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Smart Delivery Vehicles for Cancer: Categories, Unique Roles and Therapeutic Strategies

Yiyu Zeng[a1], Yijun Gao[a1], Liming He[b], Wenhui Ge[a], Xinying Wang[a], Tao Ma[a], Xiaoyan Xie[a*]

[a] Department of Stomatology, The Second Xiangya Hospital, Central South University, Changsha, 410011, P. R. China.

[b] Department of Stomatology, Changsha Stomatological Hospital, Changsha, 410004, P. R. China.

[1]These authors contributed to the work equally.

* Corresponding author

Xiaoyan Xie: **xyxie@csu.edu.cn**

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Abstract

Chemotherapy and surgery remain the primary treatment modalities for cancers; however, these techniques have drawbacks, such as cancer recurrence and toxic side effects, necessitating more efficient cancer treatment strategies. Recent advancements in research and medical technology have provided novel insights and expanded our understanding of cancer development; consequently, scholars have investigated several delivery vehicles for cancer therapy to improve the efficiency of cancer treatment and patient outcomes. Herein, we summarize several types of smart therapeutic carriers and elaborate on the mechanism underlying drug delivery. We reveal the advantages of smart therapeutic carriers for cancer treatment, focus on their effectiveness in cancer immunotherapy, and discuss the application of smart cancer therapy vehicles in combination with other emerging therapeutic strategies for cancer treatment. Finally, we summarize the bottlenecks encountered in the development of smart cancer therapeutic vehicles and suggest directions for future research. This review will promote progress in smart cancer therapy and facilitate related research.

Keywords: Therapy delivery vehicles, cancers, immunotherapy, targeted delivery

1. Introduction

Cancer is the leading cause of mortality worldwide [1]. The World Health Organization estimated that the number of cancer-related deaths will increase by 2030 [2]. Therefore, effective treatment of cancers remains urgently needed.

Surgery, radiotherapy, and chemotherapy are the first-line treatment options for most cancers [3]. Conventional chemotherapy, a fundamental approach to cancer treatment, distributes drugs through the bloodstream to various organs, where it interferes with DNA synthesis and mitosis in rapidly proliferating cells and causes cell-cycle arrest [4, 5]. However, chemotherapy is associated with multidrug

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resistance (MDR), nonspecific drug distribution, and systemic toxicities [6]. Chemotherapeutic drugs are non-selective; their cytotoxic effects can damage healthy tissue cells, leading to adverse toxic effects, such as cardiotoxicity in the case of adriamycin [7] or hepatotoxicity in the case of camptothecin [8]. In addition, conventional chemotherapeutic drugs are less bioaccessible to cancer tissues; therefore, high dosages are required, which in turn produces toxicity in normal cells and increases the likelihood of multi-drug resistance [9]. The efficacy of cancer therapy is influenced by drug tolerance, effective drug delivery, and duration of drug action, among others, which considerably restrict its application [10]. Consequently, conventional cancer treatments are associated with disadvantages, such as difficulty in achieving treatment, cancer recurrence, and side effects [11]. Despite considerable advances in cancer treatment, cancer-related morbidity and mortality rates continue to increase [12]. According to statistics, the age-standardized cancer incidence rate is 201.7/100,000 in China, 319.2/100,000 in the United Kingdom, and 352.2/100,000 in the United States. At the same time, the cancer mortality rate is 130.1 per 100,000 in China, 102.6 per 100,000 in the United Kingdom, and 91.0 per 100,000 in the United States [13]. Therefore, highly effective and less toxic strategies that can differentiate between cancer and normal cells, selectively target cancer tissue, and respond "intelligently" to the complex microenvironment of the cancer are warranted.

Precise cancer therapeutic strategies have been developed to improve clinical outcomes. Nanotechnology has great potential to improve the clinical outcomes for various diseases, including cancer [14-16].

Among them, the development and application of various smart cancer drug delivery vehicles, including polymers [17], liposomes [18], inorganic carriers [19], and polymeric hydrogels [20], have greatly compensated for the limitations in conventional cancer treatments. For example, smart cancer drug delivery vehicles can increase the targeting of tumors through functionalized modifications, thereby enabling drug accumulation in tumors [21], improving the stability of therapeutic drugs *in vivo*, and reducing drug resistance [22]. In addition, while improving therapeutic efficacy, smart cancer drug delivery vehicles can accurately monitor

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tumor-related biomarkers, which is conducive to the early diagnosis of tumors [23]. More importantly, novel therapeutic strategies, such as photothermal therapy, photodynamic therapy (PDT), gene therapy, and hormone therapy, are minimally invasive, if at all, and have demonstrated good potential for cancer treatment and prevention in preclinical studies [24, 25]. However, photosensitizers are susceptible to self-extinction during delivery and generate reactive oxygen species (ROS) with a small diffusion radius, thereby hampering the anti-tumor effect of PDT. The application of smart cancer delivery vehicles can overcome these limitations [26], and, when combined with different treatment methods, enhance the ability to kill cancer cells through synergistic effects [27, 28]. Currently, several nanoparticle-based chemotherapeutic agents have been clinically approved [29, 30], and novel chemotherapeutic drugs are at different stages of preclinical development. Therefore, the development of smart cancer delivery systems with better targeting capabilities, longer blood circulation times, and the possibility of combination therapy is important.

In this review, we discuss various smart delivery vehicles currently used in cancer therapy and their advantages, focusing on their facilitating role in cancer immunotherapy and the current challenges in their application (Fig. 1). Our findings will help to facilitate future clinical translation and propose new directions for further advancements in anti-cancer therapy.

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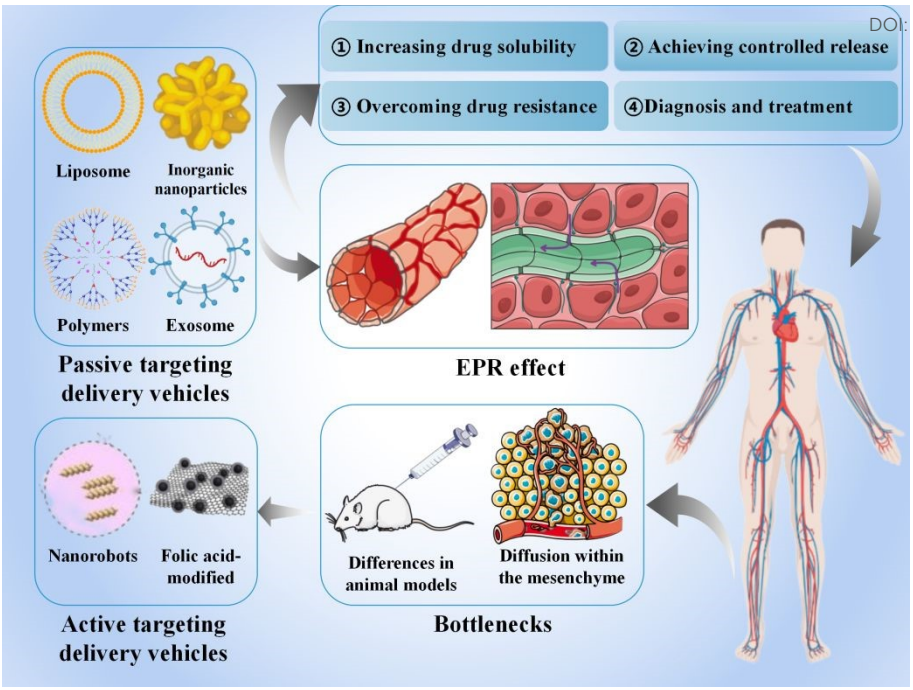

Fig. 1. Schematic diagram of the application of smart delivery vehicles in cancer treatment.

2. Status of research on smart delivery vehicles

Traditional administration methods involve non-specific biological distribution and arbitrary drug release. To improve treatment efficiency and reduce related side effects, drugs should be released in a controlled manner at specific sites of action. In this review, smart delivery vehicles are defined as a type of tool that can deliver drugs to the target site and control drug release to "intelligently" exert their effects, thereby improving treatment efficiency and reducing drug toxicity.

2.1 Passive targeting-based delivery vehicles

Passive targeting-based therapeutic vehicles loaded with therapeutic agents are widely used in various cancer treatments (Table 1).

Table 1. Summary of commonly used passive smart therapy vehicles in cancer

Type of delivery vehicles	Loaded drugs	Cancer	Mechanisms	References
Liposomes	Doxorubicin	Colorectal	Peptide connectors	[31]

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	(DOX)	cancer	respond to upregulated MMP-2 in the cancer microenvironment and enhance the capture of liposomes	
	Oxaliplatin and antisense lncRNA of MDC1	Cervical cancer	Thermosensitive release of OXA with enhanced inhibition of cervical cancer cells by co-delivery	[32]
	Anti-STAT3 siRNA	Melanoma	Enhances cell internalization and cytotoxicity, induces apoptosis, and significantly inhibits the *STAT10* gene	[33]
	Oxaliplatin and paclitaxel	Ovarian cancer	Better specific targeting ability, anti-tumor proliferative effects and prolonged drug half-life	[34]
	Irinotecan (IRI) and doxorubicin	Breast cancer	Improves drug loading and stability and promotes drug synergism through co-loading	[35]
	DOX		Increases affinity for the cell membrane, thereby facilitating drug release and entry to the	[36]

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			nucleus of the tumor cell and avoid lysosomal capture	
Polymeric nanoparticles	Doxorubicin, 5-Fluorouracil, and Methotrexate	Triple-negative breast cancer (TNBC)	Ruthenium in the dendrimer structure has anti-cancer effects and can form stable nanocomposites with drugs	[37]
	-	Chronic lymphocytic leukemia	Inhibits the proliferation of leukemia cells and promotes cell apoptosis	[38]
	Contrast agents (CAs)	Murine glioblastoma	Crosses the blood–brain barrier (BBB), enhances tumor contrast and significantly reduces toxicity	[39]
	Gemcitabine (Gem)	Pancreatic cancer	Stable formulation with pH-responsive drug release, effective accumulation at the tumor site and rapid cellular uptake	[40]
Inorganic nanoparticles	Cancer-penetrating peptide (TPP)	TNBC	Induces apoptosis by increasing ROS	[41]
	Gemcitabine	Liver and pancreatic	Improves targeting and increases synergy	[42]

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		cancer		
	TK-p53-NTR and microRNA	Lung Cancer	Improves gene transfection rates	[43]
	Methotrexate (MTX)	A-375 cancer cell line	Controls drug release and increase selectivity for tumor cells	[44]
	-	Cervical cancer	Cytotoxicity to tumor cells in a dose-dependent manner and induction of apoptosis	[45]
Polymeric micelles	TPL-NSA	Gastric cancer	Reduces the expression of collagen, FAP, and α-smooth muscle actin in cancers	[46]
	Paclitaxel (PTX), etoposide (ETP), and rapamycin (RAPA)		The pH-sensitive property was utilized to effectively control drug release in tumor cells and improve the water solubility of the drug	[47]
	Taxotere (DTX)	Hepatocellular carcinoma	Overcomes solubility and anti-proliferative activity and inhibits ascites production	[48]
	Anti-KRAS antibodies (KRAS-Ab)	Pancreatic and colorectal cancers	Block the overactivation of the KRAS-related cascade and recover the	[49]

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			influence of its mutation	
	Containing camphor sulfonamide (DK164)	Breast and lung cancer	Higher stability and cellular uptake for improved anti-cancer properties while maintaining drug activity	[50]
	2,6-bis((3-methoxy-4-hydroxyphenyl) methylene) cyclohexanone	Colon cancer	Higher selective cytotoxicity against tumor cells, arresting cell growth at the G2/M phase and inducing apoptosis earlier	[51]
Exosomes	Paclitaxel	MDR cancer	High loading efficiency and sustained drug release, resulting in more than 50-fold increase in cytotoxicity	[52]
	HChrR6-encoding mRNA	HER2 human breast cancer	Confines HChrR6 generation and CNOB activation to the cancer	[53]
	lncRNA MEG3	Osteosarcoma (OS)	Improves anti-cancer properties	[54]
	Rifampicin (RIF)		Accelerates entry of rifampicin into OS cells stalls the cell cycle in the G2/M phase and	[55]

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			leads to mitochondrial cleavage and apoptosis	
	$CaCO_3$NPs and Cur	Colon cancer	$CaCO_3$NPs with homologous targeting ability improves drug accumulation, and releases Ca^{2+} to disrupt mitochondria and induce oxidative stress	[56]
	Triptolide (TP)	Melanoma	Antiproliferative, anti-invasive, and pro-apoptotic; prolongs half-life of TP	[57]
	Hyaluronan (HA)	Human prostate cancer cell line PC3	Reduces number of associated immunosuppressive immune cells and hyaluronidase-induced tumor cell metastasis	[58]
	IL-12	B16F10 and MC38 cell line	Prolongs IL-12 retention and long-lasting immune memory	[59]

2.1.1 Liposomes

Smart delivery systems based on liposomes have advanced cancer therapy [60]. Owing to their biodegradable nature, they can be loaded with biomolecules with different properties, such as RNA, peptides, and proteins, without altering their original features. Thus, liposomes have become the most widely used carriers in

cancer therapy and the first therapeutic nanoparticles approved for clinical treatment [61].

Liposomes are spherical lipid vesicles composed of phospholipids with a bilayered structure [62]. Since their discovery in 1965, they have become versatile therapeutic carriers owing to their superior biocompatibility and biodegradability, as well as their unique ability to encapsulate hydrophobic drugs. In addition, liposomes offer controlled drug release, low toxicity, and good biocompatibility and can avoid drug leakage [63]. However, liposomes exhibit high uptake mainly by the liver and spleen [64]; therefore, different surface modifications have been applied to increase the circulation time of liposomes and improve the efficiency of chemotherapeutic drugs [65].

Xie et al. used polyethylene glycol-modified liposome surfaces, followed by binding to estrone (ES-SSL), to deliver chemotherapeutic drugs to ovarian cancer with high expression of estrogen receptors. The authors reported a prolonged drug half-life, slowed clearance, and 85.24% cancer inhibition [34]. Irinotecan (IRI) and DOX are often combined in cancer treatments; Liu et al. constructed a novel liposome carrier for the co-delivery of IRI and DOX using the triethyl octasulfate sucrose gradient loading method. The co-delivery of liposomes maintains the optimal proportion of drug action and increases the distribution of the two drugs in cancer tissues. In addition, co-loaded liposomes exhibited a stronger anti-cancer effect on 4T-1 breast cancer xenotransplantation than a mixture of single-loaded liposomes [35].

Stealth magnetic liposomes containing calcium-substituted magnesium ferrite NPs have been used as nanocarriers for curcumin delivery, which showed superparamagnetic properties, targeted cancer sites, and offered combined effects, such as magnetic heat and drug release [66]. The release of liposome-loaded drugs can be triggered by external factors, such as heat, light, and magnetic fields. Lipid bilayer-loaded protoporphyrin IX (PpIX), a hydrophobic photosensitizer, promotes the nuclear delivery of DOX and has a greater affinity for cytoplasmic membranes than liposome carriers. Such a feature encourages its separation from liposomes upon encountering cancer cells, thereby triggering the effective release of DOX and facilitating its entry to the nucleus of breast cancer cells and avoiding lysosomal

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degradation (Fig. 2A) [36]. Based on the well-established use of liposomes in cancer therapy, Chen et al. developed a novel liposome drug delivery system that mimics viruses and used a self-assembled liposome bilayer structure to mimic the viral envelope and a loaded drug to mimic the viral genome. The structure and concentration of the adsorbed polymers were adjusted to control drug release from liposomes. Owing to their ability to bypass the efflux mechanism, enhance the uptake of target cells, and provide effective internal body escape, treatment vehicle systems have demonstrated efficacy against various drug-resistant cancer cells such as HeLa cervical cancer, A549 lung cancer, MES-SA uterine cancer, and MES-SA/DX5 multidrug-resistant cancer cells (Fig. 2B) [67]. Stereochemistry can affect the biological properties of liposomes. Designing liposomes by stereospecific ionization of lipids can increase the efficiency of their mediated mRNA delivery. A novel C12-200 (stereospecific derivative)-S LNP was designed to deliver mRNA 3.8 times more efficiently than its racemate [68].

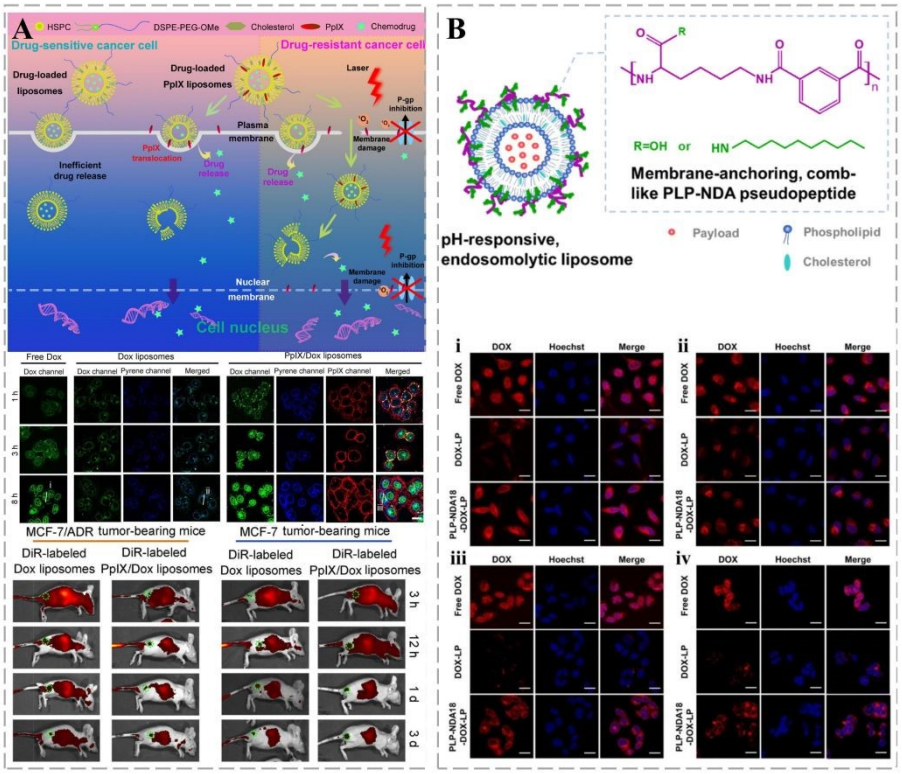

Fig. 2. Liposomes in cancer therapy. A. Schematic illustration of the plasma membrane-activatable drug release and plasma membrane-based PDT for MDR reversal. PpIX/DOX liposomes appear rapidly in cancer-bearing mice and last for more than three days. B. Schematic diagram of pH-responsive endolysis liposomes. The intensity of red fluorescence in HeLa cells (i), A549 cells (ii), MES-SA cells (iii),

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and MES-SA/DX5 cells (iv) was significantly reduced after internalization of DOX-loaded naked liposomes by endocytosis.

2.1.2 Polymeric nanoparticles

Polymeric nanoparticles (PNPs) are polymeric particles with a size range of 1–1,000 nm [69] and different structures, such as nanocapsules, nanospheres, micelles, and dendritic polymers [70]. Most materials used in PNPs have good biocompatibility and are approved by the United States Food and Drug Administration (FDA) [71]. Various small molecules, such as RNA and proteins, modify the surface of PNPs to confer different functions. In addition to targeting the delivery of loaded drugs, PNPs prevent phagocytosis by the phagocytic system and adverse reactions at other sites [72].

In addition, PNP-based drug-delivery systems can control the release rate of drugs by altering stimulus-responsive systems, such as pH and magnetic thermal environments, to prolong the duration of action in target regions (Fig. 3A) [73]. Based on the plasticity of PNP surfaces and structures, the development of PNPs with various functions for drug loading and their application in cancer-targeted therapies has been investigated.

Dendritic polymers are hyperbranched polymers with well-defined structures comprising cores, branches, gaps, and terminal groups [74]. Dendritic polymers have better physicochemical behavior than straight or branched polymers, allowing for a wide range of applications, including as adjuvants for vaccine antigens [75] or as modified contrast agents (CAs) [76]. The unique properties of dendritic macromolecules, such as uniform size and size distribution, spherical design, high branching, and functional surfaces, make them effective carriers for drug delivery [77, 78].

Magnetic resonance imaging (MRI) can be used for the early diagnosis of cancers and is particularly important for brain cancers. Paramagnetic gadolinium-based CAs are the most widely used for MRI acquisition in the brain; however, they are associated with potentially fatal nephrogenic systemic fibrosis [79]. Organic free radicals fixed to the surfaces of dendritic macromolecules have paramagnetic properties, thereby reducing the accumulation of toxic metals, and can

serve as CA for T1CA imaging. Zhang et al. investigated a third-generation water-soluble family of poly(phosphorhydrazone) radical dendrimers and developed G3-Tyr-PROXYL-ONa radical dendrimers, offering a viable alternative to metal-based MRI CA (Fig. 3B). In a mouse glioblastoma model, carriers loaded with less than four times the administered clinical dose showed appropriate contrast enhancement and selective accumulation in the brain cancer tissue, remaining within cancer tissue and allowing image acquisition over a longer period [39].

Self-assembled small amphiphilic dendrimers exhibit lipid self-assembly abilities combined with the specific structure and stability of dendrimers, allowing for high drug-loading capacity while maintaining a small size and stable formulation (Fig. 3C) [80]. The efficacy of gemcitabine (Gem) is mainly limited by its unstable metabolism and poor cellular uptake; therefore, higher doses of Gem are administered to improve efficacy, leading to severe systemic toxicity [81]. Zhao et al. first synthesized an aliphatic Gem prodrug and encapsulated it into a small amphiphilic dendritic polymer that could self-assemble into nano-micelles in water. Nano-formulations provide significant advantages, such as excellent stability to protect the loaded drug from early release, maintenance of their small size for effective accumulation at the cancer site, and effective pH-responsive drug release to increase the drug concentration at cancer sites. Dendrimer carriers have shown more potent anti-cancer activity in vitro and *in vivo* and considerably fewer adverse effects than free Gem (Fig. 3D) [40].

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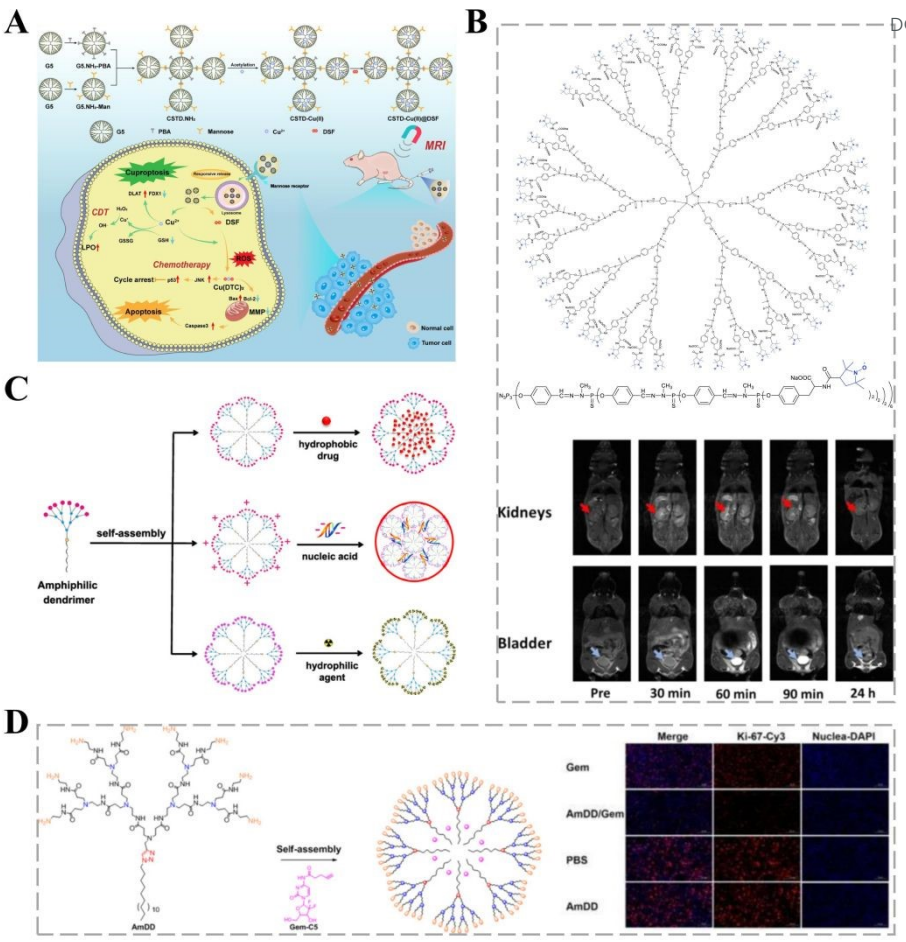

Fig. 3. Dendritic polymers for cancer therapy. A. A novel pH-responsive formulation consisting of PCAD-DMSN@DOX in which polycarboxylic acid dextran (PCAD) is electrostatically attached to the DMSN@DOX surface. Covalent coupling of CD133-RNA aptamers to the PCAD-DMSN nanoparticle surface results in specific translocation of the encapsulated anti-cancer drugs to CD133-overexpressing cancer cells. B. Structure of the G3-Tyr-PROXYL-ONa radical dendrimer. C. Self-assembly of small amphiphilic dendrimers into supramolecular dendrimers mimicking covalent construction of dendrimers. D. Self-assembling amphiphilic dendritic polymers for drug encapsulation. Immunohistochemical analysis using Ki-67, a tumor cell proliferation marker, showed that Ki-67 expression in tumor cells of AmDD/Gem-treated PC tumor-bearing mice was lower than that in the Gem group.

2.1.3 Inorganic nanoparticles

Inorganic nanoparticles (INPs), synthesized from inorganic particles and biodegradable polycations, including metals, metal oxides, carbon materials, and

mesoporous silica nanoparticles, have various sizes and shapes and a range of physical properties induced by the quantum nature of their core materials. INP-based drug delivery systems have the advantages of wide surface area coupling chemistry and multifunctional surface functionalization, which provide new strategies for designing novel therapeutic and imaging agents [82].

Since entering clinical trials, metal NPs have been widely used as probes for observing cell components under electron microscopes to detect markers [83] and as carriers for drug delivery [84]. Metal-organic framework nanoparticles (MOF-NPs) are crystalline hybrid microporous or mesoporous nanomaterials with significant potential in biomedicine owing to their drug loading and controlled release properties. Porous capsules are prepared from MIL-100 carboxylate iron nanoparticles via low-temperature spray drying, allowing for MTX encapsulation in the pores of MOF-NPs during pod formation at a high loading. Collagenase (COL) was packaged in a specific mesoporous cavity in a pot to enhance cancer treatment. Compared with naked MOF-NPs, this binding offers enhanced controlled release of the active components, MTX and COL, under simulated body fluid conditions. In addition, the selective toxicity of loaded MIL-100 capsules to A-375 cancer cells was nine times higher than that of normal HaCaT cells, indicating that the capsules could be used for the selective treatment of cancer cells [44]. Zinc ligand polymers are novel drug delivery vehicles that can protonate the ligand bonds of zinc-based organic ligand polymers in the slightly acidic cancer environment to achieve targeted drug release, exhibiting great potential for application in cancer treatment [85]. Green-synthesized ZnO nanoparticles exhibit significant cytotoxicity against SiHa cancer cell lines and improve the efficiency of treatment for cervical cancer [45].

Mesoporous silica nanoparticles (MSNPs) are commonly used inorganic non-metallic nanoparticles with superior biosafety to metal nanoparticles, higher drug loading, and faster dissolution rate [86].

Gallbladder cancer (GBC) manifests via non-specific symptoms early in the course of the disease and is often diagnosed at advanced stages. GBC is chemo-resistant, leading to poor clinical outcomes. An electrochemical probe

constructed on SiO2 nanoparticles with ENPP1 and EpCAM as dual targets has been shown to specifically detect circulating cancer cells (CTCs) in GBC and enable a more rapid and sensitive diagnosis of GBC and determination of chemoresistance than traditional invasive tissue biopsy [87]. mRNA is an unstable large molecule with very low *in vitro* effectiveness [88]. Dong et al. varied the size, porosity, surface topography, length, and width of MSNPs to optimize their effectiveness in delivering mRNA. The vehicle could achieve effective cellular uptake and intracellular escape in animal models, remain stable and active for a long time, and achieve tissue-specific mRNA expression [89].

2.1.4 Polymer micelles

Micelles are nanoscale systems of spherical or globular colloids formed by the self-assembly of amphiphilic block copolymers in aqueous solutions [90] with a hydrophobic core and a hydrophilic shell. Hydrophobic cores are used to store hydrophobic drugs, whereas hydrophilic shells enhance the solubility of the polymers and hydrophobic drugs in water [91]. Drugs bind to polymer micelles through chemical, physical, or electrostatic interactions. Polymeric micelle nanoparticles (PM-NPs) have been used as paclitaxel (PTX) nanocarrier platforms, showing good clinical performance [92]. Genenaxel PM (PEG-poly(D,L-propanediol)-paclitaxel) is the first PM preparation of PTX; it does not contain cremophor and exhibits good therapeutic efficacy and safety in advanced refractory malignant cancers [93]. pH-sensitive PMs maintain a stable state in normal tissues; however, upon reaching the cancer site, they become unstable and release the encapsulated drug in response to the low pH in cancer tissue [94]. Thus, pH-sensitive PMs can exploit the pH difference between the cancer and normal tissues to trigger drug release. Methoxypolyethylene glycol-b-poly (ε-caprolactone; mPEG-b-PCL) consists of a hydrophilic PEG shell and a hydrophobic PCL core, with the shell connected to the core via citraconic anhydride [95].

pH-sensitive mPEG-pH-PCL copolymer micelles exhibit high stability and sustained release as carriers loaded with PTX, etoposide (ETP), and rapamycin (RAPA), exploiting the low pH of the cancer microenvironment to disrupt

citraconamide bonds for rapid drug release [47]. By embedding hydrophobic bioactive substances in PEG, Schröder developed a novel micellar form, 113-b-P(CyCL3-co-CL46)-B-PEO113, based on triblock copolymer micelles of ferrocene-containing camphorsulfonamide DK164. The drug-loaded micelles are stable in aqueous media and have high encapsulation efficiency and sustained-release properties [50]. Sripetthong prepared nanomicelles loaded with curcumin analogs for colon cancer chemotherapy. CL-NBSCh showed considerable selective cytotoxicity against human colon cancer mucosal epithelial cells (HT-29). In addition, CL-NBSCh micelles more effectively induced cell growth arrest at the G2/M phase and induced apoptosis earlier in HT-29 cells than free CL [51].

2.1.5 Exosomes

Exosomes (Exos), extracellular vesicles (EVs) secreted by mesenchymal stem cells (MSCs), are produced by the vesicle outgrowth of endosomes that mature into multivesicular bodies or by vesicle outgrowth directly from the plasma membrane [96]. Exos are 30–150 nm in diameter, secreted by almost all cells [97], and retain the cancer-regulating properties of MSCs [98]. Exos can transport biomolecules, such as proteins, lipids, and RNA, to target cells through various physiological barriers, including the blood–brain barrier (BBB) [99], thereby increasing the local concentration of therapeutic agents [100]. Owing to their lipid bilayers, Exos remain stable in the blood and have low immunogenicity and good biocompatibility and, hence, are used in several *in vivo* anti-cancer drug delivery strategies [101]. Compared with cell therapy, Exos have revolutionized therapy in various diseases and enhanced drug safety [102-104].

The use of Exos as a therapeutic vehicle for drug delivery is being actively explored. In animal models, Exos carry anti-cancer drugs into the brain via receptor-mediated endocytosis, promoting the cytotoxicity of anti-cancer drugs in cancer cells, significantly reducing cancer growth [105].

Exos loaded with rifampicin (RIF) accelerated its entry into osteosarcoma (OS) cells, and the inhibition of OS proliferation, migration, and invasion by RIF was further enhanced. In mice, kinesin-related protein 1 (Drp1) was activated using

EXO-RIF and caused mitochondrial lysis and apoptosis, thereby increasing survival [55]. Sonodynamic therapy (SDT) is minimally invasive and exhibits low toxicity and the ability to treat deep tissues; however, low water-soluble acoustic sensitizers can limit its clinical application and the tumor microenvironment (TME) can affect its effectiveness. Exos facilitate communications between cells and regulate specific responses in recipient cells. Li et al. designed a bionanosystem (ECaC) by loading mesoporous calcium carbonate nanoparticles ($CaCO_3$-NPs) and acoustic sensitizer curcumin (Cur) into cancer-derived Exos to synergistically enhance the efficacy of SDT. Exos facilitated homologous targeting capabilities to $CaCO_3$-NPs and avoided clearance by the immune system. When they reach the cancer site, $CaCO_3$-NPs are degraded into Ca^{2+} in the acidic TME to disrupt the cellular mitochondria. Consequently, cancer cell respiration is disrupted, causing oxidative stress and enhancing Cur-mediated chemotherapy/SDT [56]. Gu et al. used Exos derived from human umbilical cord mesenchymal stromal cells (hUCMSCs) and cyclic peptide arginine-glycine-aspartate (cRGD) encapsulated with thujaplicin lactone (TP) to establish a bionic targeted drug delivery system (cRGD-Exo/TP). The delivery system exhibited a drug loading of 10.76 ± 1.21% and significant anti-proliferative, anti-invasive, and pro-apoptotic activities in A375 cells via the cystein cascade and mitochondrial pathway, as well as cell-cycle alterations (Fig. 4A) [57].

Surface modifications can confer additional functions to Exos, such as sensitization of TME, stimulation of immune responses, improved cancer targeting and retention, and *in vivo* imaging and transport. Feng et al. used genetic engineering and self-assembly techniques to develop Exos-PH20-FA, where Exos were modified with folic acid (FA). Exos-PH20-FA polarized macrophages to the M1 phenotype and reduced the number of associated immunosuppressive immune cells, thereby changing the immune microenvironment from immunosuppressive to immune-supportive. In addition, Exos-PH20-FA directly reduced hyaluronidase-induced cancer cell metastasis (Fig. 4B) [58]. Interleukin (IL)12 was prepared by fusion with the exosomal surface protein, PTGFRN, to generate ExoIL12. ExoIL12 exhibited longer cancer retention, greater anti-cancer activity, and more

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potent cancer growth inhibition than recombinant IL12 [59]. The aforementioned studies demonstrate that Exos play a key role in cancer treatment and can improve prognosis; therefore, Exos-based therapeutic strategies provide alternative options for cancer treatment.

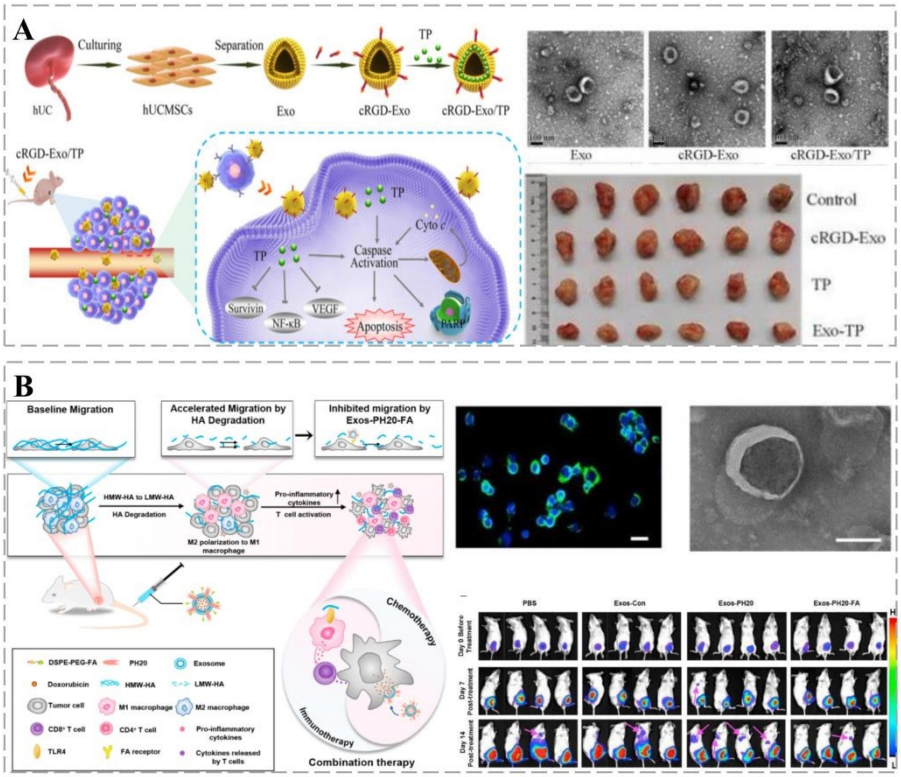

Fig. 4. Exos for cancer therapy. A. Functionalized Exo vehicles for targeted therapy of malignant melanoma. These vehicles exhibit a distinct bilayer membrane-shaped disc morphology; the cRGD-Exo/TP group significantly inhibits cancer growth. B. Folic acid-modified self-assembled and genetically engineered Exo vehicles transform the cancer microenvironment from immunosuppressive to immune-supportive and improve the efficacy of combination chemotherapy. PH20 expression can be observed on the surface of transfected 293T cells and used to produce Exos. Furthermore, after FA modification, Exos-PH20-triggered metastasis of cancer cells to the lung was significantly inhibited.

2.2 Active targeting-based delivery vehicles

Active targeting strategies are being developed to enhance tumor therapy (Table 2)

Table 2. Summary of active targeting-based delivery vehicles in cancer

Type of	Cancer	Mechanisms	Reference

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delivery vehicles			
Nanorobots	Hepatocellular carcinoma cells (Hep3B)	Manipulation of nanorobot movement using an external EMA system; real-time drug release by near-infrared laser irradiation	[106]
Folic acid (FA)	Breast cancer	Enhances cellular internalization and promotes drug uptake	[107]
	HepG2 cells	Promotes intracellular uptake of drugs by tumor cells; co-administration of drugs by chemotherapy and photothermal action for synergistic anti-tumor effects	[108]
Lactoferrin (Lf)	Prostate cancer	Delivery of drugs into drug-resistant cells to avoid drug efflux and prolong nuclear retention time	[109]
	Glioma	Modulates the STAT6 pathway and inhibits Ras/Raf/p-Erk pathway-induced mitochondrial apoptosis	[110]
	Breast cancer	Prolonged drug action; selective cytotoxicity against tumor cells	[111]

2.2.1 Nanorobots

Current drug delivery nanocarriers rely on the enhanced permeability and retention (EPR) effects and lack dynamic navigation, which limits their therapeutic efficacy. Nanorobots offer unique features as novel delivery vehicles, including

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propulsion, controlled navigation, and cargo traction and release, and can potentially penetrate tissues and rapidly transport therapeutic drugs directly to target sites, improving efficacy and reducing systemic side effects of toxic drugs. The Janus nanomotor is a small active targeting delivery system. Scientists have developed micro-robots over the past decade for precise drug delivery and controlled release [112]. These mobile microrobots can be used to target deep wounds and narrow blood vessels that are difficult to reach during surgery [112, 113]. They increase the apparent diffusion coefficient by a factor of two at low H2O2 fuel concentrations (< 3 wt%). Owing to their mesoporous structure and small size, mobile microrobots can be loaded with large amounts of cargo molecules and act as active nanocarriers for targeted delivery on chips [114]. he speed of motion of nanorobots can be regulated by changing the fuel concentration, and the direction of motion can be controlled using an external magnetic field. These assembled nanorobots can act as both autonomous engines and intelligent carriers for drug loading, targeted transport, and remotely controlled release near cells and tissues in living organisms [115]. Helical microrobots with gyroid surfaces exhibit enhanced drug-loading efficiency [106]. The microrobots, controlled by an external EMA system and equipped with iron oxide nanoparticles on their surface, can achieve real-time drug release through irradiation with a near-infrared (NIR) laser, combining photothermal and drug treatments for maximum therapeutic effect and minimal side effects (Fig. 5A).

2.2.2 Folic acid

Active targeting enhances therapeutic carrier selectivity for cancer cells, minimizing the distribution of drugs in non-specific tissues. Various ligands can be used to functionalize nanocarriers, of which surface modification of vehicles by folic acid (FA) is a promising strategy for active cancer targeting owing to its low cost, easy coupling to nanoparticles, and limited stimulation of the immune system [116]. In particular, most solid cancers, including breast cancer, exhibit overexpression of the alpha isoform, whereas its expression in normal tissues is negligible; therefore, FA-nanoparticles are a promising therapeutic strategy. Granja et al. functionalized solid lipid nanoparticle (SLN) vehicles loaded with mitoxantrone (Mito) using

diesteroyl phosphatidylethanolamine-poly(ethylene glycol)-FA (DSPE-PEG-FA) ligands. Functionalized NPs can improve the anti-cancer effect of free drugs.

In addition, confocal microscopy and flow cytometry revealed the enhanced cellular internalization of functionalized solid lipid nanoparticles (SLNs) via folate receptor (FR)-mediated endocytosis [107]. Chen successfully constructed a folic-acid-modified erythrocyte drug delivery system, DOX and ICG-PLGA@RBC nanoparticles (DIRNPs), for simultaneous transport of chemotherapeutic drugs (e.g., DOX) and photothermal agents (indocyanine green, ICG) for application in synergistic chemotherapy. FA modification effectively promoted the capture of DIRNP vehicles by HepG2 cells by promoting the level of ROS that induced apoptosis and limited cell migration. NIR laser disintegrates DIRNPs by increasing the local temperature of cancer tissues and rapidly releases the loaded drug, which in turn promotes cancer cell apoptosis. Therefore, this combination strategy is an effective method for cancer treatment [108]. Compared with non-targeted DATS and DATS-SLNs, FA-DATS-SLNs containing surface-functionalized FA are further selective for invasive TNBC MDA-MB-231 cells and more susceptible to cellular capture, which increases cytotoxicity. FA-DATS-SLNs significantly downregulate the anti-apoptotic protein Bcl2, upregulate the pro-apoptotic protein caspase-9, and enhance the apoptotic potential of functionalized agents by interfering with the intrinsic apoptotic pathway (Fig. 5B) [117].

2.2.3 Lactoferrin

Lactoferrin (Lf) is a non-toxic and inexpensive natural iron-binding glycoprotein, the anti-cancer activity of which has been observed in various cell lines, animal models, and clinical trials. The main anti-cancer mechanisms include the downregulation of the anti-apoptotic protein Bcl-2 [118], increased expression of the pro-apoptotic Bax protein [119], upregulation of Fas expression [120], and specific activation of the p53 cancer suppressor gene [121]. Since 1992, the mode of action of Lf in cancer therapy has attracted increasing attention [122-124]. Lf has been used for surface modification of drug nanocarriers since its receptor is overexpressed by cancer cells and other tissues, such as the brain. Lf acts as an excellent functional

carrier protein coupled with DOX for delivery to DU145 cells, CD44+/EpCAM+ double-positive enriched DU145 3D prostate cells, and drug-resistant ADR1000-DU145 cells, bypassing the DOX efflux to overcome chemoresistance. Iron-saturated bLf-DOX inhibits cancer development by upregulating the serum levels of anti-cancer molecules (e.g., TNF-α, IFN-γ, CCL4, and CCL17) [109]. Mo et al. co-encapsulated simvastatin and fenretinide in a TPGS-TAT-embedded Lf nanoparticle system via the LRP-1 receptor for brain-targeted bionic delivery. The Lf-nanoparticles change cancer-associated macrophages from the M2 to M1 phenotypes by modulating the STAT6 pathway and inhibiting the Ras/Raf/p-Erk pathway to induce mitochondrial apoptosis [110].

Lf-inorganic nanocarriers exert synergistic anti-cancer effects when used in combination with chemotherapy. Sharifi et al. coated highly homogeneous porous magnetite nanoparticles (PMNs) with Lf for targeted drug delivery to breast cancers. Lf-Doxo-PMNs prolonged the circulation time of DOX in the blood and reduced cancer drug resistance. In addition, combination therapies based on Lf-Doxo-PMNs, such as chemo-MF, chemo-PTT, and chemo-MF-PTT, induced apoptosis through extrinsic (TNF-α) and intrinsic (Bax) pathways and significantly reduced the volume and size of breast cancers (Fig. 5C) [111]. Lf can cross the BBB, and its receptors, LfRs, are highly expressed on the surface of glioblastoma cells [125]. Song et al. used Lf as a targeting ligand to construct an Lf@graphene oxide (GO)@Fe3O4 targeted delivery system via EDC/NHS chemistry. Lf-modified nanocarriers have higher intracellular delivery efficiency and are more cytotoxic to C6 glioma cells than free DOX and DOX@GO@Fe. These results suggest Lf-conjugated GO@Fe as a potential 3O4 nanocomposite for therapeutic applications in glioma treatment [126].

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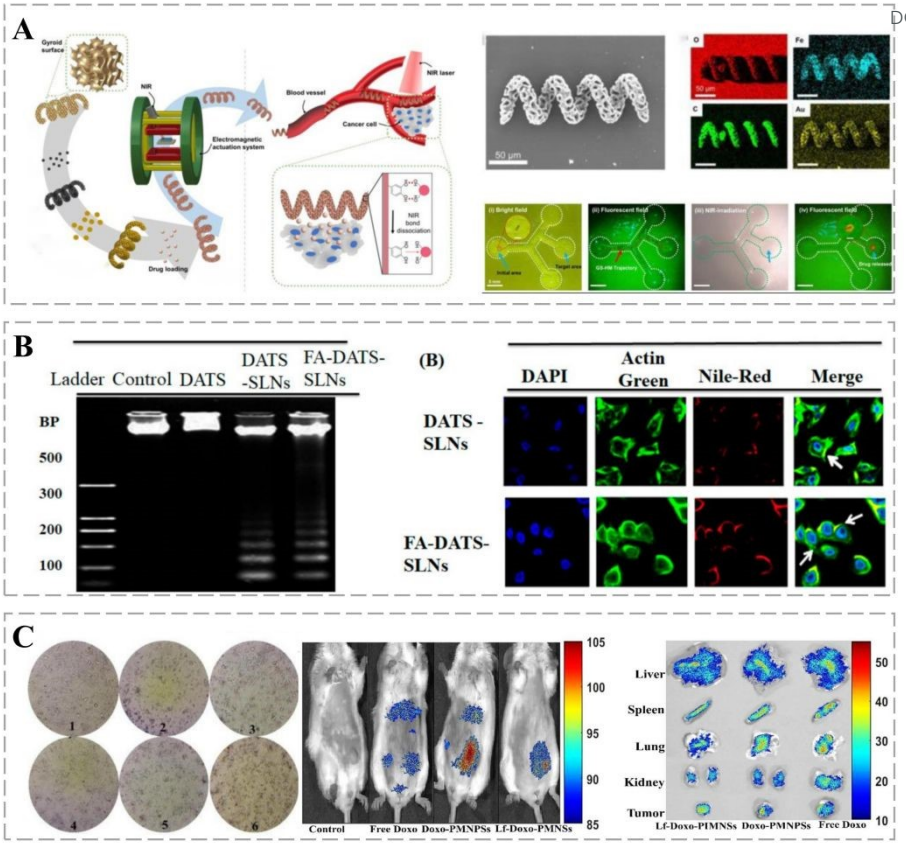

Fig. 5. Applications of active targeting vehicles. A. Magnetically guided helical microrobots with Gyroid surface coated with magnetic nanoparticles (MNPs) can achieve active motion under magnetic fields, and the use of plasmon resonance (LSPR) to modulate the robot surface coated with star-shaped gold nanoparticles (Au-nanostar) can facilitate multi-step drug release. B. The MDA-MB-231 cell line treated with FA-DATS-SLNs exhibited more apoptotic DNA fragmentation with superior DATS cell accumulation. This vehicle, with target specificity, promotes and improves the internalization of DATS cells. C. Lf-Doxo-PMNSs can stimulate 4T1 cell death by generating ROS, resulting in significant changes in cell morphology and targeted delivery of drugs.

2.2.4 Other

Escherichia coli K1 (EC-K1) can actively penetrate the BBB and induce bacterial meningitis after colonizing the brain. We have referred to the bacteria-based drug delivery system as “Trojan Bacteria.” It is used for photothermal immunotherapy of glioblastoma (GBM). The system consists of a loaded photosensitive ICG bypassing the BBB and targeting the penetration of GBM tissue, after which the ICG converts

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light energy into heat under laser irradiation to destroy cancer cells [127]. In contrast, dead EC-K1 can penetrate the BBB and does not produce bacterial virulence. Based on this feature, EC-K1 was modified by maltodextrin and extinguished under UV irradiation to construct a "dead EC-K1" drug delivery system, which significantly enhanced the accumulation of therapeutic drugs in the brain without toxicity and retained the health of the animal model [128].

3. The pharmacokinetics of smart cancer therapy delivery vehicles

Pharmacokinetics is the science of elucidating the relationship between drug concentration in different parts of the body and time by quantitatively studying the dynamic changes in the absorption, distribution, metabolism and excretion of drugs in the organism. Drugs are metabolized by different pathways in different tissues and cells [129]. Many factors can affect drug metabolism, such as cellular transporters, metabolic enzymes, pH environment and electrochemical gradients, as well as the drug itself, such as drug polarity, dosage form, and surface charge. Compared with free drugs, smart delivery vehicles have the characteristics of controllability and targeting, which can improve the bioavailability of drugs and reduce the toxicity and side effects, while their cell entry and transmembrane pathways and the mechanism of pharmacological effects are different from those of free drugs [130]. The pharmacokinetic study of smart delivery vehicles can more effectively and comprehensively evaluate and predict the efficacy of the loaded drugs and the possible toxic side effects, and can provide more important references for the design of smart delivery vehicles[131].

3.1 Absorption and transport

Smart delivery carriers enter cells mainly through endocytosis, and the main endocytosis pathways include giant cell drinking, lattice protein-mediated endocytosis, follicular protein-mediated endocytosis and lattice protein/follicular protein-independent endocytosis. The endocytosis process is closely related to the nature of the carrier itself and the nature of the cell [132, 133].

The nature of the vehicles itself mainly includes surface charge, particle size and

shape. The charge can affect the amount and pathway of the delivery vehicles into the cell. Positively charged vehicles have stronger interactions with cells, and are therefore more likely to be taken up by cells and tend to be endocytosed through the lattice protein-mediated pathway [134]. In addition, charge can also affect the organelle localization of the vehicles after it enters the cell, as negatively charged vehicles are more likely to pass through the lysosomal degradation pathway, whereas positively charged vehicles tend to bypass the lysosomal pathway. Particle size can affect the entry and transit of therapeutic carriers. It was found that the larger the particle size, the slower the internalization rate of the vehicles [135]. Studies have shown that nanocarriers exhibit excellent dissolution properties due to their smaller particle size and larger surface area. In addition, under simulated in vitro gastrointestinal conditions, nanocarriers showed faster release, higher bioaccessibility and higher permeability [136]. In addition, the cell type can also affect the cellular uptake of the delivery vehicles. The cancer cell uptake of arginine-glycine-aspartic acid (RGD)-modified DOX liposomes was higher, which was closely related to the high expression of integrin receptors on the cancer cell surface [137].

The *in vivo* blood concentration of smart delivery vehicles is usually inconsistent with the cellular level of cell entry. Differences in the nature of delivery carriers and target cells may lead to a higher distribution of highly targeted delivery vehicles in target organs and target cells, thus showing more significant drug effects. The study of cellular pharmacokinetics can be used to screen out smart delivery vehicles with high targeting ability, reduce the workload of *in vivo* experiments, and improve the efficiency of drug screening. According to the results of cellular pharmacokinetics, when designing smart delivery vehicles, we can try to change the absorption and transportation pathways of drugs by changing the charge and particle size of the vehicles, thus affecting the absorption and distribution of drugs in the body.

3.2 Distribution and metabolism

Compared with free drugs, the distribution, metabolism and efficacy of smart delivery vehicles are altered after entering cells. In MCF-7 cells, the concentration of free PTX was higher than that of CMCS-DFNS@PTX at 1 h, which may be attributed

to the fact that CMCS-DFNS@PTX needs to be endocytosed to enter the cells and needs to undergo a certain sustained release time after entering the cells to exert the drug effect. After 2 h, the drug concentration in CMCS-DFNS@ PTX had a higher drug concentration than free PTX after 2 h, and the drug concentration in the cells reached the highest after 12 h [138].

For drugs with different targets and properties, changes in intracellular transport pathways induced by smart delivery vehicles can bring about different therapeutic effects. DOX and PTX, which are physicochemically and chemically stable, can be efficiently delivered into the cell by the vehicles, whereas biomolecule drugs (e.g., peptides, proteins, siRNAs, etc.) are unstable in the lysosomal low-pH and enzyme-rich microenvironment [139], so the lysosomal escape of biomolecule drugs has to be taken into account in designing the vehicles loading drugs. Since the traditional pharmacokinetics based on plasma drug concentration often fails to fully explain the pharmacological effects of drugs on cancers, a more in-depth understanding of the mechanism of drug efficacy can be achieved by analyzing the distribution of smart delivery vehicles in cells. The design of different smart delivery vehicles according to the specific internal environment of the cell can achieve the purpose of controlling the metabolic pathway of drugs in the cell, thus providing a broader idea for cancer therapy.

3.3 Excretion

Free drugs can easily enter normal cells, but it is difficult for them to accumulate in drug-resistant cells due to the role of various exocytosis proteins. The emergence of smart delivery vehicles has solved this problem.

Ideally, the delivery vehicles should be excreted via the renal clearance route. Studies have shown that the dissolved Bi (III) ions in BiNPs can be cleared by metallothionine (a cysteine-rich protein in the kidney, and excreted in the urine). Even at high concentrations of 800 μg/mL, the nanocarriers demonstrated good blood compatibility with a hemolytic effect of less than 2%. No significant weight loss or tissue damage was observed in the animals after administration of BiNPs [140]. It was shown that free PTX in cells was significantly eliminated in the first 18 h, while the

elimination of CMCS-DFNS@PTX was relatively slow. Throughout the elimination period, the concentration of CMCS-DFNS@PTX in the cells was higher than that of free PTX, indicating that CMCS-DFNS could prolong the circulation time of PTX in the cells and significantly increase the bioavailability of PTX, thus improving the therapeutic effect [138].

In conclusion, the study of the cellular exocytosis of delivery vehicles is of great significance in improving the efficacy of drugs and designing new formulations.

Smart delivery vehicles often exhibit different cellular pharmacokinetic behaviors compared to free drugs. The study of the absorption, transport, distribution, metabolism and excretion processes of smart delivery vehicles in tissues and cells plays a crucial role in the effectiveness and safety of delivery systems. It is of great significance for the development, screening and clinical application of smart delivery ehicles to record, analyze and reveal the intracellular kinetic processes and laws of smart delivery vehicles by using analytical techniques and cellular molecular biology research techniques.

4. Advantages of smart cancer therapy delivery vehicles

4.1 Delivery of drugs with different physicochemical properties through improved solubility

The poor solubility of most anti-cancer chemotherapeutic drugs such as adriamycin and methotrexate [141], in aqueous solutions hinders their clinical application, mainly due to the difficulties in passing through the aqueous environment surrounding the cancer cells to cross the cell membrane and act on intracellular targets. In addition, some chemotherapeutic drugs can cause serious toxicity through intravenous administration, such as skin and visceral damage [142]. Therefore, the delivery of hydrophobic therapeutic agents to cancer tissues is an important breakthrough in cancer therapy.

Smart drug delivery carriers containing hydrophobic or amphiphilic materials address the problem of poor solubility of hydrophobic drugs, such as PLGA, PLA, chitosan, gelatin, polycaprolactone, and polyalkyl cyanoacrylate [143]. The high

lipophilicity and low water solubility of the oleanolic acid derivative DKS26 attribute to its very low oral bioavailability. Liposomal loading of DKS26 significantly enhances the absolute oral bioavailability [144]. Gholizadeh *et al*. prepared immunoliposomal carriers to deliver sepantronium bromide YM155 (a hydrophilic drug with low oral bioavailability and rapid renal elimination). The YM155-loaded liposomes exhibited prolonged circulation and a significantly increased half-life in cancer tissue compared to intravenous free YM155 [145]. Paclitaxel (PTX) is an effective anti-cancer drug with very low solubility in water. Meanwhile, the complex gastrointestinal environment and epithelial barriers hinder its antitumor effect. PEGylated high-density glycerylcholic acid-decorated micelles (PTX@GNPs) based on PEGylation can encapsulate PTX by π-π stacking, thereby gaining mucus-trapping escape ability and significantly improving drug targeting in the gastrointestinal tract [146]. Mitomycin C (MMC) is used for the treatment of various solid cancers; however, the application of MMC via intravenous injection is associated with toxic side effects and non-specific interpolymerization. Yang et al. synthesized PEG2k-Fmoc-ibuprofen (PEG-FIbu) micelle nanocarriers loaded with MMC. PEG-FIbu/MMC micelles exhibited superior stability, higher drug loading efficiency, slower release, longer circulation time, and higher cancer uptake and therapeutic efficiency than MMC intravenous injection [147]. Zhao et al. developed FA-PLGA/PCADK-lipid NPs (FA-PPLNPs) to encapsulate methotrexate (Mtx). The developed NPs exhibited high cellular uptake rates [148]. The amphiphilic CPT-ss-EB prodrug developed by Zhang et al. self-assembles into nanostructures with high solubility in aqueous solution while rapidly transforming into a long-term circulating nanocomplex [149]. Therefore, therapeutic carriers can enhance the solubility of hydrophobic drugs and deliver drugs with different physicochemical properties.

4.2 Controlled release of drugs

Kline and French introduced the first controlled-release formulation for the delivery of dextroamphetamine (dexedrine) in 1952. By the late 1970s, no improvements have been made in understanding the mechanism underlying controlled

drug delivery. Smart therapeutic vehicles are capable of controlled-release of the loaded drug and can improve the presentation of the drug in different temporal spaces in the body, protect the drug from clearance and degradation, and reduce the toxic effects, which can improve patient outcomes. Drug delivery technologies have advanced, from understanding drug release mechanisms to manipulating vehicle size for targeted drug delivery, which has facilitated the development of several nanoparticle-based controlled-release systems with excellent results [150, 151].

Smart stimuli-responsive nanoparticles (srNPs) have undergone substantial progress as effective drug-delivery vehicles for cancer immunotherapy. srNPs use unique cancer microenvironments or external stimuli, such as weak acidity, high glutathione (GSH) concentrations, overexpression of cancer site enzymes, and ROS, as triggers for the precise delivery and controlled release of drugs. This function can improve the bioavailability of the drug and reduce its toxic effects [152]. Stimulus-responsive delivery systems exhibit more dynamic activity than non-stimulus-responsive nanocarriers, allowing for more precise drug release [153].

The structure and metabolism of cancers result in an acidic microenvironment [154], which provides favorable conditions for cancer growth, affecting the immune surveillance of cancer cells and possibly leading to the immune escape of the cancer. Cancer-targeting smart nanoparticle carriers can alter this microenvironment based on different pH values: the surface potential of the carrier shifts from negative to neutral (pH 6.5–7.0), which facilitates cellular uptake of the drug, whereas, at pH 4.5–6.5, the carriers dissociate, inducing endosomal escape and releasing the drug into the cytoplasm. Meanwhile, smart nanoparticles modified with the cancer-penetrating peptide iNRG were used as cancer-targeting molecules. In an acidic environment (pH 6.8), this carrier promoted the uptake of the drug by cancer cells (Fig. 6A) [155]. The polyion complex (PIC) micelles prepared by Hsieh et al. demonstrated good colloidal stability at different pH values. Controlled permeability of the micelles can be achieved by adjusting the degree of cross-linking and accelerating drug release at low pH conditions [156]. ROS plays an important role in cancerigenesis; elevated ROS levels have been reported in several cancer cells [157]. Wang et al. designed a

therapeutic system containing a ROS marker that oxidizes and hydrolyzes TSPBA in the presence of ROS, resulting in sustained release of gemcitabine (GEM) and aPDL1 (anti-PD-L1 blocking antibody) to enhance anti-cancer responses [158]. In addition, enzyme-responsive cancer drug delivery systems offer new solutions for cancer therapy. Wang et al. synthesized PEG5k-GL2-IMDQ micelles using imidazoquinoline-like TLR7/8 agonists. The micelles form vesicles in aqueous media that can be specifically degraded by endosomal enzymes and can control drug delivery through an enzymatic response at the tidal junctions. Once micellar vesicles accumulate in the cancer region, effector proteases are depleted, leading to local drug release (Fig. 6B) [159]. Under hypoxic conditions, macrophages and neutrophils are easily transformed into the cancer-promoting M2 phenotype, thereby inhibiting the killing effects of T and NK cells [160]. However, as the levels of anaerobic metabolites increase, the production of interferon γ (IF-γ) is affected and impairs the function of connective tissue growth factors. Therefore, the design of low-oxygen-responsive nanomaterials will enhance cancer therapy. Nanovesicular carriers were assembled from hypoxia-responsive amphiphilic polymer-grafted manganese ferrite nanoparticles (MFN), with DOX loaded into an aqueous cavity. Under hypoxic conditions, the nanocarriers rapidly dissociate into individual MFNs, releasing DOX and inducing cancer breakdown of H_2O_2, relieving cancer hypoxia, and contributing to cancer treatment [161].

Multi-responsive therapeutic regimens can amplify anti-cancer responses. Nanocarriers containing therapeutic peptide components respond to dual stimuli in the cancer extracellular matrix with targeted delivery to cancer and on-demand release of a short d-peptide antagonist of programmed cell death ligand 1 (DPPA-1) and an isoindolamine 2,3-dioxygenase inhibitor (NLG919). By blocking immune checkpoint and tryptophan metabolism, the local release of DPPA-1 and NLG919 facilitates cytotoxic T lymphocyte survival and activation, ultimately inhibiting melanoma progression (Fig. 6C) [162]. Zhang et al. designed a drug delivery vehicle that responded sequentially to the triple response of MMP-2, pH, and GSH for co-immunotherapy of TNBC. The therapeutic vehicle undergoes structural

transformation to achieve optimal size and shape changes according to therapeutic needs. It synergistically amplified the ROS cascade response, increased H_2O_2 and •OH levels, induced immunogenic cell death (ICD) responses, and promoted anti-TNBC immunity by enhancing the interaction between dendritic cells (DCs) and dying cancer cells [163]. Stimuli-responsive drug delivery systems have considerable potential to improve the efficiency of cancer treatment by controlling drug release and degradation and combining them with multiple treatment options to minimize side effects.

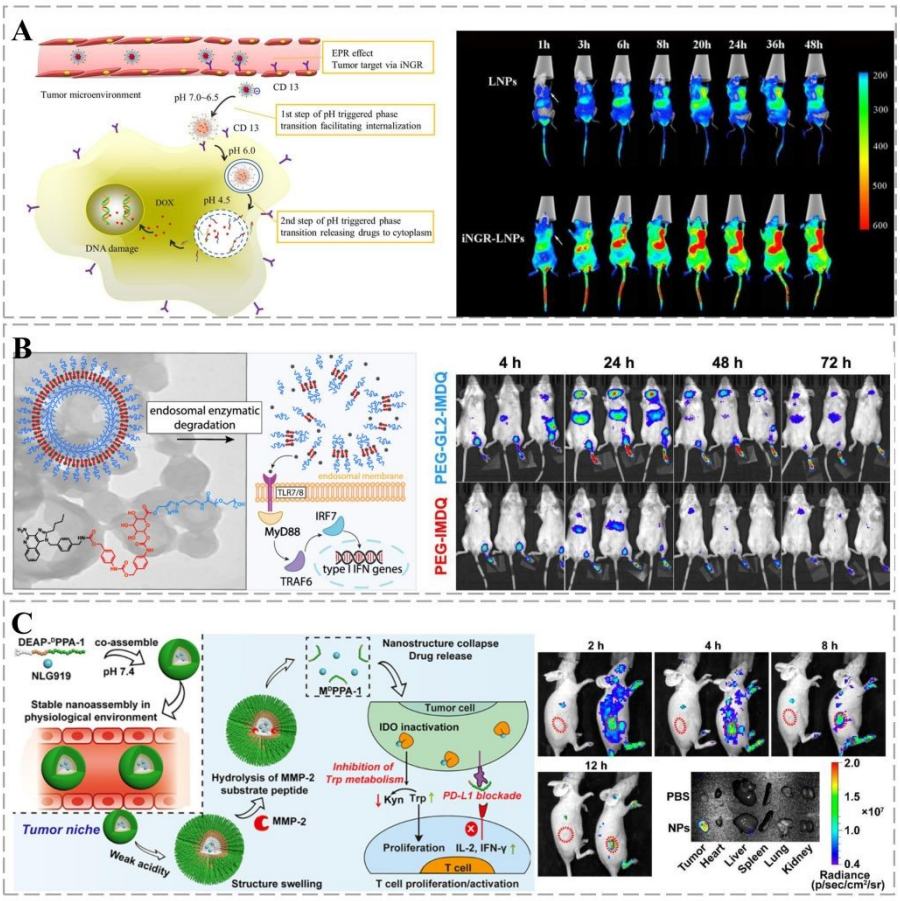

Fig. 6. Smart therapeutic vehicles enabling controlled drug release. A. Schematic diagram of the two-step phase transition of pH-triggered iNGR-LPNs. iNGR-LPNs alter the biodistribution of free DOX, exhibiting long circulation and cancer-specific distribution properties while avoiding the cardiac distribution. iNGR-LPNs administered to mice first recognize cancer neovascularization, induce high levels of particle accumulation at the cancer site, and promote cancer-specific cellular uptake via CD13 receptor-mediated endocytosis and pH-triggered particle phase transition to

promote cancer-specific cellular uptake. B. Upon endocytosis by antigen-presenting cells, the self-assembled nanovesicles are degraded and release native IMDQ, which bound to TLR7/8 receptors and trigger immune activation. One week after injection, PEG5k-GL2-IMDQ vesicle signals can be detected in mice, suggesting that sustained degradation and release of IMDQ prolong immune stimulation due to IMDQ, thereby reducing the frequency of dosing and inducing a more effective immunomodulatory effect. C. Schematic diagram of the composition of DEAP-DPPA-1 and the anti-cancer mechanism of NLG919@DEAP-DPPA-1 nanoparticles. The peptide-assembled nanoparticles have a high sensitivity to pH. TRITC fluorescence shows nanoparticles predominantly distributed in tumors.

4.3 Overcoming multi-drug resistance and synergistic treatment to improve efficacy

The underlying principles of various cancer combination therapies have been investigated to achieve optimal clinical outcomes [164]. Compared with monotherapy, combination therapy significantly improves clinical outcomes, effectively overcomes clonal heterogeneity, and reduces drug toxicity in humans [165].

MDR affects the efficacy of chemotherapy and leads to chemotherapy failure. When treatment doses are increased to avoid drug resistance, the resulting drug toxicity damages healthy organs and tissues. Smart drug delivery carriers have been proven effective in overcoming MDR using several mechanisms. Degradable poly (lactic acid-glycolic acid) (PLGA) NPs loaded with both DOX and Cur effectively inhibited the growth of DOX-resistant esophageal cancer (Fig. 7A) [166]. Zhen et al. constructed DEB/TQR@PMP micelles by encapsulating a near-infrared fluorophore (DEB-BDTO) as a photosensitizer with the drug resistance inhibitor tariquidar (TQR) in a polymeric pre-drug (PMP). The micelles exhibited synergistic lethal effects on SKOV-3 and SKOV-3/MDR cells, significantly enhancing the inhibition of cancer growth [167]. Xing et al. dissolved IR780 (a photosensitizer) in D-α-tocopheryl polyethylene glycol succinate (TPGS) micelles and loaded clusters of polydopamine (PDA) NPs on their surface for the combined treatment of drug-resistant breast

cancer. Mediated by PDA, the system exhibited significant quenching of fluorescence emission and inhibition of singlet oxygen generation upon exposure to NIR light, facilitating efficient PTT treatment. Furthermore, micellar carriers significantly enhanced the intracellular accumulation of adriamycin hydrochloride, and photothermolysis promoted its release. Such findings suggest that smart therapeutic carrier-loaded drugs can enable complementary interactions between photothermal/photodynamic therapy/chemotherapy, thereby improving the efficiency of combination therapy for multi-drug resistant cancers (Fig. 7B) [168].

Smart therapeutic carriers can also overcome MDR by inhibiting energy metabolism and blocking ion-mediated signaling pathways. Ruan et al. developed a mitochondrial temperature-responsive drug delivery system that prevents adriamycin efflux and promotes adriamycin accumulation and mitochondrial targeting in drug-resistant cancers using thermally responsive nanocarriers. Thermoresponsive nanocarriers effectively enhanced the cytotoxicity of adriamycin and reversed drug resistance in cancer-bearing mice (Fig. 7C) [169]. Such effects inhibit cellular respiration and downregulate HIF-1α expression to suppress P-glycoprotein biosynthesis. Additionally, Ca^{2+} burst-induced respiratory inhibition blocks intracellular ATP production, leading to P-glycoprotein insufficiency. Thus, TCANG enhanced the proliferative effect of IC50DOX on MCF-7/ADR cells by approximately 30-fold and the proliferation of drug-resistant cancers by approximately 13-fold (Fig. 7D) [170].

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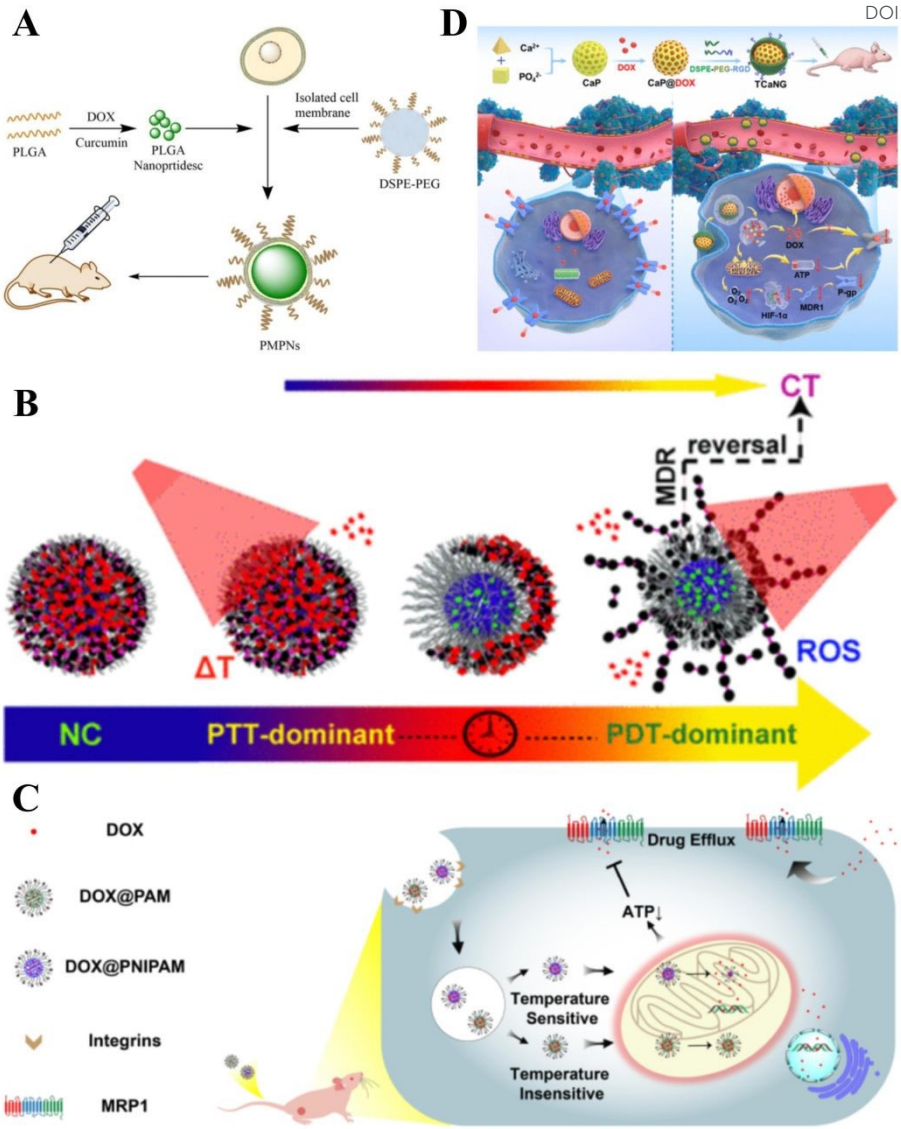

Fig. 7. Smart therapeutic vehicles to overcome MDR. A. PLGA loaded with DOX and Cur to form PLGA-NP, followed by the addition of isolated TE10 cell membranes and DSPE-PEG and self-assembly on PLGA-NP to form PMPN. Application of bionanodrug PMPN to the *in vivo* treatment of MDR esophageal cancer. B. Photoresponsive nanocluster (NC) system enabling combination chemotherapy (CT)/photothermal therapy (PTT)/PDT for drug-resistant breast cancer. C. Mitochondrial temperature-responsive drug delivery in a DOX-resistant model of small cell cancer. The thermoresponsive nanocarrier PNIPAM can release DOX at high mitochondrial temperatures compared with the non-thermoresponsive nanocarrier PAM, thereby damaging mitochondria and reversing DOX resistance. D. Cancer-targeted “calcium nano-generator” (TCANG) safely and effectively reverses

drug resistance in cancer cells through a nano-activated intracellular calcium explosion resistance.

4.4 Diagnosis and treatment

Cancer therapeutic carriers can be loaded with various CA and fluorescent agents to effectively deliver drugs. Owing to their optical properties, these carriers can be used in the diagnosis of cancers.

Zhou et al. developed NRh-G-NPs, which can specifically respond to GGT overexpressed in U87MG cancer cells and selectively illuminate cancers for image-guided therapy. Furthermore, restoring photothermal properties in the cancer region can improve the accuracy of cancer-targeted therapy and reduce side effects (Fig. 8A) [171]. Pan used circulating EV vehicles to assess cancer-specific drug-target interactions in patient blood samples, such as Exos small molecule chemical occupancy and protein expression monitoring (ExoSCOPE). The use of such technology in cancer diagnosis and treatment monitoring allows for accurate classification of disease status and rapid differentiation of the outcome of targeted therapies within 24 h of treatment [172]. Nanodroplets (NDS), a noninvasive delivery strategy, can enhance both ultrasound imaging and therapeutic efficacy. Zhao et al. constructed novel SP94 peptide-modified and doxorubicin-loaded ultrasound nanodroplets (SP94-DOX-NDs) to target and treat castrate prostate cancer (CRPC). *In vitro* and *in vivo* experiments showed that SP94-DOX-NDs could specifically deliver DOX to 22RV1 cells under ultrasound guidance and, therefore, exhibited strong anti-cancer effects (Fig. 8B) [173]. Narmani et al. used a polyethylene glycol-modified and folate-functionalized PAMAM G4 dendrimer as a smart, low-toxicity nanocarrier. The nanocarrier exhibited excellent potential for delivering 5-FU chemotherapeutic agents to breast cancer cell lines, and cancer accumulation studies demonstrated its targeting ability. In addition, imaging studies of targeted radiotracers confirmed the excellent performance of the nanocomplexes in a cancer-bearing mouse model. In conclusion, novel smart synthetic nanocomplexes are suitable for cancer treatment, tracking, and imaging (Fig. 8C) [174]. Kong et al. designed a novel nanocarrier based on HA conjugated with Gd3+ and loaded it with

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806 therapeutic drugs for combined magnetic resonance imaging (MRI)-guided cancer
807 chemotherapy and MRI-photothermal treatment. HA-Gd-DOX exhibited high
808 photothermal conversion efficiency and photothermal stability; its pH-responsive
809 release properties and photothermal effects allowed for the gradual release of DOX.
810 HA-Gd-DOX was also efficient in MRI-guided cancer monitoring (Fig. 8D) [175].
811 Owing to the limitations of the BBB, it is difficult to maintain high concentrations of
812 therapeutic drugs in the brain. The use of Lf-modified dual-target magnetic
813 polydiethylene glycol nanocarriers (PDNCs) can improve BBB crossing efficiency for
814 treating brain cancers. The magnetic Lf-modified PDNCs exhibited MRI and
815 dual-targeting capabilities and could enhance PDNC transport to the BBB to track and
816 target gliomas [176]. In addition, highly fluorescent CdTe quantum dots (QDs) were
817 coupled with Lf-targeted nanocapsules. The covalent bond between Lf and QDs
818 prevents Cd from entering the circulatory system and ensures that QDs are released
819 only at the cancer site. Upon conjugation to Lf (OFF state), QDs luminesced in vitro
820 owing to an electron/energy transfer mechanism. Upon intracellular uptake into
821 MCF-7 cells, the luminescence was restored (ON state) as the surface-bound ligand
822 was separated from QDs in the cytoplasm. *In vivo*, cancer tissue from
823 Lf-QDs-CS-NC-treated mice exhibited higher fluorescence intensity than the liver
824 and kidney tissue, demonstrating the efficient localization of QDs in cancer tissue
825 [177].

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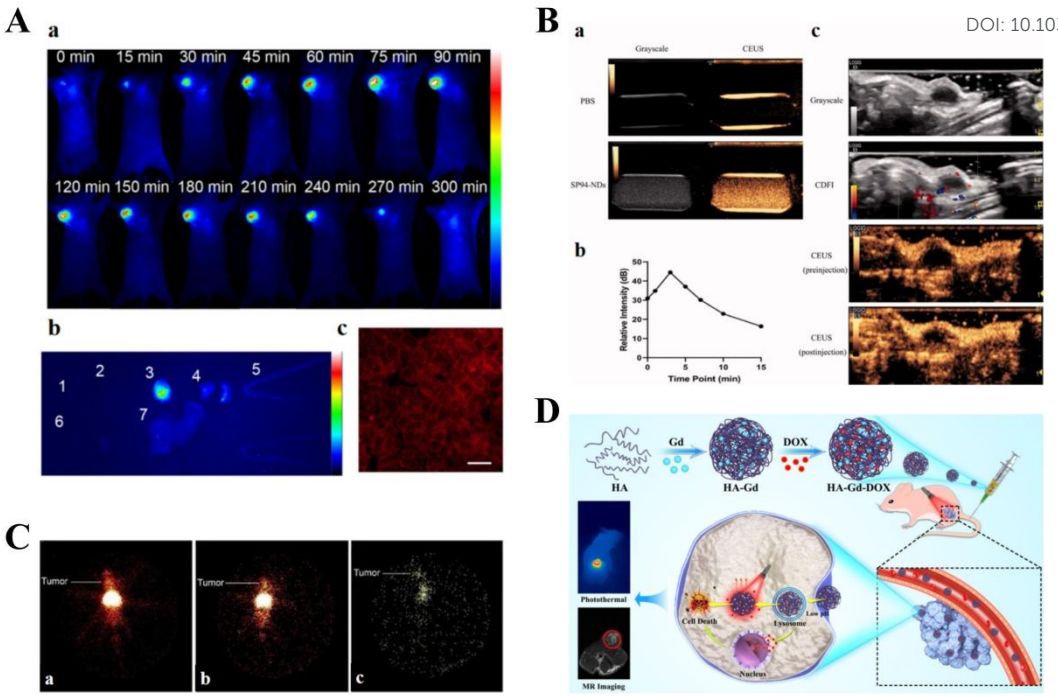

826

827 Fig. 8. Smart therapeutic vehicle for simultaneous diagnosis and treatment. A.
828 NRh-G-NPs indicate the cancer location by passive targeting and can be used for
829 effective real-time non-invasive imaging of GGT in cancers. B. SP94-NDs achieve
830 significant ultrasound enhancement. C. P-PA-Suc-99mTc nanocomplex is localized to
831 the specific site of the cancer following intravenous injection. D. HA-GD-DOX
832 performs photothermal/chemotherapy guided by MRI for cancer treatment.

833

834 **5. Smart cancer therapy delivery systems enhancing immunotherapy**

835 Immunomodulation plays an important role in the treatment of cancers and has
836 given rise to a range of therapeutic modalities for advanced cancers [178].
837 Immunomodulation has several advantages, such as high specificity and few side
838 effects, thereby killing cancer cells by prolonging cancerigenesis, inhibiting cancer
839 growth, preventing recurrence, and suppressing metastasis [179]. Current primary
840 cancer immunotherapy strategies include immune checkpoint blockers [180],
841 monoclonal antibody technology [181], and cancer vaccines [182]. However, the
842 limited response rate of patients to conventional immunotherapy, poor efficacy in
843 solid cancers, and potentially serious toxic side effects limit the clinical use of
844 immunotherapy in cancer treatment [183]. The development of smart cancer therapy

delivery systems has optimized cancer immunotherapy strategies to overcome the shortcomings of conventional immunotherapy [184] while working synergistically with established immunotherapies to improve cancer response rates to drugs and patient survival [185, 186].

5.1 Elimination of immune escapes

Cancers can use various immune-escape mechanisms to weaken or even silence the body's anti-cancer immunity [187] and are, therefore, prone to invasion and metastasis [188]. PD-L1 is a ligand for programmed death 1 (PD-1) protein that enables cancer cells to evade the body's immune system. Thus, blocking the interaction between PD-1 and PD-L1 enhances the immune response and anti-cancer activity [189, 190], making PD-L1 an effective target for eliminating cancer immune escape [191]. The promoter-specific CRISPR/Cas9 system (F-PC/pHCP) proposed by Zhao et al. can achieve permanent disruption of the PD-L1 genome and trigger a multifaceted anti-cancer immune response to enhance immunotherapy (Fig. 9A). The system comprises an encapsulated fluorinated dendrimer containing chlorine e6 and an HSP70 promoter-driven CRISPR/Cas9 system. Under a 660 nm laser, F-PC/pHCP activates HSP70 to specifically express Cas9 protein, thereby disrupting the PD-L1 gene and preventing immune escape, demonstrating excellent anti-cancer efficacy [192].

The event of cancer cell death promoting anti-cancer immune responses is known as ICD [193]. Cancer cells undergoing ICD promote the activation of antigen-presenting cells (APC) by releasing damage-associated molecular pattern (DAMP), which increases the activation of antigen-specific T-cells, enhancing the anti-cancer effect. The combination of low doses of Nano-Folox and free 5-FU significantly promotes CRC cancer regression through OxP-mediated immunogenic cell death (Fig. 9B) [194].

Most cancer treatment approaches, such as chemotherapy and immunotherapy, enhance the immune response by increasing antigen exposure, mainly by triggering the apoptosis of target cells [195, 196]. However, apoptosis is considered a form of immune silencing, and the immune effects of chemotherapy may be severely affected

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by apoptosis. Scorch death is another type of programmed cell death that can be used to enhance the immunogenicity of cancer cells; however, immune evasion involving myeloid-derived suppressor cells (MDSC) limits the use of immunotherapy based on scorch death. MOF-based nano-delivery systems trigger apoptosis-scarring death transition and counter MDSC-based immune escape. (M+H)@ZIF/HA nano-delivery systems convert cancers into a reservoir of antigens that stimulate a powerful immune response while suppressing immune escape. It triggers a strong cytotoxic T-cell response that eliminates cancers and establishes a long-term immune memory response that prevents further metastasis (Fig. 9C) [197].

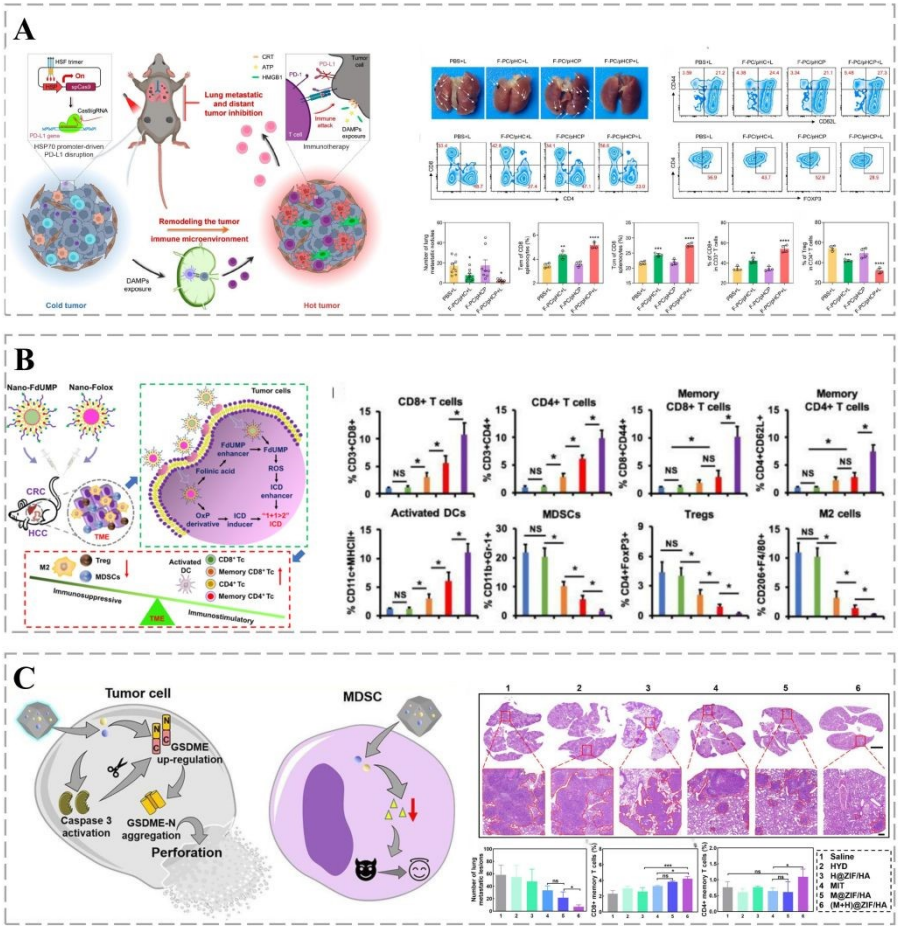

Fig. 9. Smart treatment vehicles eliminate immune escape. A. HSP70-Promoter-Driven CRISPR/Cas9 system activated by ROS for multifaceted anti-cancer immune response and multifaceted anti-cancer immune response (immunosuppression). The CRISPR/Cas9 system inhibits distant cancer growth and lung metastasis with the highest percentage of Tem and Tcm cells and significantly

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reduces the percentage of CD8 T^+ cells in distant cancers by 56.6% following F-PC/pHCP$^+$L treatment. Treg cell numbers (immunosuppression). B. Nanopreparations containing FdUMP (Nano-FdUMP) in combination with nanoformulations containing OxP derivatives and FnA (Nano-Folox) for CRC and HCC treatment. The combination of the two nanoformulations shifts the cancer microenvironment from "cold" to "hot", with CD8 T cells, CD4 T cells, and dendritic cells (DCs) being significantly activated by the combined strategy, while MDSCs, regulatory T cells (Tregs), and cancer-associated macrophages (M2) being significantly downregulated in cancer. C. Schematic representation of the role of (M+H)@ZIF/HA in cancer cells and MDSCs. (M+H)@ZIF/HA treatment resulted in a significant reduction in metastatic nodules and an increase in the percentage of CD8 Tcms and CD4 Tcms in mice, indicating that this vehicle can stimulate T-cell immune memory responses to suppress cancer metastasis.

5.2 Improvement of cancer immunosuppressive microenvironment

The TME consists of various cell types (e.g., immune cells, fibroblasts, endothelial cells, and lymphocytes), extracellular matrix, blood vessels, and chemokines and directly affects immunotherapy efficacy [198]. The TME affects the penetration of therapeutic agents into cancer and is associated with MDR and low response rates in the organism; therefore, smart therapeutic vehicles targeting the TME can enable cancer-specific therapy [199, 200].

Immunosuppressive cells, such as tumor-associated macrophages (TAMs), regulatory cells (Tregs), and MDSCs, can promote cancer development and resist immunotherapy by providing nutrition to cancer cells. However, they can also exert anti-cancer effects by enhancing phagocytic and oxidative functions [201]. Currently, cancer drug development is shifting from targeting the intrinsic properties of cancer cells to the cancer immune microenvironment and the body's immune system [202]. Multiple delivery vehicles have been designed to target TAMs and MDSCs to deliver drugs that improve the therapeutic impact of the cancer immunosuppressive microenvironment by inducing apoptosis, inhibiting cell infiltration activation, or modulating cancer cell differentiation [203]. In addition, T-cell hypofunction can lead

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to poor outcomes in cancer immunotherapy. Therefore, activating T-cell function in the cancer microenvironment enhances anti-cancer effects [204]. Tang et al. proposed using protein nanogels (NGs) to "package" large amounts of drugs onto T-cells and selectively release them upon T-cell receptor activation. Compared with the systemic use of free cytokines, the release of NGs resulted in a 16-fold expansion of T-cell numbers, whereas no significant cytotoxicity at increasing drug doses was observed [205].

Smart cancer therapy delivery systems have also been applied to enhance the infiltration of immune cells into the TME, specifically promoting the infiltration of effector T-cells with anti-cancer effects into the cancer tissue, thereby improving the cancer immune microenvironment. The cancer acid-reactive nanoparticle delivery system NP-siCD47/CCL25 significantly increased CCR9+CD8+ T-cell infiltration and downregulated CD47 expression in cancers. It sequentially released CCL25 protein and CD47 siRNAs, thereby downregulating cancer development and metastasis through T-cell-dependent immunosuppression. The combination of NP-siCD47/CCL25 with the PD-L1 antibody synergistically enhanced their anti-cancer effect [206].

Cancers are associated with fibroblasts at all stages of development, including metastasis [207]. In addition to immune cells in the TME, smart cancer therapy delivery systems have been designed to target non-immune cells, such as cancer-associated fibroblasts (CAFs). CAFs improve immunosuppression by increasing the proportion of ECM in the TME to reconstitute the microenvironment [208]. CAFs contribute to the evolution of MDR cancer phenotypes through various mechanisms [209]. Kovács et al. developed Au@Ag NPs and demonstrated their indirect effect on the metastatic activity of cancer by weakening the pro-cancer capacity of CAFs and regulating their secretion (Fig. 10A) [210]. In addition, gold-nucleated nanoparticles (AuNPs) can reduce the density of fibroblasts within cancers and improve the chemotherapeutic effects of cisplatin (Fig. 10B) [211].

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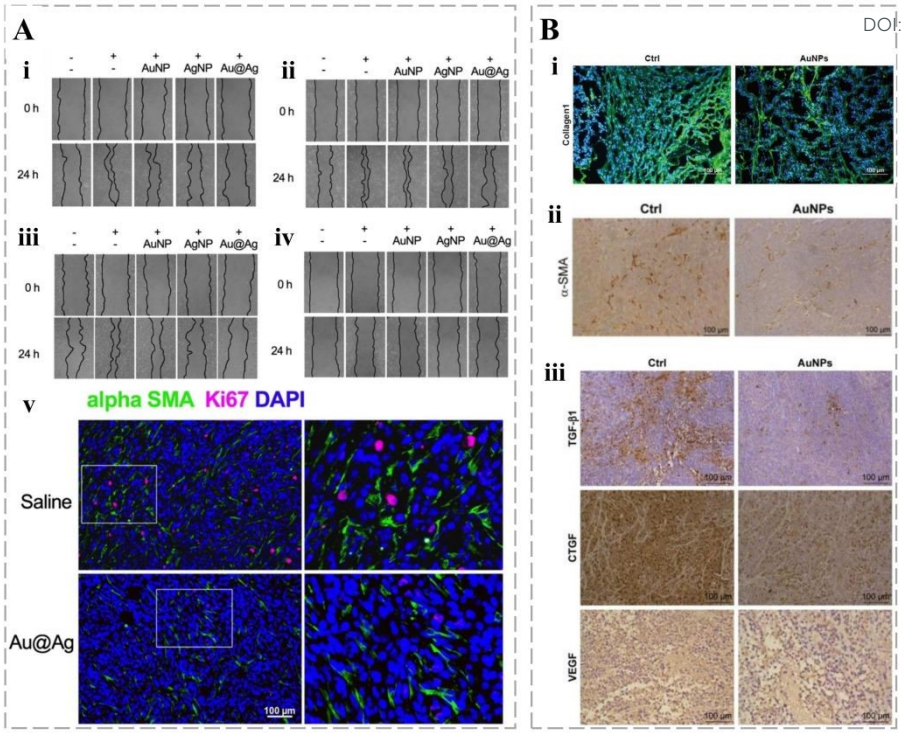

Fig. 10. Smart treatment vehicles improve the cancer immunosuppressive microenvironment. A. AgNP and Au@Ag treatments significantly inhibit the cancer cell-promoting activity of fibroblasts, characterized by reduced wound closure, thereby slowing the migration of adenocarcinoma cells. In addition, vehicles reduce the number of proliferating cancer cells in fibroblast-rich cancer microdomains. B. (i) AuNP rapidly inhibits collagen I expression in cancers, decreasing pericancer blood flow; (ii) AuNPs reduced α-SMA-positive CAF density in SW620 cancers; (iii) AuNPs reduced pro-fibroblast cytokine levels in plasma and SW620 cancers.

5.3 Enhancement of anti-cancer effect of the peripheral immune system

The successful clinical use of immune checkpoint inhibitors has led to the establishment of immunotherapy as a key component of cancer treatment [212]. Immune checkpoint blockade therapy has been applied in various cancers, and its applications are broadening [213]. Preclinical and clinical data suggest that the antibody blockade of immune checkpoints significantly enhances the anti-cancer effects of immunotherapy [214]. The activated immune system promotes immunosurveillance and eliminates cancers while establishing an immune protection mechanism against cancer recurrence [215]. Therapeutic vehicles can target immune cells such as effector T-cells, DCs, natural killer (NK) cells, and TAMs to

significantly enhance their anti-cancer effects [185]. Several immune checkpoint-based therapeutic strategies have been developed, such as PD-1/PD-L1 and CTLA-4, to promote T-cell activation and control cancer progression [216, 217]. Mao et al. reported a biomacromolecular delivery system that delivers monocyte chemotactic molecules to cancer tissue and attenuates the acidic microenvironment surrounding cancer tissues. This nanodrug carrier significantly inhibits cancer growth through the anti-cancer immune action of T cells, facilitating a cascade amplification of peripheral anti-cancer effects [218]. Therapeutic vehicles can enhance the activation of cancer antigen-specific T-cells by the targeted delivery of cancer antigens to antigen-presenting cells in the peripheral lymph nodes or spleen. The use of antigen-capturing nanocarrier particles (AC-NPs) can improve cancer immunotherapy. AC-NPs can be enriched in lymph nodes, enhance the presentation of cancer antigens by APCs, and increase the activation of CD8+ T-cells. AC-NPs cause the expansion of $CD8^+$ cytotoxic T-cells and significantly increase the ratio of $CD4T^+$/Tregs and $CD8T^+$/Tregs. Targeted delivery of mRNA encoding cancer antigens to splenic APCs was achieved by altering the surface charge of the vehicle, which enhanced the activation of antigen-specific $CD8^+$ T-cells and improved the inhibition of aggressively growing murine cancers [219]. PLE-IL-12-NPs, prepared using cytokine therapy, selectively bind to cancer cells and remain stable on the cell surface, releasing IL-12 over the course of 24 h to activate T-cells [220]. Sun et al. have developed an immunostimulatory delivery system for STING agonists that enhanced coordination and promotes nanoparticle self-assembly by exploiting the unique coordination kinetics between the drug and metal ions, supplemented with polyhistidine. The resulting Zinc-Mn-CDN Particle (ZMCP) elicits strong cellular and humoral immune responses, leading to a robust anti-tumor immune response and inhibition of tumor growth [221].

The development of cancer immunotherapy has brought hope for more patients and significantly improved their prognosis and survival rate. However, the clinical efficacy of traditional immunotherapy still faces challenges, prompting scientists to explore better solutions. The smart delivery vehicles solve the current challenges of

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cancer immunotherapy by eliminating immune escapes, improving the tumor immunosuppressive microenvironment, and enhancing the anti-tumor effect of the peripheral immune system. The widespread application of smart delivery vehicles in cancer immunotherapy still need to address some issues, such as the immunogenicity and biocompatibility issues mediated by therapeutic vectors. In addition, the excessive activation of the immune system by immunotherapy drugs can affect the activity of normal cells, so it is necessary to design delivery vehicles reasonably to control the release of therapeutic drugs. In summary, the use of smart delivery vehicles for cancer immunotherapy is of great significance.

6. Smart therapy vehicles in other cancer treatments

Cancer immunotherapy has progressed rapidly; however, its widespread use is hindered by low patient response rates [222]. Therefore, scientists have developed several therapeutic modalities to combine with immunotherapy, such as chemotherapy, radiotherapy, and phototherapy, and enhance anti-cancer immune responses [223]. Furthermore, the combination of smart therapeutic vehicles loaded with multiple therapeutic agents offers targeted delivery and controlled release, which can enhance the efficiency of combined immunotherapy [224, 225].

6.1 PDT

PDT has been used clinically to treat various cancers as a local treatment modality that activates photosensitizers in the target organ under light and induces chemical damage through ROS [226]. However, the current clinical application of PDT suffers from poor blood circulation, limited cancer accumulation, and the inability of the photosensitizer excitation wavelength to reach the target *in vivo* [227]. Nanoparticle-based PDT employs photosensitizers that generate toxic ROS after laser irradiation, acting as *in situ* vaccines to destroy cancer cells and enhance cancer immunogenicity [228]. Therefore, PDT combined with immunotherapy is an effective strategy for cancer treatment.

Bai et al. successfully developed a nano-interference vehicle for small interfering RNA (siRNA) blocking Cdk4 (siCdk4) delivery in combination with photodynamic

therapy. siCdk4y blocked the cell cycle, inhibited cancer cell proliferation, and interfered with PD-L1 expression, promoting cancer antigen presentation. Upon laser irradiation, immunogenic cancer antigens are released under PCN-mediated PDT, enhancing the anti-cancer immune response and the binding of anti-PD-L1 antibodies. This strategy enhances the synergistic effects of PDT and immunotherapy and delays cancer progression [229]. Based on the hypoxic cancer microenvironment, oxygen nanobubbles were protein-modified to enhance their cancer-targeting and apoptosis-inducing abilities. Copper phthalocyanine has been used as a photosensitizer for cancer combination therapy with anti-HER2 scFv-nCytcl, which exhibited superior z-treatment and alleviated cancer hypoxia *in vivo* (Fig. 11B) [230]. NPs were produced using clinically approved human serum albumin as a nanoreactor to encapsulate the photosensitizer chlorin e6 (CA-NPs). CA-NPs produced more ROS and exhibited excellent resistance to photobleaching. Furthermore, CA-NPs were efficiently internalized and localized in lysosomes by cancer cells, and upon irradiation, they rapidly translocated into the cytoplasm, inducing significant cytotoxicity. More importantly, ROS generation and apoptosis experiments demonstrated that the vehicle induced positive PDT effects [231].

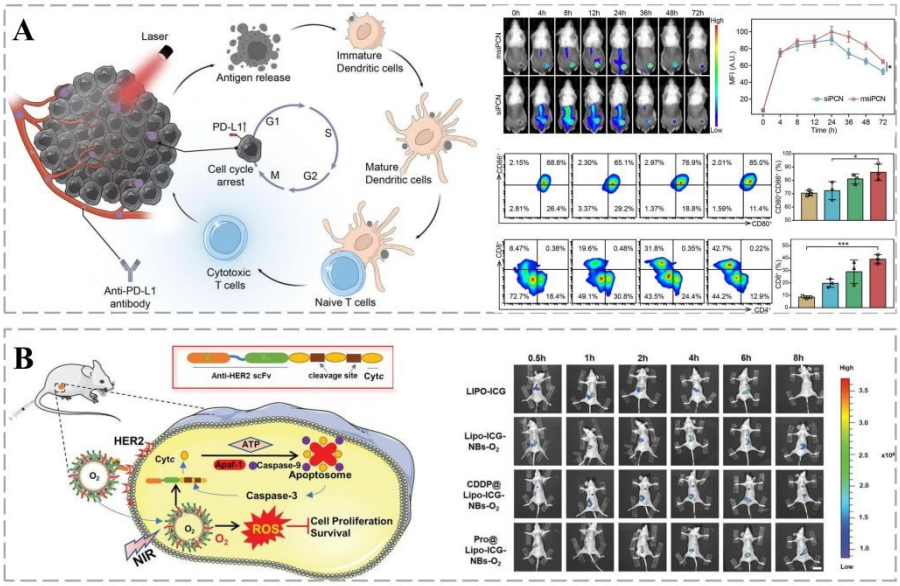

Fig. 11. Smart therapeutic vehicles mediate cancer immune-PDT therapy. A. Schematic diagram of nano-interferon combined with anti-PD-L1 antibody to promote cancer photoimmunotherapy. siPCN and msiPCN rapidly target cancer sites

for a long duration following administration. cdk4 inhibition in synergy with PDT can induce the release of strong immunogenic antigens through ICD, allowing for full DC penetration; B. Pro@Lipo-PS-NBs-O_2 combined with NIR irradiation can be concentrated in cancers following endocytosis. Pro@Lipo-ICG-NBs-O_2 has long cycling characteristics in mice and is highly concentrated in the cancer region at 8 h post-injection.

6.2 Gene therapy

Cancers are closely related to genetic alternation, and the emergence of gene therapy is a major breakthrough in the treatment of gene-related diseases [232]. Currently, several gene therapy drugs have been clinically approved [233]. Owing to their short half-life, naked nucleic acids are susceptible to rapid degradation in circulation *in vivo*. In addition, both DNA and cell membranes carry negative charges, which impede DNA from approaching the cell membrane [234], leading to a low nucleic acid capture rate by the target cells. Therefore, effective and safe gene delivery systems are urgently needed. Ideal vehicles should protect nucleic acids from degradation and maintain their long-term stability in circulation; however, they should also improve the recognition of target cells and promote their uptake efficiency [235].

The cationic polymer polyethylene glycol (PEI) plays a key role in gene delivery. The molecular weight of PEI can affect its transfection efficiency and cytotoxicity; therefore, by effective chemical modification, it is possible to improve PEI transfection activity and reduce its toxicity. ROS-responsive PEI-based fluoropolymers (TKPV) with different degrees of fluorination have excellent therapeutic properties: (1) fluorinated PEI-based fluoropolymers reduce the positive charge density and impart hydrophobic and lipophilic properties to the carrier to resist the effects of serum; (2) the fluorophilic effect makes cellular uptake more effective; (3) ROS-responsive TK linkers allow for the decomposition of polymorphic forms to reduce their cytotoxicity and improve drug release from targets [236]. Debele et al. encapsulated polyplexes in methoxy glycol (mPEG)-modified liposomes loaded with DOX in combination with siRNA. The lipid polymer successfully released DOX at low pH, inducing cancer cell death and the siRNA to leave the endosome and inhibit

the translation of the FAK protein (Fig. 12A) [237]. Liu et al. developed a charge conversion biological platform with a three-layer core-shell structure, which effectively resolved the problem of siRNA delivery to glioblastoma (GBM). The resulting nanocomposites can prolong the blood circulation of nucleic acids, have high BBB transmembrane performance, effectively accumulate in cancers, and can be specifically ingested by target cells. In addition, further destruction of the red blood cell membrane (RBCm) and the effective release of siRNA can trigger negative to positive charge transfer in cancer cells, silencing highly effective target genes with strong anti-GBM effects (Fig. 12B) [238].

The long-term safety of vehicle-mediated gene therapy for cancers has not been fully assessed. For example, the autoimmune system may recognize the new substances produced by gene therapy as “foreign” substances, leading to autoimmune diseases. Furthermore, the widespread use of emerging gene-editing therapies has led to related legal issues and adverse consequences. Therefore, the adoption of vehicle-mediated gene therapy for cancers requires long-term follow-up of patients to assess its long-term effect on suppressing cancer progression.

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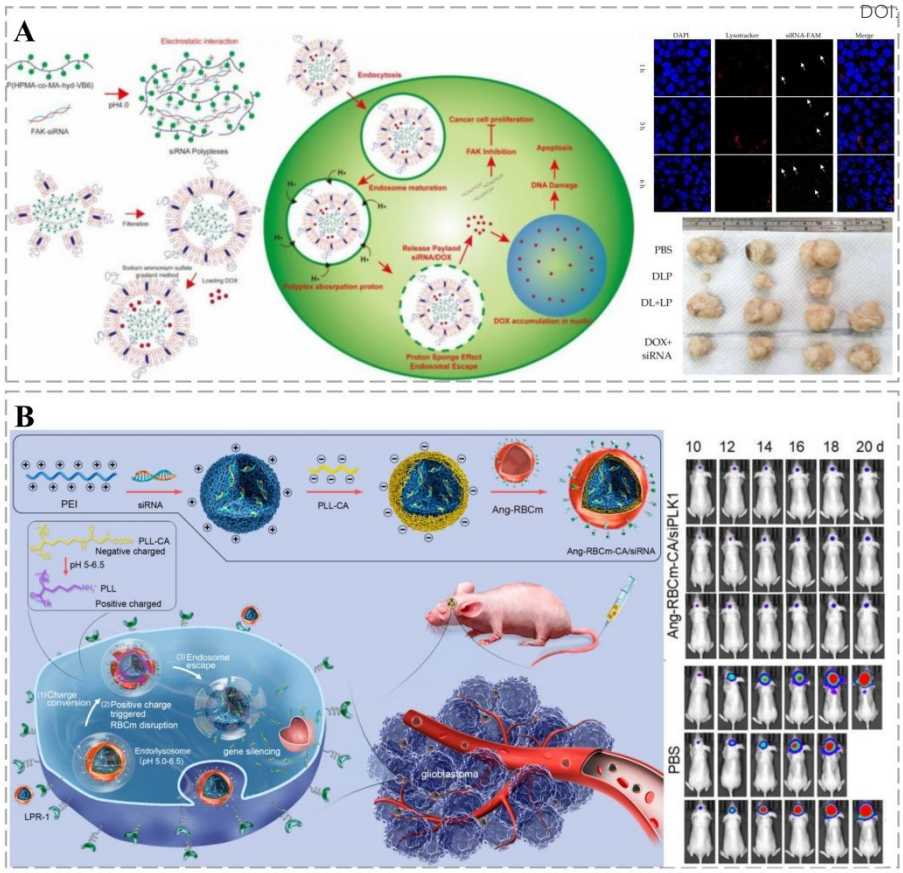

Fig. 12. Smart therapeutic vehicles mediate cancer immune-gene therapy. A. Schematic diagram of lipopolyplexes loaded with DOX for cancer chemotherapy-gene therapy. siRNA and DOX labeled by fluorescence can be observed in tumor cells, suggesting that lipopolyplexes can deliver drugs into tumor cells and release them. The co-delivery of DOX and siRNA through lipopolyplexes significantly inhibits tumor growth through a synergistic effect and was significantly more effective than free drugs. B. Schematic diagram of RNAi therapy using pH-responsive charge-switching bionanocomplex (Ang-RBCm-CA/ siRNA) to promote *in situ* glioblastoma. Ang-RBCm-CA/siRNA with long circulation time and high BBB penetration *in vivo* is effective in treating glioblastoma in nude mice through charge conversion, low pH-induced membrane disruption, and siRNA release.

7. Bottlenecks of smart cancer treatment vehicles in cancer therapy

Smart therapeutic carriers can overcome the limitations of traditional therapeutic modalities, including low bioavailability, poor specificity, and drug resistance.

Furthermore, they exhibit advantages, such as targeted and controlled drug release and rich and variable drug loading strategies, which are promising for applications in cancer therapy. However, despite the numerous promising cancer therapeutic strategies, the application of smart cancer therapeutic delivery vehicles remains challenging, and only a few studies have successfully applied them clinically.

7.1 EPR effect

Matsumura and Maeda first proposed the EPR effect in cancer targeting in 1986; solid cancers exhibit such an effect [239]. Owing to the dysfunction of lymphatic drainage in the cancer TME, carriers with a particle size of < 200 nm can enter the interstitial tissue through the blood vessel wall; therefore, drug-loaded carriers exhibit preferential accumulation in solid cancers. It is believed that passive processes dominate the accumulation of nanocarriers in cancer tissues. Current drug-loaded therapeutic vehicles that accumulate in cancers rely on the EPR effect, which is the basis for the passive targeting of vehicles [240, 241]. Their therapeutic effectiveness is influenced by the different stages of the cancer, intensity of the EPR effect, and physiological barriers [242].

Despite their widespread clinical use, passive targeting strategies have many limitations owing to the heterogeneous distribution of blood vessels in solid cancers, resulting in heterogeneous permeability. For small cancers not characterized by angiogenesis or those that metastasize, the efficiency of passive targeting based on the EPR effect is limited [243]. In addition, drug delivery vehicles that are based on the EPR effect have limited accumulation in cancers and are highly heterogeneous [244]. Therefore, treatment of patients with multiple cancers may fail owing to the lack of the EPR effect. Notably, compared with clinical cancers, it is believed that experimental animal cancer models exhibit more significant EPR effects [245] and that nanoparticles have very low delivery efficiency in human cancers.

Other routes have been suggested to address the limited accumulation of drugs in cancers based on the EPR effect (Table 3), such as increasing cancer vascular permeability through physical strategies or using drugs to achieve an increased EPR effect, such as thalidomide.

Table 3. Bottlenecks of smart cancer treatment vehicles and the corresponding solution measures

Treatment Bottleneck	Specific methods	Examples	References
EPR Effect	Physical Strategy	Thermotherapy, ultrasound, photodynamic therapy	[246-248]
	Regulation of cancer vascular permeability	Thalidomide, NO	[249-251]
	Increase carrier penetration	iRGD	[137]
Intra-stromal spread of cancer	Reduces cancer interstitial pressure	Water splitting, decomposition of cancer mesenchyme	[252, 253]
	Rational drug distribution	Ultrasmall gold nanosatellite	[254]

7.2 Diffusion of therapeutic vehicles within the cancer mesenchyme

For smart carriers to deliver drugs to cancer tissues through extravascular penetration, they must be near and enter the cancer cells before exerting their anti-cancer effects. The cancer mesenchyme determines the efficiency of passive targeting. Unlike normal tissues, cancers exhibit high interstitial pressure, especially in their central part, whereas the elevated interstitial fluid pressure (TIP) may create physiological barriers to drug delivery in solid cancers [255]. Both the absence of lymphatic vessels and the lack of lymphatic return result in the retention of tissue fluid in the cancer interstitium [256]. Excessive TIP can impede the flow of blood and drugs from blood vessels; therefore, only a few nanocarriers may reach the site of action in solid cancers [257]. This low delivery efficiency hinders the use of cancer nanodelivery systems in solid cancer treatment (Table 3).

NPs are transported into the cancer mesenchyme via a net force between mesenchymal pressure and drug concentration. Fu et al. grew Ag_2S NPs in situ on the ultrathin WS2 surface and designed a "nanomotor" to fabricate the Z-type photocatalytic drug AWS@M. AWS@M can reduce TIP by splitting the water in the interstitium to produce O_2, which rapidly enters cancer tissues. At the same time, O_2 can be converted into ROS and combined with thermal therapy, increasing the local temperature of the cancer and eliminating deep cancer cells. Upon irradiation with a 660 nm laser, the "nanomotor" can effectively reduce TIP levels in cervical and pancreatic cancers, enhancing intra-cancer drug delivery and inhibiting cancer growth. This nanomotor successfully addresses the issue of blocked intracancer drug delivery and provides a multifunctional strategy for effective cancer growth inhibition [258]. The self-assembly of a thermosensitive polymer, superparamagnetic MnFe2O4 nanoparticles, and DOX produced DOX-MTM, which exhibited high drug loading efficiency. Owing to the high content of superparamagnetic nanoparticles, DOX-MTM exhibited good SAR and magneto-thermally sensitive drug release, with a suitable LCST of 42.3 ℃. Therefore, the *in vitro* cytotoxicity was substantially increased through magneto-thermal dependent DOX release and endocytosis. Subsequently, DOX was effectively released under the influence of MH and enhanced the penetration depth into the cancer tissue [259].

7.3 Differences between animal models and clinical cancers

Most current studies on the performance of smart vehicles in cancer therapy are based on data from animal models, whereas their translation into human applications remains unexplored. *In vivo* animal models and clinical cancer patients present a large variability [260]; for example, cancer patients often have a combination of underlying diseases and are influenced by psychiatric factors and conditions that cannot be replicated in animal models. Although some preclinical and clinical studies have examined the pharmacokinetics (PK) of different species, detailed data for predicting the safety and efficacy of therapeutic vehicles in clinical settings using animal models are lacking. In addition, even in animal models, drugs do not fully exploit the EPR effect to achieve positive efficacy [261]. The efficiency of smart carrier drug delivery

based on the EPR effect is correlated with the individual size, which in turn affects the distribution and stability of the carrier *in vivo*. Previous studies have used the weight of animal models to determine the amount of drug loaded onto the therapeutic vehicle. However, the timing of drug delivery and treatment duration should be adjusted according to the specific clinical condition of the patient. The drug clearance rate in animal models fundamentally differs from that in humans, leading to inconsistencies in treatment duration compared with clinical practice. Therefore, results obtained from animal models do not accurately reflect the potential effects on clinical patients, limiting the translation of therapeutic vehicles from animal models to clinical practice.

8. Conclusion and outlook

Smart cancer delivery systems have been under development, and scientists have made several advances to actively develop and apply them to promote the effectiveness of cancer treatments. Smart cancer therapeutic delivery vehicles exhibit numerous advantages over traditional drug delivery methods; an essential advantage is their modifiability, which allows them to be designed in various sizes, shapes, and functions as needed. They can be modified or loaded with various drugs to enable the targeted delivery of therapeutic agents. Furthermore, smart carriers can exploit the EPR effect, facilitating the accumulation of drugs within cancerous tissues. Moreover, the complex TME during cancer development necessitates precise drug release at specific locations and periods. Smart therapeutic carriers possess unique properties that prevent drug degradation while releasing them in response to specific stimuli.

However, the efficacy of smart delivery systems has not met expectations, and their clinical application remains limited. The field of clinical translation is in its early stages. Furthermore, the EPR effects in cancer tissues of different patients can be inconsistent, and active targeting systems remain underdeveloped, rendering cancer drug delivery systems unstable for cancer treatment applications. Meanwhile, animal cancer models are not representative of clinical cancers, leading to discrepancies between the preclinical and clinical trial efficacies of smart drug delivery systems, thereby reducing the success rate of clinical translation.

Therefore, to improve the clinical translation, the development of multifunctional

biomaterials that can overcome most biological barriers, such as humanized animal models, is required. At the same time, appropriate smart delivery vehicles should be selected for cancer treatment, and FDA-approved drugs, such as liposomes or polymers, should be used first in clinical practice to accelerate clinical translation and immunomodulation. In addition to controlling the toxicity of immune drugs themselves, the physical and chemical properties of smart delivery vehicles, including size, shape, structure, and surface charge, should also be adjusted to reduce the side effects of nanoparticles and enhance their potential in cancer treatment [262]. In addition, the surface functionalization of smart delivery vehicles is another important factor affecting cancer treatment. Surface functionalization can affect intracellular uptake of delivery vehicles, and even affect their processing [263]. Therefore, appropriate surface functionalization should also be considered in the future development of smart delivery vehicles. Smart delivery vehicles can combine immunotherapy with other therapies such as PDT and gene therapy, significantly enhancing treatment effectiveness and reducing toxic side effects. Further exploration is needed to determine the rationale for combining different treatment regimens and optimize the timing and sequence of drug release. For instance, the timing of PTX or cyclophosphamide injections can impact the anti-cancer T-cell response induced by CD47 blockade. Additionally, the effectiveness of therapeutic vehicles can vary among patients due to individual heterogeneity. Therefore, personalizing the design of therapeutic vehicles according to each patient's needs is necessary to achieve optimal therapeutic performance. Furthermore, more extensive screening of cancer therapeutic targets should be conducted to identify suitable regimens and optimize personalized combination protocols. The development of smart cancer therapeutic vehicles holds great potential for addressing challenges in cancer treatment. These vehicles can substantially reduce the adverse events associated with immunotherapy. Current advances in diagnostic imaging, immune response monitoring, and prognosis have enhanced the versatility of smart therapeutic vehicles in cancer treatment.

Smart delivery vehicles compensate for the shortcomings of conventional cancer therapies, and their application to all types of cancers has yielded excellent

therapeutic results. The study and optimization of biomaterials have expanded the prospects for the broader application of smart delivery carriers in cancer therapy.

List of abbreviations

AC-NPs: antigen-capturing nanocarrier particles;
APC: antigen-presenting cells;
aPDL1: anti-PD-L1 blocking antibody;
AuNPs: gold nucleated nanoparticles;
BBB: blood-brain barrier;
CA: contrast agents;
CAF: cancer-associated fibroblasts;
CA-NPs: chlorin e6 nanoparticles;
COL: collagenase;
CPT: camptothecin;
CRPC: castrate prostate cancer;
CT: combination chemotherapy;
Cur: curcumin;
DAMP: damage associated molecular pattern;
DCs: dendritic cells;
DOX: doxorubicin;
DOX: Doxorubicin;
ePC: egg phosphatidylcholine;
EPR: enhanced permeability and retention;
ER: estrogen receptor;
ES: estrone;
ETP: etoposide;
Exos: exosomes;
FA: folic acid;
FR: folate receptor;
GBM: glioblastoma;

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GEM: gemcitabine;

GSH: glutathione;

GS-HM: Gyroid Surface Helical Microrobot;

HA: hyaluronic acid;

HD: hydrodynamic diameter;

HMON: hollow mesoporous organosilicon nanoparticles;

HYD: hydrazine;

ICD: immunogenic cell death;

ICG: indocyanine green;

IF-γ: interferon γ;

IMDQ: imidazoquinoline;

IRI: irinotecan; Lf: lactoferrin;

MDR: multidrug resistance;

MDSCs: myeloid-derived suppressor cells;

MFN: manganese ferrite nanoparticles;

Mito: mitoxantrone;

MMC: mitomycin C;

MNP: magnetic nanoparticles;

mPEG: methoxy glycol;

MRI: magnetic resonance imaging;

MSCs: mesenchymal stem cells;

Mtx: methotrexate;

NC: nanocluster;

NDS: nanodroplets;

NGs: nanogels;

NIR: near infra-red;

NK: natural killer;

NPs: nanoparticles;

OS: osteosarcoma;

PAA: polyacrylic acid;

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PCAD: polycarboxylic acid dextran;

PDA: polydopamine;

PDNCs: polydiacetylene nanocarriers;

PDT: photodynamic therapy;

PEG-FIbu: PEG2k-Fmoc-ibuprofen;

PEI: cationic polyethylene glycol;

PIC: polyion complex;

PK: pharmacokinetics;

PLGA: poly(lactic acid-glycolic acid);

PLL: poly-L-lysine;

PM: polymeric micelles;

PMNs: porous magnetite nanoparticles;

PMP: polymeric pre-drug;

PNPs: polymeric nanoparticles;

PpIX: protoporphyrin IX;

PTT: photothermal therapy;

PTX: paclitaxel;

QDs: quantum dots;

RAPA: rapamycin;

RBCm: red blood cell membrane;

RIF: rifampicin;

ROS: reactive oxygen species;

SDT: sonodynamic therapy;

siRNA: small interfering RNA;

SLNs: solid lipid nanoparticles;

srNPs: smart stimuli-responsive nanoparticles;

TAMs: tumor-associated macrophages;

TIP: interstitial fluid pressure;

TME: tumor microenvironment;

TNBC: triple-negative breast cancer;

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TPGS: D-α-tocopheryl polyethylene glycol succinate;

TPP: two-photon polymerization;

TQR: tariquidar;

Tregs: regulatory cells;

ZIF-8: zeolite imidazolate framework-8.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no known competing financial interests or personal relationships.

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Author contributions

XX: conceived the conceptualization and designed the manuscript. YZ and YG: manuscript writing. LH and WG: collated and produced relevant figures for the manuscript. XW and TM: participated in discussions. All authors read and approved the final manuscript.

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