

Nanoscale Advances

Accepted Manuscript

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Data Availability Statement

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



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

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26 Abstract

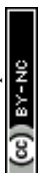
27 Chemotherapy and surgery remain the primary treatment modalities for cancers;
28 however, these techniques have drawbacks, such as cancer recurrence and toxic side
29 effects, necessitating more efficient cancer treatment strategies. Recent advancements
30 in research and medical technology have provided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

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

46 1. Introduction

47 Cancer is the leading cause of mortality worldwide [1]. The World Health
48 Organization estimated that the number of cancer-related deaths will increase by 2030
49 [2]. Therefore, effective treatment of cancers remains urgently needed.

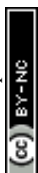
50 Surgery, radiotherapy, and chemotherapy are the first-line treatment options for
51 most cancers [3]. Conventional chemotherapy, a fundamental approach to cancer
52 treatment, distributes drugs through the bloodstream to various organs, where it
53 interferes with DNA synthesis and mitosis in rapidly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



55 resistance (MDR), nonspecific drug distribution, and systemic toxicities [6].
56 Chemotherapeutic drugs are non-selective; their cytotoxic effects can damage healthy
57 tissue cells, leading to adverse toxic effects, such as cardiotoxicity in the case of
58 adriamycin [7] or hepatotoxicity in the case of camptothecin [8]. In addition,
59 conventional chemotherapeutic drugs are less bioaccessible to cancer tissues;
60 therefore, high dosages are required, which in turn produces toxicity in normal cells
61 and increases the likelihood of multi-drug resistance [9]. The efficacy of cancer
62 therapy is influenced by drug tolerance, effective drug delivery, and duration of drug
63 action, among others, which considerably restrict its application [10]. Consequently,
64 conventional cancer treatments are associated with disadvantages, such as difficulty in
65 achieving treatment, cancer recurrence, and side effects [11]. Despite considerable
66 advances in cancer treatment, cancer-related morbidity and mortality rates continue to
67 increase [12]. According to statistics, the age-standardized cancer incidence rate is
68 201.7/100,000 in China, 319.2/100,000 in the United Kingdom, and 352.2/100,000 in
69 the United States. At the same time, the cancer mortality rate is 130.1 per 100,000 in
70 China, 102.6 per 100,000 in the United Kingdom, and 91.0 per 100,000 in the United
71 States [13]. Therefore, highly effective and less toxic strategies that can differentiate
72 between cancer and normal cells, selectively target cancer tissue, and respond
73 “intelligently” to the complex microenvironment of the cancer are warranted.

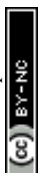
74 Precise cancer therapeutic strategies have been developed to improve clinical
75 outcomes. Nanotechnology has great potential to improve the clinical outcomes for
76 various diseases, including cancer [14-16].

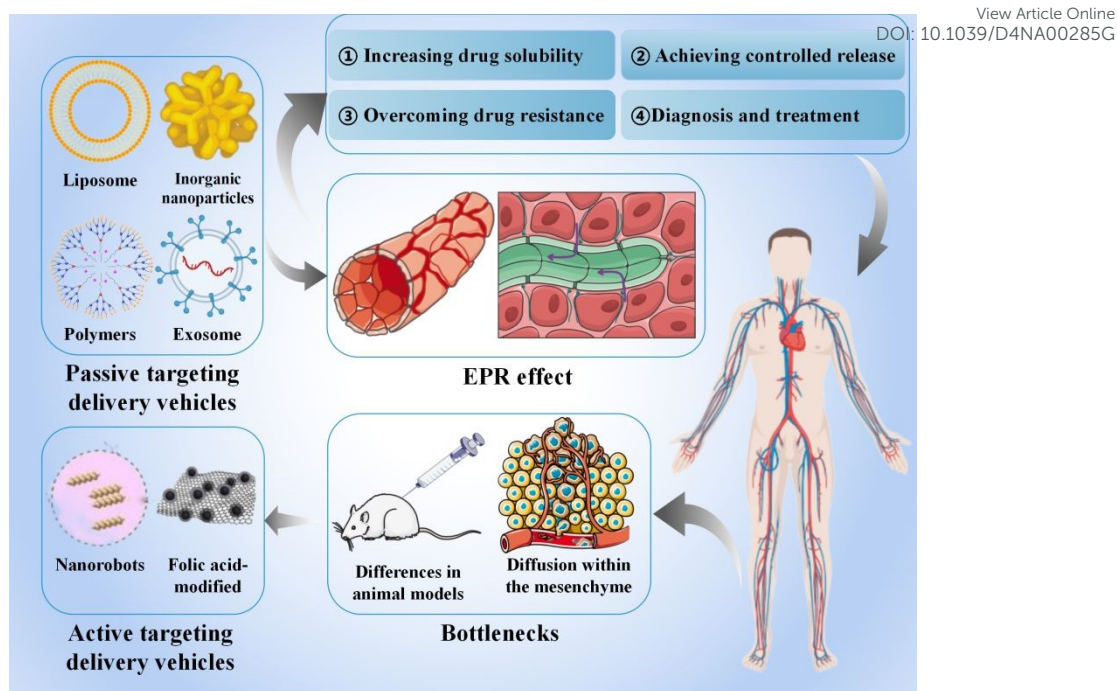
77 Among them, the development and application of various smart cancer drug
78 delivery vehicles, including polymers [17], liposomes [18], inorganic carriers [19],
79 and polymeric hydrogels [20], have greatly compensated for the limitations in
80 conventional cancer treatments. For example, smart cancer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



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

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





105

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

107 treatment.

108

109 **2. Status of research on smart delivery vehicles**

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

116 **2.1 Passive targeting-based delivery vehicles**

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

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

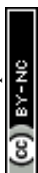
Type of delivery vehicles	Loaded drugs	Cancer	Mechanisms	References
Liposomes	Doxorubicin	Colorectal	Peptide connectors	[31]



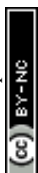
	(DOX)	cancer	respond to upregulated MMP-2 in the cancer microenvironment and enhance the capture of liposomes	
	Oxaliplatin and antisense lncRNA of MDC1	Cervical cancer	Thermosensitive release of OXA with enhanced inhibition of cervical cancer cells by co-delivery	[32]
	Anti-STAT3 siRNA	Melanoma	Enhances cell internalization and cytotoxicity, induces apoptosis, and significantly inhibits the <i>STAT10</i> 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]



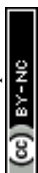
			nucleus of the tumor cell and avoid lysosomal capture	View Article Online DOI: 10.1039/D4NA00285G
Polymeric nanoparticles	Doxorubicin, 5-Fluorouracil, and Methotrexate	Triple-negative breast cancer (TNBC)	Ruthenium in the dendrimer structure has anti-cancer effects and can form stable nanocomposites 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]



		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]



			influence of its mutation	View Article Online DOI: 10.1039/D4NA00285G
	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]



			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]

120

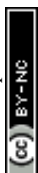
121 **2.1.1 Liposomes**

122 Smart delivery systems based on liposomes have advanced cancer therapy [60].

123 Owing to their biodegradable nature, they can be loaded with biomolecules with

124 different properties, such as RNA, peptides, and proteins, without altering their

125 original features. Thus, liposomes have become the most widely used carriers in

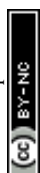


126 cancer therapy and the first therapeutic nanoparticles approved for clinical treatment
127 [61].

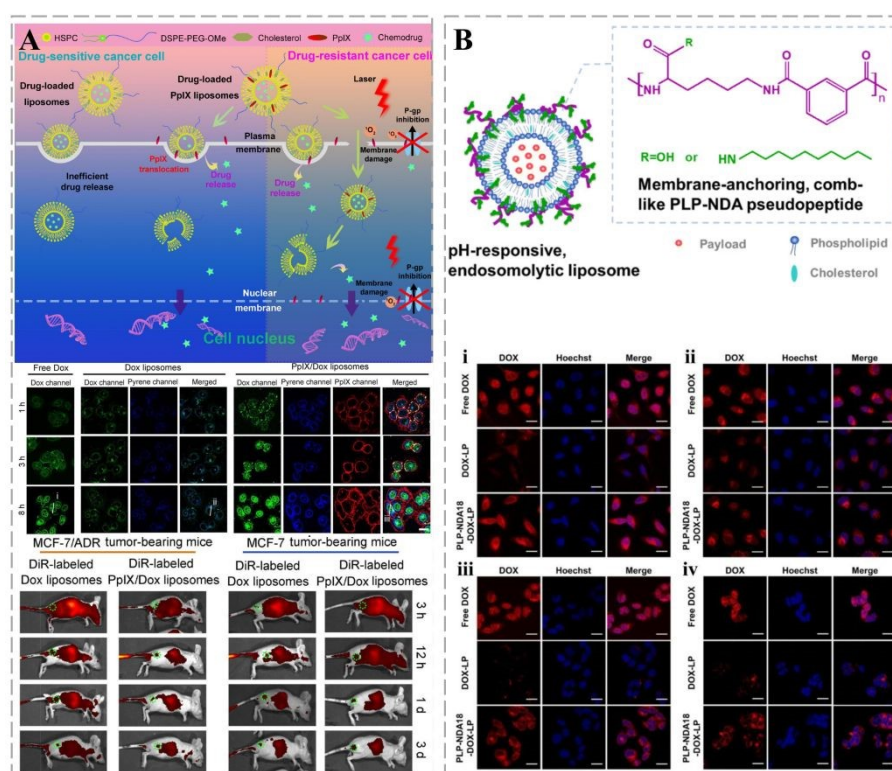
128 Liposomes are spherical lipid vesicles composed of phospholipids with a
129 bilayered structure [62]. Since their discovery in 1965, they have become versatile
130 therapeutic carriers owing to their superior biocompatibility and biodegradability, as
131 well as their unique ability to encapsulate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

137 Xie et al. used polyethylene glycol-modified liposome surfaces, followed by
138 binding to estrone (ES-SSL), to deliver chemotherapeutic drugs to ovarian cancer
139 with high expression of estrogen receptors. The authors reported a prolonged drug
140 half-life, slowed clearance, and 85.24% cancer inhibition [34]. Irinotecan (IRI) and
141 DOX are often combined in cancer treatments; Liu et al. constructed a novel liposome
142 carrier for the co-delivery of IRI and DOX using the triethyl octasulfate sucrose
143 gradient loading method. The co-delivery of liposomes maintains the optimal
144 proportion of drug action and increases the distribution of the two drugs in cancer
145 tissues. In addition, co-loaded liposomes exhibited a stronger anti-cancer effect on
146 4T-1 breast cancer xenotransplantation than a mixture of single-loaded liposomes
147 [35].

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



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



172
 173 Fig. 2. Liposomes in cancer therapy. A. Schematic illustration of the plasma
 174 membrane-activatable drug release and plasma membrane-based PDT for MDR
 175 reversal. PpIX/DOX liposomes appear rapidly in cancer-bearing mice and last for
 176 more than three days. B. Schematic diagram of pH-responsive endolysosomal liposomes.
 177 The intensity of red fluorescence in HeLa cells (i), A549 cells (ii), MES-SA cells (iii),



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

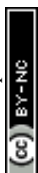
180 2.1.2 Polymeric nanoparticles

181 Polymeric nanoparticles (PNPs) are polymeric particles with a size range of 1–
182 1,000 nm [69] and different structures, such as nanocapsules, nanospheres, micelles,
183 and dendritic polymers [70]. Most materials used in PNPs have good biocompatibility
184 and are approved by the United States Food and Drug Administration (FDA) [71].
185 Various small molecules, such as RNA and proteins, modify the surface of PNPs to
186 confer different functions. In addition to targeting the delivery of loaded drugs, PNPs
187 prevent phagocytosis by the phagocytic system and adverse reactions at other sites
188 [72].

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

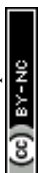
195 Dendritic polymers are hyperbranched polymers with well-defined structures
196 comprising cores, branches, gaps, and terminal groups [74]. Dendritic polymers have
197 better physicochemical behavior than straight or branched polymers, allowing for a
198 wide range of applications, including as adjuvants for vaccine antigens [75] or as
199 modified contrast agents (CAs) [76]. The unique properties of dendritic
200 macromolecules, such as uniform size and size distribution, spherical design, high
201 branching, and functional surfaces, make them effective carriers for drug delivery [77,
202 78].

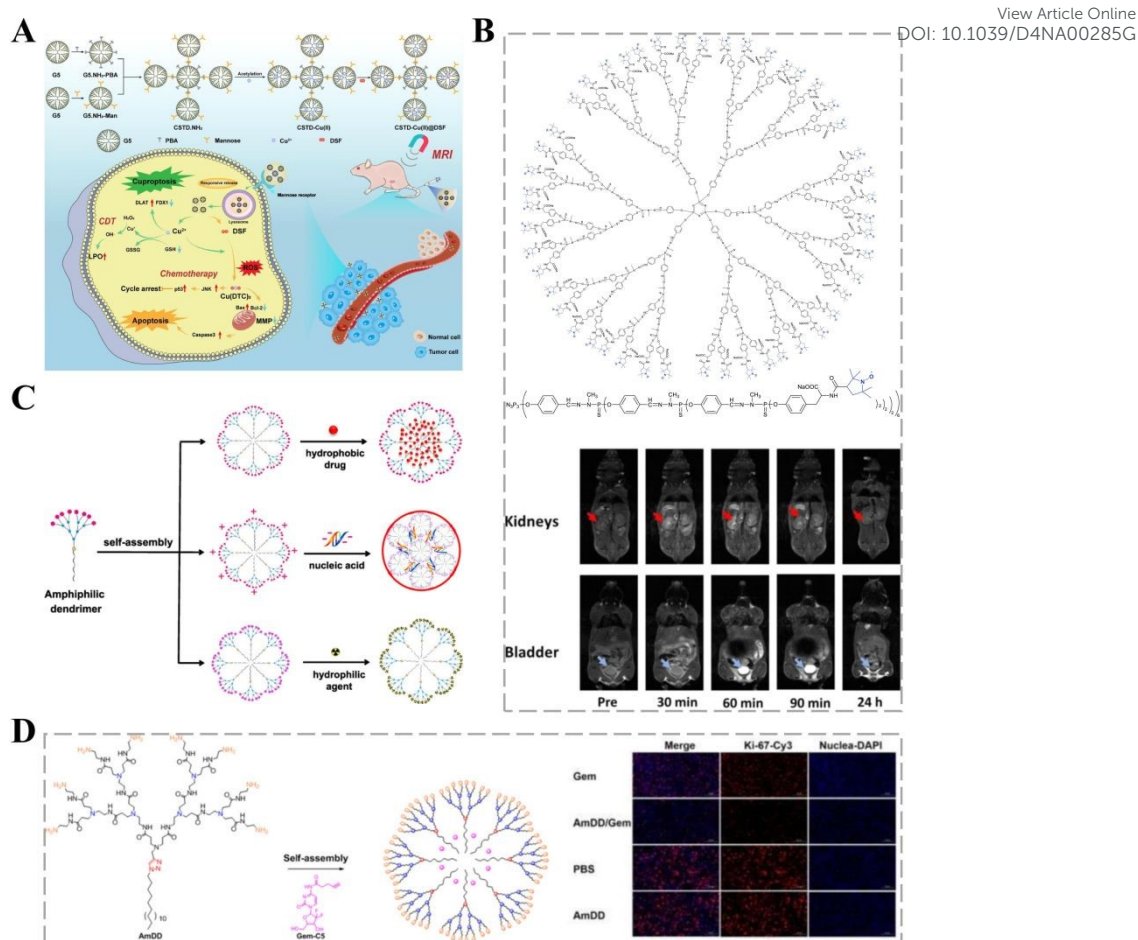
203 Magnetic resonance imaging (MRI) can be used for the early diagnosis of
204 cancers and is particularly important for brain cancers. Paramagnetic
205 gadolinium-based CAs are the most widely used for MRI acquisition in the brain;
206 however, they are associated with potentially fatal nephrogenic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



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

216 Self-assembled small amphiphilic dendrimers exhibit lipid self-assembly abilities
217 combined with the specific structure and stability of dendrimers, allowing for high
218 drug-loading capacity while maintaining a small size and stable formulation (Fig. 3C)
219 [80]. The efficacy of gemcitabine (Gem) is mainly limited by its unstable metabolism
220 and poor cellular uptake; therefore, higher doses of Gem are administered to improve
221 efficacy, leading to severe systemic toxicity [81]. Zhao et al. first synthesized an
222 aliphatic Gem prodrug and encapsulated it into a small amphiphilic dendritic polymer
223 that could self-assemble into nano-micelles in water. Nano-formulations provide
224 significant advantages, such as excellent stability to protect the loaded drug from
225 early release, maintenance of their small size for effective accumulation at the cancer
226 site, and effective pH-responsive drug release to increase the drug concentration at
227 cancer sites. Dendrimer carriers have shown more potent anti-cancer activity *in vitro*
228 and *in vivo* and considerably fewer adverse effects than free Gem (Fig. 3D) [40].





229

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

241 2.1.3 Inorganic nanoparticles

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



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

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

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

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



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

283 2.1.4 Polymer micelles

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

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



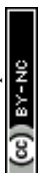
304 citraconamide bonds for rapid drug release [47]. By embedding hydrophobic
305 bioactive substances in PEG, Schröder developed a novel micellar form,
306 113-b-P(CyCL3-co-CL46)-B-PEO113, based on triblock copolymer micelles of
307 ferrocene-containing camphorsulfonamide DK164. The drug-loaded micelles are
308 stable in aqueous media and have high encapsulation efficiency and sustained-release
309 properties [50]. Sripetthong prepared nanomicelles loaded with curcumin analogs for
310 colon cancer chemotherapy. CL-NBSCh showed considerable selective cytotoxicity
311 against human colon cancer mucosal epithelial cells (HT-29). In addition, CL-NBSCh
312 micelles more effectively induced cell growth arrest at the G2/M phase and induced
313 apoptosis earlier in HT-29 cells than free CL [51].

314 2.1.5 Exosomes

315 Exosomes (Exos), extracellular vesicles (EVs) secreted by mesenchymal stem
316 cells (MSCs), are produced by the vesicle outgrowth of endosomes that mature into
317 multivesicular bodies or by vesicle outgrowth directly from the plasma membrane
318 [96]. Exos are 30–150 nm in diameter, secreted by almost all cells [97], and retain the
319 cancer-regulating properties of MSCs [98]. Exos can transport biomolecules, such as
320 proteins, lipids, and RNA, to target cells through various physiological barriers,
321 including the blood–brain barrier (BBB) [99], thereby increasing the local
322 concentration of therapeutic agents [100]. Owing to their lipid bilayers, Exos remain
323 stable in the blood and have low immunogenicity and good biocompatibility and,
324 hence, are used in several *in vivo* anti-cancer drug delivery strategies [101]. Compared
325 with cell therapy, Exos have revolutionized therapy in various diseases and enhanced
326 drug safety [102-104].

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

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

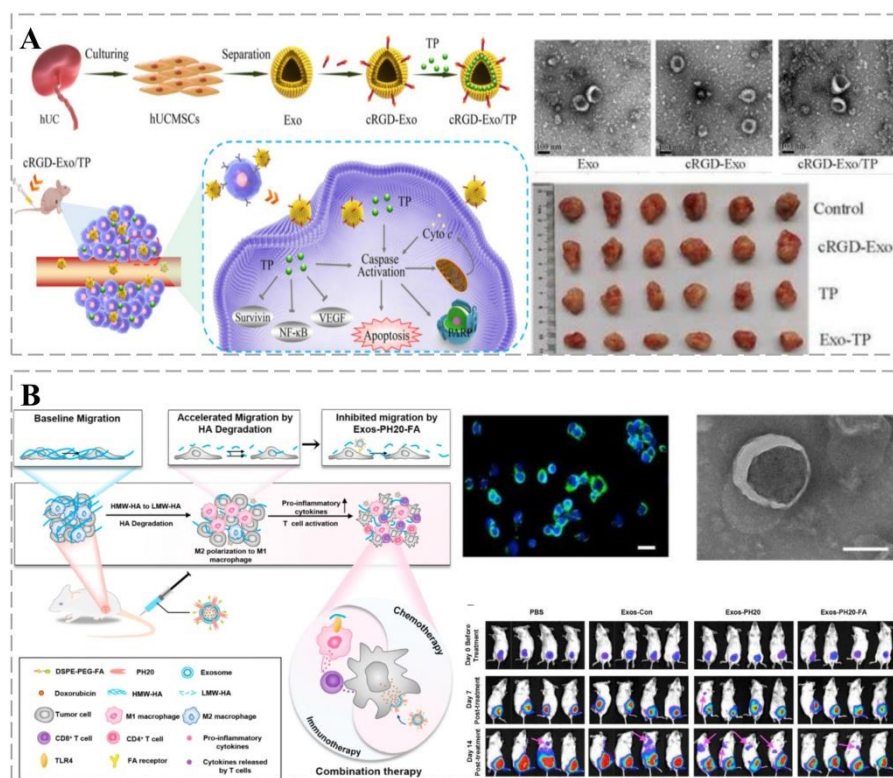


334 EXO-RIF and caused mitochondrial lysis and apoptosis, thereby increasing survival
335 [55]. Sonodynamic therapy (SDT) is minimally invasive and exhibits low toxicity and
336 the ability to treat deep tissues; however, low water-soluble acoustic sensitizers can
337 limit its clinical application and the tumor microenvironment (TME) can affect its
338 effectiveness. Exos facilitate communications between cells and regulate specific
339 responses in recipient cells. Li et al. designed a bionanosystem (ECaC) by loading
340 mesoporous calcium carbonate nanoparticles (CaCO₃-NPs) and acoustic sensitizer
341 curcumin (Cur) into cancer-derived Exos to synergistically enhance the efficacy of
342 SDT. Exos facilitated homologous targeting capabilities to CaCO₃-NPs and avoided
343 clearance by the immune system. When they reach the cancer site, CaCO₃-NPs are
344 degraded into Ca²⁺ in the acidic TME to disrupt the cellular mitochondria.
345 Consequently, cancer cell respiration is disrupted, causing oxidative stress and
346 enhancing Cur-mediated chemotherapy/SDT [56]. Gu et al. used Exos derived from
347 human umbilical cord mesenchymal stromal cells (hUCMSCs) and cyclic peptide
348 arginine-glycine-aspartate (cRGD) encapsulated with thujaplicin lactone (TP) to
349 establish a bionic targeted drug delivery system (cRGD-Exo/TP). The delivery system
350 exhibited a drug loading of 10.76 ± 1.21% and significant anti-proliferative,
351 anti-invasive, and pro-apoptotic activities in A375 cells via the cystein cascade and
352 mitochondrial pathway, as well as cell-cycle alterations (Fig. 4A) [57].

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



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



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

378 2.2 Active targeting-based delivery vehicles

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

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

Type of	Cancer	Mechanisms	Reference
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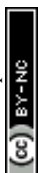


delivery vehicles			View Article Online DOI: 10.1039/D4NA00285G
Nanorobots	Hepatocellular carcinoma cells (Hep3B)	Manipulation of nanorobot movement using an external EMA system; real-time drug release by near-infrared laser irradiation	[106]
Folic acid (FA)	Breast cancer	Enhances cellular internalization 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]

381

382 2.2.1 Nanorobots

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



386 propulsion, controlled navigation, and cargo traction and release, and can potentially
387 penetrate tissues and rapidly transport therapeutic drugs directly to target sites,
388 improving efficacy and reducing systemic side effects of toxic drugs. The Janus
389 nanomotor is a small active targeting delivery system. Scientists have developed
390 micro-robots over the past decade for precise drug delivery and controlled release
391 [112]. These mobile microrobots can be used to target deep wounds and narrow blood
392 vessels that are difficult to reach during surgery [112, 113]. They increase the
393 apparent diffusion coefficient by a factor of two at low H₂O₂ fuel concentrations (< 3
394 wt%). Owing to their mesoporous structure and small size, mobile microrobots can be
395 loaded with large amounts of cargo molecules and act as active nanocarriers for
396 targeted delivery on chips [114]. The speed of motion of nanorobots can be regulated
397 by changing the fuel concentration, and the direction of motion can be controlled
398 using an external magnetic field. These assembled nanorobots can act as both
399 autonomous engines and intelligent carriers for drug loading, targeted transport, and
400 remotely controlled release near cells and tissues in living organisms [115]. Helical
401 microrobots with gyroid surfaces exhibit enhanced drug-loading efficiency [106]. The
402 microrobots, controlled by an external EMA system and equipped with iron oxide
403 nanoparticles on their surface, can achieve real-time drug release through irradiation
404 with a near-infrared (NIR) laser, combining photothermal and drug treatments for
405 maximum therapeutic effect and minimal side effects (Fig. 5A).

406 2.2.2 Folic acid

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

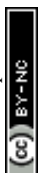


416 diesteroyl phosphatidylethanolamine-poly(ethylene glycol)-FA (DSPE-PEG-FA)
417 ligands. Functionalized NPs can improve the anti-cancer effect of free drugs.

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

436 2.2.3 Lactoferrin

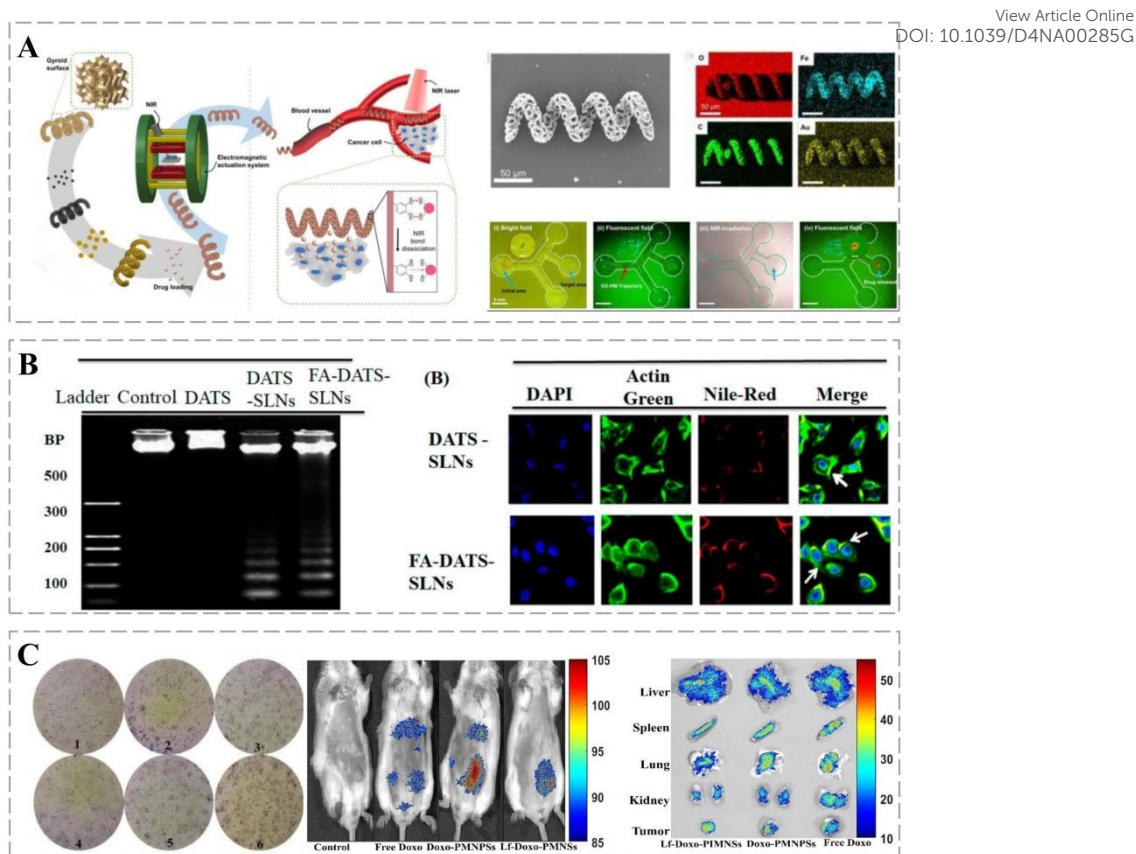
437 Lactoferrin (Lf) is a non-toxic and inexpensive natural iron-binding glycoprotein,
438 the anti-cancer activity of which has been observed in various cell lines, animal
439 models, and clinical trials. The main anti-cancer mechanisms include the
440 downregulation of the anti-apoptotic protein Bcl-2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



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

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





470

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

481 2.2.4 Other

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



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

493

494 **3. The pharmacokinetics of smart cancer therapy delivery vehicles**

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

510 **3.1 Absorption and transport**

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

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



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

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

543 3.2 Distribution and metabolism

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



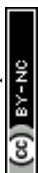
547 to the fact that CMCS-DFNS@PTX needs to be endocytosed to enter the cells and
548 needs to undergo a certain sustained release time after entering the cells to exert the
549 drug effect. After 2 h, the drug concentration in CMCS-DFNS@ PTX had a higher
550 drug concentration than free PTX after 2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

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

566 3.3 Excretion

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

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



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

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

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

593 **4. Advantages of smart cancer therapy delivery vehicles**

594 **4.1 Delivery of drugs with different physicochemical properties through** 595 **improved solubility**

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

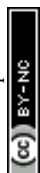
604 Smart drug delivery carriers containing hydrophobic or amphiphilic materials
605 address the problem of poor solubility of hydrophobic drugs, such as PLGA, PLA,
606 chitosan, gelatin, polycaprolactone, and polyalkyl cyanoacrylate [143]. The high



607 lipophilicity and low water solubility of the oleanolic acid derivative DKS26 attribute
608 to its very low oral bioavailability. Liposomal loading of DKS26 significantly
609 enhances the absolute oral bioavailability [144]. Gholizadeh *et al.* prepared
610 immunoliposomal carriers to deliver sepantronium bromide YM155 (a hydrophilic
611 drug with low oral bioavailability and rapid renal elimination). The YM155-loaded
612 liposomes exhibited prolonged circulation and a significantly increased half-life in
613 cancer tissue compared to intravenous free YM155 [145]. Paclitaxel (PTX) is an
614 effective anti-cancer drug with very low solubility in water. Meanwhile, the complex
615 gastrointestinal environment and epithelial barriers hinder its antitumor effect.
616 PEGylated high-density glycerylcholic acid-decorated micelles (PTX@GNPs) based
617 on PEGylation can encapsulate PTX by π - π stacking, thereby gaining mucus-trapping
618 escape ability and significantly improving drug targeting in the gastrointestinal tract
619 [146]. Mitomycin C (MMC) is used for the treatment of various solid cancers;
620 however, the application of MMC via intravenous injection is associated with toxic
621 side effects and non-specific interpolymerization. Yang *et al.* synthesized
622 PEG2k-Fmoc-ibuprofen (PEG-FIbu) micelle nanocarriers loaded with MMC.
623 PEG-FIbu/MMC micelles exhibited superior stability, higher drug loading efficiency,
624 slower release, longer circulation time, and higher cancer uptake and therapeutic
625 efficiency than MMC intravenous injection [147]. Zhao *et al.* developed
626 FA-PLGA/PCADK-lipid NPs (FA-PPLNPs) to encapsulate methotrexate (Mtx). The
627 developed NPs exhibited high cellular uptake rates [148]. The amphiphilic
628 CPT-ss-EB prodrug developed by Zhang *et al.* self-assembles into nanostructures with
629 high solubility in aqueous solution while rapidly transforming into a long-term
630 circulating nanocomplex [149]. Therefore, therapeutic carriers can enhance the
631 solubility of hydrophobic drugs and deliver drugs with different physicochemical
632 properties.

633 4.2 Controlled release of drugs

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



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

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

652 The structure and metabolism of cancers result in an acidic microenvironment
653 [154], which provides favorable conditions for cancer growth, affecting the immune
654 surveillance of cancer cells and possibly leading to the immune escape of the cancer.
655 Cancer-targeting smart nanoparticle carriers can alter this microenvironment based on
656 different pH values: the surface potential of the carrier shifts from negative to neutral
657 (pH 6.5–7.0), which facilitates cellular uptake of the drug, whereas, at pH 4.5–6.5, the
658 carriers dissociate, inducing endosomal escape and releasing the drug into the
659 cytoplasm. Meanwhile, smart nanoparticles modified with the cancer-penetrating
660 peptide iNRG were used as cancer-targeting molecules. In an acidic environment (pH
661 6.8), this carrier promoted the uptake of the drug by cancer cells (Fig. 6A) [155]. The
662 polyion complex (PIC) micelles prepared by Hsieh et al. demonstrated good colloidal
663 stability at different pH values. Controlled permeability of the micelles can be
664 achieved by adjusting the degree of cross-linking and accelerating drug release at low
665 pH conditions [156]. ROS plays an important role in cancerigenesis; elevated ROS
666 levels have been reported in several cancer cells [157]. Wang et al. designed a

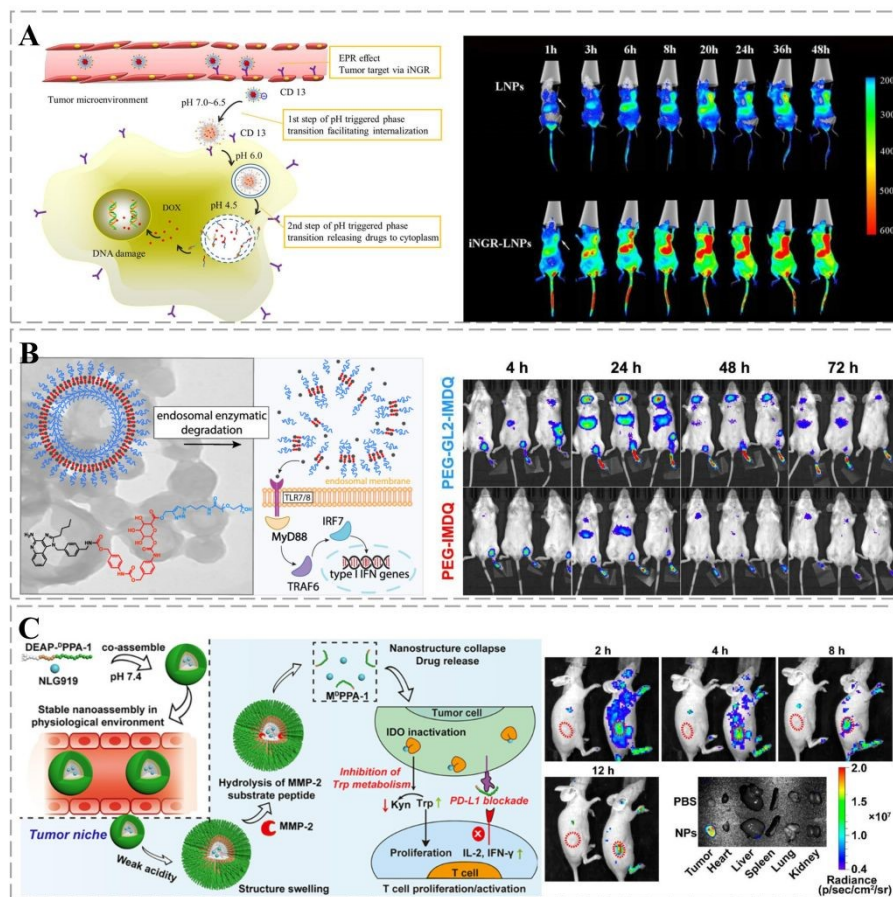


667 therapeutic system containing a ROS marker that oxidizes and hydrolyzes TSPBA in
668 the presence of ROS, resulting in sustained release of gemcitabine (GEM) and aPDL1
669 (anti-PD-L1 blocking antibody) to enhance anti-cancer responses [158]. In addition,
670 enzyme-responsive cancer drug delivery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

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



697 transformation to achieve optimal size and shape changes according to therapeutic
 698 needs. It synergistically amplified the ROS cascade response, increased H_2O_2 and
 699 $\bullet\text{OH}$ levels, induced immunogenic cell death (ICD) responses, and promoted
 700 anti-TNBC immunity by enhancing the interaction between dendritic cells (DCs) and
 701 dying cancer cells [163]. Stimuli-responsive drug delivery systems have considerable
 702 potential to improve the efficiency of cancer treatment by controlling drug release and
 703 degradation and combining them with multiple treatment options to minimize side
 704 effects.



705
 706 Fig. 6. Smart therapeutic vehicles enabling controlled drug release. A. Schematic
 707 diagram of the two-step phase transition of pH-triggered iNGR-LPNs. iNGR-LPNs
 708 alter the biodistribution of free DOX, exhibiting long circulation and cancer-specific
 709 distribution properties while avoiding the cardiac distribution. iNGR-LPNs
 710 administered to mice first recognize cancer neovascularization, induce high levels of
 711 particle accumulation at the cancer site, and promote cancer-specific cellular uptake
 712 via CD13 receptor-mediated endocytosis and pH-triggered particle phase transition to



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

723 **4.3 Overcoming multi-drug resistance and synergistic treatment to improve** 724 **efficacy**

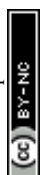
725 The underlying principles of various cancer combination therapies have been
726 investigated to achieve optimal clinical outcomes [164]. Compared with
727 monotherapy, combination therapy significantly improves clinical outcomes,
728 effectively overcomes clonal heterogeneity, and reduces drug toxicity in humans
729 [165].

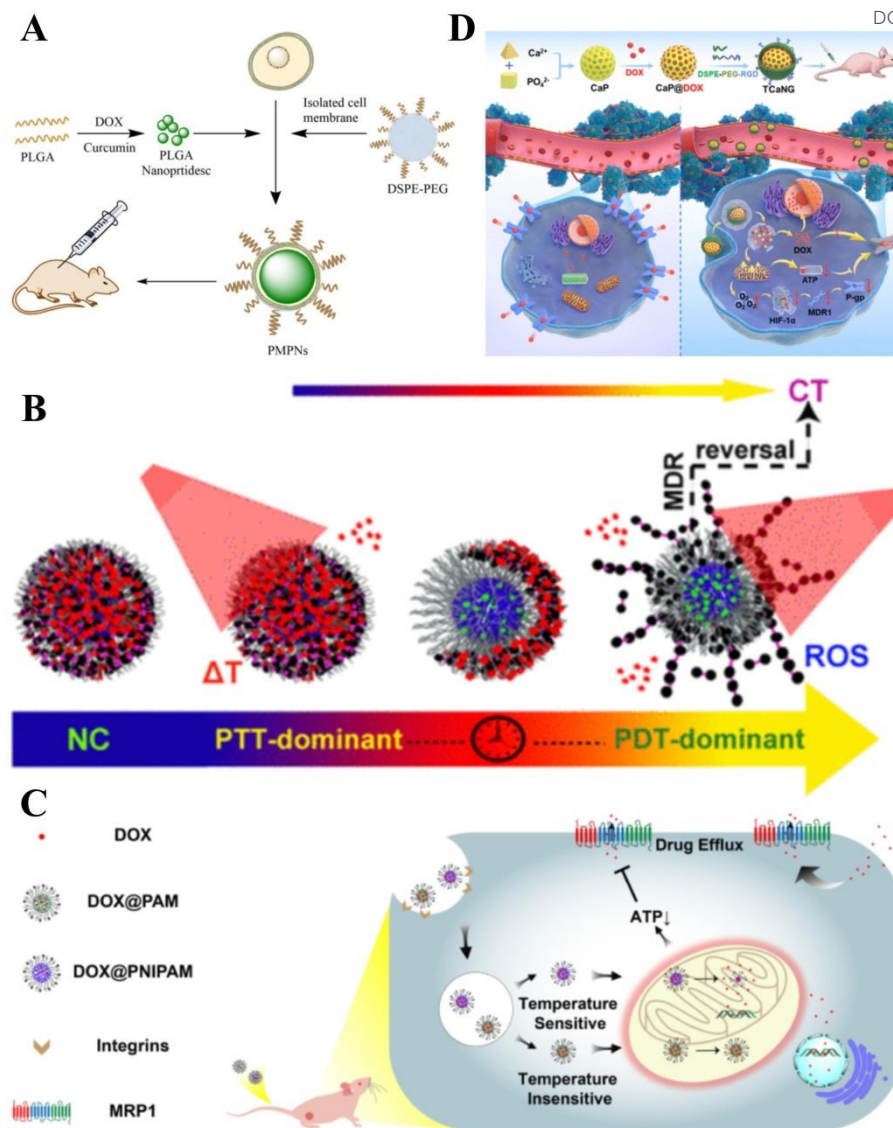
730 MDR affects the efficacy of chemotherapy and leads to chemotherapy failure.
731 When treatment doses are increased to avoid drug resistance, the resulting drug
732 toxicity damages healthy organs and tissues. Smart drug delivery carriers have been
733 proven effective in overcoming MDR using several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



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

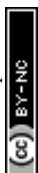
751 Smart therapeutic carriers can also overcome MDR by inhibiting energy
752 metabolism and blocking ion-mediated signaling pathways. Ruan et al. developed a
753 mitochondrial temperature-responsive drug delivery system that prevents adriamycin
754 efflux and promotes adriamycin accumulation and mitochondrial targeting in
755 drug-resistant cancers using thermally responsive nanocarriers. Thermoresponsive
756 nanocarriers effectively enhanced the cytotoxicity of adriamycin and reversed drug
757 resistance in cancer-bearing mice (Fig. 7C) [169]. Such effects inhibit cellular
758 respiration and downregulate HIF-1 α expression to suppress P-glycoprotein
759 biosynthesis. Additionally, Ca²⁺ burst-induced respiratory inhibition blocks
760 intracellular ATP production, leading to P-glycoprotein insufficiency. Thus, TCANG
761 enhanced the proliferative effect of IC50DOX on MCF-7/ADR cells by
762 approximately 30-fold and the proliferation of drug-resistant cancers by
763 approximately 13-fold (Fig. 7D) [170].





764

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

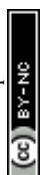


776 drug resistance in cancer cells through a nano-activated intracellular calcium
777 explosion resistance.

778 4.4 Diagnosis and treatment

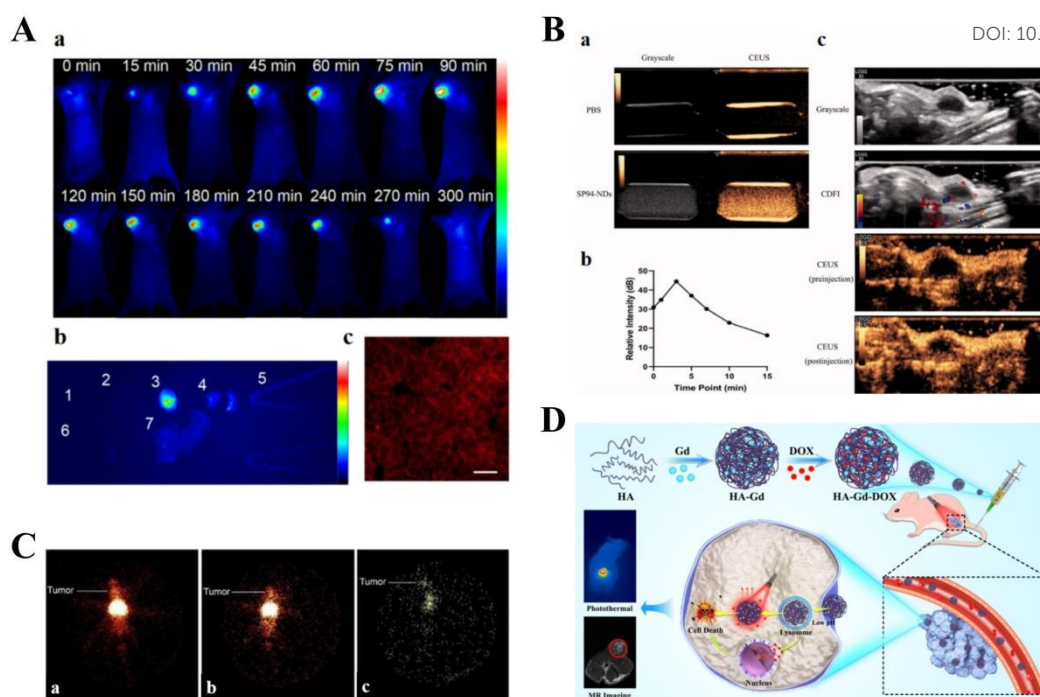
779 Cancer therapeutic carriers can be loaded with various CA and fluorescent agents
780 to effectively deliver drugs. Owing to their optical properties, these carriers can be
781 used in the diagnosis of cancers.

782 Zhou et al. developed NRh-G-NPs, which can specifically respond to GGT
783 overexpressed in U87MG cancer cells and selectively illuminate cancers for
784 image-guided therapy. Furthermore, restoring photothermal properties in the cancer
785 region can improve the accuracy of cancer-targeted therapy and reduce side effects
786 (Fig. 8A) [171]. Pan used circulating EV vehicles to assess cancer-specific drug-target
787 interactions in patient blood samples, such as Exos small molecule chemical
788 occupancy and protein expression monitoring (ExoSCOPE). The use of such
789 technology in cancer diagnosis and treatment monitoring allows for accurate
790 classification of disease status and rapid differentiation of the outcome of targeted
791 therapies within 24 h of treatment [172]. Nanodroplets (NDS), a noninvasive delivery
792 strategy, can enhance both ultrasound imaging and therapeutic efficacy. Zhao et al.
793 constructed novel SP94 peptide-modified and doxorubicin-loaded ultrasound
794 nanodroplets (SP94-DOX-NDs) to target and treat castrate prostate cancer (CRPC). *In*
795 *vitro* and *in vivo* experiments showed that SP94-DOX-NDs could specifically deliver
796 DOX to 22RV1 cells under ultrasound guidance and, therefore, exhibited strong
797 anti-cancer effects (Fig. 8B) [173]. Narmani et al. used a polyethylene
798 glycol-modified and folate-functionalized PAMAM G4 dendrimer as a smart,
799 low-toxicity nanocarrier. The nanocarrier exhibited excellent potential for delivering
800 5-FU chemotherapeutic agents to breast cancer cell lines, and cancer accumulation
801 studies demonstrated its targeting ability. In addition, imaging studies of targeted
802 radiotracers confirmed the excellent performance of the nanocomplexes in a
803 cancer-bearing mouse model. In conclusion, novel smart synthetic nanocomplexes are
804 suitable for cancer treatment, tracking, and imaging (Fig. 8C) [174]. Kong et al.
805 designed a novel nanocarrier based on HA conjugated with Gd³⁺ and loaded it with



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].





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



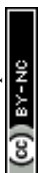
845 delivery systems has optimized cancer immunotherapy strategies to overcome the
846 shortcomings of conventional immunotherapy [184] while working synergistically
847 with established immunotherapies to improve cancer response rates to drugs and
848 patient survival [185, 186].

849 **5.1 Elimination of immune escapes**

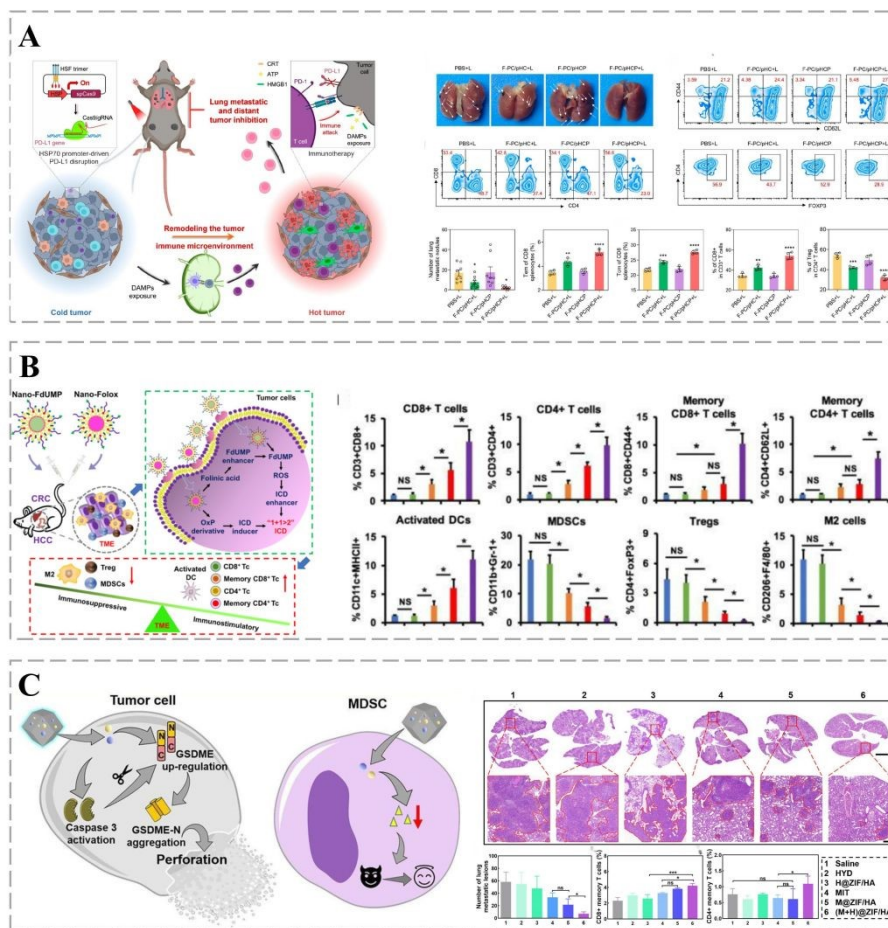
850 Cancers can use various immune-escape mechanisms to weaken or even silence
851 the body's anti-cancer immunity [187] and are, therefore, prone to invasion and
852 metastasis [188]. PD-L1 is a ligand for programmed death 1 (PD-1) protein that
853 enables cancer cells to evade the body's immune system. Thus, blocking the
854 interaction between PD-1 and PD-L1 enhances the immune response and anti-cancer
855 activity [189, 190], making PD-L1 an effective target for eliminating cancer immune
856 escape [191]. The promoter-specific CRISPR/Cas9 system (F-PC/pHCP) proposed by
857 Zhao et al. can achieve permanent disruption of the PD-L1 genome and trigger a
858 multifaceted anti-cancer immune response to enhance immunotherapy (Fig. 9A). The
859 system comprises an encapsulated fluorinated dendrimer containing chlorine e6 and
860 an HSP70 promoter-driven CRISPR/Cas9 system. Under a 660 nm laser, F-PC/pHCP
861 activates HSP70 to specifically express Cas9 protein, thereby disrupting the PD-L1
862 gene and preventing immune escape, demonstrating excellent anti-cancer efficacy
863 [192].

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

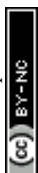
871 Most cancer treatment approaches, such as chemotherapy and immunotherapy,
872 enhance the immune response by increasing antigen exposure, mainly by triggering
873 the apoptosis of target cells [195, 196]. However, apoptosis is considered a form of
874 immune silencing, and the immune effects of chemotherapy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



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



884
 885 Fig. 9. Smart treatment vehicles eliminate immune escape. A.
 886 HSP70-Promoter-Driven CRISPR/Cas9 system activated by ROS for multifaceted
 887 anti-cancer immune response and multifaceted anti-cancer immune response
 888 (immunosuppression). The CRISPR/Cas9 system inhibits distant cancer growth and
 889 lung metastasis with the highest percentage of Tem and Tcm cells and significantly



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

903 5.2 Improvement of cancer immunosuppressive microenvironment

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

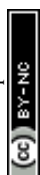
910 Immunosuppressive cells, such as tumor-associated macrophages (TAMs),
911 regulatory cells (Tregs), and MDSCs, can promote cancer development and resist
912 immunotherapy by providing nutrition to cancer cells. However, they can also exert
913 anti-cancer effects by enhancing phagocytic and oxidative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

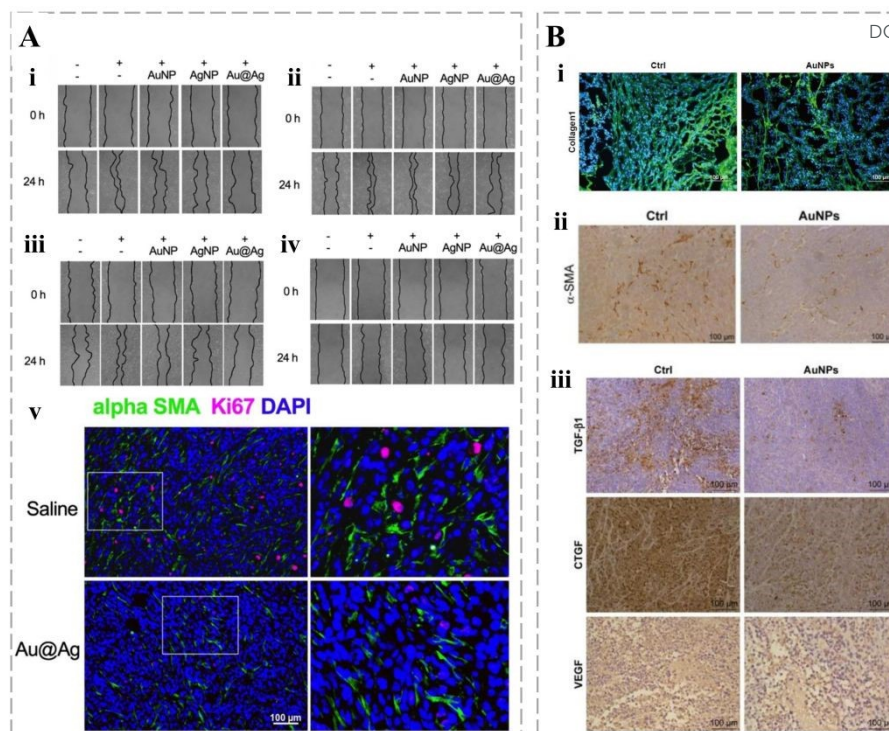


920 to poor outcomes in cancer immunotherapy. Therefore, activating T-cell function in
921 the cancer microenvironment enhances anti-cancer effects [204]. Tang et al. proposed
922 using protein nanogels (NGs) to “package” large amounts of drugs onto T-cells and
923 selectively release them upon T-cell receptor activation. Compared with the systemic
924 use of free cytokines, the release of NGs resulted in a 16-fold expansion of T-cell
925 numbers, whereas no significant cytotoxicity at increasing drug doses was observed
926 [205].

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

937 Cancers are associated with fibroblasts at all stages of development, including
938 metastasis [207]. In addition to immune cells in the TME, smart cancer therapy
939 delivery systems have been designed to target non-immune cells, such as
940 cancer-associated fibroblasts (CAFs). CAFs improve immunosuppression by
941 increasing the proportion of ECM in the TME to reconstitute the microenvironment
942 [208]. CAFs contribute to the evolution of MDR cancer phenotypes through various
943 mechanisms [209]. Kovács et al. developed Au@Ag NPs and demonstrated their
944 indirect effect on the metastatic activity of cancer by weakening the pro-cancer
945 capacity of CAFs and regulating their secretion (Fig. 10A) [210]. In addition,
946 gold-nucleated nanoparticles (AuNPs) can reduce the density of fibroblasts within
947 cancers and improve the chemotherapeutic effects of cisplatin (Fig. 10B) [211].





948

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

957 5.3 Enhancement of anti-cancer effect of the peripheral immune system

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



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

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



997 cancer immunotherapy by eliminating immune escapes, improving the tumor
998 immunosuppressive microenvironment, and enhancing the anti-tumor effect of the
999 peripheral immune system. The widespread application of smart delivery vehicles in
1000 cancer immunotherapy still need to address some issues, such as the immunogenicity
1001 and biocompatibility issues mediated by therapeutic vectors. In addition, the excessive
1002 activation of the immune system by immunotherapy drugs can affect the activity of
1003 normal cells, so it is necessary to design delivery vehicles reasonably to control the
1004 release of therapeutic drugs. In summary, the use of smart delivery vehicles for cancer
1005 immunotherapy is of great significance.

1006

1007 **6. Smart therapy vehicles in other cancer treatments**

1008 Cancer immunotherapy has progressed rapidly; however, its widespread use is
1009 hindered by low patient response rates [222]. Therefore, scientists have developed
1010 several therapeutic modalities to combine with immunotherapy, such as
1011 chemotherapy, radiotherapy, and phototherapy, and enhance anti-cancer immune
1012 responses [223]. Furthermore, the combination of smart therapeutic vehicles loaded
1013 with multiple therapeutic agents offers targeted delivery and controlled release, which
1014 can enhance the efficiency of combined immunotherapy [224, 225].

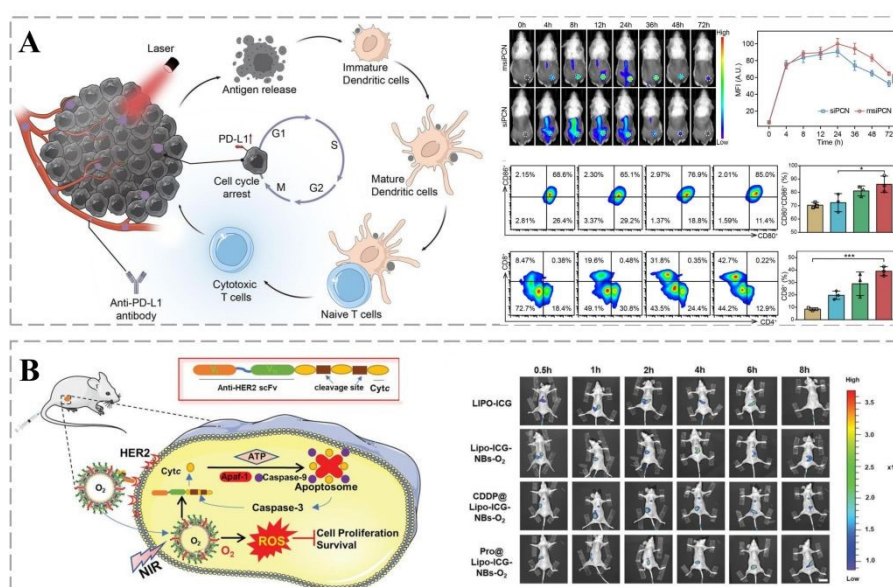
1015 **6.1 PDT**

1016 PDT has been used clinically to treat various cancers as a local treatment
1017 modality that activates photosensitizers in the target organ under light and induces
1018 chemical damage through ROS [226]. However, the current clinical application of
1019 PDT suffers from poor blood circulation, limited cancer accumulation, and the
1020 inability of the photosensitizer excitation wavelength to reach the target *in vivo* [227].
1021 Nanoparticle-based PDT employs photosensitizers that generate toxic ROS after laser
1022 irradiation, acting as *in situ* vaccines to destroy cancer cells and enhance cancer
1023 immunogenicity [228]. Therefore, PDT combined with immunotherapy is an effective
1024 strategy for cancer treatment.

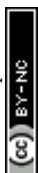
1025 Bai et al. successfully developed a nano-interference vehicle for small interfering
1026 RNA (siRNA) blocking Cdk4 (siCdk4) delivery in combination with photodynamic



1027 therapy. siCdk4y blocked the cell cycle, inhibited cancer cell proliferation, and
 1028 interfered with PD-L1 expression, promoting cancer antigen presentation. Upon laser
 1029 irradiation, immunogenic cancer antigens are released under PCN-mediated PDT,
 1030 enhancing the anti-cancer immune response and the binding of anti-PD-L1 antibodies.
 1031 This strategy enhances the synergistic effects of PDT and immunotherapy and delays
 1032 cancer progression [229]. Based on the hypoxic cancer microenvironment, oxygen
 1033 nanobubbles were protein-modified to enhance their cancer-targeting and
 1034 apoptosis-inducing abilities. Copper phthalocyanine has been used as a
 1035 photosensitizer for cancer combination therapy with anti-HER2 scFv-nCytcl, which
 1036 exhibited superior z-treatment and alleviated cancer hypoxia *in vivo* (Fig. 11B) [230].
 1037 NPs were produced using clinically approved human serum albumin as a nanoreactor
 1038 to encapsulate the photosensitizer chlorin e6 (CA-NPs). CA-NPs produced more ROS
 1039 and exhibited excellent resistance to photobleaching. Furthermore, CA-NPs were
 1040 efficiently internalized and localized in lysosomes by cancer cells, and upon
 1041 irradiation, they rapidly translocated into the cytoplasm, inducing significant
 1042 cytotoxicity. More importantly, ROS generation and apoptosis experiments
 1043 demonstrated that the vehicle induced positive PDT effects [231].



1044
 1045 Fig. 11. Smart therapeutic vehicles mediate cancer immune-PDT therapy. A.
 1046 Schematic diagram of nano-interferon combined with anti-PD-L1 antibody to
 1047 promote cancer photoimmunotherapy. siPCN and msiPCN rapidly target cancer sites



1048 for a long duration following administration. cdk4 inhibition in synergy with PDT can
1049 induce the release of strong immunogenic antigens through ICD, allowing for full DC
1050 penetration; B. Pro@Lipo-PS-NBs-O₂ combined with NIR irradiation can be
1051 concentrated in cancers following endocytosis. Pro@Lipo-ICG-NBs-O₂ has long
1052 cycling characteristics in mice and is highly concentrated in the cancer region at 8 h
1053 post-injection.

1054 6.2 Gene therapy

1055 Cancers are closely related to genetic alternation, and the emergence of gene
1056 therapy is a major breakthrough in the treatment of gene-related diseases [232].
1057 Currently, several gene therapy drugs have been clinically approved [233]. Owing to
1058 their short half-life, naked nucleic acids are susceptible to rapid degradation in
1059 circulation *in vivo*. In addition, both DNA and cell membranes carry negative charges,
1060 which impede DNA from approaching the cell membrane [234], leading to a low
1061 nucleic acid capture rate by the target cells. Therefore, effective and safe gene
1062 delivery systems are urgently needed. Ideal vehicles should protect nucleic acids from
1063 degradation and maintain their long-term stability in circulation; however, they should
1064 also improve the recognition of target cells and promote their uptake efficiency [235].

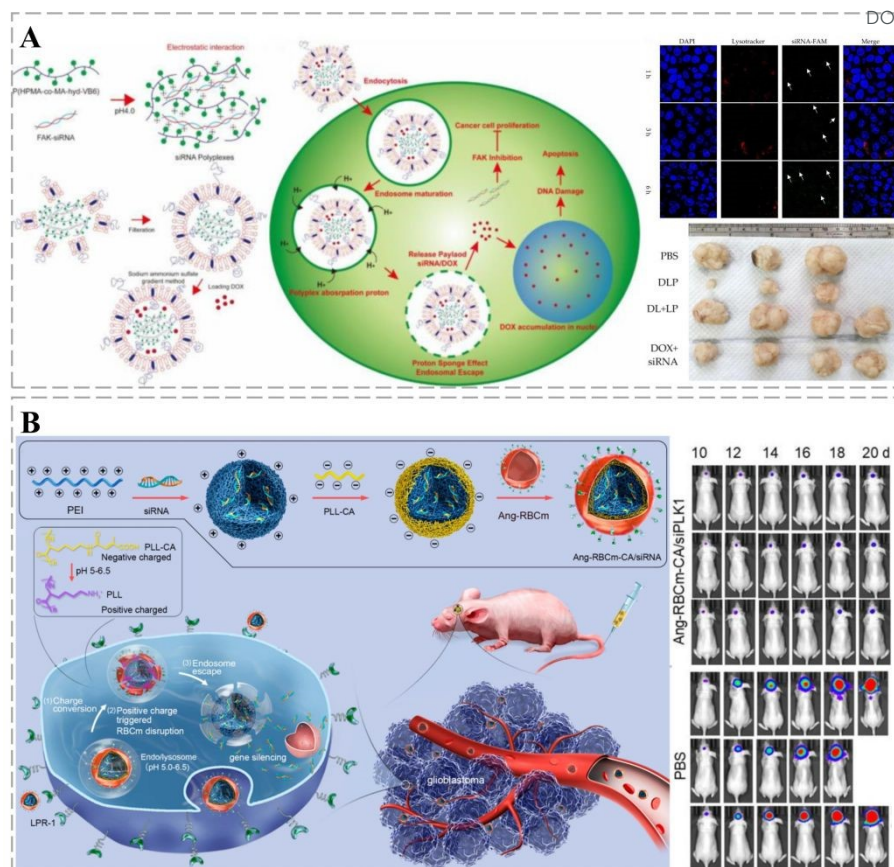
1065 The cationic polymer polyethylene glycol (PEI) plays a key role in gene
1066 delivery. The molecular weight of PEI can affect its transfection efficiency and
1067 cytotoxicity; therefore, by effective chemical modification, it is possible to improve
1068 PEI transfection activity and reduce its toxicity. ROS-responsive PEI-based
1069 fluoropolymers (TKPV) with different degrees of fluorination have excellent
1070 therapeutic properties: (1) fluorinated PEI-based fluoropolymers reduce the positive
1071 charge density and impart hydrophobic and lipophilic properties to the carrier to resist
1072 the effects of serum; (2) the fluorophilic effect makes cellular uptake more effective;
1073 (3) ROS-responsive TK linkers allow for the decomposition of polymorphic forms to
1074 reduce their cytotoxicity and improve drug release from targets [236]. Debele et al.
1075 encapsulated polyplexes in methoxy glycol (mPEG)-modified liposomes loaded with
1076 DOX in combination with siRNA. The lipid polymer successfully released DOX at
1077 low pH, inducing cancer cell death and the siRNA to leave the endosome and inhibit



1078 the translation of the FAK protein (Fig. 12A) [237]. Liu et al. developed a charge
1079 conversion biological platform with a three-layer core-shell structure, which
1080 effectively resolved the problem of siRNA delivery to glioblastoma (GBM). The
1081 resulting nanocomposites can prolong the blood circulation of nucleic acids, have
1082 high BBB transmembrane performance, effectively accumulate in cancers, and can be
1083 specifically ingested by target cells. In addition, further destruction of the red blood
1084 cell membrane (RBCm) and the effective release of siRNA can trigger negative to
1085 positive charge transfer in cancer cells, silencing highly effective target genes with
1086 strong anti-GBM effects (Fig. 12B) [238].

1087 The long-term safety of vehicle-mediated gene therapy for cancers has not been
1088 fully assessed. For example, the autoimmune system may recognize the new
1089 substances produced by gene therapy as “foreign” substances, leading to autoimmune
1090 diseases. Furthermore, the widespread use of emerging gene-editing therapies has led
1091 to related legal issues and adverse consequences. Therefore, the adoption of
1092 vehicle-mediated gene therapy for cancers requires long-term follow-up of patients to
1093 assess its long-term effect on suppressing cancer progression.



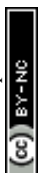


1094

1095 Fig. 12. Smart therapeutic vehicles mediate cancer immune-gene therapy. A.
 1096 Schematic diagram of lipopolyplexes loaded with DOX for cancer
 1097 chemotherapy-gene therapy. siRNA and DOX labeled by fluorescence can be
 1098 observed in tumor cells, suggesting that lipopolyplexes can deliver drugs into tumor
 1099 cells and release them. The co-delivery of DOX and siRNA through lipopolyplexes
 1100 significantly inhibits tumor growth through a synergistic effect and was significantly
 1101 more effective than free drugs. B. Schematic diagram of RNAi therapy using
 1102 pH-responsive charge-switching bionanocomplex (Ang-RBCm-CA/ siRNA) to
 1103 promote *in situ* glioblastoma. Ang-RBCm-CA/siRNA with long circulation time and
 1104 high BBB penetration *in vivo* is effective in treating glioblastoma in nude mice
 1105 through charge conversion, low pH-induced membrane disruption, and siRNA
 1106 release.

1107 7. Bottlenecks of smart cancer treatment vehicles in cancer therapy

1108 Smart therapeutic carriers can overcome the limitations of traditional therapeutic
 1109 modalities, including low bioavailability, poor specificity, and drug resistance.



1110 Furthermore, they exhibit advantages, such as targeted and controlled drug release
1111 and rich and variable drug loading strategies, which are promising for applications in
1112 cancer therapy. However, despite the numerous promising cancer therapeutic
1113 strategies, the application of smart cancer therapeutic delivery vehicles remains
1114 challenging, and only a few studies have successfully applied them clinically.

1115 **7.1 EPR effect**

1116 Matsumura and Maeda first proposed the EPR effect in cancer targeting in 1986;
1117 solid cancers exhibit such an effect [239]. Owing to the dysfunction of lymphatic
1118 drainage in the cancer TME, carriers with a particle size of < 200 nm can enter the
1119 interstitial tissue through the blood vessel wall; therefore, drug-loaded carriers exhibit
1120 preferential accumulation in solid cancers. It is believed that passive processes
1121 dominate the accumulation of nanocarriers in cancer tissues. Current drug-loaded
1122 therapeutic vehicles that accumulate in cancers rely on the EPR effect, which is the
1123 basis for the passive targeting of vehicles [240, 241]. Their therapeutic effectiveness
1124 is influenced by the different stages of the cancer, intensity of the EPR effect, and
1125 physiological barriers [242].

1126 Despite their widespread clinical use, passive targeting strategies have many
1127 limitations owing to the heterogeneous distribution of blood vessels in solid cancers,
1128 resulting in heterogeneous permeability. For small cancers not characterized by
1129 angiogenesis or those that metastasize, the efficiency of passive targeting based on the
1130 EPR effect is limited [243]. In addition, drug delivery vehicles that are based on the
1131 EPR effect have limited accumulation in cancers and are highly heterogeneous [244].
1132 Therefore, treatment of patients with multiple cancers may fail owing to the lack of
1133 the EPR effect. Notably, compared with clinical cancers, it is believed that
1134 experimental animal cancer models exhibit more significant EPR effects [245] and
1135 that nanoparticles have very low delivery efficiency in human cancers.

1136 Other routes have been suggested to address the limited accumulation of drugs in
1137 cancers based on the EPR effect (Table 3), such as increasing cancer vascular
1138 permeability through physical strategies or using drugs to achieve an increased EPR
1139 effect, such as thalidomide.



1140 Table 3. Bottlenecks of smart cancer treatment vehicles and the corresponding
1141 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]

1142

1143 7.2 Diffusion of therapeutic vehicles within the cancer mesenchyme

1144 For smart carriers to deliver drugs to cancer tissues through extravascular
1145 penetration, they must be near and enter the cancer cells before exerting their
1146 anti-cancer effects. The cancer mesenchyme determines the efficiency of passive
1147 targeting. Unlike normal tissues, cancers exhibit high interstitial pressure, especially
1148 in their central part, whereas the elevated interstitial fluid pressure (TIP) may create
1149 physiological barriers to drug delivery in solid cancers [255]. Both the absence of
1150 lymphatic vessels and the lack of lymphatic return result in the retention of tissue
1151 fluid in the cancer interstitium [256]. Excessive TIP can impede the flow of blood and
1152 drugs from blood vessels; therefore, only a few nanocarriers may reach the site of
1153 action in solid cancers [257]. This low delivery efficiency hinders the use of cancer
1154 nanodelivery systems in solid cancer treatment (Table 3).



1155 NPs are transported into the cancer mesenchyme via a net force between
1156 mesenchymal pressure and drug concentration. Fu et al. grew Ag₂S NPs in situ on the
1157 ultrathin WS₂ surface and designed a “nanomotor” to fabricate the Z-type
1158 photocatalytic drug AWS@M. AWS@M can reduce TIP by splitting the water in the
1159 interstitium to produce O₂, which rapidly enters cancer tissues. At the same time, O₂
1160 can be converted into ROS and combined with thermal therapy, increasing the local
1161 temperature of the cancer and eliminating deep cancer cells. Upon irradiation with a
1162 660 nm laser, the “nanomotor” can effectively reduce TIP levels in cervical and
1163 pancreatic cancers, enhancing intra-cancer drug delivery and inhibiting cancer
1164 growth. This nanomotor successfully addresses the issue of blocked intracancer drug
1165 delivery and provides a multifunctional strategy for effective cancer growth inhibition
1166 [258]. The self-assembly of a thermosensitive polymer, superparamagnetic MnFe₂O₄
1167 nanoparticles, and DOX produced DOX-MTM, which exhibited high drug loading
1168 efficiency. Owing to the high content of superparamagnetic nanoparticles,
1169 DOX-MTM exhibited good SAR and magneto-thermally sensitive drug release, with
1170 a suitable LCST of 42.3 °C. Therefore, the *in vitro* cytotoxicity was substantially
1171 increased through magneto-thermal dependent DOX release and endocytosis.
1172 Subsequently, DOX was effectively released under the influence of MH and enhanced
1173 the penetration depth into the cancer tissue [259].

1174 7.3 Differences between animal models and clinical cancers

1175 Most current studies on the performance of smart vehicles in cancer therapy are
1176 based on data from animal models, whereas their translation into human applications
1177 remains unexplored. *In vivo* animal models and clinical cancer patients present a large
1178 variability [260]; for example, cancer patients often have a combination of underlying
1179 diseases and are influenced by psychiatric factors and conditions that cannot be
1180 replicated in animal models. Although some preclinical and clinical studies have
1181 examined the pharmacokinetics (PK) of different species, detailed data for predicting
1182 the safety and efficacy of therapeutic vehicles in clinical settings using animal models
1183 are lacking. In addition, even in animal models, drugs do not fully exploit the EPR
1184 effect to achieve positive efficacy [261]. The efficiency of smart carrier drug delivery



1185 based on the EPR effect is correlated with the individual size, which in turn affects the
1186 distribution and stability of the carrier *in vivo*. Previous studies have used the weight
1187 of animal models to determine the amount of drug loaded onto the therapeutic vehicle.
1188 However, the timing of drug delivery and treatment duration should be adjusted
1189 according to the specific clinical condition of the patient. The drug clearance rate in
1190 animal models fundamentally differs from that in humans, leading to inconsistencies
1191 in treatment duration compared with clinical practice. Therefore, results obtained
1192 from animal models do not accurately reflect the potential effects on clinical patients,
1193 limiting the translation of therapeutic vehicles from animal models to clinical practice.

1194 **8. Conclusion and outlook**

1195 Smart cancer delivery systems have been under development, and scientists have
1196 made several advances to actively develop and apply them to promote the
1197 effectiveness of cancer treatments. Smart cancer therapeutic delivery vehicles exhibit
1198 numerous advantages over traditional drug delivery methods; an essential advantage
1199 is their modifiability, which allows them to be designed in various sizes, shapes, and
1200 functions as needed. They can be modified or loaded with various drugs to enable the
1201 targeted delivery of therapeutic agents. Furthermore, smart carriers can exploit the
1202 EPR effect, facilitating the accumulation of drugs within cancerous tissues. Moreover,
1203 the complex TME during cancer development necessitates precise drug release at
1204 specific locations and periods. Smart therapeutic carriers possess unique properties
1205 that prevent drug degradation while releasing them in response to specific stimuli.

1206 However, the efficacy of smart delivery systems has not met expectations, and
1207 their clinical application remains limited. The field of clinical translation is in its early
1208 stages. Furthermore, the EPR effects in cancer tissues of different patients can be
1209 inconsistent, and active targeting systems remain underdeveloped, rendering cancer
1210 drug delivery systems unstable for cancer treatment applications. Meanwhile, animal
1211 cancer models are not representative of clinical cancers, leading to discrepancies
1212 between the preclinical and clinical trial efficacies of smart drug delivery systems,
1213 thereby reducing the success rate of clinical translation.

1214 Therefore, to improve the clinical translation, the development of multifunctional



1215 biomaterials that can overcome most biological barriers, such as humanized animal
1216 models, is required. At the same time, appropriate smart delivery vehicles should be
1217 selected for cancer treatment, and FDA-approved drugs, such as liposomes or
1218 polymers, should be used first in clinical practice to accelerate clinical translation and
1219 immunomodulation. In addition to controlling the toxicity of immune drugs
1220 themselves, the physical and chemical properties of smart delivery vehicles, including
1221 size, shape, structure, and surface charge, should also be adjusted to reduce the side
1222 effects of nanoparticles and enhance their potential in cancer treatment [262]. In
1223 addition, the surface functionalization of smart delivery vehicles is another important
1224 factor affecting cancer treatment. Surface functionalization can affect intracellular
1225 uptake of delivery vehicles, and even affect their processing [263]. Therefore,
1226 appropriate surface functionalization should also be considered in the future
1227 development of smart delivery vehicles. Smart delivery vehicles can combine
1228 immunotherapy with other therapies such as PDT and gene therapy, significantly
1229 enhancing treatment effectiveness and reducing toxic side effects. Further exploration
1230 is needed to determine the rationale for combining different treatment regimens and
1231 optimize the timing and sequence of drug release. For instance, the timing of PTX or
1232 cyclophosphamide injections can impact the anti-cancer T-cell response induced by
1233 CD47 blockade. Additionally, the effectiveness of therapeutic vehicles can vary
1234 among patients due to individual heterogeneity. Therefore, personalizing the design of
1235 therapeutic vehicles according to each patient's needs is necessary to achieve optimal
1236 therapeutic performance. Furthermore, more extensive screening of cancer therapeutic
1237 targets should be conducted to identify suitable regimens and optimize personalized
1238 combination protocols. The development of smart cancer therapeutic vehicles holds
1239 great potential for addressing challenges in cancer treatment. These vehicles can
1240 substantially reduce the adverse events associated with immunotherapy. Current
1241 advances in diagnostic imaging, immune response monitoring, and prognosis have
1242 enhanced the versatility of smart therapeutic vehicles in cancer treatment.

1243 Smart delivery vehicles compensate for the shortcomings of conventional cancer
1244 therapies, and their application to all types of cancers has yielded excellent



1245 therapeutic results. The study and optimization of biomaterials have expanded the
1246 prospects for the broader application of smart delivery carriers in cancer therapy.

1247

1248 **List of abbreviations**

1249 AC-NPs: antigen-capturing nanocarrier particles;

1250 APC: antigen-presenting cells;

1251 aPDL1: anti-PD-L1 blocking antibody;

1252 AuNPs: gold nucleated nanoparticles;

1253 BBB: blood-brain barrier;

1254 CA: contrast agents;

1255 CAF: cancer-associated fibroblasts;

1256 CA-NPs: chlorin e6 nanoparticles;

1257 COL: collagenase;

1258 CPT: camptothecin;

1259 CRPC: castrate prostate cancer;

1260 CT: combination chemotherapy;

1261 Cur: curcumin;

1262 DAMP: damage associated molecular pattern;

1263 DCs: dendritic cells;

1264 DOX: doxorubicin;

1265 DOX: Doxorubicin;

1266 ePC: egg phosphatidylcholine;

1267 EPR: enhanced permeability and retention;

1268 ER: estrogen receptor;

1269 ES: estrone;

1270 ETP: etoposide;

1271 Exos: exosomes;

1272 FA: folic acid;

1273 FR: folate receptor;

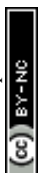
1274 GBM: glioblastoma;



- 1275 GEM: gemcitabine;
- 1276 GSH: glutathione;
- 1277 GS-HM: Gyroid Surface Helical Microrobot;
- 1278 HA: hyaluronic acid;
- 1279 HD: hydrodynamic diameter;
- 1280 HMON: hollow mesoporous organosilicon nanoparticles;
- 1281 HYD: hydrazine;
- 1282 ICD: immunogenic cell death;
- 1283 ICG: indocyanine green;
- 1284 IF- γ : interferon γ ;
- 1285 IMDQ: imidazoquinoline;
- 1286 IRI: irinotecan; Lf: lactoferrin;
- 1287 MDR: multidrug resistance;
- 1288 MDSCs: myeloid-derived suppressor cells;
- 1289 MFN: manganese ferrite nanoparticles;
- 1290 Mito: mitoxantrone;
- 1291 MMC: mitomycin C;
- 1292 MNP: magnetic nanoparticles;
- 1293 mPEG: methoxy glycol;
- 1294 MRI: magnetic resonance imaging;
- 1295 MSCs: mesenchymal stem cells;
- 1296 Mtx: methotrexate;
- 1297 NC: nanocluster;
- 1298 NDS: nanodroplets;
- 1299 NGs: nanogels;
- 1300 NIR: near infra-red;
- 1301 NK: natural killer;
- 1302 NPs: nanoparticles;
- 1303 OS: osteosarcoma;
- 1304 PAA: polyacrylic acid;



- 1305 PCAD: polycarboxylic acid dextran;
- 1306 PDA: polydopamine;
- 1307 PDNCs: polydiacetylene nanocarriers;
- 1308 PDT: photodynamic therapy;
- 1309 PEG-FIbu: PEG2k-Fmoc-ibuprofen;
- 1310 PEI: cationic polyethylene glycol;
- 1311 PIC: polyion complex;
- 1312 PK: pharmacokinetics;
- 1313 PLGA: poly(lactic acid-glycolic acid);
- 1314 PLL: poly-L-lysine;
- 1315 PM: polymeric micelles;
- 1316 PMNs: porous magnetite nanoparticles;
- 1317 PMP: polymeric pre-drug;
- 1318 PNPs: polymeric nanoparticles;
- 1319 PpIX: protoporphyrin IX;
- 1320 PTT: photothermal therapy;
- 1321 PTX: paclitaxel;
- 1322 QDs: quantum dots;
- 1323 RAPA: rapamycin;
- 1324 RBCm: red blood cell membrane;
- 1325 RIF: rifampicin;
- 1326 ROS: reactive oxygen species;
- 1327 SDT: sonodynamic therapy;
- 1328 siRNA: small interfering RNA;
- 1329 SLNs: solid lipid nanoparticles;
- 1330 srNPs: smart stimuli-responsive nanoparticles;
- 1331 TAMs: tumor-associated macrophages;
- 1332 TIP: interstitial fluid pressure;
- 1333 TME: tumor microenvironment;
- 1334 TNBC: triple-negative breast cancer;



1335 TPGS: D- α -tocopheryl polyethylene glycol succinate;

1336 TPP: two-photon polymerization;

1337 TQR: tariquidar;

1338 Tregs: regulatory cells;

1339 ZIF-8: zeolite imidazolate framework-8.

1340

1341

1342 **Ethics approval and consent to participate**

1343 Not applicable.

1344

1345 **Consent for publication**

1346 Not applicable.

1347

1348 **Availability of data and materials**

1349 No data was used for the research described in the article.

1350

1351 **Competing interests**

1352 The authors declare that they have no known competing financial interests or
1353 personal relationships.

1354

1355 **Funding**

1356 This study was funded by the Natural Science Foundation of Hunan Province,
1357 China (2023JJ60089).

1358

1359 **Author contributions**

1360 XX: conceived the conceptualization and designed the manuscript. YZ and YG:
1361 manuscript writing. LH and WG: collated and produced relevant figures for the
1362 manuscript. XW and TM: participated in discussions. All authors read and approved
1363 the final manuscript.

1364



1365 **Acknowledgements**

1366 Not applicable.

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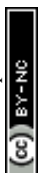
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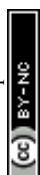
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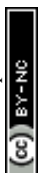
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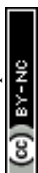
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