with drug loading expressed more significant cancer cell cytotoxicity. Cancer cells uptake P-EVs by cytoplasmic membranes or endocytosis to transit anticancer agents. However, humans' DOX-P-EVs internalization by cancer cells and cancer cell cytotoxicity is lower than that in rats', we still need more research to verify whether this phenomenon appears owing to normal cells' competitiveness internalization or the role of PLT granules content. Simultaneously, the risk of thrombosis cannot be neglected. Blood clotting promoting P-EVs is correlated with coagulation factors VIII and Va, thrombin, and phosphatidyl serine or P-selectin [82]. Hence, evaluating the risk of pro-coagulation and thrombogenicity before therapeutic by P-EVs is vital for patients' lives. Thrombin generation assay (TGA) related to the evaluation of thrombotic potential of p-EVs, even clotting time assays, activated partial thromboplastin time, and prothrombin time could be applied to the evaluation of procoagulant potential [83]. Another risk is the proinflammatory cytokines IL-1, IL-6, and TNF of p-EVs, which might induce excessive pro-inflammatory role in anticancer treatment [84]. Based on these limitations, preclinical research of long-lasting safety and efficacy in therapy is still urgent to conduct, and deeper-level experiments on the safety and efficacy of allogeneic p-EVs. Circulating tumor cells (CTCs) disseminate to distant organs *via* circulatory metastasis. Activated PLTs and fibrin are physically associated with the blood circulation microenvironment of CTCs. Li *et al.* enlightened by this connection proposed a PLTM-functionalized silica particle to combine specific cytokine TRAIL, which induced tumor cell apoptosis [85]. These particles integrated with CTC-relevant microthrombus in the lung remarkably reduced the lung metastases in breast cancer.

Platelet-derived microparticles were obtained from activated, stressed, or apoptotic plasma membranes of PLTs. Kailashiya *et al.* designed a natural vector, PMPs loaded with DOX, to target tumor sites [86]. PMP-DOX with excellent biocompatibility targets leukemia cells naturally, its leukemia cells toxicity is superior to free drugs, and there is less extravascular escape. PMP-DOX crosses the blood-brain barrier to locate diseased tissues, and P-selectin and integrins might play a significant role in the PMP uptake by cancer cells. However, the intermolecular interactions are complex and intricate, further research is required to confirm whether other molecules are involved in the therapeutic process.

4.1.2. RBCs

RBCs with an extended circulation duration of around 120 d render them well-suited for the persistent delivery of long-lasting medications into the bloodstream [87,88]. The maturity of RBCs in blood transfusion reflects their low immunological rejection and side effects. RBCs protect their intracellular agents in drug delivery by reducing their immunogenicity while avoiding drug degradation. Agents also combinate to the surface of RBCs, utilizing their natural markers to reduce adverse immunological reactions of agents.

4.1.2.1. Living RBCs-based drug delivery systems. RBC encapsulates L-ASP acquired promising effects in AML, L-ASP catalyzes ASN to reduce to disrupt the function of cancer cells and eliminate them, even decreasing the anaphylaxis of L-ASP [89]. Domenech *et al.* carried out RBC encapsulates L-ASP in clinical phase I/II trials. First relapsing

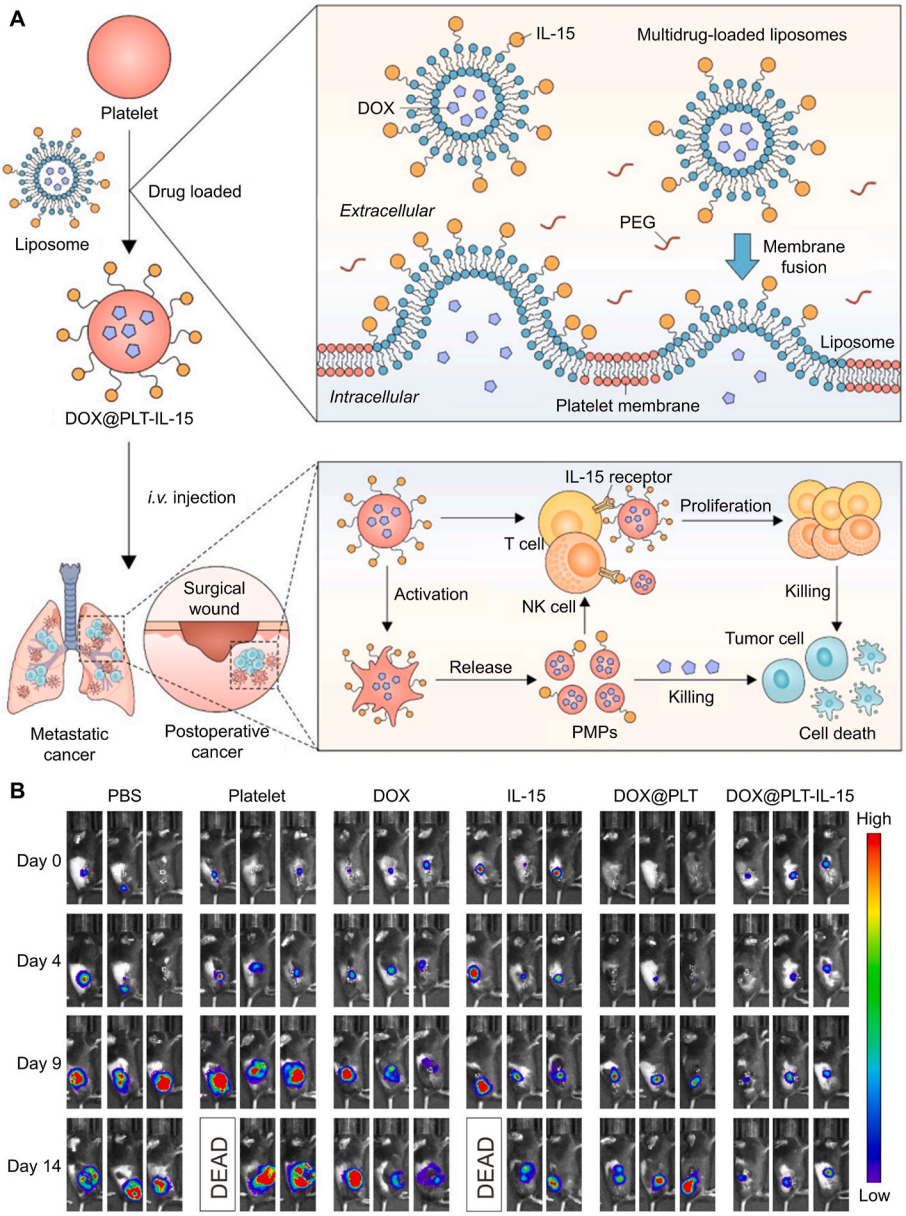

Fig. 4. Schematic of DOX@PLT-IL-15 engineered *via* one-step fusion. (A). Illustration depicting the synthesis of DOX@PLT-IL-15 and its impact on combating tumor metastasis and postoperative recurrence, as well as stimulating the immune response. (B). *In vivo* tumor bioluminescence images of postoperative mice receiving different treatments [70]. © 2024 Wiley-VCH GmbH.

grown-up and child patients with 150 IU/kg L-ASP manifested low concentration of ASN and low anaphylaxis, even getting a 40 d half-life of encapsulated L-ASP [90]. In geriatric patients, 100 IU/kg L-ASP is practicable without by-effect. Nevertheless, the total survival rate was low, which was disillusionary and might ameliorate effects by enhancing the injection frequency [91]. In the presence of anti-L-ASP antibodies, encapsulated L-ASP exhibits lower anaphylaxis and prolongs L-ASP activity compared to free L-ASP [92]. In pancreatic tumors, the expression of ASN synzyme is notable downregulation. Nutrition is cut off *via* depleting the ASN in the cancer microenvironment, which leads to tumor cell apoptosis [93,94]. Bachet *et al.* carried out RBC encapsulates L-ASP in transferability pancreatic tumors phase I clinical study. No drug-relevant dose-limiting poisonousness was manifested in patients [95]. Subsequently, a phase II clinical trial continued in late-stage pancreatic tumor patients. RBC encapsulates L-ASP combined with Chemotherapy agents improving patients' survival [96]. The short circulation half-life and low tumor accumulation of carboplatin drugs can greatly limit their efficacy in the body. Wang's group developed a novel platinum (IV) anticancer prodrug that can "hitchhike" on RBCs [97]. It effectively and stably binds to RBCs, showing an 18.5-fold longer circulation half-life in mice compared to carboplatin. This extended circulation half-life also allows the platinum drug to accumulate 7.7 times higher than carboplatin and maintain stability in the tumor.

4.1.2.2. Engineered RBCs biomaterials. Checkpoint inhibitors and T cell therapies have demonstrated that T cells are vital in the anti-cancer immune response. However, the limitations associated with these treatments have driven the need for alternative approaches. Zhang and colleagues transformed RBCs into artificial antigen-presenting cells (aAPCs) and used them to present a peptide bound to major histocompatibility complex I, the co-stimulatory ligand 4-1BBL, and IL-12 [98]. These engineered RBCs were capable of inducing effective antigen-specific T cell expansion, memory formation, immune activation, tumor control, and antigen spreading *in vivo* tumor models. The

allogeneic aAPC (RTX-321) consists of human leukocyte antigen-A*02:01 presenting the human papillomavirus (HPV) peptide HPV16 E711-19 and surface-expressed 4-1BBL and IL-12, which can activate HPV-specific T cells and promote effector functions *in vitro*. Collectively, RTX-321 is an effective *in vivo* cellular immunotherapy that can be used to treat HPV-positive cancers, including cervical cancer and head and neck cancers.

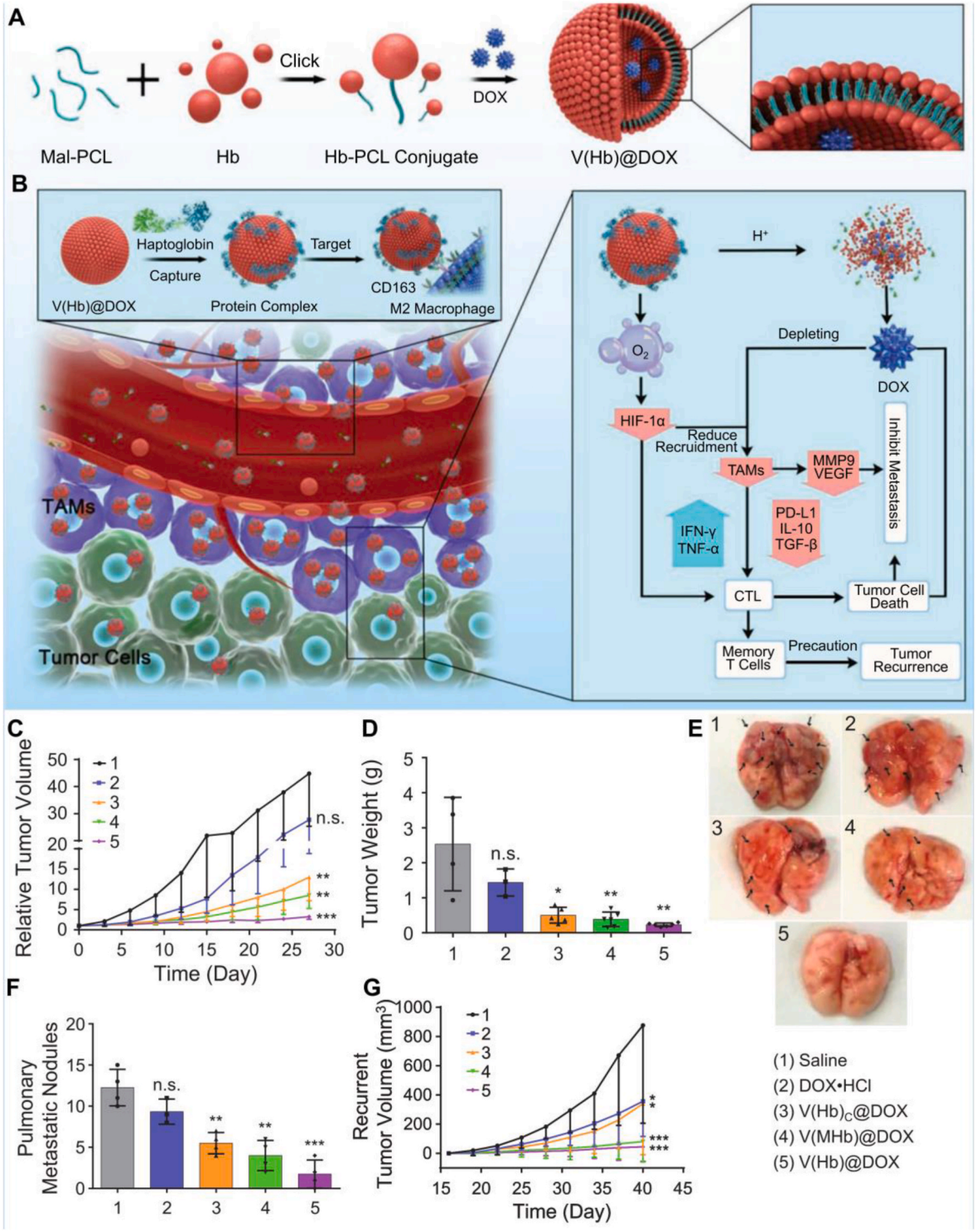

Fig. 5. Schematic depiction of an engineered, endogenous TAM-targeting biomimetic nano-RBC platform designed to enhance cancer chemoimmunotherapy through TIME reprogramming. (A). The schematic representation showcases the construction of the DOX-loaded biomimetic nano-RBC system (V(Hb)@DOX). (B). Illustration of the mechanism by which the endogenously targeted V(Hb)@DOX NPs interact with TAMs, leading to improved chemo-immunotherapeutic outcomes via TIME modulation. (C). Curves of tumor growth following administration of different treatments. (D). The mean tumor weight was harvested from mice on day 27 following the initiation of the respective treatment regimens. (E). Illustrative pulmonary metastatic nodules (indicated by arrow) in mice upon completion of the treatment regimen. (F). The mean count of pulmonary metastatic nodules observed after the treatment period. (G). Growth curves of recurrent tumors 25 days following surgical excision of the original tumors [99].

4.1.2.3. Biomimetic RBCs biomaterials. Immunotherapy holds broad application prospects. However, due to the presence of complex immunosuppressive TME, the response rate of immunotherapy is often low. Huang's group designed a self-assembled biomimetic nano-erythrocyte (nano-RBC) system conjugated with hemoglobin-poly (ε-caprolactone) (Hb-PCL) (V(Hb)) and used it to deliver the chemotherapeutic drug DOX and oxygen to reprogram TIME (Fig. 5A and B) [99]. The Hb component in V(Hb)@DOX can bind to endogenous plasma Hb and specifically target M2-type tumor-associated macrophages (TAMs) through the CD163 surface receptor, thereby effectively killing cells, achieving the most significant inhibition of tumor volume and tumor weight (Fig. 5C and D). Additionally, the O_2 released by Hb can alleviate tumor hypoxia and further enhance the antitumor immune response by recruiting fewer M2-type macrophages. The gross inspection as well as the histopathological evaluation of the lungs revealed a notable reduction in the number and size of metastatic tumor nodules following treatment with V(Hb)@DOX (Fig. 5E and F). Tumor recurrence was observed in just a single mouse out of a cohort of six, and the volume of the recurrent tumor was notably smaller (Fig. 5G).

Malaria-infected RBCs can utilize the parasite protein VAR2CSA to bind to a unique CS and achieve placenta-specific tropism. Many cancers also express similar CS, known as oncofetal CS (of CS). In light of this, the Fang's research group designed a novel drug delivery platform to effectively mimic infected RBCs and their specificity for of CS [100]. The authors functionalized recombinant VAR2CSA (rVAR2) onto RBCs membrane-coated drug carriers using a lipid-capture-tag conjugation system. These malaria-mimicking erythrocyte NPs (MMENPs) were able to effectively load docetaxel (DTX) and specifically target and kill melanoma cells *in vitro*. The researchers further demonstrated the significant tumor targeting and therapeutic efficacy of these MMENPs in a xenograft melanoma model, providing proof of concept for the use of malaria-biomimetic materials in targeted tumor drug delivery. Since of CS is widely present in various types of malignant tumors, these biomimetic NPs hold significant potential for targeted cancer therapy against a variety of tumor indications. Poorly regulated drug-releasing and limitation of drug-delivery capacity restrict the intracellular

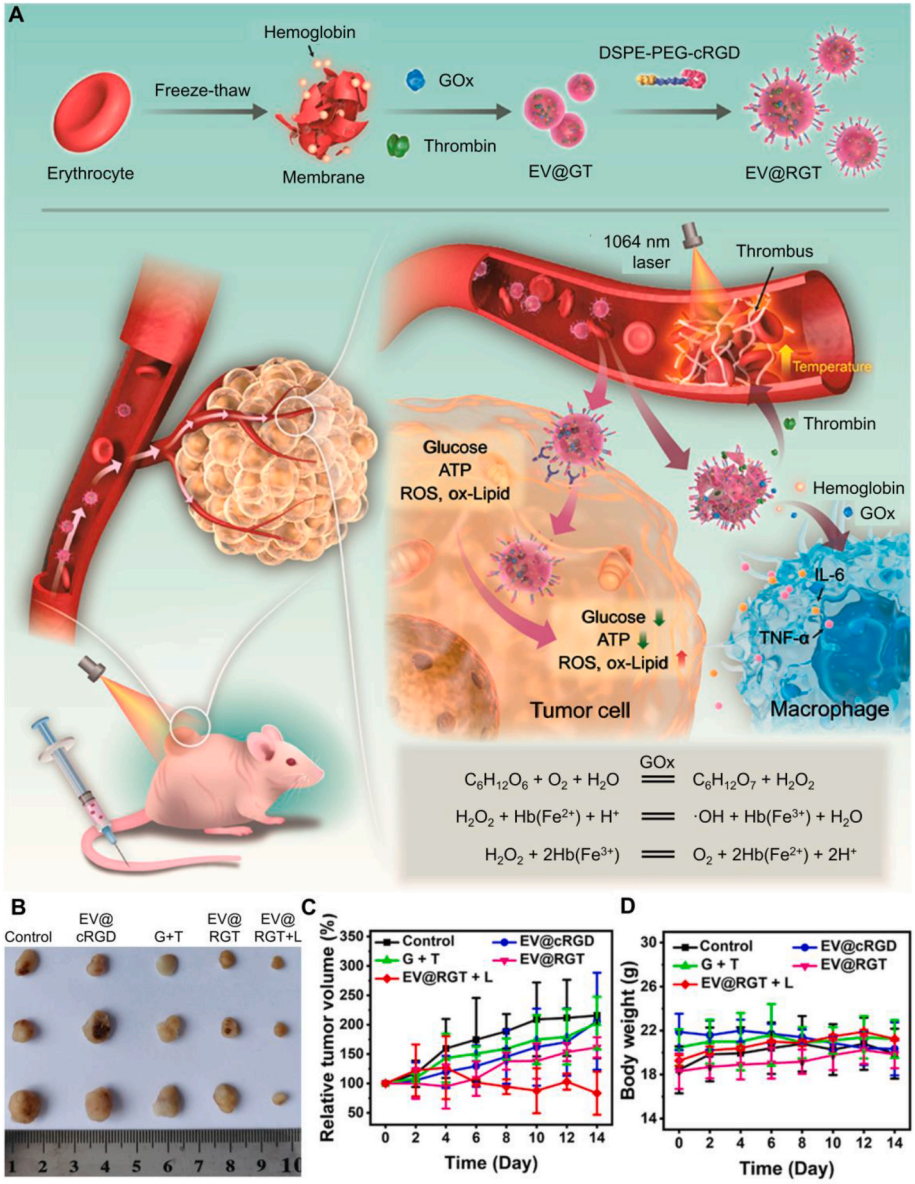

Fig. 6. (A). Representation of the synthesis process for EV@RGT and the mechanism of its anticancer action. (B). Images of excised tumors from euthanized mice captured on the 15th day post-treatment. (C). Growth trajectories of tumor volume in mice subjected to various treatments. (D). Body weight changes in mice subjected to various treatments [105]. Copyright © 2023, American Chemical Society.

medicine delivery of RBCs. Based on that, unique RBC membrane-camouflaged NPs (RCNPs) have been proposed for drug delivery, which unites the peculiarity of RBC membranes and therapeutical actions of synthetic NPs. RBC membrane as the coat for NPs provides lower immunoreaction and circulated durability [101,102]. It also protects against the leakage of agents from porous NPs [103].Intend to utilize the RCNPs targeting cancer sites to receive the effect of specific targeting and reduced dosage. Su et al. integrated tumor-homing peptide iRGD on RBC membrane to heighten RBC membrane-camouflaged NPs' (consisting of paclitaxel-loaded polymeric core and RBC membrane, RVPNs) tumor infiltration ability for treating metastatic breast cancer [104]. Meanwhile, RVPNs/iRGD exhibited a half-life longer than detected NPs in the bloodstream. It manifested over 90 % cancer growth suppression and 95 % inhibition of pulmonary metastasis.

4.1.2.4. RBCs-derived vesicle delivery systems. Starvation therapy is considered a promising strategy in cancer treatment for altering the TME and eliciting a series of therapeutic effects. Li's group utilized glucose oxidase (GOx) and thrombin combined with erythrocyte vesicles (EV) modified with cyclic (Arg-Gly-Asp) (cRGD) peptides, denoted as EV@RGT, to synthesize a precision tumor nutrition deprivation system and sequentially induce second near-infrared (NIR-II) photothermal therapy (PTT) and immune activation (Fig. 6A) [105]. This EV@RGT can specifically accumulate at the tumor site and release enzymes at the acidic TME. The combination of GOx and thrombin depletes tumor glucose while blocking nutrient supply, leading to severe energy deficiency and ROS enrichment within tumor cells. Subsequently, due to the presence of hemoglobin, the abundant clotted erythrocytes in tumor vessels exhibit significant local NIR-II PTT, aiding in the eradication of cancer. Moreover, the enriched ROS produced by enhanced starvation therapy repolarizes resident macrophages to an antitumor M1 phenotype through the DNA damage-induced STING/NF-κB pathway, ultimately contributing to tumor elimination (Fig. 6B–D).

4.2. Immune cells

4.2.1. Neutrophils

Neutrophils, the most prevalent type of white blood cell in the bloodstream, are classified into two functional subsets in the context of cancer: N1 and N2 neutrophils. N1 neutrophils possess anti-tumor effects, whereas N2 neutrophils contribute to tumor growth and immune suppression. Moreover, neutrophils, with their inherent capacity to respond to inflammation and traverse physical barriers, along with their byproducts such as membranes and EVs, are emerging as innovative vectors for the targeted delivery of therapeutic agents, enhancing the efficacy of anti-tumor treatments [106].

4.2.1.1. Living neutrophils-based delivery systems. Oncolytic bacteria are among the most promising tumor-targeting vectors. However, the challenge of finding a balance between their therapeutic efficacy and safety remains. The key metric for maintaining this balance is the improvement of bacterial tumor colonization. Liu *et al.* constructed a delivery system that allows for the controlled release of attenuated *Salmonella typhimurium* (VNP) after being loaded into neutrophils, significantly increasing the tumor-targeting ability of VNP and enhancing its therapeutic effect in a melanoma lung metastasis model [107]. Attenuated *Salmonella typhimurium* (VNP20009) is the only *Salmonella* strain assessed in clinical trials and is a potential bacterium for tumor therapy. In this work, the study confirmed that neutrophils are a key factor for VNP colonization. To improve the synergistic therapeutic effect, an engineered strain capable of secreting PD1 nanobodies (NE(PD1nb)) was used. NE(PD1nb) activates the differentiation of DC cells and stimulates M1-like differentiation of macrophages, and induces the maturation of $CD4^+$ T cells and the activation of cytotoxic $CD8^+$ T cells through DC tumor antigen presentation, thereby reshaping the TME to suppress tumor metastasis. Efficient delivery of anticancer drugs to the TME is crucial for successful cancer therapy. Consequently, drug carriers must be capable of navigating the tumor vasculature and possess a high drug payload. Wang's group has discovered that light-induced inflammatory responses could recruit neutrophils to the TME, and these neutrophils can transport NPs, enabling them to penetrate the tumor blood barrier [108]. The results indicate that this strategy achieves a tumor delivery efficiency of 5 % ID/g for NPs, which is independent of NP size (30–200 nm) and dose (10^8 to 10^{11} NPs). To effectively deliver anticancer drugs to tumors *via* neutrophils, the researchers prepared carrier-free paclitaxel nanocrystals (PTX NCs). Experimental findings showed that neutrophil uptake of PTX NCs does not diminish their tumor infiltration, and the sustained release of PTX in the tumor was regulated by paclitaxel-protein complexes, significantly prolonging the survival of two preclinical mouse models. This study demonstrated that neutrophil-mediated delivery of nanocrystal drugs was a promising approach for the effective treatment of various cancers and further elucidates the mechanism by which neutrophils release drugs within tumors. Immune checkpoint inhibitors (ICIs) have shown promise in treating triple-negative breast cancer, however, a little patients benefit from this therapy. Activation of the STING pathway, an innate immune stimulator, can enhance antitumor immunity and make tumors more sensitive to ICIs. However, the efficient delivery of STING agonists to tumors remains a significant challenge. To address this issue, Hao and collaborators have developed a tumor-penetrating neutrophil cytopharmaceutical (NEs@STING-Mal-NP) that utilizes liposomal STING agonists conjugated to the surface of neutrophils. Unlike traditional neutrophil cytopharmaceuticals, which load drugs inside the neutrophils, this approach leverages the inherent properties of neutrophils for enhanced tumor penetration and delivery [109]. The premise of using neutrophils to transport NPs is the construction of NP-neutrophil complexes, for which there are currently two distinctly different strategies. The first involves assembling NPs into neutrophils *in vitro*, while the second strategy uses NPs to hitchhike on neutrophils *in situ* (*i.e.*, during circulation). In practical applications, the former strategy is limited by the short lifespan of neutrophils (~7 h), premature degradation of cargo within cells, high costs, insufficient yield of harvested cells, and the risk of contamination *in vitro*, all of which reduce cell viability. The *in situ* hitchhiking strategy is more conducive to clinical practice, and it is essential to rationally design NPs that highly associate with neutrophils. In light of this, Wang's group has proposed a strategy using nano pathogens (NPNs) that mimic pathogens to hitchhike on circulating neutrophils [110]. The concept of mimicking pathogens originates from the way neutrophils combat invading pathogens (such as bacteria, fungi, and viruses) in nature. By encapsulating NPs with bacterial outer membrane vesicles (OMVs), the authors could create nanoscale mimics of pathogens with similar pathological activities. Since the synthetic NPNs were non-replicating, they may also pose fewer potential toxicity issues compared to live or attenuated bacteria. NPNs were recognized by pattern recognition receptors (PRRs) on neutrophils, which identified pathogen-associated molecular patterns (PAMPs) on the NPNs, thereby hitchhiking on circulating neutrophils and overcoming biological barriers to actively aggregate at tumor sites. Once NPNs entered the tumor tissue, they were released from neutrophils during the formation of neutrophil extracellular traps (NETs).

4.2.1.2. Engineered neutrophils. Engineered neutrophils drug-free systems have been proven to exert antitumor effects without the additional loading of drugs. Mitragotri's group investigated the potential of neutrophil-based cancer immunotherapy using cyto-adhesive micropatches (CAMPs) as a non-drug approach to activate tumor-associated neutrophils (TANs) and elicit antitumor responses [111]. CAMPs efficiently attach to neutrophils without internalization: CAMPs were designed to be large enough to adhere to neutrophil surfaces but small enough to avoid being engulfed. They were functionalized with

anti-CD11b Fab, a molecule that specifically binds to CD11b receptors on neutrophils, facilitating attachment. CAMPs activated neutrophils and promoted an antitumor phenotype: Upon attachment, CAMPs triggered neutrophil activation, leading to increased secretion of myeloperoxidase (MPO) and other pro-inflammatory cytokines. This activation also results in the upregulation of N1-related genes, including MHC-II, CD95, and CD54, indicating a shift towards an antitumor phenotype. CAMP-activated neutrophils enhance the antitumor immune response: *In vitro*, CAMP-activated neutrophils activated surrounding immune cells, including $CD8^+$ T cells, NK cells, DC cells, and macrophages, further potentiating the antitumor response. Systemic administration of CAMP-activated neutrophils reduced tumor burden and improved survival. In murine models of B16F10 and 4T1 breast cancer, intravenous injection of CAMP-activated neutrophils led to significant reductions in tumor growth and improved survival rates. The combination of CAMP-activated neutrophils with anti-CTLA4 or anti-PD1 checkpoint inhibitors further improved antitumor efficacy. The use of CAMPs to activate neutrophils offers a potential "off-the-shelf" approach to cancer immunotherapy, eliminating the need for complex genetic modification or patient-specific cell sourcing. Further research is needed to optimize the design of CAMPs and explore their potential in clinical settings.

4.2.1.3. Biomimetic neutrophils biomaterials. The short lifespan of neutrophils severely limits their application, but this challenge can be addressed by extracting and utilizing the neutrophil membrane. The precise recognition and eradication of cancer cells by immune cells that do not rely on antigen recognition holds great promise, yet their design and preparation remain challenging. Inspired by neutrophils. Qu's group designed and constructed a tumor-discriminating nanodevice based on the differential expression of histone H1 subtypes [112]. In this nanodevice, the camouflage of the neutrophil membrane and the unlocking effect of GSH on the iron porphyrin metal-organic framework structure ensure selectivity for cancer cells. The released porcine pancreatic elastase (PPE) mimics the action of neutrophils, inducing histone H1 release-dependent selective cancer cell killing. Meanwhile, the nuclear localization signal (NLS) peptide-labeled porphyrin (Porphyrin-NLS) acted as an *in situ* singlet oxygen generator, amplifying histone H1 nuclear-cytoplasmic translocation by inducing DNA double-strand breaks under laser irradiation, further promoting the clearance of cancer cells. Qin *et al.* developed a self-synergistic nanoplatform for targeted tumor therapy, overcoming the limitations of current pyroptosis-based immunogenic cell death (ICD) strategies [113]. This platform combines a neutrophil camouflaging shell and a polymer core loaded with indocyanine green (ICG) and β-lapachone to achieve tumor-specific and amplified ROS generation and induce potent antitumor immune responses. The outer shell of neutrophil membranes provided stealthy properties and enhanced tumor accumulation through active targeting and the enhanced permeability and retention (EPR) effect. Lap-mediated endogenous ROS production via upregulating NADPH expression, which catalyzed Lap to produce endogenous ROS. This amplifies the ICD effect by further stimulating Caspase-3 activation and GSDME-mediated pyroptosis. The release of damage-associated molecular patterns (DAMPs) during pyroptosis further promoted DC maturation and T-cell activation, thereby reshaping the TME and activating systemic antitumor immunity.

4.2.1.4. Neutrophil-derived vehicles delivery systems. Neutrophil-derived exosomes (N-Ex) have been used in antitumor therapy due to their innate targeting and penetrating capabilities. Zhang *et al.* explored the potential of N-Ex and exosome-like nanovesicles (NNVs) in targeted cancer therapy. N-Ex was found to effectively inhibit the proliferation and mediate apoptosis of different types of tumor cells [114]. This effect was attributed to the activation of the caspase signaling pathway and the presence of cytotoxic proteins like FasL, granzyme A, granzyme B, and perforin within the exosomes. However, this work had some limitations, N-Ex tended to accumulate in the liver and spleen after intravenous injection, limiting their therapeutic efficacy at the tumor site. Therefore, the authors further designed superparamagnetic iron oxide NPs-decorated N-Ex (SPION-Ex, allowing for rapid magnetic separation and improved tumor targeting under an external magnetic field. Finally, DOX-loaded SPION-Modified NNVs (SPION-NNV-DOX) achieved dual therapeutic effects: SPION-NNV-DOX demonstrated both drug and NNV-mediated antitumor effects, leading to significant tumor growth inhibition and prolonged survival in xenograft mouse models. The treatment of aggressive gliomas remains a significant hurdle due to their invasive growth patterns, resistance to chemotherapy, and the presence of the blood-brain barrier (BBB). To address these challenges, Wang's group has proposed a bioinspired approach N-Ex for the delivery of DOX to glioma cells [115]. N-Ex leveraged the natural inflammatory chemotaxis and BBB-crossing abilities of neutrophils. Studies using zebrafish and C6-Luc glioma-bearing mice models have demonstrated the ability of N-Ex to rapidly penetrate the BBB and target brain tumors. Furthermore, *in vitro* BBB models and mouse brain inflammation studies have confirmed the chemotactic response of N-Ex to inflammatory stimuli, allowing them to target infiltrating tumor cells within inflamed brain tumors.

4.2.2. Macrophages

Macrophages are pivotal in cancer progression and metastasis. Pro-inflammatory M1 macrophages can phagocytose tumor cells, whereas anti-inflammatory M2 macrophages, including TAMs, contribute to tumor growth. Research has demonstrated that modifying macrophages to modulate the tumor immune microenvironment can significantly enhance the effectiveness of cancer therapies [116].

4.2.2.1. Living macrophages-based delivery systems. Living macrophages possess good active tumor-targeting capabilities. Zhang's group loaded DOX-containing liposomes onto the surface of macrophages through biotin-avidin interactions [117]. Compared to traditional liposomes, the macrophage-liposome (MA-Lip) system can further increase the accumulation efficiency of DOX at the tumor site and penetrate deeper into the tumor tissue to enhance the antitumor immune response. Since the MA-Lip system is composed of materials with high biocompatibility, it also has a higher long-term safety profile. Zhu's group has developed an active tumor-targeting drug delivery system featuring NPs carrying DOX on the surface of macrophages (DOX@MPF127-MCP-1, DMPM) through interaction with the CCR2/MCP-1 axis [118]. Initially, the study carboxylated the amphiphilic block copolymer Pluronic F127 (PF127) to create MPF127, which was then modified with MCP-1 peptides to prepare MPF127-MCP-1 (MPM). During the self-assembly process of MPM, the researchers encapsulated DOX within MPM to construct approximately 100 nm DMPM nanomicelles. DMPM spontaneously bound to macrophages, forming an active targeting delivery system of macrophage-DMPM (MA-DMPM). The study found that DOX in MA-DMPM could be released in a pH-responsive manner in the acidic TME, increasing the accumulation of DOX in the TME and enhancing the efficacy of tumor treatment.

4.2.2.2. Engineered macrophage biomaterials. Activating the antitumor properties of TAMs while suppressing the anti-phagocytic signaling expression of tumor cells can enable macrophages to phagocytose and kill tumor cells, providing a novel approach to cancer treatment. Feng and colleagues have developed an editable palladium biorthogonal nanoplatform combined with the antitumor prodrug alloc-DOX to enhance the antitumor phagocytic function of TAMs [119]. The authors effectively linked metabolizable palladium clusters with CRISPR/Cas9 and modified the surface with targeting materials to achieve precise drug delivery to tumor cells. Upon reaching the tumor cells, the palladium cluster-induced Fenton-like catalytic reaction promotes the

accumulation of ROS, which are used for chemodynamic therapy and the M1 polarization of TAMs. Additionally, the palladium cluster-induced biorthogonal catalytic reaction activates the antitumor prodrug alloc-DOX for chemotherapy. Furthermore, CRISPR/Cas9 reprograms tumor cells to inhibit the expression of surface anti-phagocytic protein CD47 and adipocyte membrane-associated protein, significantly enhancing the phagocytic efficiency of macrophages and thereby suppressing tumor cell proliferation and metastasis. Hua's research group has integrated modified macrophages with engineered antitumor bacteria to develop a novel therapy based on a dual-engineered macrophage-microorganism system (Du-EMME) [120]. These engineered macrophages (R-GEM cells) express RGD peptides on their extracellular membrane, enhancing their binding to tumor cells and enriching efficiency within tumors. The study co-cultured R-GEM cells with the attenuated *Salmonella typhimurium* VNP20009 to construct a macrophage-microorganism system (R-GEM/VNP cells). The bacteria within the cells remained biologically active for over 24 h, and the bacteria released by R-GEM/VNP cells within the tumor continued to exert the bacterially mediated antitumor effects. The research found that the chemotactic and camouflaging abilities of macrophages could enhance the enrichment and biocompatibility of bacteria within tumors. R-GEM cells were able to load and secrete IFNγ-producing strains (VNP-IFNγ) to form R-GEM/VNP-IFNγ cells. Experimental results showed that therapies based on these cells effectively prevented the progression of metastatic tumors in the lungs in three mouse tumor models (breast cancer, melanoma, and colorectal cancer). The phagocytic action of TAMs can negatively remove apoptotic tumor cells through LC3-associated phagocytosis (LAP), reducing the efficiency of tumor antigen presentation and causing an immunosuppressive TME. Therefore, Shang and colleagues constructed TAM-targeted nanopores (PC-CW) by using the cell wall of rice sporidia to camouflage and encapsulate poly(styrenesulfonate) (PSS)-coated polyethyleneimine (PEI)-shRNA nanocomplexes [121]. PC-CW can block LAP and delay the degradation of tumor debris engulfed by TAMs, which not only enhances antigen presentation but also initiates a domino effect of antitumor immune responses through the STING signaling pathway and the repolarization of TAMs.

4.2.2.3. Biomimetic macrophage biomaterials. SDT is a non-invasive antitumor therapy technology, however, its clinical application is often limited due to factors such as low tumor accumulation of SDT drugs, the hypoxic microenvironment of tumors, and the cytoprotective effects of autophagy. Based on this, Wang's research group has developed surface-engineered Chlorella (Chl, a type of green algae) as a targeted drug carrier and sustainable oxygen supplier (*via* photosynthesis) to significantly improve SDT by alleviating hypoxia and inhibiting autophagy with chloroquine [122]. Macrophage membranes are coated on Chl to form macrophage-mimicking Chl (MChl), which increases its biocompatibility. At the same time, the targeting of tumor accumulation is enhanced by the inflammatory homing effect driven by the macrophage membrane. Moreover, the membrane coating on Chl allows for the insertion of lipids to produce β-cyclodextrin (β-CD) modified MChl (CD-MChl). Subsequently, a supramolecular conjugate of MChl-NP is constructed through the host-guest interaction between CD-MChl and adamantine (ADA) modified liposomes (ADA-NP). The anchored liposomes work in conjunction with CD-MChl to enter tumor tissue, co-delivering Chl, hematoporphyrin, and chloroquine (loaded in ADA-NP).

4.2.2.4. Macrophages-derived vehicles delivery systems. The durable response rate of immune checkpoint blockade therapy remains relatively low, primarily due to the limited presence of $CD8^+$ T cells in tumor tissues, which creates an immunosuppressive microenvironment. Therefore, Yang's group developed macrophage-derived engineered microvesicles (MPs) that overexpressed alpha-fetoprotein (AFP) and utilized them to load resiquimod (R848@M2pep-MPsAFP) for enhancing anti-PD-1 therapy in hepatocellular carcinoma (HCC). R848@M2pep-MPsAFP could target M2-like immunosuppressive TAMs and reprogram them into M1-like phenotypes. At the same time, the reprogrammed TAMs by R848@M2pep-MPsAFP acted as aAPCs, which not only presented the AFP antigen to trigger $CD8^+$ T cell-mediated anticancer effect but also provided intratumoral niches to maintain and differentiate stem cell-like $CD8^+$ T cells. The study found that the immunotherapy combined with anti-PD-1 antibodies could generate robust anti-tumor immune memory and induced plenty of stem cell-like $CD8^+$ T cells to proliferate and differentiate, thereby enabling long-term immune surveillance of orthotopic and autologous HCC preclinical models. The BBB and the hypoxic microenvironment often greatly limit the efficiency of SDT. Given this, Liu's group encapsulated catalase (CAT) into silicon dioxide NPs (CAT@SiO2) to alleviate tumor hypoxia and further loaded the sonosensitizer ICG to prepare a biodegradable nanoplatforms (CSI) [123]. Inspired by the ability of macrophages to cross the BBB, the experiment further utilized AS1411 aptamer-modified macrophage exosomes to encapsulate CSI, resulting in the preparation of CSI@Ex-A, and demonstrated its efficient BBB penetration capability and good tumor cell targeting performance. After being endocytosed by tumor cells, the highly expressed GSH triggers the biodegradation of the nanoplatforms, thereby releasing CAT to catalyze the production of O_2 from H_2O_2, alleviating tumor hypoxia.

4.2.3. T cells

4.2.3.1. Engineered T cells. Adoptively transferred T cells and drugs aimed at blocking the CD47-SIRPα axis are promising cancer therapies that can activate different branches of the immune system. However, the use of anti-CD47 antibodies in combination with adoptively transferred T cells has not shown significant therapeutic benefits due to the rapid clearance of CAR T cells mediated by macrophages. Mackall's group has reported an engineered CD47-expressing CAR T cell therapy [124]. This CD47 variant, CD47(Q31P)(47E), bound to SIRPα and delivered a "do not eat me" signal that was not blocked by anti-CD47 antibodies. TCR or CAR T cells expressing 47E were resistant to macrophage clearance after treatment with anti-CD47 antibodies and mediated substantial and sustained recruitment of macrophages to the TME. Macrophages have been identified as a major regulator of T cell persistence and highlight the fundamental challenge of combining T cell-directed therapies with macrophage activation therapies. Engineered CD47 provided a treatment approach that could simultaneously harness the antitumor effects of both T cells and macrophages, enhancing the cytotoxicity against solid tumors. Although B6H12 is a research-grade antibody, the CD47 variants generated in this study also resist binding to the clinical-grade antibody TJC4 (lemzoparlimab), suggesting that 47E could pair adoptive therapies with clinical-grade anti-CD47 antibodies. The dense extracellular matrix of tumors results in poor infiltration of CAR T cells, and the suppressive TME can also cause the dysfunction and exhaustion of CAR T cells. Gu's research group has proposed a strategy for preparing active biomaterials using lyophilized muscle tissue [125]. The researchers preserved the key components and porous matrix structure within the lymph nodes using freeze-drying technology, thus loading and delivering CAR T cells that can specifically recognize and clear tumors. After lyophilization, the lymph nodes acquire a loose and porous structure capable of accommodating T cells. Meanwhile, the lyophilized lymph nodes, having had the moisture removed, exhibit enhanced water absorption. The CAR T cell suspension can be easily absorbed into the interior of the lymph nodes. The drug-loaded lyophilized lymph nodes can be implanted back into the cavity left by the tumor after surgical resection, serving as a reservoir for CAR T cells that continuously release the drug to clear locally residual microtumors and inhibit postoperative recurrence. The antitumor effects, the number of activated CAR T cells within the tumor, and the production of cytotoxic factors after treatment

with lyophilized lymph node-loaded CAR T cells are significantly better than those of the same dose of CAR T cells loaded onto artificially synthesized hyaluronic acid gel carriers. The lymph node material, derived from the patient's own body, unlike the artificially synthesized hyaluronic acid gel, does not induce a strong inflammatory response when implanted back into the body. The efficacy of oncolytic viruses is first hampered by the insufficient uptake of the virus by tumor cells and its ability to upregulate the expression of immune checkpoints in various cancer cells and immune cells. Hence, Chen *et al.* harnessed oncolytic adenoviruses (OAs) shielded by engineered biomembranes that display T cell-specific antigens and made them physically anchored to the T cell surface by recognizing TCRs or CARs [126]. This anchoring strategy does not impair T cell function, and once the carrier T cells reach the tumor cells and recognize their homologous tumor-specific antigens, the OAs can be easily released. The OAs are internalized by cancer cells and promote specific viral infections. After infection, the OA constructs encoding the Cas9 editor can disrupt the PDL1 gene in tumor cells and infiltrating immune cells, downregulate their PD-L1 expression levels, alleviate the immunosuppressive TME, and facilitate T cell therapy and tumor lysis. However, targeting this system to solid tumors with lacks or no antigens is challenging.

In conclusion, engineered T cells, such as CD47-expressing CAR-T cells, enhance antitumor effects by resisting macrophage clearance and recruiting macrophages to the tumor microenvironment. In contrast, T cell programming using lyophilized lymph nodes as a biomaterial reservoir improves CAR T cell infiltration and persistence, outperforming synthetic carriers. Oncolytic viruses, when anchored to T cells, can disrupt tumor cell immunity but face challenges in targeting antigen-poor solid tumors.

4.2.3.2. Biomimetic T-cells biomaterials. Glioblastoma stem cells (GSCs) are a subset of tumor-initiating cells responsible for glioblastoma (GBM) occurrence and recurrence. Due to the distinct pathological characteristics of vascular endothelial cells and GSCs, achieving dual inhibition of both remains a significant challenge. Tang's group has designed a combined holistic strategy to realize localized photothermal therapy (PTT) [127]. By coating gene-engineered T cell membranes (CM) on aggregation-induced emission (AIE) NPs, they designed NPs with AIE properties that can mimic T cells (CM@AIE NPs). The designed CM shell is capable of targeting CD133 and epidermal growth factor receptor (EGFR), which also provides the possibility of targeting GBM cells and GSCs for cancer treatment. Additionally, CM@AIE NPs can also act as tight junction (TJ) modulators, triggering intracellular signaling cascades that lead to TJ disassembly and actin cytoskeleton reorganization, allowing CM@AIE NPs to "silently" cross the BBB.

4.2.3.3. T cells-derived vehicles delivery systems. Although T cell therapy represents a significant breakthrough in the field of cancer immunotherapy, its efficacy in the treatment of solid tumors is often limited. The main reason for T cell exhaustion in solid tumors is the immunosuppressive mechanisms of the tumor, primarily mediated by programmed death ligand 1 (PD-L1) and transforming growth factor-β (TGF-β). Kim's group has constructed T cell-derived nanovesicles (TCNVs), which are produced by the continuous extrusion of cytotoxic T cells through membranes with micro/nanopores [128]. These TCNVs can inhibit T cell exhaustion and maintain antitumor activity in the immunosuppressive TME. The surface of TCNVs is programmed with cell death protein 1 and TGF-β receptors, which can block PD-L1 on cancer cells and clear TGF-β in the immunosuppressive TME, thereby preventing the exhaustion of cytotoxic T cells. Additionally, TCNVs can directly kill cancer cells through granzyme B. Paclitaxel (PTX)-based chemotherapy remains a primary method for treating cancer, but its use is limited by systemic toxicity. Due to the presence of tumor-targeting CARs and cytotoxic granules (granzyme B and perforin) in CAR T cell-derived exosomes, they are considered potential delivery vehicles for PTX. However, the low drug-loading capacity of exosomes and their hepatotropic nature pose barriers to their application in extrahepatic cancers. Recently, Huang's group designed and prepared Lip-CExo@PTX by fusing exosomes derived from bispecific CAR T cells targeting mesothelin (MSLN) and programmed death-ligand 1 (PD-L1) with lung-targeting liposomes to achieve immunochemotherapy for cancer (Fig. 7A) [129]. Lip-CExo@PTX significantly inhibits the growth of metastatic lung cancer (Fig. 7B and C). After 55 days of treatment, it maintains an 80 % survival rate in mice (Fig. 7D), with a notable upward trend in body weight (Fig. 7E). This effect can be attributed to the enhanced targeting of lung cancer cells by Lip-CExo, as well as its superior ability to stimulate T-cell anti-tumor responses.

4.2.4. NK cells

4.2.4.1. Living NK cell-based delivery systems. NK cells are a type of cell that can be used for adoptive tumor immunotherapy, but their therapeutic efficacy in solid tumors is still not ideal. Given this, Sang's group developed a hybrid module consisting of injectable hydrogels and hydroxyapatite (HAp) nanoribbons, which was used for the controlled delivery of NK cells to enhance the treatment of solid tumors (Fig. 8A) [130]. The surface-functionalized HAp nanoribbons were modified with agonistic antibodies against NKG2D and 4-1BB, as well as cytokines IL-2 and IL-21, to support survival and dynamic activation. Therefore, the HAp-modified chitosan thermosensitive hydrogel not only improved the retention time of NK cells in the body (more than 20 d) but also enhanced the functionality of NK cells by more than twofold. The unique structure of the biomaterial complex can protect NK cells from the adverse effects of the tumor environment and improve anti-tumor efficacy. This study demonstrates that using a biocompatible hydrogel reservoir to generate a transient inflammatory niche for NK cells can provide a new approach to preventing the recurrence of resectable tumors.

4.2.4.2. Engineered NK cells. NK cell immunotherapy has received extensive attention in recent years. Nevertheless, this way still faces challenges like decreased functionality, insufficient infiltration, and immunosuppression in the microenvironment when applied in practice [131,132]. Therefore, many researchers are attempting to address these challenges by tailoring NK cells with biomaterials. For instance, Qu's group constructed NK cells armed with a photoreponsive porphyrin iron array (NK@p-Fe), which can regulate cellular behavior through bioorthogonal catalysis [133]. The authors engineered a catalytic array with photocollecting capability by installing cholesterol-modified porphyrin iron molecules on the surface of NK cells. This functionality transforms NK cells into cellular factories, capable of photocatalytically producing active agents. The study found that NK@p-Fe can generate the active anti-tumor drug DOX through biorthogonal reactions, thereby enhancing the cytotoxic functions of NK cells. NK@p-Fe can also bioorthogonally catalyze the production of the FDA-approved immunostimulant imiquimod (IMQ). Kim and colleagues have utilized pluripotent transcription factors and optimized reprogramming culture media to directly reprogram human somatic cells into NK cells with $CD56^{bright}$ and $CD16^{bright}$ phenotypes [134]. Direct reprogramming of either NK cells with cancer-specific CARs or NK cells bound to antibodies results in selective and enhanced anti-cancer effects. The direct reprogramming of human somatic cells into NK cells facilitates the production of both autologous and allogeneic NK cells, which will aid in the combination of cancer immunotherapy with other treatments. Zhang's group designed a strategy to anchor exogenous proteins onto the membrane of live cells using DNA templates, enabling the programmable functionalization of live cells (Fig. 8B and C) [135]. Under the condition of using DNA as a scaffold, model cell membranes can be easily modified by proteins. Through predictable DNA hybridization, researchers precisely control the density and ratio of proteins and their interactions. The authors

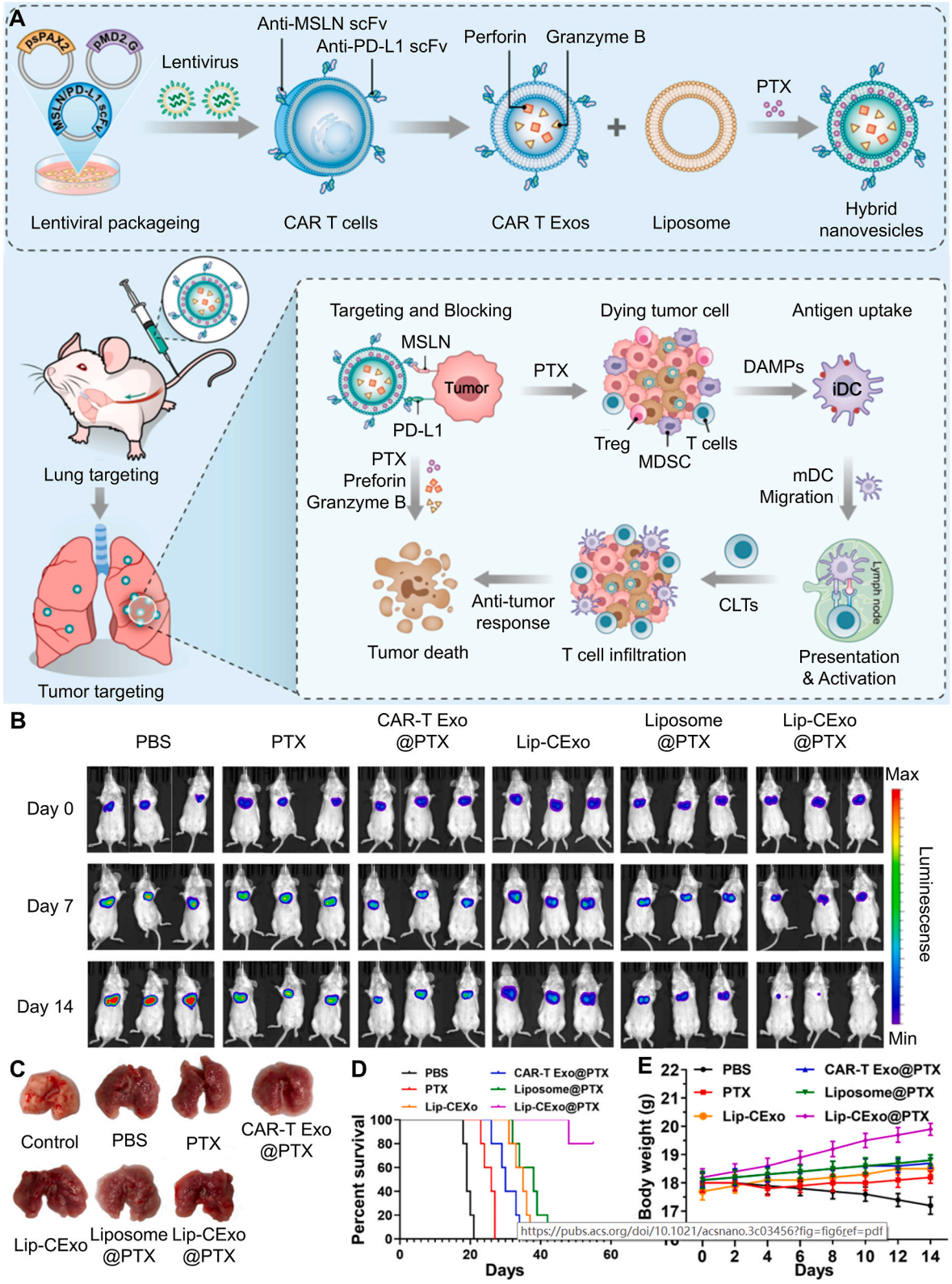

Fig. 7. (A). Representation of the hybrid nanovesicles comprising bispecific CAR T cell-derived exosomes and liposomes for the treatment of lung cancer. (B). Bioluminescence and tumor growth on days 0, 7, and 14 of treatment. (C). Representative lung images from tumor-bearing mice across different treatment groups. (D). Survival curves and (E). body weight changes of tumor-bearing mice in various treatment groups [129]. Copyright © 2023, American Chemical Society.

modified NK cells to eliminate immune checkpoint signals at the NK-tumor synapse, significantly enhancing the activation efficiency of NK cells in the process of immunotherapy.

4.2.4.3. Biomimetic NK cell biomaterials. NK cells are not only capable of recognizing and eliminating abnormal cells but also recruiting and re-educating immune cells to protect the host. However, the function of NK cells is often restricted in the immunosuppressive TME. Based on

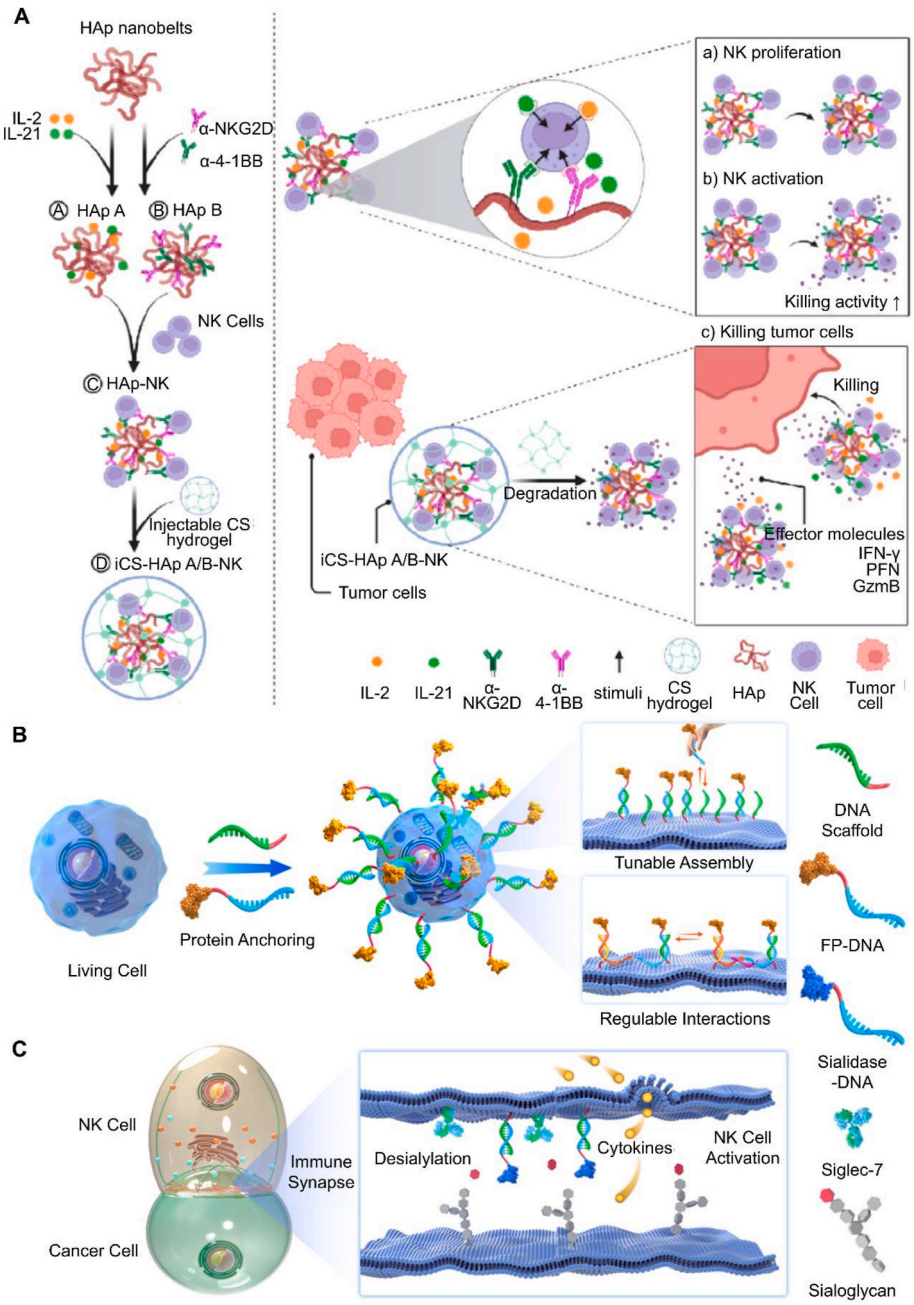

Fig. 8. (A). Illustration of the Injectable iCS-HAp A/B-NK Complex Schema [130]. Copyright © 2024, American Chemical Society (B). DNA frameworks are engineered on cellular surfaces to enable precise and controlled attachment of proteins. (C). The NK cells modified with sialidase effectively overcome the inhibitory effects of sialic acids at the tumor-NK cell interface, thereby amplifying the immune response [117]. Copyright © 2023, American Chemical Society.

this, Zhang's group designed an artificial NK cell (aNK) that is less restricted by the TME and can re-educate macrophages to inhibit tumor growth [136]. The authors used RBC membranes (RBCM) to encapsulate perfluorohexane (PFC) and GOX to construct aNK. aNK can directly kill tumor cells by consuming glucose and generating H_2O_2. Moreover, the generated H_2O_2 also serves as a cytokine and chemokine to recruit immune cells and re-educate surviving macrophages to attack tumor cells. Additionally, the oxygen-carrying PFC can enhance the catalytic reaction of GOX and improve the hypoxic TME.

4.2.5. *DC cells*

4.2.5.1. Living DC cell delivery systems. DC vaccines are a safe and effective method for tumor immunotherapy. However, the low activity of DCs and their limited migration to lymphoid organs restrict their clinical application. In response to this, Xu's group designed a novel 3D-printed DC vaccine that can effectively prolong the survival of DCs in the body, promote their continuous migration to lymph nodes, and significantly enhance the antitumor effects of DC vaccines [137]. The 3D-printed DC vaccine consists of bone marrow-derived DCs (BMDCs), gene-edited tumor cell membrane vesicles with high expression of PD1 (PD1-CVs), and methacrylated hydrogel (GelMA). GelMA provides a living environment for DCs, and encapsulating DCs in a porous scaffold printed with GelMA further improves their survival. PD1-CVs act as immunomodulators for DCs, stimulating their maturation while blocking PD-L1 on their surface, thereby enhancing the antitumor effects of DCs. The personalized 3D-printed DC vaccine is used to fill the tumor defect after surgery, improving the survival rate of postoperative mice.

4.2.5.2. Biomimetic DC cell biomaterials. Currently, a variety of bioactive materials have been developed for the ex *vivo* expansion of T cells and adoptive T cell immunotherapy, and they are also referred to as artificial aAPCs. However, almost all reported design strategies use biomolecules that activate T cells to modify relatively smooth surfaces, which do not well simulate the dendritic morphological features of DCs, a type of natural antigen-presenting cell (APC) with a high specific surface area. In light of this, Liu's group designed a hydrophilic monomer-mediated surface morphology control strategy to synthesize biocompatible dendritic poly(N-isopropylacrylamide) microspheres, which were used to construct aAPCs that mimic the surface morphology of natural APCs such as DCs [138]. The study found that, while maintaining the same ligand density, aAPCs based on dendritic polymer microspheres (DPM beads) were able to expand $CD8^+$ T cells more effectively than smooth-surfaced aAPCs. The adoptive transfer of antigen-specific $CD8^+$ T cells expanded by DPM beads showed significant antitumor effects in B16-OVA tumor-bearing mice. DC vaccines are a method that can induce potent antigen-specific immune responses to eliminate tumor cells. However, this strategy still faces many challenges, such as loading of tumor-associated antigens (TAAs), lymph node homing, quality control, and other restrictive factors. In light of this, the Wang group developed a personalized DC-like nanovaccine (nanoDCs) for stimulating TAAs-specific T cell populations [139]. They utilized nanoparticles with dendritic structures and membranes derived from mature bone marrow-derived cells (BMDCs) to prepare the nanoDCs. Mature BMDCs can be stimulated by nanostructures assembled from *E. coli* and tumor cells to effectively deliver TAAs and induce BMDC maturation through the STING pathway. By maintaining co-stimulatory markers, class I molecule (MHC-I) antigen complexes, and lymphocyte homing receptors, the nanoDCs can effectively migrate to lymph nodes and generate a robust antigen-specific T cell response.

The stimulation and proliferation of T cells are key steps in generating an immune response, and these steps also depend on the effective presentation of tumor antigens and co-stimulatory molecules by DCs. The Tang group developed a biomimetic AIE photosensitizer, DC@AIEdot, by coating DC cell membranes on the surface of nanoclusters of aggregation-induced emission molecules (AIEgens) [140]. Studies have shown that the AIE molecules within DC@AIEdot can selectively aggregate in the lipid droplets of tumor cells, while the external cell membrane can promote the "hitchhiking" of DC@AIEdots onto endogenous T cells, increasing their tumor delivery efficiency by approximately 1.6-fold. Additionally, DC@AIEdots are also capable of stimulating the proliferation and activation of T cells *in vivo*, thereby triggering an immune response. The Wang group developed poly (lactic-co-glycolic acid) (PLGA) nanocomposite coated by activated and matured DCs membranes (aDCM) and loaded with rapamycin (RAPA), named aDCM@PLGA/RAPA, which can precisely traverse the blood-brain barrier (BBB) and improve the immune microenvironment [141]. *In vitro* cell uptake and results in a blood-brain barrier model showed that aDCM@PLGA/RAPA can effectively enhance homotypic targeting and crossing of the BBB. The immune responses generated by aDCM@PLGA/RAPA both *in vitro* and *in vivo* can stimulate immature DCs to a mature state, thereby further activating immune cells like tumor-infiltrating T cells and NK cells and inducing subsequent immune responses through both direct and indirect means. The study found that aDCM@PLGA/RAPA treatment not only significantly inhibits the growth of orthotopic gliomas but also has good potential to induce glioma differentiation.

4.2.5.3. DC cells-derived vehicle delivery systems. DC cell-derived EVs (DEVs) are considered an effective alternative to DC vaccines. However, current clinical trials of DEV-based immunotherapy often have limited efficacy. In response to this, Wang's group developed a strategy using DCs as cellular reactors that can efficiently excrete aggregates of DEV-like aggregation-induced emission (AIE) NPs (DEV-AIE NPs) for synergistic photodynamic immunotherapy [142]. The extracellularly secreted DEV-AIE NPs not only inherit the immunomodulatory proteins of the parental DCs, which can activate T cells but also load the AIE photosensitizer MBPN-TCyP, which can induce immunogenic cell death (ICD) by selectively accumulating in the mitochondria of tumor cells. Studies have shown that DEV-AIE-based synergistic photodynamic immunotherapy can trigger a significant immune response and effectively eradicate primary tumors, inhibit distant tumors, and prevent tumor metastasis. Li and colleagues constructed a non-cell-based tumor vaccine strategy using DC-derived exosomes, providing a new reference for the clinical development of personalized precision tumor vaccines [143]. Researchers selected highly specific and strongly immunogenic antigen targets from patient tumor samples. The DC-derived exosome system was evaluated in melanoma and colon cancer mouse models, and it was found to have a good storage effect at the injection site and lymph node targeting ability; activating multiple immune responses, it significantly inhibited the growth of various tumors and prolonged the survival of mice. In addition, the system effectively eliminated lung metastasis, forming a long-term preventive tumor immune memory protection, thus delaying tumor onset. Further mechanism studies found that it promotes the release of various tumor immune factors, activates more anti-tumor T cell immune infiltration to play a role in clearing tumors, and at the same time activates B cells to secrete plenty of antigen-specific antibodies, achieving a synergistic effect of humoral and cellular immunity.

4.3. Tumor cells

4.3.1. Engineered tumor cells

Tumor cells' targeting capabilities allow them to precisely identify and gather at the lesion site. Due to the inadequate distribution of chemotherapeutic drugs in the bone marrow and their potential tissue toxicity, Gu et al. utilized the migratory capacity of AML cells to the spinal cord for AML therapy [144]. These non-proliferating and non-pathogenic liquid nitrogen-treated AML (LNT) cells successfully carried the chemotherapeutic drug DOX across the blood-brain barrier to eliminate leukemia in the spinal cord. LNT cells with the body's immune response stimulating work synergistically with DOX to combat leukemia. This indicates that a combination of LNT cells and adjuvants may be used for preimmunization to shield the body from malignant cell invasion. Drugs' poor retention in the metastatic lung tissue, alterations in an inflammatory microenvironment, and the heightened expression of adhesive molecules present significant challenges in treating triple-negative breast cancer (TNBC). Li *et al.* advanced the technique of loading TNBC cells with programmed death protein 1 inhibitor (PD-1) and DOX for a combined chemo-immunotherapy approach targeting lung metastasis (Fig. 9A) [145]. These modified TNBC cells preserved their antigen-presenting capacity, while the release of PD-1 and DOX significantly enhanced drug retention in metastatic sites, which manifested as a significant inhibition of metastatic foci (Fig. 9B and C). Additionally, the microenvironment underwent reconstruction through the action of DAMPs and PD-1 blockade, which collectively contributed to prolonged survival in mice.

4.3.2. Biomimetic tumor cell biomaterials

The combination of PDT with tumor immunotherapy is expected to awaken the host immune system, thereby eliminating residual tumor cells. The Tu group designed a tumor cell membrane-coated NPs and utilized it to combine PDT, TLR7 agonist, and tumor antigens to enhance the therapeutic effect on tumors [146]. The biomimetic NPs (CCMV/LTNPs) prepared by the authors can specifically kill tumor cells through photodynamic therapy and induce a strong antitumor immune response in the host with the help of immunoadjuvants and tumor antigens on the tumor cell membrane, to clear residual tumor cells [147]. Similarly, the Liu group designed a hybrid cell membrane camouflage strategy, which involves preparing therapeutic nanocomposites

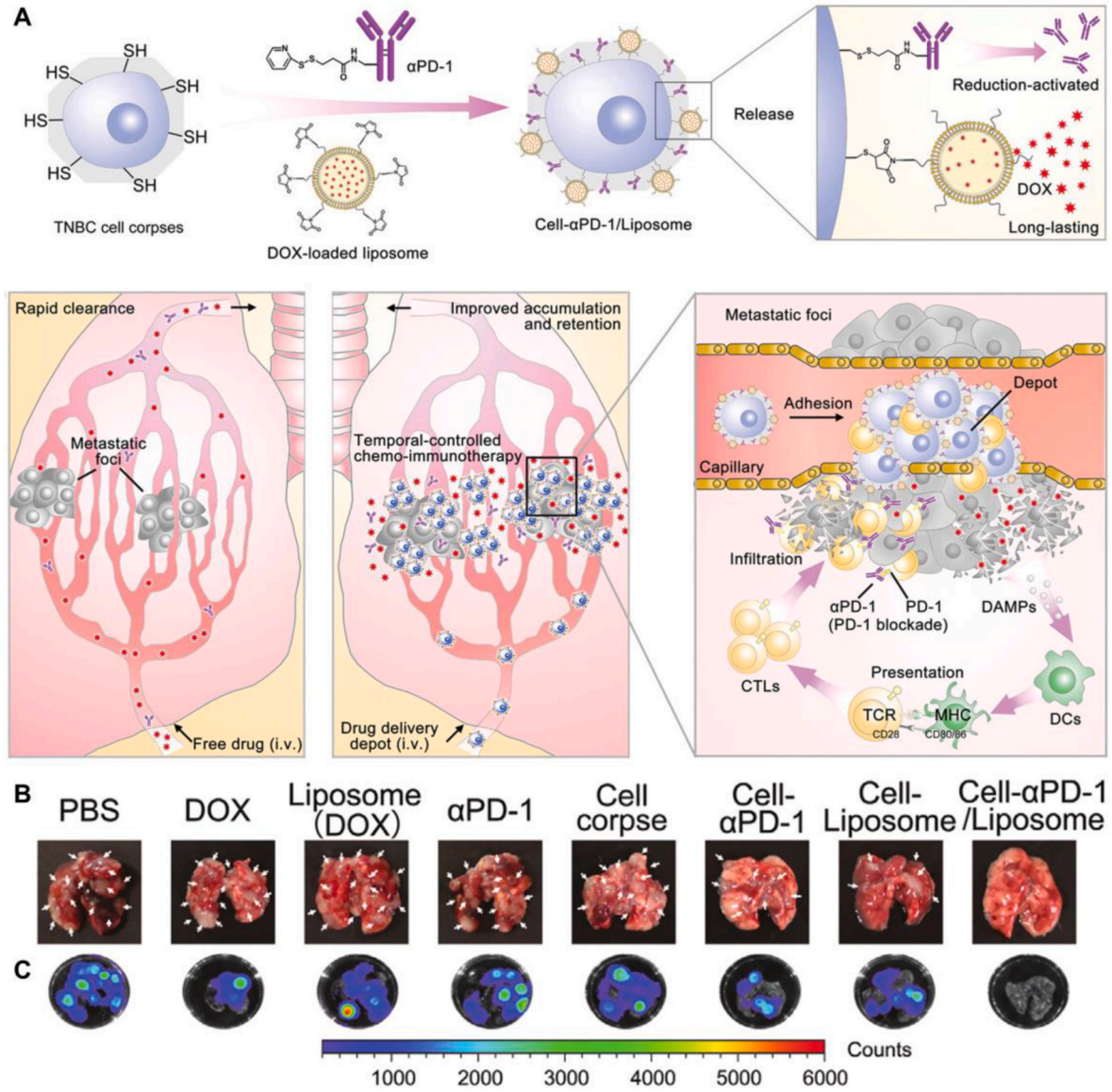

Fig. 9. (A). Diagram showing TNBC cells loaded with PD-1 and DOX for a combined chemo-immunotherapy approach targeting lung metastasis. (B). Illustrative images of lungs from each group, with metastatic lesions indicated by white arrows. (C). Typical bioluminescent scans show metastatic lung lesions across the groups [145]. © 2022 Wiley-VCH GmbH.

composed of brain metastatic breast cancer cell membranes and glioma cell membranes through a simple membrane fusion method [148]. The experiment constructed a biomimetic therapeutic formulation (HMGINPs) by coating HM on drug-loaded NPs, which can simultaneously inherit the BBB penetrating ability of both cell types and the capability to target homologous glioma. Nanovaccines based on cell membranes have received continuous academic attention due to their inherent multi-antigen nature and the ability to be formulated with adjuvants. The Fang group reported cell nanodiscs made from cancer cell membranes, which were combined with lipid-based adjuvants to achieve antitumor vaccination [149]. The cell nanodiscs are small and disc-shaped, easily absorbed by aAPCs, and effectively drain to the lymph nodes. Due to their highly immunostimulatory properties, the nanodisc vaccines effectively stimulate the immune system and promote tumor-specific immunity.

5. Conclusions and future outlooks

Despite advancements in medical science, cancer treatments remain limited, with metastasis and recurrence posing significant risks. Synthetic biomaterials show promise but face biocompatibility and biodegradability issues. Cell-inspired biomaterials offer a solution with inherent advantages and diverse functionalities, including drug-loading capacity for combined therapies. The development of cell-inspired antitumor biomaterials represents a transformative approach in the fight against cancer. The potential for personalized medicine through the application of cells in the construction of these biomaterials is an exciting avenue for future exploration. Advances in materials science, cell engineering, and nanotechnology will continue to drive innovation in this field, promising more effective and less toxic cancer treatments. This review aims to provide a novel paradigm and a foundational framework for the ongoing evolution of cell-inspired antitumor biomaterials, ultimately contributing to the development of more precise and effective cancer therapies. Looking forward to the future, new aspects of biomaterial synthesis and delivery systems, the complex interactions between cell-inspired biomaterials and tumor cells, potential technologies for tailoring cells, screening new targets, and clinical transformation are opportunities in the future (Fig. 10). For biomaterial

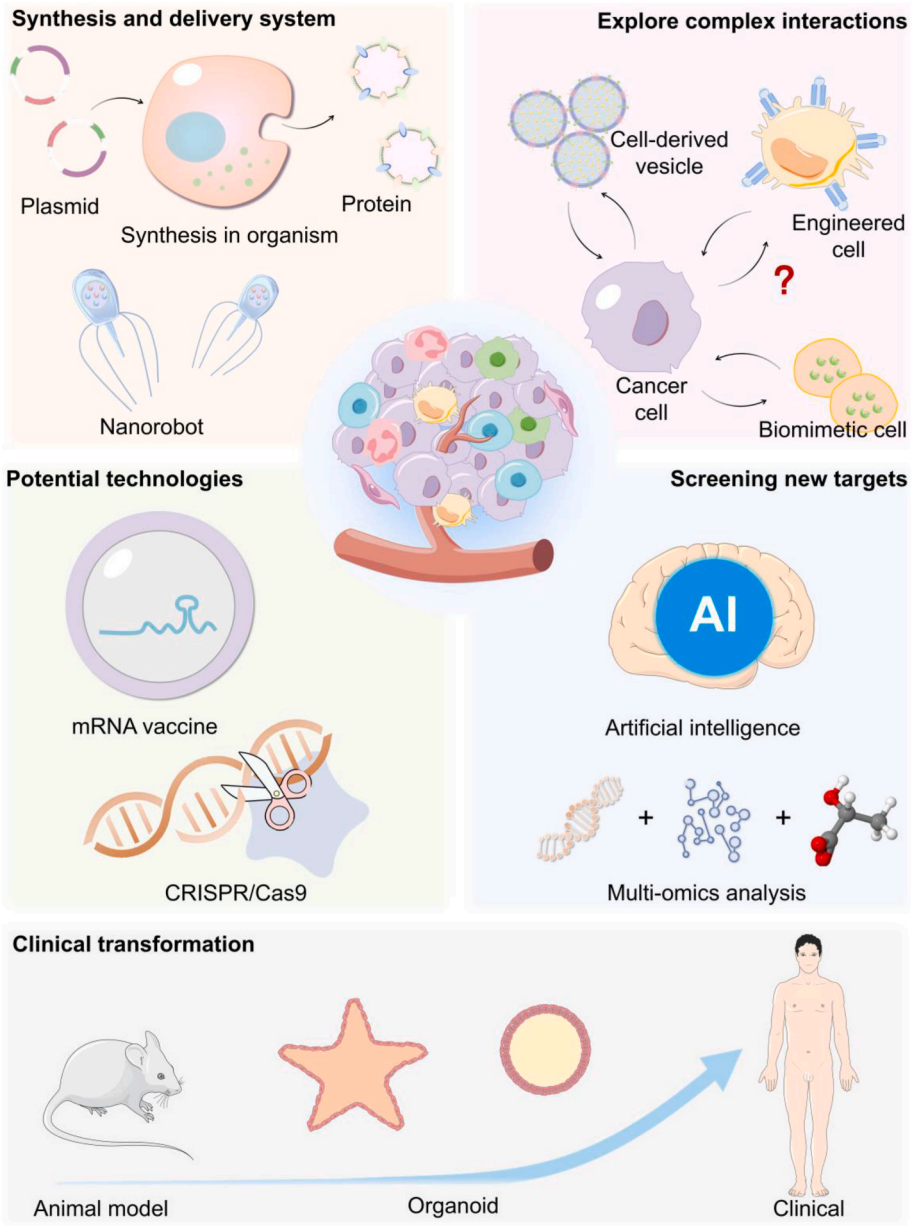

Fig. 10. Perspectives of cell-inspired biomaterials for cancer therapy. Presently, cell-inspired biomaterials for cancer therapy have made obvious progress. Looking to the future, it's recommended to 1) explore new aspects of biomaterial synthesis and delivery systems; 2) understand the complex interactions between cell-inspired biomaterials and tumor cells; 3) develop potential technologies to tailor cells for antitumor therapy; 4) screen new targets; 5) facilitate clinical transformation.

synthesis and delivery systems, nanorobots have promise potential for targeting tumor cells precisely [150,151]. Specifically, the advantages of nano-robots include precise targeting, deep penetration, sustained release, and multifunctionality. Consequently, they have been utilized for targeted delivery of chemotherapy drugs, photodynamic therapy drugs, etc., to improve tumor treatment efficacy and reduce side effects. The emerging technology of synthesis in organisms enables the synthesis of biomaterials within cells by mimicking and harnessing the natural cellular processes [152]. The advantages of *in vivo* biosynthesis of biomaterials include: 1) Excellent biocompatibility: These materials are either derived from the cells themselves or share similarities with cellular components, ensuring their compatibility with the biological environment; 2) Controllable: The synthesis rate, structure, and functionality of biomaterials can be precisely controlled by regulating cellular metabolic pathways and synthetic mechanisms; 3) Multifunctionality: The synthesis of biomaterials can be integrated with other cellular functions, enabling multifunctionalities, such as imaging, diagnostics, and therapy; 4) Environmental adaptability: Cells can adjust the synthesis of biomaterials in response to environmental changes, allowing them to adapt to various conditions. It reduces the reliance on delivery systems and may potentially address the challenges associated with the large-scale production of biomaterials. The intricate interactions between tumor cells and other cells are yet to be fully explored, necessitating a deeper investigation into cell-inspired biomaterials and the mechanisms of tumor cell crosstalk [153]. For tailoring cells *via* potential technologies, mRNA vaccines are capable of swiftly generating substantial quantities of proteins within cells, making them a viable option for treating cancers linked to protein abnormalities [154,155]. The application of mRNA vaccines in constructing biomaterials for cancer therapy encompasses several methods: 1) Fabrication of targeted NPs: By utilizing mRNA vaccine technology, mRNA sequences encoding target-specific proteins or peptides are designed; 2) Development of immunotherapeutic biomaterials: mRNA vaccine technology is harnessed to design mRNA sequences encoding tumor antigens

or immunomodulatory factors; 3) Construction of imaging biomaterials: mRNA vaccine technology is utilized to design mRNA sequences encoding fluorescent proteins or magnetic resonance imaging probes. These biomaterials can be employed for imaging diagnostics of tumors. The advent of CRISPR/Cas9 gene editing technology has furnished a potent instrument for altering cell structures and components [156,157]. The advantages of using CRISPR/Cas9 to construct anti-tumor biomaterials include: 1) Precision: CRISPR/Cas9 can accurately edit specific genes in cells, enabling precise modification of biomaterials; 2) Flexibility: Different gRNAs can be designed as needed to edit various genes, constructing anti-tumor biomaterials with diverse functions; 3) Efficiency: CRISPR/Cas9 can efficiently edit genes in cells, enhancing the construction efficiency of biomaterials. However, it is important to note that CRISPR/Cas9 may cut off-target genes, leading to cellular dysfunction. For screening new targets, the integration of multi-omics analysis and artificial intelligence (AI) can identify novel and efficient therapeutic targets [158,159]. Multi-omics sequencing provides comprehensive biological information encompassing genomics, transcriptomics, proteomics, and metabolomics, while AI excels in efficiently analyzing and pattern recognition of these massive datasets. By integrating multi-omics data, AI can identify key genes, signaling pathways, and metabolic routes associated with tumor development, enabling precise screening of potential anti-tumor targets. For clinical transformation, one significant bottleneck in the translation of biomaterials is the discrepancy between current animal models and human biology. While large mammals offer a relatively accurate representation of human tissues, conducting experiments on these animals is both costly and subject to stringent ethical considerations. Advancements in organoid engineering hold the potential to address this issue [160–162]. Furthermore, the complex and costly experimental procedures involving cells have significantly hindered the development and application in this field. The emergence of new technologies such as microbial cell factories, modular production systems, closed production systems, and functional hydrolysates has provided new support for reducing the production costs of cell-derived biomaterials, simplifying experimental procedures, and promoting clinical translation [163]. Successful clinical translation requires a collaborative effort involving scientists, entrepreneurs, governments, patients, and healthcare professionals [164,165]. The advent of numerous groundbreaking technologies presents possibilities for overcoming challenges in this domain.

CRediT authorship contribution statement

Qi-Hui Wang: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Shi Cheng:** Writing – review & editing, Writing – original draft, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation. **Chun-Yu Han:** Validation, Software, Project administration, Methodology. **Shuang Yang:** Methodology, Investigation, Data curation, Conceptualization. **Sheng-Rui Gao:** Resources, Investigation, Formal analysis. **Wan-Zhong Yin:** Software, Investigation. **Wen-Zhi Song:** Writing – review & editing, Writing – original draft, Supervision, Resources, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Wenzhi Song reports financial support was provided by International Cooperation Project of the Jilin Department of Science and Technology. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

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

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