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REVIEW ARTICLE

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(Nano)platforms in breast cancer therapy: Drug/gene delivery, advanced nanocarriers and immunotherapy

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Abstract

Breast cancer is the most malignant tumor in women, and there is no absolute cure for it. Although treatment modalities including surgery, chemotherapy, and radiotherapy are utilized for breast cancer, it is still a life-threatening disease for humans. Nanomedicine has provided a new opportunity in breast cancer treatment, which is the focus of the current study. The nanocarriers deliver chemotherapeutic agents and natural products, both of which increase cytotoxicity against breast tumor cells and prevent the development of drug resistance. The efficacy of gene therapy is boosted by nanoparticles and the delivery of CRISPR/Cas9, Noncoding RNAs, and RNAi, promoting their potential for gene expression regulation. The drug and gene codelivery by nanoparticles can exert a synergistic impact on breast tumors and enhance cellular uptake via endocytosis. Nanostructures are able to induce photothermal and photodynamic therapy for breast tumor ablation via cell death induction. The nanoparticles can provide tumor microenvironment remodeling and repolarization of macrophages for antitumor immunity. The stimuli-responsive nanocarriers, including pH-, redox-, and light-sensitive, can mediate targeted suppression of breast tumors. Besides, nanoparticles can provide a diagnosis of breast cancer and detect biomarkers. Various kinds of nanoparticles have been employed for breast cancer therapy, including carbon-, lipid-, polymeric- and metal-based nanostructures, which are different in terms of biocompatibility and delivery efficiency.

KEYWORDS
breast cancer, cancer therapy, clinical application, nanotechnology, stimuli-responsive nanocarriers

1 | INTRODUCTION

One of the malignant diseases negatively affecting the life quality of women around the world is breast cancer.[1] Breast cancer is the most aggressive tumor, and its incidence rate is gradually increasing. According to estimates, up to 2.2 million females with breast cancer were diagnosed in 2020.[2] About 11.7% of new cancer cases are related to

breast cancer, and almost 279,100 cases will have been diagnosed with breast cancer by the end of 2020.[2,3] There are a number of factors affecting breast cancer development and initiation, including sex, family history, estrogen, gene mutations, and race.[4,5] Breast cancer is commonly observed in the glandular epithelial tissue of the breast, and upon exposure to tumorigenesis agents or abnormal events occurring in breast tissue, benign tumors or metastatic cancers may develop. One of the factors that significantly reduces the survival rate of breast cancer patients is metastasis to various organs, including bone, liver, lung, brain and lymph nodes.[6,7] Breast cancer is divided into various subtypes, including luminal A, luminal B, HER2 + B2, HER-2 overexpression and triple-negative breast cancer, among others.[8] The classification of breast cancer into subtypes is important for predicting the response of patients to therapy and finding relevant solutions.[9] The surgery is a promising approach for the treatment of breast cancer. A combination of surgery and adjuvant radiation appears to be effective in improving the survival rate of patients and reducing the chance of recurrence. It has been reported that among 10,801 breast cancer patients who have undergone mass resection, application of radiotherapy significantly improves their survival rate and decreases their 10-year recurrence rate.[10] Utilization of nanoradiosensitizers composed of high atomic number elements has been shown to significantly improve cancer therapy efficacy.[11–13] Furthermore, chemotherapy or its combination with surgery or radiotherapy can be employed in breast cancer therapy.[14,15] In recent years, immunotherapy approaches such as application of checkpoint inhibitors have been developed for breast cancer treatment and to improve the overall survival of patients. However, as most breast cancer patients are diagnosed at advanced stages, the aforementioned therapeutic modalities appear to be less effective, and resistance can be commonly observed. Although recent preclinical experiments have focused on the application of novel therapeutics such as gene therapy and phytochemicals with antitumor activity, breast cancer treatment is still a challenge. Various studies have shown that cancer treatment is achieved using an interdisciplinary approach. Both engineering and biology can be combined in the treatment of breast cancer, and nanotechnology and its introduction in breast cancer therapy for drug and gene delivery, immunotherapy and bioimaging can make significant progress in the treatment of breast cancer.[16–20]

The current review article focuses on nanotechnological approaches in the treatment of breast cancer. At first, the role of nanostructures in the delivery of genes and drugs and their codelivery is discussed, and it is shown how nanocarriers can improve the potential of aforementioned therapies in breast cancer suppression. Then, the focus is directed toward the role of nanoparticles in breast cancer immunotherapy and bioimaging. Then, surface modification of nanoparticles and their increased selectivity towards breast cancer cells are discussed, and finally, challenges and opportunities for clinical application are described.

2 | DRUG DELIVERY

2.1 | Phytochemicals

Among various kinds of anticancer agents employed for breast cancer therapy, plant-derived natural compounds are of importance. Compared to synthetic drugs, phytochemicals are more affordable, and they have negligible adverse impacts. Besides, due to the capacity of phytochemicals to target various types of signaling networks involved in tumor progression, they can effectively suppress tumor growth and invasion. More importantly, when tumor cells develop resistance to synthetic compounds, phytochemicals with a different mechanism of action can be used to sensitize tumor cells to chemotherapy drugs, and since phytochemicals display pleiotropic function, they are promising compounds for mediating chemosensitivity. However, clinical application of plant-derived natural compounds is low due to their poor bioavailability, which diminishes their therapeutic index.[21,22] Notably, various kinds of nanoparticles have been developed for the delivery of phytochemicals in effective cancer therapy. An experiment has developed mesoporous silica nanostructures (MSNs) for curcumin delivery in breast cancer suppression. Large surface area, high biocompatibility and ease of modification are among the benefits of MSNs (Figure 1).[23] The prepared MSNs were modified with hyaluronic acid or folic acid, and then curcumin, as the

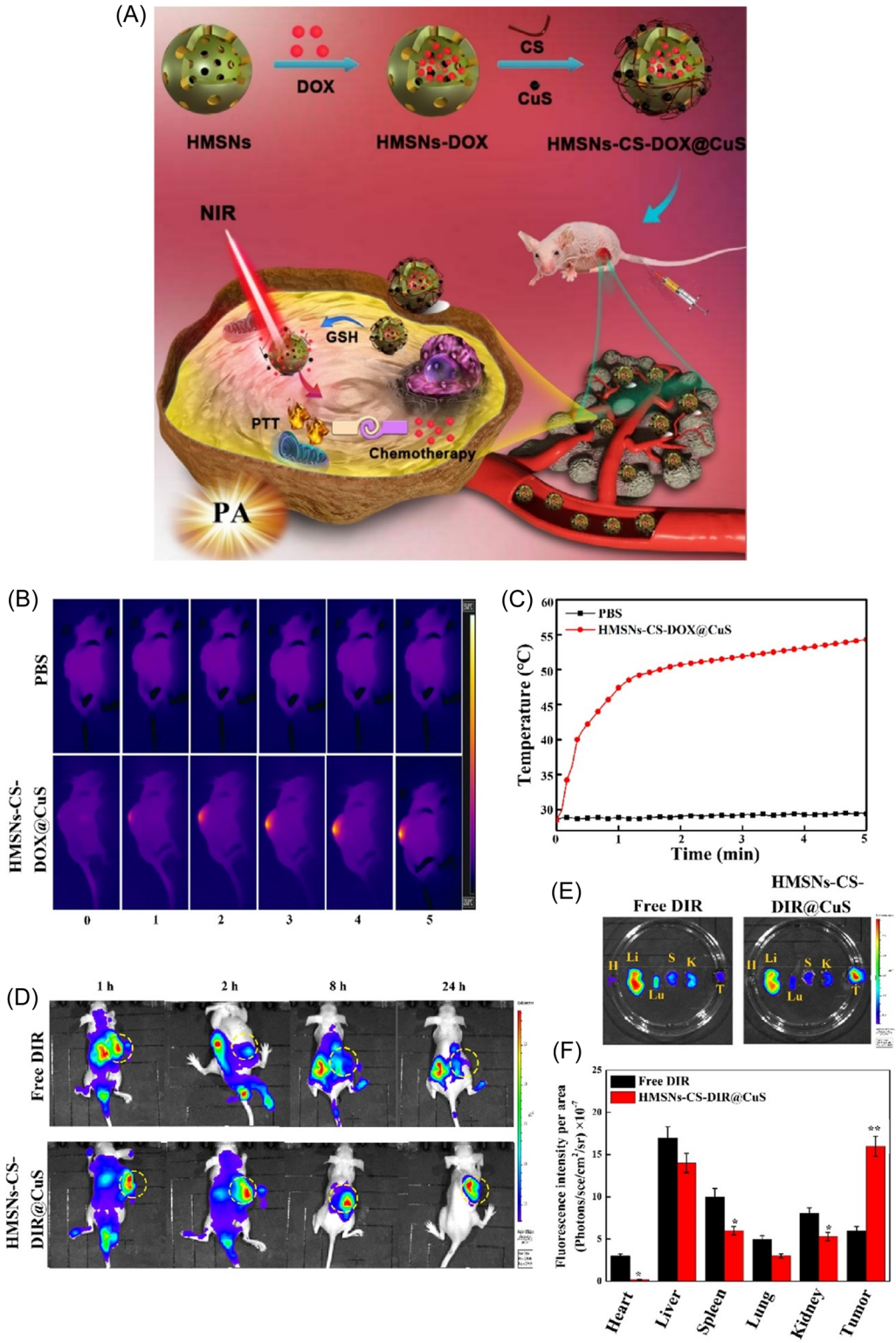

FIGURE 1 (A) Mechanism of action in tumor cells, (B) Thermal images, and (C) corresponding tumor temperature, (D) in vivo fluorescent images, (E) ex vivo images, and (F) fluorescent intensity in different organs. Reprinted with permission from[23] Elsevier. [Color figure can be viewed at wileyonlinelibrary.com]

anticancer agent, was loaded on MSNs. Cellular uptake of curcumin-loaded MSNs enhances due to functionalization, while folic acid modification has a better impact compared to hyaluronic acid. By accumulating at the tumor site, nanoparticles promoted curcumin delivery to cancer cells, and a significant increase in its cytotoxicity occurred, while its biocompatibility and safety profile were maintained.[24] In addition to curcumin, quercetin has also been loaded onto silica. The resulting quercetin-loaded silica nanostructures had 82 nm size and they induced apoptosis. Furthermore, quercetin-loaded silica nanoparticles remarkably decreased the viability.[25]

In addition to MSNs, polymeric nanostructures have been designed to deliver natural compounds in breast tumor suppression. Polymeric nanoparticles from poly-glycerol-malic acid-dodecanedioic acid (PGMD) have been fabricated, and then, curcumin was loaded on these polymeric nanoparticles with 110 and 218 nm size and −18.9 and −17.5 mV zeta potential, with 75%–81% EE. The curcumin-loaded PGMD nanostructures suppressed the carcinogenesis, induced apoptosis and nuclear anomalies. The IC_{50} value of curcumin-loaded PGMD nanostructures was around 30–45 μM.[26] Another study developed chitosan-protamine nanostructures for curcumin delivery. The curcumin-loaded chitosan-protamine induced apoptosis through Bcl-2 suppression, and they decreased breast cancer cell survival and levels of NF-κB, TNF-α and IL-6.[27] Due to the potential of chitosan in improving the safety, this linear polysaccharide is extensively utilized for pharmaceutical approaches.[28,29] The chitosan nanostructures were prepared for quercetin and had an encapsulation efficiency of 83%. Loading quercetin onto nanostructures promoted their particle size to 490–502 nm, and cargo release accelerated at pH 5.0. The quercetin-embedded nanostructures suppressed the progression and metabolism, and they preferentially aggregated in cancer tissue while their biocompatibility and safety profile were high.[30]

Metal nanostructures are another kind of nanocarrier utilized for phytochemical. Berberine was loaded onto gold nanoparticles and they were internalized through clathrin-mediated endocytosis and autophagy, and they significantly decreased the viability. Apoptosis was responsible for the decreased progression of breast tumor by berberine-loaded gold nanoparticles, and upregulation of Bax and p21 were observed.[31] The resveratrol-loaded gold nanostructures had 30.75 nm size and −32.8 mV zeta potential. The resveratrol-loaded gold nanoparticles suppressed the growth and metastasis of breast cancer cells via through suppressing MMP-9 and COX-2.[32] Low particle size, good zeta potential and stability are among the advantageous of metal-based nanostructures.[33] However, the biocompatibility of gold nanoparticles is a challenging issue, and their modification with natural compounds such as chitosan can be employed to enhance their biocompatibility.

Carbon-based nanostructures are also suitable carriers for naturally occurring compounds. A recent experiment has developed graphene quantum dots (GQDs) to deliver curcumin. The modification of GQDs with glucosamine (GlcN) was performed to selectively target overexpressed GlcN receptor-tumor cells. The curcumin-loaded GQDs displayed 20–30 nm size, prolonged delivery of curcumin and more release at pH 5.5 (37%) instead of pH 7.4 (17%). The GQDs internalized in MCF-7 cells through endocytosis and decreased cancer cell viability.[34] The reduced graphene oxide (GO) sheets are also appropriate carriers for phytochemicals because of stability and zeta potential (−20 mV).[35] It is worth mentioning that GO nanostructures can provide photothermal therapy for synergistic impact with antitumor agents.[36] Improved half-life, prolonged circulation time, increased internalization in tumor cells and promoted anticancer activity result from the nanoarchitectures for delivery of phytochemicals in breast tumor suppression (Table 1).[45,56–61]

2.2 | Synthetic molecules

In addition to naturally occurring compounds, synthetic molecules can also be delivered by nanostructures. Tumor cells have the capacity to develop resistance to chemotherapeutic agents including doxorubicin (DOX), cisplatin (CP), paclitaxel (PTX) and docetaxel (DTX), among others. The GQDs were modified with scFv as an antibody to selectively target the EGFR. The CP-loaded GQDs had −31.3 mV zeta potential, showing stability. The drug loading was 50%, and they released CP in a pH-responsive manner. These nanocarriers internalized in cells and suppressed

TABLE 1 The nanostructures for phytochemical delivery in breast cancer therapy.

Nanoarchitecture	Features	Cargo	Remarks	References
Lipid nanoarchitectures	302.5 nm +41.4 mV	Curcumin	Increased internalization in tumor cells, reducing tumor progression and enhancing radio-sensitivity	[37]
Solid lipid nanoparticles	30-50 nm −25.3 mV 72.47%	Curcumin	Apoptosis induction Enhanced Bax/Bcl-2 expression Downregulation of cyclin D1 and CDK4	[38]
Copper complex micelle nanostructures	248 nm −0.11 mV 80%	Curcumin	Enhanced stability Promoting curcumin's Anticancer function Suppressing growth	[39]
HAS nanoparticles	180 and 220 nm −7 mV	Curcumin	Apoptosis induction, increased stability and inhibiting tumor progression	[40]
PLGA nanostructures	347.4 nm	Curcumin GANT61	Spherical shape with smooth surface morphology Apoptosis and autophagy induction to reduce tumor cell viability	[41]
Phenylboronic acid-functionalized ZnO nanostructures	166.3, 284.96 and 413.63 nm 17.9, −4.7 and −16.4 mV	Curcumin	Selective targeting of tumor cells due to PBA modification, pH-sensitive release at tumor microenvironment and inducing oxidative stress by curcumin and Zn^{2+} ions	[42]
Folic acid-modified polymeric nanoparticles	186.52 nm −18.87 mV 97.64% (doxorubicin) 78.13% (curcumin)	Doxorubicin Curcumin	Enhanced cellular uptake, apoptosis induction and reducing tumor progression	[43]
SPC-TPGS nanoparticles	71 nm −40.8 mV 98.24%	Pterostilbene	Enhanced water solubility High bioavailability of pterostilbene	[43]
Layer-by-layer nanostructures	217 nm +45 mV	Resveratrol Tamoxifen	High biocompatibility, increased cellular uptake, antitumor activity and decreasing colony formation capacity	[44]
Solid lipid nanoparticles	169 and 203 nm −27.8 and −25.6 mV	Resveratrol	Increased cellular uptake, mitochondrial dysfunction, apoptosis induction and enhanced cytotoxicity against tumor cells	[45]
Gold nanostructures	22.28 nm	Resveratrol	Suppression of MMP-9 and COX-2 expression	[32]

TABLE 1 (Continued)

Nanoarchitecture	Features	Cargo	Remarks	References
Chondroitin sulfate-based nanostructures	169.83 nm −19.71 mV	Quercetin Chlorin e6 Paclitaxel	NIR irradiation enhances ROS overgeneration, mitochondrial damage and suppressing progression of breast tumor cells	[46]
Chitosan-functionalized copper oxide nanostructures	50 nm −17.6 mV	Quercetin	Exerting anticancer activity and reducing progression of breast tumor via p53 overexpression and elevating levels of cytochrome C and caspase-3	[47]
Mesoporous silica nanoparticles	200 nm −25 mV	Quercetin	Enhanced internalization due to selective targeting of cells overexpressing folate receptor Enhanced drug bioavailability Apoptosis induction and cell cycle arrest Inhibiting Akt signaling and promoting Bax expression	[48]
Gold nanoparticles	3-4.5 nm	Quercetin	Apoptosis induction Enhancing nuclear condensation Bax and caspase-3 overexpression and Bcl-2 suppression Inhibiting EGFR signaling and its downstream target PI3K/Akt/mTOR/GSK-β axis	[49]
Superparamagnetic magnetite nanoparticles	20 nm 6.14 mV	Quercetin	Enhanced cytotoxicity of quercetin against breast tumor cells	[50]
PCL-TPGS nanostructures	235 nm −7.4 mV	Quercetin	Boosting anticancer activity of quercetin by 2.9 times compared to quercetin alone	[51]
MOEG-PLA nanostructures	155.3 nm −3.14 mV 5.3%	Quercetin	Sustained release of quercetin Apoptosis induction Cell lysis and preventing proliferation in vivo	[52]
Lipid nanoparticles	-	Quercetin	High internalization of quercetin in tumor cells Inhibiting P-gp activity Cell cycle arrest at G2 phase Stimulation of apoptosis and autophagy	[53]
PLA nanoparticles	152 nm 62%	Quercetin	Elimination of 50% of breast tumor cells	[54]
Porous silicon nanoparticles	-	Quercetin	Improving cytotoxicity of DOX against breast tumor cells	[55]

their progression; simultaneously, they provided bioimaging.[62] Another study developed GO/polymeric nanocomposites for DOX delivery. The nanocomposites had 51 nm size and an encapsulation efficiency of 82%. DOX was conjugated to GO/polymeric nanocomposite and its release mainly occurred at acidic pH (41.2%), making GO/polymeric nanocomposites suitable carriers for breast cancer therapy. The GO nanocomposites internalized into cancer cells and reduced breast tumor viability.[63] Furthermore, two chemotherapeutic agents can be codelivered by GO nanocomposites. In an effort, polyhydroxyethyl PHEMA was bound to reduced GO and. DOX and CP were loaded onto PHEMA/reduced GO nanocomposites via hydrogen bonding and π−π stacking, with 75% and 82% EE, respectively. The nanocarriers had 70 nm size, and they showed high cellular uptake. They triggered apoptosis and cell cycle arrest and provided a synergistic impact between DOX and CP.[64] Therefore, carbon-based nanomaterials are ideal candidates.[65,66]

Liposome-mediated drug delivery has been of importance.[67] In an effort, TPGS-modified liposomal nanocarriers were designed for DOX delivery. The resulting DOX-loaded liposomal nanocarriers had 98.2 and 117.6 nm size, zeta potentials of −38.7 and −36.4 mV, and encapsulation efficiencies of 66.8% and 73.5%, respectively. The liposomes demonstrated prolonged release of DOX, and they released 83.6% and 69.8% of DOX in 72 h. They had high hemocompatibility and effectively reduced breast cancer progression. The modification of liposomes with TPGS improves their stability and stealth feature, as well as their anticancer activity.[68] The overexpression of P-gp is responsible for DOX resistance. The DOX-loaded liposomes and modified with apolipoprotein A1 was performed to promote their cellular uptake. The liposomal nanoparticles provided a burst release of DOX and suppressed breast cancer progression. Furthermore, by reducing off-targeting, DOX-loaded liposomes reduce adverse impacts on heart.[69] It is also worth mentioning that liposomes show more internalization, making them appropriate nanocarriers for treatment and reversal of chemoresistance in breast tumors.[70]

The lipid-based nanoparticles can mediate the codelivery of DOX and CP in synergistic tumor removal. Then, DOX and CP were embedded onto lipid nanostructures. The antitumor activity of drugs enhanced by lipid nanoparticles exerted synergistic impact and effectively suppressed carcinogenesis.[71] Pluronic prodrug micelles can deliver DOX to breast cancer cells (MCF-7). They showed high stability and have the capacity to release at the cancer place due to cleavage of β-carboxylic amide bonds in acidic TME. Due to the modification of micelles by phenylboric acid (PBA), their internalization in MCF-7 cells was elevated, and simultaneously, their adverse impacts on healthy cells and organs were reduced. These DOX-loaded micelles prevented multidrug resistance in breast cancer and inhibited tumor progression up to 78% due to the synergistic impact between DOX and F127.[72] Another experiment developed mixed micelles from PPG-grafted HA copolymers (PPG-g-HA) and loaded with pluronic L61. High stability, good biocompatibility and high internalization in MCF-7 cells are characteristics of polymeric micelles. The DOX-loaded PPG-g-HA/L61 showed high anticancer role against breast tumor, while their toxicity on fibroblast L929 cells was low. They suppressed drug resistance and improved the anticancer activity of DOX, which are of importance for breast cancer therapy.[73] The bioavailability and blood circulation time of irinotecan have also been enhanced by micelles to effectively suppress breast cancer progression.[74]

The employment of nanoarchitectures enables the stimulation of more apoptosis in breast tumor compared to free drug,[75] and when they selectively deliver drug to the tumor site, their systemic toxicity significantly diminishes.[76] The internalization in tumor cells is mediated by endocytosis.[77] A recent experiment developed L-lysine-conjugated gold nanoparticles for CP delivery. They had 85 nm size and −25 mV zeta potenial, showing their capacity to internalize in breast tumor cells, and they also had high stability.[78] It is worth mentioning that a number of nanocarriers, such as gold nanoparticles, have anticancer activity via enhancing reactive oxygen species (ROS) generation to mediate cell death and sensitize tumor cells to chemotherapy. Furthermore, gold nanostructures can provide simultaneous chemotherapy and bioimaging, which are discussed in detail in the next sections (Table 2).[96,97]

TABLE 2 The nanostructures delivery aims.

Nanostructures	Characteristics	Cargo	Remarks	References
PEGylated PLGA nanoparticles	137.5 and 124.7 nm −26.1 mV 57.27%	Doxorubicin	Reducing drug release at blood circulation pH-sensitive release of DOX Increased cellular uptake Suppressing tumor growth up to 85.53%	[79]
Metal-organic framework nanostructures	258.49 nm	Doxorubicin	Prolonging residence time of DOX at tumor tissue Increasing internalization in cancer cells via endocytosis Providing simultaneous chemotherapy and immunotherapy	[80]
Serum albumin nanostructures	173.57 nm	Doxorubicin MDR1-siRNA	Reducing P-gp expression and promoting DOX internalization to suppress breast cancer progression	[80]
PLGA nanoparticles	113.5 and 148 nm −23 and −6.63 mV 73%	Doxorubicin	Inhibiting Notch, Wnt, estrogen, progesterone and HER2 pathways Reducing P-gp expression High biocompatibility	[81]
PTMC nanoparticles	140-230 nm	Doxorubicin	Preventing proliferation of breast tumor and increased DOX's cytotoxicity	[82]
Chitosan-coated polymeric nanoparticles	169.5 nm +4.47 mV	Trastazumab	Increased cellular uptake, nuclear and membrane-patterned deposition High cytotoxicity	[83]
Chitosan nanoparticles	30.5 and 26.9 mV	Cisplatin	High cytotoxicity Apoptosis induction Chromatin condensation	[84]

(Continues)

TABLE 2 (Continued)

Nanostructures	Characteristics	Cargo	Remarks	References
Core-shell nanoparticles	110–130 nm 17.7% and 29.8%	Cisplatin	High stability Reducing blood clearance and enhancing tumor accumulation ROS overgeneration Reducing breast tumor progression	[85]
Polymeric nanoparticles	162.9–182.9 nm 70%	Paclitaxel Curcumin	Suppressing breast cancer progression and integrin-mediated targeting	[86]
Magnetic nanoparticles	35 nm −29 mV 77.6%	Paclitaxel	Aptamer conjugation promoted internalization of paclitaxel in breast tumor cells and inhibiting tumor growth	[87]
Magnetic nanoparticles	10 nm 84.5% (paclitaxel) 77.6% (trastazumab)	Paclitaxel Trastuzumab	Spherical shape, cytotoxic activity, apoptosis induction and reducing tumor burden	[88]
Chitosan-NPDP nanoparticles	-	Paclitaxel Dendrophthoe pentandra leaves	Suppressing proliferation rate Decreasing TUBB3 and MAP4 expression	[89]
Polydopamine nanoparticles	179.3 nm −27.4 mV	Paclitaxel	Significant anticancer activity Apoptosis induction Reducing colony formation capacity	[90]
Polymeric nanoparticles	60 nm −10 to −16 mV	Gemcitabine Paclitaxel	Increased internalization of drugs in tumors Improving anticancer activity of drugs	[91]

TABLE 2 (Continued)

Nanostructures	Characteristics	Cargo	Remarks	References
$CSCaCO_3$ nanoparticles	63.9, 83.9, 78.2, and 87.2 nm	Paclitaxel Gefitinib	High solubility in acidic pH medium Prolonged release Enhanced anticancer activity	[92]
Polysaccharide hybrid nanoparticles	187.5 nm −25.20 mV 49.25% (paclitaxel) 54.71% (baicalein)	Paclitaxel Baicalein	Release of cargo at tumor site Remodeling of tumor microenvironment Polarization of M2 macrophages to M1 ones Reducing tumor progression	[93]
Albumin-based nanostructures	142.2 and 128.1 nm −30 mV 7.5%	Paclitaxel	Binding to P-selectin on activated platelets to target cancer cells using platelets as a bridge Enhancing PTX efficacy in cancer suppression Mediating hyperthermia and exerting synergistic impact	[93]
Paclitaxel palmitate albumin nanoparticles	87.63 nm 11.7 mV 97.71%	Paclitaxel	Decreased side effects on normal organs Prolonged release of paclitaxel Suppressing proliferation of tumors	[94]
Silicon nanoparticles	165 nm	Camptothecin	Reducing proliferation Decreased metastasis	[95]

2.3 | Phytochemical and synthetic molecule codelivery

The previous sections revealed that nanotechnological approaches elevate the cytotoxicity of anticancer drugs and mediating effective breast cancer suppression.[98] The synergistic impact between natural and synthetic drugs has resulted in their co-application for breast cancer. An experiment has developed amphiphilic copolymeric micelles for codelivery of DOX and curcumin. The downregulation of P-gp expression and ATP depletion (impairing P-gp activity) prevent the efflux of DOX from breast cancer cells,.[99] Overall, P-gp upregulation stimulates chemoresistance.[100–102] A study has developed multifunctional lipid nanostructures for PTX and curcumin codelivery in breast cancer suppression. The folate-modified lipid nanoparticles containing curcumin and PTX reduced P-gp expression to inhibit drug resistance. The nanocarriers enhanced the internalization and accumulation of curcumin and PTX in cells via endocytosis and suppressed breast cancer progression.[103]

The MSNs are important for delivery because of entrapping drugs in their pores. For codelivery of curcumin and PTX, an experiment prepared MSNs with a size of 115 nm and a pore size of 2.754 nm via an etching technique. The surface coating of MSNs with a thickness of 10-15 nm was then done with a PEGylated lipid bilayer. The lipid bilayer was fabricated using film hydration method, and then curcumin and PTX were loaded in lipid bilayer-coated MSNs. The encapsulation efficiencies for PTX and curcumin were 77.48% and 30.70%, respectively. The nanocarriers had a spherical shape, uniform dispersion, and the ability for sustained release of curcumin and PTX that remarkably elevated their cytotoxicity against breast cancer.[104] The PEGylated lipid bilayer-coated MSNs can be administered via intravenous and intratumoral routes and suppress tumor in vivo. They localized in lysosomes and mitochondria, and by increasing the internalization of curcumin and PTX, they effectively suppressed breast cancer progression.[105] The curcumin- and DTX-embedded solid lipid nanostructures were prepared with 247.5 nm size, and 73.88% EE. Enhanced cellular uptake and decreased cancer cell viability result from curcumin- and PTX-loaded nanoarchitectures.[106] Therefore, codelivery of natural compounds and synthetic molecules by nanoplatforms improves cancer therapy (Figure 2).[57]

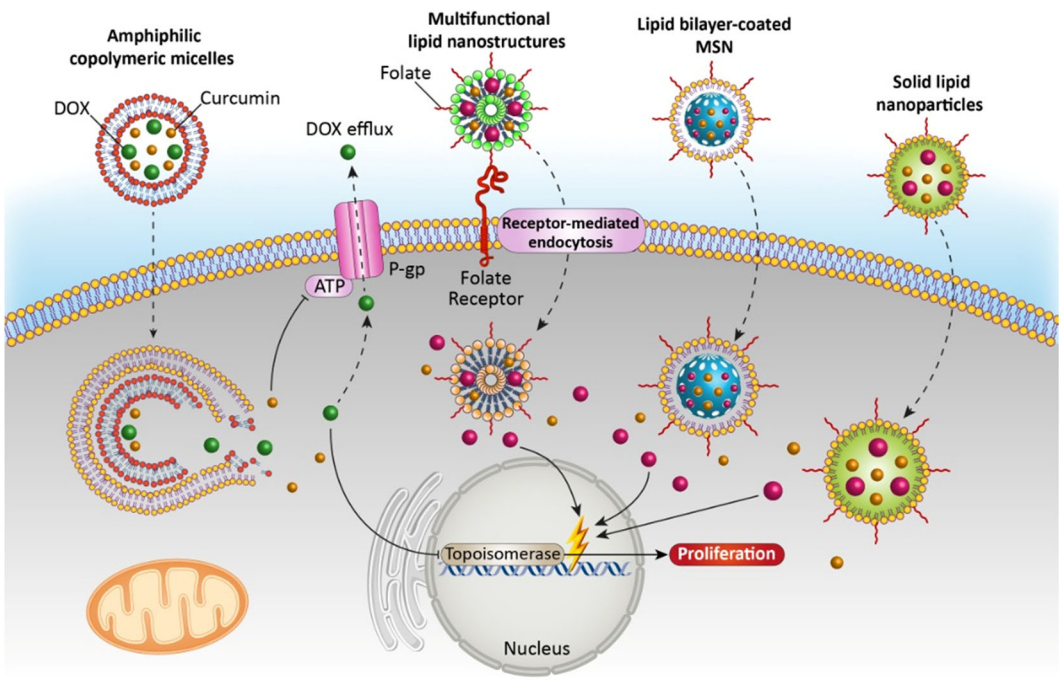

FIGURE 2 The application of nanostructures for delivery of synthetic agents and their codelivery. [Color figure can be viewed at wileyonlinelibrary.com]

3 | GENE DELIVERY

3.1 | RNA interference (RNAi)

RNAi was first discovered in 1998 in *Caenorhabditis elegans* and is considered an evolutionary cellular mechanism started by double-stranded RNAs (dsRNAs) that can silence target messenger RNA (mRNA) to prevent protein synthesis. Small interfering RNA (siRNA) is the most well-known tool of RNAi that is widely employed for gene expression regulation. The task of siRNA is to silence target gene and suppress its activity in targeted cells. However, the potential of siRNA and another RNAi tool, known as short hairpin RNA (shRNA), is limited due to enzymatic degradation in blood circulation, low accumulation in tissue sites and off-targeting features. These drawbacks are complexly obvious in cancer therapy, which urges scientists to find solutions, of which the application of nanostructures is one.[107–111]

The effective treatment of breast cancer by RNAi depends on identification of critical factors involved in its progression and malignancy. For instance, PRDM14 shows low expression in healthy cells, while its expression level undergoes upregulation in breast tumors, leading to stemness, invasion and drug resistance. Clinically, PRDM14 demonstrates overexpression in 23.8% of breast cancer patients. In an attempt, branched PEGylated poly-L-ornithine (PLO) nanoarchitectures were developed for specific delivery of PRDM14-siRNA. After intravenous administration, siRNA-loaded PLO nanoparticles significantly reduced PRDM14 expression, decreased tumor proliferation and prevented breast tumor metastasis in vivo. These nanoparticles improved the survival of tumor-bearing mice and showed high biocompatibility in serum.[112] However, this experiment did not investigate the characteristics of nanostructures and how they can affect siRNA complexation and its role in gene silencing. Noteworthy, the cellular uptake of naked siRNA appears to be low, and its degradation by enzymes in blood circulation is another challenge. In an effort, non-ionic surfactant vesicles (niosomes) were prepared, and then Lifeguard (LFG)-siRNA was loaded in hydrophobic core. To improve the internalization of siRNA-loaded niosomes in breast cancer cells, superparamagnetic iron oxide nanostructures were embedded into bilayer of niosomes. The prepared nanostructures demonstrated particle sizes of 127 and 145 nm. The zeta potential of nanocarriers reached −37.9 from −41.1 mV due to the connection between negatively charged niosome surface and positively charged polyplexes. These nanoparticles effectively diminished expression level of LFG and enhanced sensitivity of breast tumor cells to erlotinib or trastuzumab chemotherapy. The external magnetic field boosted intracellular accumulation of nanostructures and induced apoptosis to reduce breast cancer viability.[113] Therefore, it appears that delivery of siRNA by nanostructures is a promising strategy in potentiating anticancer activity of chemotherapeutic drugs.[108]

The interactions occurring in TME are responsible for increasing the progression of cancers. A similar story occurs in breast cancer, and TME remodeling is followed for its treatment. The ion gelation method was employed for preparation of PEG and MTC conjugates, and then VEGF- and MED1-siRNAs were loaded onto nanostructures. The siRNA-loaded nanoparticles effectively decreased VEGF and MED1 expression and suppressed growth and metastasis of breast cancer cells. The nanoarchitectures had high stability and promoted intracellular accumulation of siRNAs. Furthermore, siRNA-loaded nanostructures mediated polarization of M2 macrophages to M1 macrophages for TME remodeling and inhibiting breast cancer progression.[114] Another important target in breast cancer therapy is heat shock protein gp96, which has the capacity to transfer from reticulum to tumor surface. A research group has developed CDO14 as a peptide cationic liposome and modified it with gp96 inhibitor, helical polypeptide p37. Then, survivin-siRNA was loaded onto these liposomes to treat breast cancer. These liposomes effectively target breast tumor cells overexpressing gp96 on the cell membrane. The liposomal nanocarriers had positive charge and high stability. They reduced survivin expression by siRNA in breast tumor cells to impair their viability. The nanostructures promoted the accumulation of siRNA in breast tumor cells, and they effectively inhibited tumor growth in vivo. Furthermore, delivery efficacy was boosted by surface-modified liposomes.[115] Overall, studies highlight the fact that siRNA is a potential tool for treatment of breast cancer, and the employment

of nanocarriers significantly enhanced cellular uptake of siRNA and its efficacy in gene silencing and suppressing the progression of breast cancer cells.[114,116,117]

Another RNAi tool in breast cancer therapy is shRNA. The conventional methods include conjugation of anticancer drugs with genetic tools and their application in cancer therapy. However, such complexes have low stability, and their drug loading efficacy is poor. An experiment has developed polylactide (PLA) micelles for codelivery of MDR1-shRNA and DOX in breast cancer therapy. At first, PLA-DNA conjugates were developed that were further assembled into micelles. Then, DNA was used as a promoter, and rolling circle transcription was employed to synthesize poly-shRNA on nanostructures. The nanoparticles accumulated in breast cancer cells and led to a significant decrease in MDR1 expression, promoting DOX internalization, apoptosis induction and improving therapeutic index.[118]

The *RAN GTP* (*RAN*) gene is another factor in increasing the metastasis of breast cancer cells via affecting molecular pathways such as Ras and PI3K/Akt pathways. The PLGA nanoparticles were synthesized for delivery of *RAN*-siRNA. The resulting nanocarriers had a particle size of 237.71 nm, a zeta potential of −1.17 mV and an encapsulation efficiency of 80%. These biodegradable nanostructures released shRNA in MDA-MB-231 cells and reduced *RAN* expression to suppress metastasis of breast cancer cells.[118] The PEI nanostructures are considered promising carriers for gene delivery. The DSPEI is a stimuli-responsive kind of PEI that is used in nanoparticle synthesis. An experiment has developed PEG-DSPI nanostructures and modified them with RGD to enhance their selectivity towards breast tumor cells. Then, p65-shRNA was loaded into nanocomplexes to suppress NF-κB pathway. Both GSH and NIR can mediate the release of p65-shRNA from nanocarriers and significantly reduce the growth and metastasis of breast cancer cells. The cellular uptake of nanocarriers in breast cancer cells increased via RGD-mediated endocytosis. Nanocarriers had particle sizes of 12 and 50 nm and a zeta potential of 48.7 mV, showing their high stability (Figure 3).[119] Therefore, nanoparticles have opened a new window for treatment of breast cancer via shRNA delivery.[120]

3.2 | CRISPR/Cas9 system

CRISPR/Cas9 is a potential tool for genomic screening to find novel targets for cancer therapy.[121] The CRISPR/Cas9 system is a part of immune defense system in prokaryotes that has been employed in recent years in breast cancer treatment. Different kinds of genes can be regulated by CRISPR/Cas9 system, and this tool is beneficial in understanding the function of certain genes in breast cancer progression to provide new insights for their targeting in future experiments. For instance, miRNA-3662-HBP1 and FOXP3 can be modulated by CRISPR/Cas9 system to reduce breast tumor progression. Proliferation and cell cycle progression of these malignant tumors and their therapy response are also modulated by CRISPR/Cas9 system.[121–128] Noteworthy, delivery of CRISPR/Cas9 system can pave the way for improving its efficacy in gene expression regulation, which is the focus of the current section.

Most of the experiments have focused on delivery of RNAi and noncoding RNAs (ncRNAs) by nanostructures in breast cancer therapy. However, there are two experiments showing CRISPR/Cas9 delivery for breast cancer. An experiment has designed proton-activatable DNA-based nanosystems for codelivery of Cas9/sgRNA and DNAzyme in breast cancer therapy. The scaffold of the nanosystem contained an HhaI enzyme cleavage site, a DNAzyme sequence and ultra-long ssDNA chains containing sequences for identification of sgRNA in Cas9/sgRNA. The mechanism of action of nanosystem was interesting, so that DNAzyme cofactor Mn^{2+} compressed DNA chains for forming nanostructures. The surface modification of nanostructures was performed with acid-degradable polymer-coated HhaI enzymes that undergo degradation in response to protons in lysosomes. Then, HhaI enzymes identify the cleavage site and cut it off, leading to release of Cas9/sgRNA and DNAzyme for affecting gene expression for the purpose of breast cancer therapy.[129] Another experiment has developed core-shell nanoparticles for delivery of dual plasmids (pHR-pCas9) in breast cancer treatment. The nanostructures had a particle size of 140 nm and a zeta

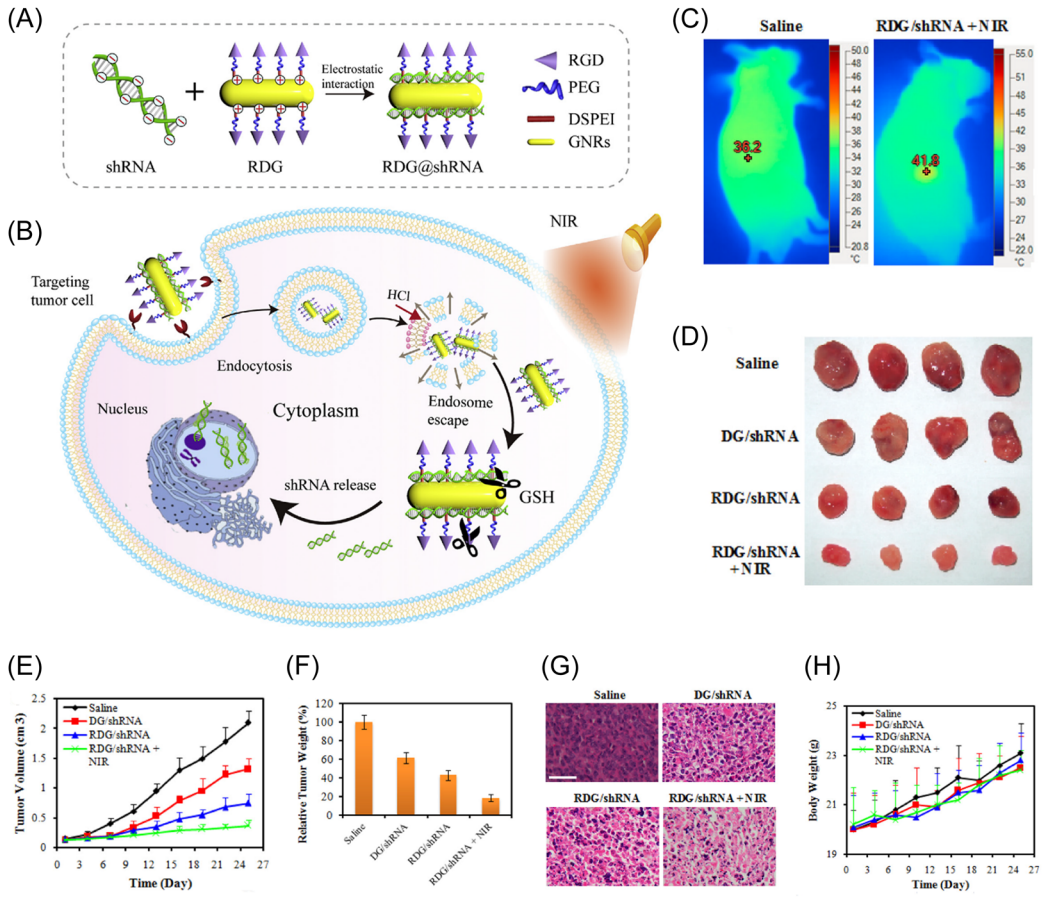

FIGURE 3 (A, B) Development of nanocarriers and their internalization in tumor cells, (C) Infrared thermal images, (D) Collected tumors, (E) Tumor volume, (F) Tumor weight, (G) Histopathological analysis and (H) Bodyweight. Reprinted with permission from[119] Elsevier. [Color figure can be viewed at wileyonlinelibrary.com]

potential of 26.4 mV. These nanoparticles promote cellular uptake of Cas9 mediated by γGTP and provide endosomal escape, resulting in accurate expression of *CTCF* gene. After *CTCF* upregulation, a significant decrease occurs in expression of STOM protein, which is vital for suppressing the proliferation (colonization) and metastasis of breast tumor cells (Figure 4).[129]

3.3 | Noncoding RNAs

A large section of the genome is comprised of ncRNAs that do not translate any proteins. Although their function was under shadow after their discovery, more advances in biology revealed the role of ncRNAs in evolutionary mechanisms and biological functions in cells. MicroRNAs (miRNAs), long noncoding RNAs (lncRNAs) and circular RNAs (circRNAs) are the most well-known categories of ncRNAs that show abnormal expression in various tumors, especially breast cancer. Apoptosis, proliferation rate, metastasis and therapy response are tightly regulated by ncRNAs in breast cancer, and therefore, modulation of their expression is of importance in breast cancer therapy[130–134] that can be boosted by nanostructures.

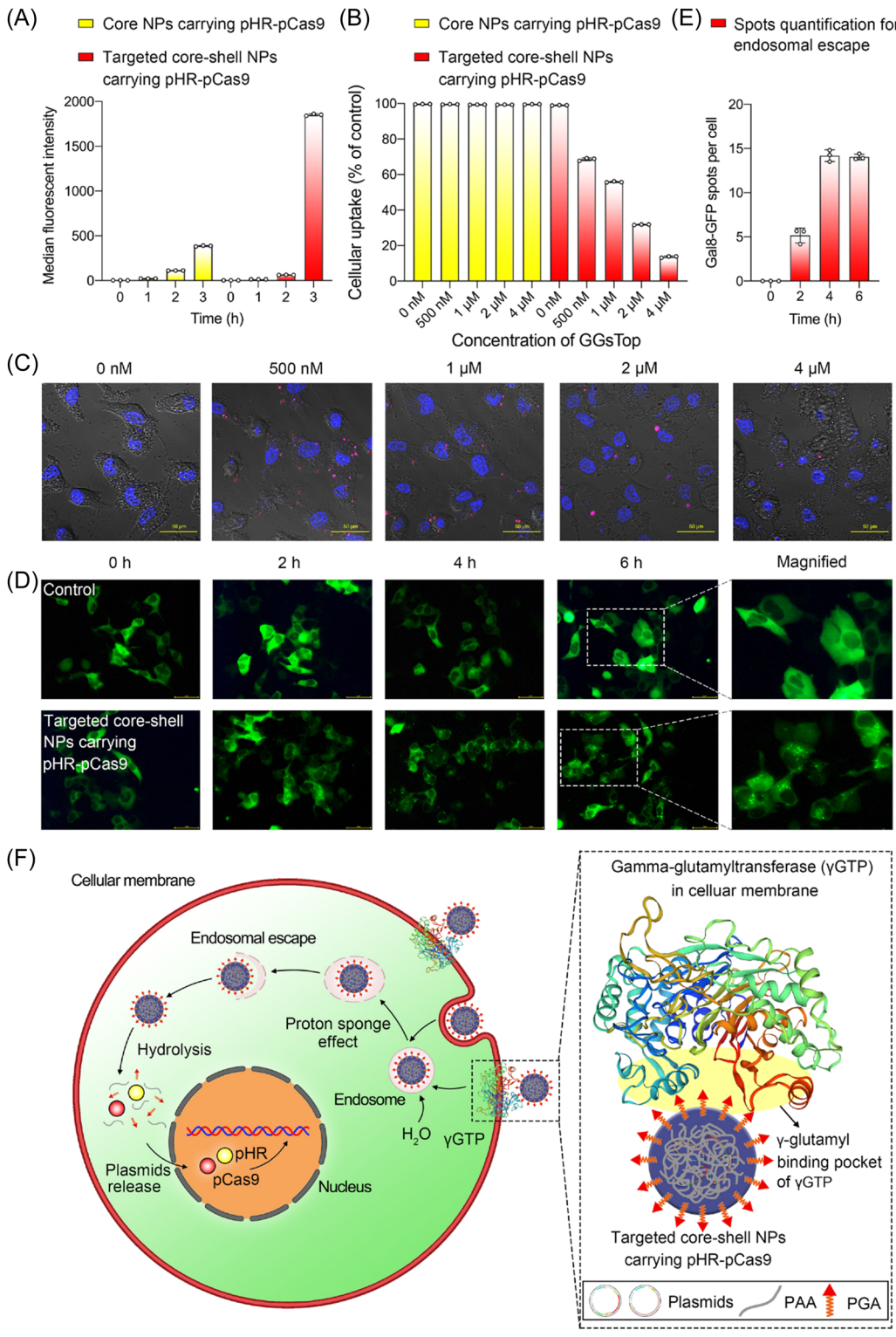

FIGURE 4 (See caption on next page)

A recent experiment has prepared layer-by-layer nanostructures for miRNA delivery in breast cancer suppression. The spherical core of nanoparticles was prepared by poly(lactic-co-glycolic acid), and it was surrounded by different layers of poly-L-lysine (PLL) and miRNA-34a. The breast tumor cells demonstrate high cellular uptake of layer-by-layer nanoparticles compared to polyplexes containing PLL and miRNA. A significant amount of miRNA-34a was delivered to cytosol, which then decreased expression of CCND-1, Notch-1, Bcl-2, survivin and MDR-1, leading to growth suppression and cell cycle arrest.[135] Another study designed silica dioxide nanoparticles for miRNA-34a delivery in breast cancer suppression. The miRNA-34a was effectively delivered to both normal and tumor cells in vitro without adverse impacts. The miRNA-34a-loaded silica dioxide nanoparticles suppressed breast cancer growth in vitro and in vivo.[136] Therefore, nanoparticles are promising candidates for miRNA delivery in breast tumor therapy, and their efficacy in gene silencing and tumor progression suppression can be elevated by nanostructures.[137] The miRNA-loaded nanoparticles are also beneficial in preventing drug resistance. The polymeric nanoparticles were prepared using chitosan and hyaluronic acid, and then miRNA-34a and doxorubicin were loaded. The nanoparticles demonstrated a particle size of 214 nm, a zeta potential of −33 mV and encapsulation efficiencies of 48.3% and 91% for DOX and miRNA-34a, respectively. The released miRNA-34a inhibited breast cancer progression via Notch-1 downregulation, and then, potential of DOX in apoptosis induction was enhanced via Bcl-2 inhibition. Furthermore, this combination therapy and delivery by nanoparticles prevented drug resistance in breast cancer.[138] Another study also prepared PEI-PLGA nanostructures for DOX and miRNA-542-3p codelivery and surface modification with HA promoted selectivity of nanoparticles towards CD44-overexpressed breast tumor cells. They had a particle size of 131.7 nm and a zeta potential of −7.8 mV. These HA-modified PEI-PLGA nanostructures delivered miRNA-542-3p to mediate survivin downregulation and p53 upregulation in apoptosis induction, leading to a significant increase in DOX sensitivity.[139] In addition to miRNA delivery by nanoparticles in breast cancer therapy,[140] circRNA delivery has been conducted. The circRNA-0001073 demonstrates downregulation in breast cancer, and it is associated with an undesirable prognosis. Upregulation of circRNA-0001073 stimulates apoptosis via caspase-3/9 overexpression and suppresses growth rate. Furthermore, circRNA-0001073 inhibits the metastasis of breast tumor cells via EMT inhibition. The circRNA-loaded nanoparticles and their intratumoral injection could suppress tumor growth in animal models.[141] Notably, lncRNAs also demonstrate aberrant expression in breast tumor, and their expression can be regulated by siRNA-loaded nanoparticles (Table 3).[151,152] The delivery of siRNA by nanoparticles was discussed in previous sections.

4 | DRUG AND GENE CODELIVERY

Nanostructures have capacity to provide a platform for codelivery of drugs and genes in breast cancer therapy. The gene therapy can promote sensitivity of breast cancer cells to chemotherapy. The overexpression of STAT3 and its nuclear translocation can lead to reduced sensitivity of breast cancer cells to PTX chemotherapy. The polymeric micelles from PCL were prepared, and then PTX was loaded into nanostructures via hydrophobic interaction. At the next step, siRNA-STAT3 was condensed into PEI via electrostatic interaction. The surface modification of micelles with HA changed the surface charge into a negative one. These HA-modified micelles selectively targeted CD44-overexpressed

FIGURE 4 (A) Time-dependent cellular uptake, (B) γGTP-mediated cellular uptake, (C) γGTP-mediated cellular uptake, (D, E) Endosomal escape capability, Quantification of Gal8-GFP spots and (F) Illustration for γGTP-mediated cellular uptake and endosomal escape of targeted core-shell NPs carrying pHR-pCas9. Reprinted with permission from[129] Elsevier. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 The nanostructures for gene delivery in breast cancer therapy.

Nanovehicle	Particle size (nm) Zeta potential (mv) Encapsulation efficiency or drug loading (%)	Cargo	Remarks	References
Liposomal nanoparticles	200 nm	Docetaxel	Reducing tumor burden up to 78% via enhancing DTX accumulation at tumor site	[142]
	20 mV	SIRT1-shRNA	Synergistic impact of chemotherapy and gene therapy	
	70%			
RGD-modified cationic DSPEI nanocomplexes		Np65-shRNA	Interaction of negatively charged shRNA and cationic DSPEI	[119]
			Cytosolic release of shRNA	
			RGD-mediated endocytosis for entering into cells	
			Combination with NIR irradiation	
PEI-functionalized carbon nanotubes	150 nm	Bcl-xL-shRNA	Modification with 5 TR1 aptamer for selective targeting of breast tumor cells	[143]
	6.3-30.8 mV		Increased transfection efficiency by 8.5-10 folds	
Carbamate-mannose-modified PEI nanostructures	140 nm	NF-κB-shRNA	High biocompatibility and transfection efficiency	[144]
	+10 mV		Inhibiting migration and colony formation in breast tumor	
			Preventing stemness via reducing cancer stem cell population	
			Apoptosis induction and sensitizing to chemotherapy	
PAMAM-functionalized graphene oxide	+24.1 mV	Doxorubicin	High transfection efficiency and stability in serum	[145]
		MMP9-shRNA	Reducing expression level of MMP-9	
			Good biocompatibility	
Magnetic nanoparticles	197 nm	Paclitaxel	Simultaneous delivery of drug and gene	[146]

TABLE 3 (Continued)

Nanovehicle	Particle size (nm) Zeta potential (mv) Encapsulation efficiency or drug loading (%)	Cargo	Remarks	References
	−7.8 mV	FAM-siRNA	pH-sensitive release and suppressing breast cancer progression	
Stronium nanoparticles	190 nm −8 mV	siRNA	Downregulation of MAPK and AKT in suppressing progression of breast tumor cells	[147]
Hyaluronate-conjugated TAT-chitosan-SPION nanostructures	118 nm +30 mV	STAT3 and HIF-1α-siRNA	Apoptosis induction Suppressing proliferation and invasion of breast tumor cells Downregulation of STAT3 and HIF-1α Enhancing number of cytotoxic T lymphocytes	[148]
Peptide-modified PEG-PEI nanostructures	80 nm	EGFR and BRD4-siRNA	Decreased expression level of EGFR and BRD4 in suppressing progression of breast tumor cells	[149]
Dual responsive-core/shell nanoparticles	176.7 nm −9.14 mV	Plk1-siRNA	High biocompatibility and reducing expression level of Plk1 to suppress breast cancer progression	[150]
PLGA nanoparticles	122 nm +32 mV	miRNA-34a	Release of miRNA-34a in cytoplasm and upregulation of miRNA-34a Suppressing CCND1, Notch1, survivin, Bcl-2 and MDR1 genes in breast tumor inhibition	[135]
Hyaluronic acid-coated PEI-PLGA nanoparticles	131.7 nm −7.8 mV	miRNA-542-3p	Selective targeting of CD44-overexpressed breast tumor cells and upregulation of miRNA-542-3p to suppress survivin expression, while enhance p53 expression in inhibiting breast cancer progression	[139]

breast cancer cells, and their internalization in endo/lysosomes led to degradation of HA by hyaluronidase. This combination suppressed the proliferation and invasion of breast tumor cells.[153] Another study developed PEI/TPGS nanostructures for codelivery of PTX and Twist-shRNA to impair the progression of breast cancer cells. These nanostructures significantly enhanced cellular uptake of shRNA and PTX and suppressed metastasis of breast tumor cells up to 91%. The blood circulation time of PTX and shRNA elevates by nanoparticles and promoted accumulation in lung and cancer site. The growth rate of breast tumor decreased, and their metastasis was inhibited.[154] Therefore, codelivery of PTX and genetic tools such as siRNA and shRNA are beneficial in impairing breast cancer progression.[155]

A similar strategy has been utilized for codelivery of DOX and genetic tools. The PEI-modified silk fibroin nanostructures were prepared for codelivery of DOX and siRNA-survivin. The nanostructures had a particle size of 207.6 nm and a zeta potential of 30.45 mV. The nanoparticles provided endosomal escape of DOX and siRNA, and promoted their accumulation in cytoplasm of breast tumor cells. These siRNA- and DOX-loaded nanoparticles decreased the expression level of survivin at mRNA level. The nanoparticles preferentially accumulated at tumor site, stimulated apoptosis and reduced breast tumor progression.[156] The biological part should be focused on targeting important factors involved in drug resistance. For instance, GCN5 is a regulator of P-gp in cancer. The pH- and redox-sensitive nanostructures for codelivery of DOX and siRNA-GCN5 have been successful for reducing GCN5 expression, impairing function of P-gp, promoting internalization of DOX in breast tumor cells and interfering with their progression.[116] These studies highlight the fact that codelivery of synthetic molecules and genetic tools can effectively suppress breast cancer progression.[157–160]

It is also worth mentioning that codelivery of genetic tools and phytochemicals in synergistic breast cancer therapy is followed. An experiment developed hybrid lipid nanoparticles for codelivery of IGF-1R and lycopene in breast cancer therapy. These nanoparticles induced apoptosis and cell cycle arrest to impair breast cancer progression.[161] Another study has designed liposomes for codelivery of siRNA-P-gp and gedunin in breast cancer. The drug-loaded liposomal nanocarriers had a particle size of 97 nm, a zeta potential of +42 mV and an encapsulation efficiency as high as 80%. These nanoparticles suppressed proliferation of breast cancer cells and impaired stem cells. Furthermore, they decreased expression levels of ABCB1, cyclin D1, Bax, p53 and survivin to impair breast tumor progression.[162]

5 | STIMULI-RESPONSIVE NANOCARRIERS

Stimuli-responsive drug delivery systems have evolved gradually in the past two decades after the development of passive and active delivery systems. The nanomaterials, which are designed to passively penetrate through the tumor environment, rely on enhanced permeation and retention, and their physical properties are a decisive factor in the efficacy of these systems.[163] Although their bioavailability and biocompatibility have improved compared to free chemotherapeutic drugs, their accumulation throughout the tumor is still not desirable. One step further was designing ctivee targeting drug delivery systems, which are being widely used in cancer therapy. Regarding to binding of some specific ligands on the surface of these systems, they can actively attach to the targeted receptor, followed by endocytosis and inducing the therapeutic effects.[164] Under the umbrella of active targeting, there is a category called stimuli-sensitive or smart delivery systems. These materials are able to change their physicochemical properties in response to a specific stimulator and/or microenvironment. Based on the type of stimulation, they are divided into internal (redox, pH, enzyme, etc.) and external (light, magnetic field, ultrasound, etc.) stimuli delivery systems (Table 4).[176]

5.1 | pH responsive

The tumor environment is known to have an acidic pH ranging from 5.4 to 6.5, whereas the healthy tissue possesses a pH of 7.4. The high amounts of glycolysis are the reason why the tumor tissue has this character.

TABLE 4 The endogenous stimuli-responsive nanocarriers in breast cancer therapy.

Nanovehicle	Particle size (nm) Zeta potential (mV) Encapsulation efficiency or drug loading (%)	Cargo	Stimulus-responsive	Remarks	References
Hyaluronic acid-carbon dots	150 nm (pH 7.4) 40 nm (pH 6.5) 8-35 mV (pH 4-7.5) 16.50% % per 10 mg of the carrier	Doxorubicin	pH	In the exposure of acidic medium, the carrier undergoes a change in the surface charge and hydrophilicity to hydrophobicity ratio resulting in the dissociation of particles and a burst release. The pH-responsivity nature of carrier causes a significant decrease in size under acidic conditions which improves deep penetration and cellular uptake.	[165]
His_6-metal assemblies	295 nm +30.4 mV 50.7%	Doxorubicin	pH	Three different breast cancer cell lines (MCF-7, MDA-MB-231, and MDA-MB-453) were treated with the developed nanocarrier. The nanocarrier with pH-responsiveness nature and high efficacy inhibited the growth of all three cell lines.	[166]
Legumain-specific melittin micelles	45.9 nm −0.83 ± 0.11 mV 95.6 ± 0.5% %	Cabazitaxel	pH	The micelles could specifically reach to the primary and metastatic tumors followed by being endocytosed by cancer cells and release the cargo inside lysosomes/endosomes.	[167]
2,3-dimethylmaleic-anhydride-PEG-ε-poly-L-lysine micelles	86.92 ± 1.82 nm -	Doxorubicin-lapatinib	pH	The micellar carrier was developed for pH-responsive codelivery of two chemotherapeutic drugs. Along with doxorubicin release in endo/lysosomes, the other drug synergized and improved the efficacy of therapy.	[168]

(Continues)

TABLE 4 (Continued)

Nanovehicle	Particle size (nm) Zeta potential (mV) Encapsulation efficiency or drug loading (%)	Cargo	Stimulus-responsive	Remarks	References
	5.2% % (Doxorubicin)−53.1% % (lapatinib)			In vivo studies on MCF-7 breast tumor revealed effective accumulation of the micelles in the tumor followed by curtailing the tumor's growth.	
Calcium phosphate-capped-hyaluronic acid-SS-tetradecyl micelles	146.56 ± 2.73 nm −14.60 ± 0.42 mv 33.64%	Sulforaphane	Glutathione	The micelles were found to respond to highly reducing media and mild acidic medium. They could effectively target breast cancer cells bearing $CD44^{+}$.	[169]
Dendron-like hyaluronic acid	87 ± 12 nm −29 ± 2 mv -	Docetaxel	Glutathione	The drug molecules were incorporated inside of glycodendronized hyaluronic acid. The morphology and surface charge of nanoparticles were spherical and negative leading to improved stability in blood circulation and better tumor accumulation. The drug-loaded carrier showed potent antitumor activity and eliminated the side-effects of free docetaxel.	[170]
Metal-organic framework	280–350 nm - 72.6 nmol mg^{-1}	Doxorubicin	Adenosine triphosphate	The metal-organic framework was coated with an ATP-responsive hydrogel. The cytotoxicity of hydrogel-coated sample towards MD-MBA-231 cancer cells was higher than non-modified one.	[171]

TABLE 4 (Continued)

Nanovehicle	Particle size (nm) Zeta potential (mV) Encapsulation efficiency or drug loading (%)	Cargo	Stimulus-responsive	Remarks	References
Near infrared (NIR) dye (IR820)	36 ± 2.4 nm - -	Docetaxel	Matrix metalloproteinase- glutathione	Attachment of a peptide called CF27 on the nanoparticles improved the targeting ability and cellular uptake. The carrier itself was a photosensitizer responsive to light and in combination with drug release, 97.5% % of tumor cells were inhibited.	[172]
Polyethylenimine–polylysine copolymers-modified mesoporous silica	249 nm 22.3 mV -	Doxorubicin-Bcl-2 siRNA	Glutathione-pH	The release was triggered by both acidic medium and glutathione. Bcl-2 effectively silenced MDA-MB-231 cells and improved therapy efficacy.	[173]
PEG-hyaluronic acid–stearic acid	185.2 ± 3.5 nm −27.5 ± 1.7 mV 31.8 ± 4.2% %	paclitaxel	pH-glutathione	The carrier was chemically stable at physiological media while releasing the drug molecules at tumorous pH and reductive and oxidative conditions. The maximum value for breast cancer cells (MDA-MB-231) inhibition was 93.71% %.	[174]
Protamine-poly(AA-*b*-NIPAAm) copolymer (PAA-*b*-PNIPAAm)	92.52 ± 3.46 nm −20.60 ± 0.78 mV 54.9% %	Doxorubicin	Temperature, pH, and enzyme	The nanoparticles could pass the cell membrane and internalize into the multidrug resistant MCF-7/ADR breast cancer cells Along with pH- and enzyme-responsiveness, applying cold shock (4°C) caused a burst release of doxorubicin and increased the treatment's efficacy.	[175]

Moreover, the pH is even more acidic at subcellular levels; the pH of endosome and lysosome is in the range of 4.5–5.5, and so after being endocytosed, the nanocarrier has an opportunity to release its cargo at these organelles.[177] Various acid-responsive chemical groups have been used, among which phosphoric acid, amines, acid-labile bonds, carboxylic acid groups, and so forth. can be enumerated. In the case of breast cancer, different types of pH-sensitive carriers with various compositions have been designed.[166,172,174,175] Polymeric nanocarriers are at the epicenter of designing pH-responsive systems for breast cancer therapy. One of most well-known compositions is pH-responsive liposomes. Based on a phosphoethanolamine lipid, a liposome carrier modified with an acid-responsive group (cholesteryl hemisuccinate) was developed; the carrier was endowed with fusogenic properties upon exposure to a mild acid environment, resulting in the carrier's disruption and drug release.[178] Polymeric micelles are of particular interest because of their easy-to-tailor structure.[179,180] Paclitaxel drug molecules were entrapped in an acid-labile, bone-modified, PEGylated micellar system. Thanks to PEG, the dispersion of micelles was excellent, and the drug molecules were liberated in the cancer cells (MDA-MB-231) due to disassembly of the micelles in an acidic medium.[181] Elsewhere, a dual-pH-responsive micelle was reported as a carrier for paclitaxel. The micelles had a core-shell structure in which there is a pH-responsive center coated with an acid-cleavable shell, leading to a significant increase in the 4T1 tumor accumulation and inducing a stronger cytotoxicity towards cancerous cells compared to free drug. It was revealed that the carrier was successful in inhibiting the tumor growth and metastasis.[182] Another approach through micellar systems is to take the advantage of using two drugs simultaneously. For this purpose, poly(2-ethyl-2-oxazoline)-poly(D,L-lactide) micelles were loaded with paclitaxel and honokiol for combinational therapy, and the results implied that the synergistic effect of both drugs caused a potent effect against tumor metastasis in vitro and in vivo.[183] A programed targeting micellar system, which has been functionalized with legumain-specific melittin, was synthesized for breast cancer metastasis. Cabazitaxel, a well-known anticancer drug that is a strong microtubular inhibitor, was entrapped inside the micelles. Due to high expression of legumain in the tumor microenvironment, the micelles could specifically penetrate throughout the tumors and accumulate there, followed by being activated inside the cancer cells in response to a change in pH. The in vivo studies revealed the successful delivery of micelles into the primary and metastatic tumors, a significant decrease in the tumor's size, and a notable suppression of lung metastasis (Figure 5).[167]

There are other pH-sensitive polymeric systems reported for breast cancer therapy. A polymeric system loaded with doxorubicin composed of poly(L-histidine)-poly(lactidecoglycolide)-tocopheryl polyethylene glycol (PEG) succinate was developed and tested against MCF-7 breast cancer cells. It was found that at subcellular level, the nanoparticles were accumulated through lysosome and released the cargo in response to the acidic medium, and they performed significantly better and caused higher cytotoxicity than free doxorubicin.[184] A ternary polymeric system comprised of starch, polysorbate 80, and polymethacrylic acid was formulated and then loaded with doxorubicin against breast cancer.[185] pH-responsivity of dendric polymers was tested at pH 5, and the release rate was observed to increase at this pH resulted due to cleavage of hydrazone bonds. Moreover, the in vivo results complemented the in vitro results and indicated antitumor activity of the dendric polymer against 4T1 breast tumor model while leaving no toxicity effects behind in vivo.[186] Besides polymeric matrices, pH-responsive inorganic nanomaterials are being extensively used in breast cancer therapy, including iron oxide, mesoporous and hollow silica, and so forth.[187–189] Through the adoption of a cleavable hydrazine bond, PEGylated polydopamine has been coated over doxorubicin-loaded hollow silica and tested against a xenograft model, resulting in the inhibition of breast tumor growth.[190] Amine-functionalized mesoporous silica was synthesized as a dual-responsive platform—pH and photodynamic therapy (PDT). The functionalization led to an improvement in the cellular uptake and induced cytotoxicity against MCF-7 cells.[191] The combination of chemotherapy and PDT was designed by using doxorubicin and a photosensitizer in a calcium carbonate carrier to increase the antitumor efficacy of platform. The nanoparticles exhibited a good stability at the physiological pH while effectively releasing the drug molecules when the pH decreased.[192]

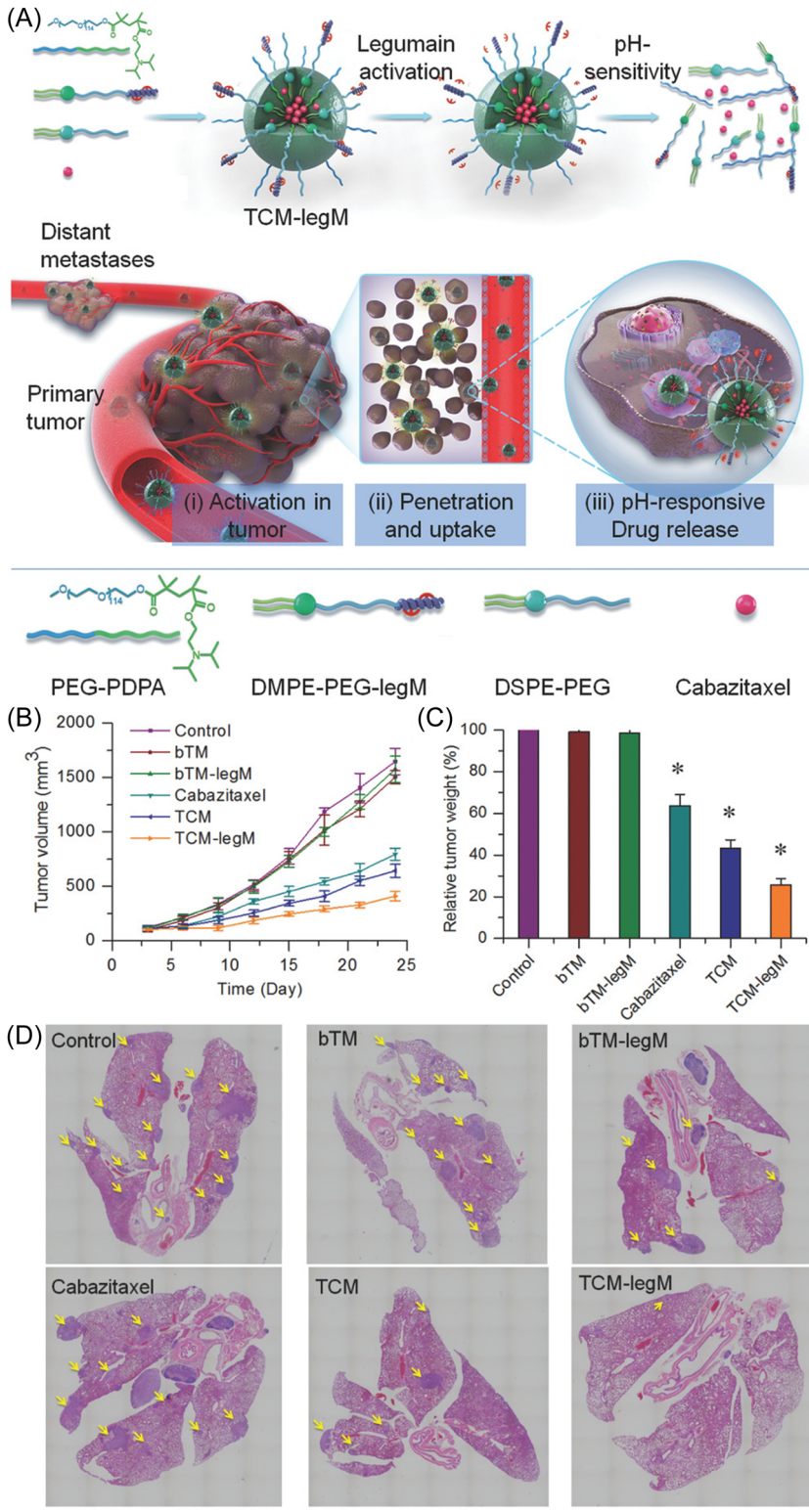

FIGURE 5 (See caption on next page)

5.2 | Redox responsive

The design of redox-responsive nanocarriers for anticancer purposes is based on using disulfide linkages, which can be as a cross-linker or in the main or side chain.[193] The general mechanism is the release of the anticancer drug molecules once they are endocytosed in the exposure of glutathione; it is known that the tumor tissues were observed to have significantly higher amounts of glutathione in their cytosol than healthy tissues.[194] An active-targeting, redox-responsive micellar nanocarrier was developed for the delivery of paclitaxel; the micelle's composition was based on hyaluronic acid and deoxycholic acid, which has been conjugated with cystamine. The drug release rate was found to be faster when the drug-loaded carrier had been dispersed in the glutathione-containing solution (20 mM). The cytotoxicity potential of micelles against MDA-MB-231 cell line was compared with Taxol, and the potency was competitively higher. The distribution of micelles was significantly enhanced in the tumor site compared with the liver and healthy tissues.[195] This group conducted another study in which they shed light on the type of internalization of these stimuli-responsive carriers. They found that the rapid and efficient endocytosis of the carriers occurs through CD44 receptor-mediated endocytosis.[196] A hierarchical ternary nanoparticulate system comprised of PEG-hyaluronic acid and stearic acid, which had been conjugated through a disulfide bond, was synthesized. The loaded paclitaxel inside was found to release faster in the presence of oxidative and reductive media with an acidic pH. Thanks to PEG, the carrier's circulation time in the blood stream was prolonged, followed by being accumulated in the tumor environment and subsequently internalized by MDA-MB-231 cells through CD44-mediated endocytosis (Figure 6).[174]

Loading more than one anticancer drug/gene into a carrier is advantageous because the cell proliferation inhibition takes place in a more efficacious way.[138] To come up with a more potent breast cancer treatment, siRNA and paclitaxel were codelivered through a hyaluronic-based redox-responsive nanocarrier. In the presence of glutathione, the liberation rates of both siRNA and paclitaxel were increased, and both therapeutic agents were successfully delivered to MDA-MB-231 cells, followed by imparting an antitumor activity much more potent than that of nonresponsive carriers.[197] To circumvent the multidrug resistance of breast cancer cells, mesoporous silica was used as a potent carrier to load both siRNA (P-glycoprotein modulator) and doxorubicin against MCF-7/ADR cancer cells.[198] A lot of effort has been made to improve the antitumor activity of nanocarriers, and one of these methods is to equip a stimuli-responsive carrier with some specific signaling molecules that can in particular recognize breast cancer cells.[199] To achieve this, a research group reported the design of a folate-conjugated carrier that was also pH and redox-responsive. The dual responsiveness led to a faster release in the presence of both stimuli—glutathione and acidic medium. Two control groups, including free doxorubicin and non-folate-modified drug-loaded carriers were simultaneously tested, and the folate-modified carrier indicated better tumor growth inhibition than the others.[200] Antibody-conjugated (anti-Trop2) redox-responsive nanoparticles were developed and the in vitro results exhibited that the doxorubicin release rate got faster in the presence of stimulus besides better uptake into MDA-MB-231 cells because of the antibody.[201]

FIGURE 5 A pH-responsive micellar system targeting primary and metastasis breast cancer. (A) A schematic on the preparation of TCM-legM system and how it acts against the cancer cells; it first actively accumulates in the tumor microenvironment due to the high expression of legumain and internalized into the cells and release the cargo due to the change in the acidity of the medium. (B) The relative tumor volume after being treated with different samples up to 25 days. (C) The relative tumor weight (%) after treatment with different samples at the end treatment time (*$p < 0.05$). (D) The histological analysis made on the different parts of lung through H&E staining; the yellow arrows point at the metastatic lesions. Reprinted from[167] with permission from Wiley. [Color figure can be viewed at wileyonlinelibrary.com]

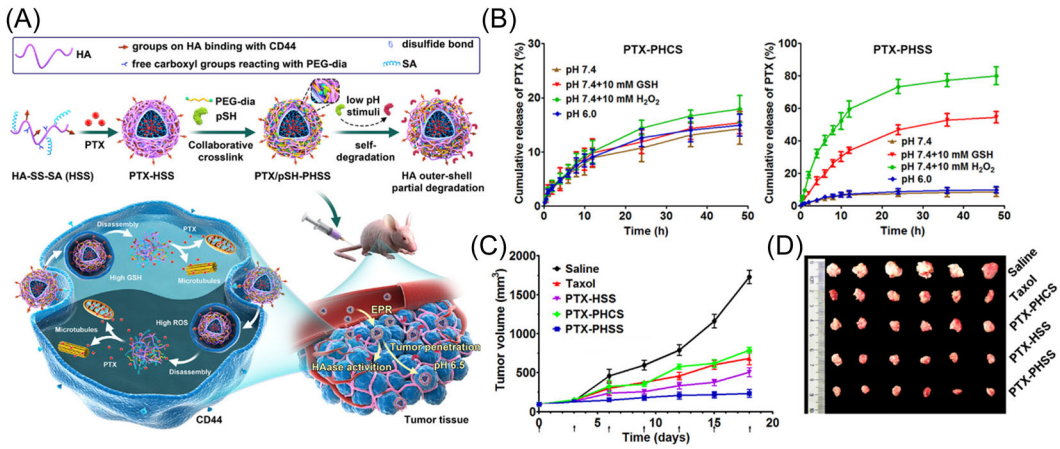

FIGURE 6 A redox-responsive ternary carrier for active breast cancer therapy. (A) Schematic on the preparation of paclitaxel-loaded ternary nanoparticulate system followed by being internalized through CD44-mediated endocytosis. (B, C) The cumulative release of PTX-PHCS and PTX-PHSS samples at different conditions. (C) Tumor volume after being treated with different samples; the black arrows show the administration times. (D) The excised tumors at the end of treatment time after applying treatment with different samples. hyaluronic acid (HA), stearic acid (SA), poly(ethylene glycol) diamine (PEG-dia), paclitaxel (PTX), pH-stimulated hyaluronidase (pSH), HA-SA containing disulfide linkages (PHSS) while with carbon bonds (HCS). Reprinted from[174] with permission from ACS. [Color figure can be viewed at wileyonlinelibrary.com]

5.3 | Enzyme responsive

Until now, multiple types of nanostructures have been used in cancer treatment, such as the development of polymeric lipid prodrug cocktails and self-assembled DHA–cabazitaxel conjugates to suppress progression even in drug-resistant tumors.[202,203] The main reason for using nanostructures in cancer therapy is to improve the cellular uptake of drugs,[204] and to increase this ability in cancer cell internalization, nanocarriers are modified with macrophage membrane.[205] In recent years, enzyme-responsive nanomaterials have piqued the interest of cancer researchers. Due to dysregulation of enzyme activity in the tumor microenvironment, designing smart nanocarriers in a way that is sensitive to the function of enzymes, can also lead to site-specific release of drug at the tumor site.[206]

One of the main challenges in the effective treatment of breast cancer is metastasis, in which degradation of tumor extracellular matrix takes place.[207] The main degradative agents are proteolytic enzymes, which are abundant in cancer cells. Therefore, through the adoption of short peptides and/or esters, the carrier would undergo cleavage in the presence of proteases or esterases.[208] A multicompartment carrier composed of docetaxel-loaded micelles was developed for breast cancer therapy and then incorporated inside of an enzyme-sensitive liposome. The anticancer potential of nanocarrier was tested against 4T1 cells in the presence of matrix metalloproteinase, and a better cellular uptake and faster liberation of docetaxel were obtained. The efficacy of drug-loaded carrier was also tested in vivo in comparison to Taxotere®, and a significantly greater tumor growth inhibition was achieved.[209] Paclitaxel was incorporated into an enzyme-sensitive beta-cyclodextrin carrier and tested against breast cancer in vivo (MDA-MB-231). The control group with which the carrier was compared had been treated with Taxol®, and the tumor volume after being treated with the carrier and Taxol was 50 and 3500 mm^3, respectively. It can be seen that the enzyme-responsive carrier caused the tumor to almost disappear.[210] A polymersome-based drug delivery system modified with iRGD peptide was fabricated; the peptide was responsible for making an interaction with the neuropilin-1 and integrin receptors located on the cancer cells' surface. It is well known that neuropilin-1 is expressed on breast cancer cells. Tracking the internalization of samples revealed that only the polymersomes modified with the peptide could enter the cell after three hours, and

the induced toxicity by the modified samples was 76% while the nonmodified ones had no effect.[211] An enzyme-responsive micellar platform consisting of a hydrophilic PEG and a hydrophobic dendron was designed and loaded with Nile red dye. Although the results implied that in the presence of penicillin G amidase, the release of dye got faster, more in vitro and in vivo studies are required to assess the carrier's true potential in breast cancer.[212] To target and reverse multidrug resistance, a paclitaxel-loaded micellar platform was proposed to release the encapsulated drug molecules faster in the presence of collagenases IV, and as a result, the mechanism of drug efflux was inhibited.[212] Diagnostic stimuli-responsive nanocarriers are of particular interest in cancer therapy because they make treatment tracking possible besides imaging. Having an imaging agent inside the nanocarrier provides an opportunity to observe if the nanoparticles have accumulated in the tumor's site and to what extent the therapeutic material is efficacious.[213] A diagnostic enzyme-responsive hybrid nanomaterial was designed to encapsulate doxorubicin and is being used for theranostic applications. Through adopting a confocal microscopy assay and making a comparison with free doxorubicin, it was observed that the hybrid nanomaterial selectively penetrated into the cancerous cells and more internalization had occurred than with free doxorubicin.[214]

6 | EXTERNAL-STIMULI RESPONSIVE

External stimuli-responsive relates to those carriers that can be controlled by an agent or agents outside of the body; these agents are capable of affecting the drug release behavior, steering the carrier to a targeted site, introducing an extra therapeutic way, etc. Various types of external stimuli systems have been reported for cancer therapy, including light, magnetic field, ultrasound, and so forth.[215–217] One of the most common external stimuli for purpose of cancer therapy is the development of nanostructures that can be sensitive to NIR light, and this results in immunogenic cell death that is of importance for purpose of immunotherapy and future insights towards development of cancer vaccines.[218] In this section, some of those techniques that have been applied more in breast cancer therapy are summarized.

6.1 | Photothermal and PDT

Photothermal therapy (PTT) is a localized treatment for various kinds of solid cancers present in different regions of the body. Infrared and electromagnetic radiation are employed during PTT to excite a photosensitizer.[219,220] During PTT, the photosensitizer absorbs light or energy, which is then converted to heat to mediate hyperthermia and provide tumor ablation.[221] PDT uses oxygen to interrelate with targeted cells and tissues. During PDT, an increase in levels of ROS occurs to mediate oxidative stress and cell death. Less energy and a longer wavelength are used for PTT compared to PDT, making it more safe for the purpose of cancer therapy and reducing adverse impacts on normal cells and tissues.[222] Various experiments have used nanostructures for PTT and PDT to suppress breast cancer progression. A recent experiment has developed injectable hydrogels for PTT in breast tumor. The Pluronic F127 hydrogels were coated with titanium carbide (Ti_3C_2). The nanoparticles showed high stability at low temperatures for at least 2 weeks. The hydrogels demonstrated a loosely meshed structure, and Ti_3C_2 nanoarchitectures had a shuttle-shaped structure. Interestingly, hydrogels did not influence photothermal activity of nanoparticles, and in turn, no negative impact on temperature sensitivity of hydrogels was observed. Exposure of these nanoarchitecture-coated hydrogels to 808 nm NIR laser led to PTT effect, enhancing temperature up to 40–50°C and suppressed tumor growth in vitro and in vivo.[223] Noteworthy, PTT can be helpful in preventing breast tumor recurrence after surgery. In this way, an experiment has developed a thermosensitive and injectable hydrogel containing porous microspheres and IR820 that induces hyperthermia (more than 50°C) upon exposure to NIR irradiation and eliminates breast tumor cells in vitro. Besides, this hydrogel prevents breast tumor recurrence after surgery in vivo and inhibits migration and invasion (Figure 7).[224] Furthermore, a photosensitizer and chemotherapy

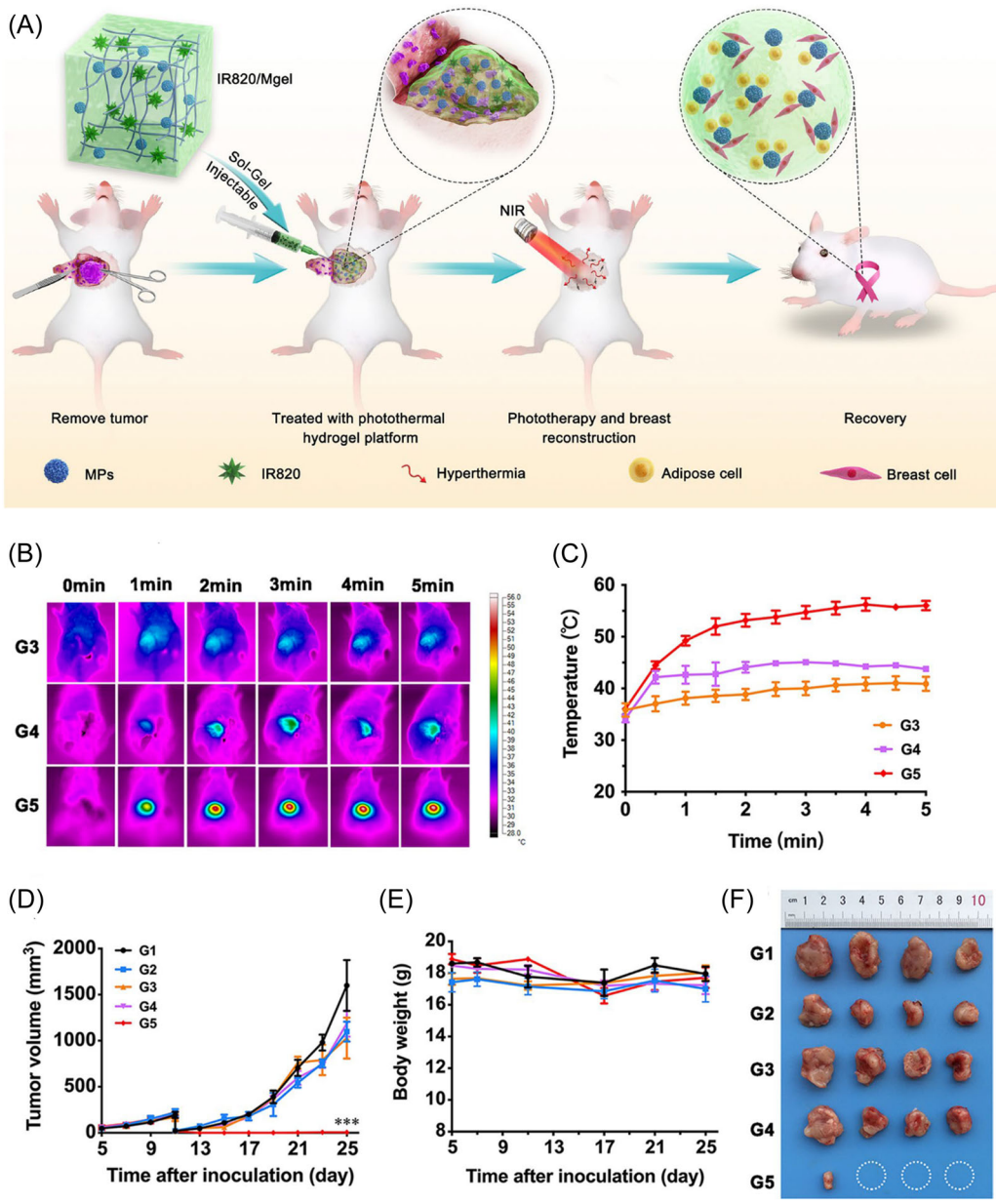

FIGURE 7 (A) The hydrogel platform and its application for preventing tumor recurrence, (B) The dynamic photothermal images, (C) temperature–time profile, (D) Tumor volume, (E) Bodyweight, and (F) Excised tumors. Reprinted with permission from[224] BMC. [Color figure can be viewed at wileyonlinelibrary.com]

drug can be wrapped and assembled into nanostructures to increase ROS generation for PDT and mediate chemotherapy and PDT of cancer cells.[225]

One of the mechanisms applied in treatment of breast cancer is ferroptosis, which is based on Fenton reaction. However, efficacy of ferroptosis in breast tumor suppression is limited due to interactions occurring in TME that reduce its efficacy. A recent experiment has developed a novel strategy for Fenton-independent ferroptosis for breast tumor ablation. This study designed iron redox pair (Fe^{2+}/Fe^{3+})-containing hollow mesoporous Prussian blue

(HMPB) nanocubes for providing iron source and then developed iron-loaded liposomes (HMPB@Lip). The resulting nanocarriers induced ferroptosis in breast tumor via catalyzing lipid peroxidation, providing PTT for cancer ablation.[131] Notably, PTT can significantly enhance potential of chemotherapy in breast tumor ablation while having high biocompatibility and safety profile.[226] In this way, an experiment has developed hybrid mesoporous silica nanoparticles for delivery of disulfiram and PTT. The anticancer drug was loaded inside the mesoporous and hollow interior, while CuS ultrasmall nanostructures were loaded on surface of nanoparticles. Exposure to NIR irradiation mediated PTT and after Cu^{2+} release into TME, disulfiram, a nontoxic agent, was changed into diethyldithiocarbamate (DTC)-copper complex as a toxic agent to suppress breast tumor progression. This combination of chemotherapy and PTT can improve breast tumor treatment (Figure 8).[133] Another target for effective treatment of breast tumor is cancer stem cells (CSCs), which are responsible for metabolism, renewal of tumor population and cancer recurrence.[227] A recent experiment has developed dendritic polyglycerol-conjugated gold nanostars in breast cancer therapy. In the structure of nanocomposite, triphenyl phosphonium (TPP) was used as a mitochondrial

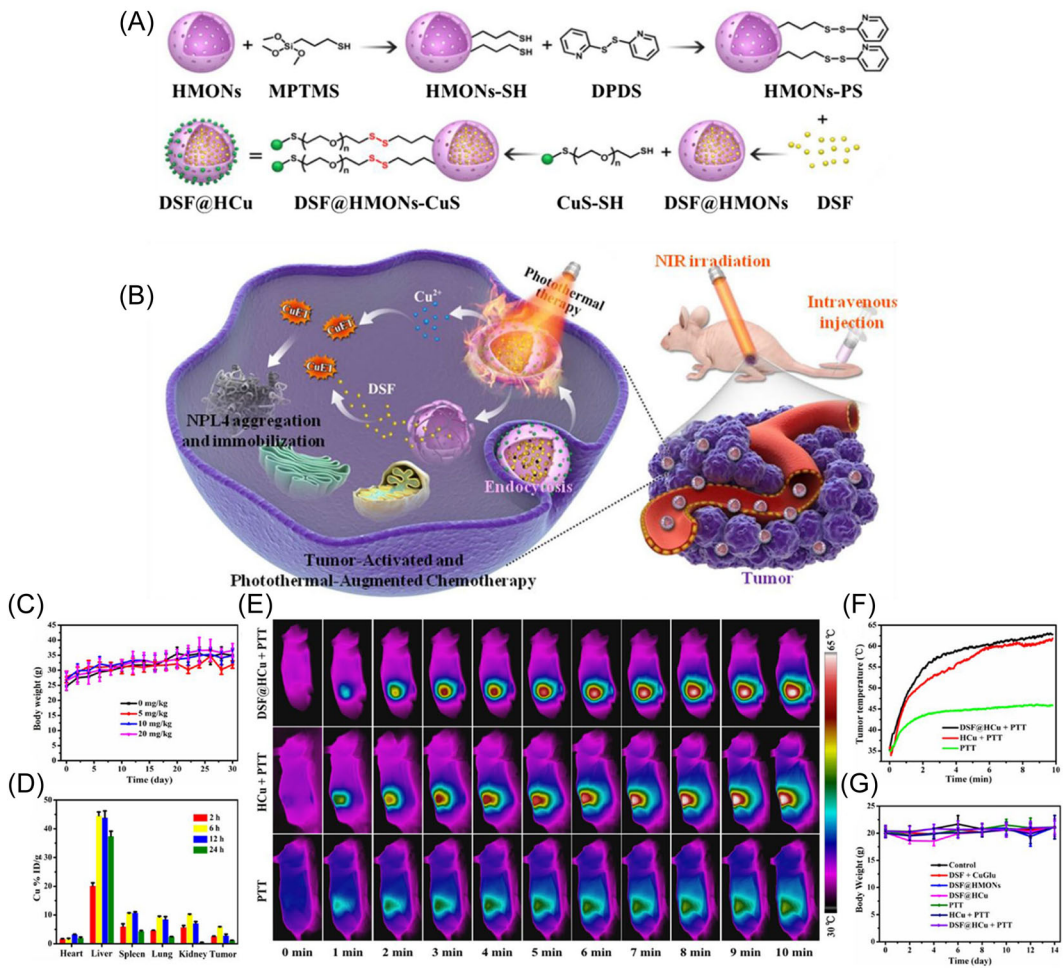

FIGURE 8 (A, B) Preparation of nanoparticles and their Anticancer activity, (C) Bodyweight, (D) Body distribution of Cu in the major organs (heart, liver, spleen, lung, and kidney) and tumor after administration of HCu for varied time durations (2, 6, 12, and 24 h), (E) Temperature elevation in tumor site, (F) Corresponding heating curve, (G) Bodyweight changes of 4T1 tumor-bearing mice with different treatment. Reprinted with permission from[133] from BMC. [Color figure can be viewed at wileyonlinelibrary.com]

targeting agent, 3-bromopyruvate (3BP) as hexokinase-2 (HK2) inhibitor and hyaluronic acid (HA) as a specific agent for targeting CSCs. The nanocomposites demonstrated high biocompatibility, and after NIR irradiation, they induced apoptotic cell death via providing PTT. Furthermore, they suppressed glycolysis in CSCs via HK2 downregulation, and HA helped in specific targeting of CSCs overexpressing CD44 receptor.[228]

Noteworthy, experiments have also focused on PDT for breast tumor ablation. In an effort, polymeric nanoparticles composed of mPEG and poly(asparagyl diisopropylethylenediamine-co-phenylalanine) (P(Asp(DIP)-co-Phe)) have been developed for pH-sensitive delivery. The polymeric nanoparticles self-assembled into nanovesicles and were utilized for encapsulation of tirapazamine and dihydrogen porphin (chlorin e6) as a photosensitizer. Exposure to NIR irradiation mediates PDT to induce hypoxia in TME. Then, activation of tirpazamine as a prodrug occurs to induce chemotherapy and breast tumor ablation.[229] In addition to chemotherapy, PDT can also help boost breast cancer immunotherapy. A recent experiment has developed manganese dioxide (MnO_2)-loaded liposomes labeled with LyP-1 peptide for breast tumor ablation. Zoledronic acid (Zol) was loaded in hydrophilic cavity of liposomes, while IR780 as photosensitizer was embedded in lipid bilayer. In response to H_2O_2 in TME, MnO_2 in structures of liposomes generated O_2 bubbles. Then, liposome membrane degradation occurred to release Zol, increasing O_2 generation and mediating PDT. Notably, phagocytosis of Zol by macrophages occurs, which subsequently induces cell death in macrophages or changes their polarization from M2 to M1 to prevent immunosuppression. Besides, surface modification with LyP-1 peptide provides targeted delivery to breast tumor cells, and IR780 enhances ROS generation upon NIR irradiation for PDT and mild immune induction.[230] These studies highlight the fact that both PDT and PTT are beneficial for breast tumor ablation, but PTT is generally preferred to PDT due to its safety profile. Both PDT and PTT can enhance cytotoxicity of chemotherapeutic agents and are beneficial in preventing drug resistance development. Furthermore, PDT and PTT can induce antitumor immunity that is suppressed in breast cancer (Table 5).[232,239,241–251]

Magnetic field is known to penetrate throughout the tissues and is generally used for imaging. Moreover, the magnetic field has been shown to have therapeutic effects, including affecting drug release behavior, steering magnetic-responsive particles to the intended target, and inducing hyperthermia.[252] Through altering the magnetic field intensity and applied frequency, it has been reported that controlling the produced heat is possible.[253] Iron oxide is one of the most reputable magnetic-responsive materials in medicine because of its high magnetization saturation and superparamagnetic property.[254] In combination with curcumin, iron oxide coated with pluronic F68 has been applied to breast cancer therapy. The anticancer potential of drug-loaded iron oxide and free curcumin was tested in vitro in the exposure of MDA-MB-231 cells with and without applying an external magnetic field. It was observed that a burst release (about 50%) occurred in the first 5 days of treatment, followed by a sustained release up to 28 days. The combination of iron oxide and curcumin reduced cell viability from 100% to 38%.[255] Chitosan-coated iron oxide was reported somewhere else for breast cancer therapy. Gemcitabine was used as the drug model, and MCF-7 and SKBR-3 were used for in vitro studies. Applying an external magnetic field led to accumulation of superparamagnetic nanoparticles in the intended location, and the IC_{50} of drug-loaded chitosan-modified iron oxide was seen to be significantly lower than free gemcitabine, showing the effectiveness of carrier against both breast cancer cell lines.[256] A magnetic nanosystem was formulated based on loading of artemisinin onto the chitosan-modified magnetic nanoparticles. The release trend of artemisinin was tested in vitro with three formulations and revealed a release range of 62-78%. Through in vivo models (4T1-breast tumor-bearing mice), the targeting ability of drug-loaded carriers was determined. The applied external magnetic field (1000 gauss) at the first hour resulted in the accumulation of nanoparticles in the cancer tissue rather than healthy ones.[257] One of the problems revolving around magnetic nanoparticles is undesirable aggregation due to dipole-dipole interactions between the nanoparticles. An effective solution to this problem is introducing a polymer coating over those nanoparticles.[258] Doxorubicin-loaded PEG-dicarboxylic acid-coated iron oxide was developed for breast cancer therapy. The surface modification culminated in the better colloidal stability of magnetic nanoparticles. The in vitro studies performed on the MCF-7 cells exhibited that the applied magnetism improved the nanoparticles' internalization into the cells.[259] The heat generation capability of chitosan-coated magnetic nanoparticles, besides

TABLE 5 The nanostructures applied for purpose of PDT and PTT in breast cancer.

Nanovehicle	Particle size (nm) Zeta potential (mV) Encapsulation efficiency or drug loading (%)	Cargo	PDT or PTT	Remarks	References
CuS-Nd nanoparticles	-	Doxorubicin	PTT	Providing PTT upon irradiation at 808 nm Exerting EPR effect and release of DOX at tumor site Synergistic impact in breast cancer therapy	[231]
Cancer cell membrane-coated biomimetic black phosphorus quantum dots	30 nm −24.1 mV	-	PTT	High photothermal conversion efficiency and elimination of cancer cells Inducing dendritic cell maturation	[232]
Gadolinium-doped carbon dots	2.8 nm −16.31 mV	Doxorubicin	PTT	Converting light to heat and suppressing breast cancer progression via providing PTT and chemotherapy	[233]
Mesoporous silica nanoparticles	69.15 nm −15 mV 91.6%	Doxorubicin	PTT	Modification with hyaluronic acid for selective targeting of breast tumor cell overexpressing CD44 Conjugation of DOX to hyaluronic acid on the surface of nanostructures Accumulation at tumor site and providing both PTT and chemotherapy	[234]
Injectable hydrogel	-	-	PTT	Photothermal conversion efficiency as much as 63.1% and suppressing tumor progression up to 99.3%	[235]
ZIF-PQ-PDA-AUN nanoplatforms	10 nm −14.3 mV	-	PTT	Providing PTT for breast tumor ablation and increasing antitumor immunity via inducing infiltration of T lymphocytes	[236]
Fe^{2+}@UCM-BBD nanoparticles	-	Doxorubicin	PDT	Converting 980 nm light to red and green light to generate singlet oxygen for PDT	[237]

TABLE 5 (Continued)

Nanovehicle	Particle size (nm) Zeta potential (mV) Encapsulation efficiency or drug loading (%)	Cargo	PDT or PTT	Remarks	References
				pH-sensitive release of DOX to induce apoptosis and DNA damage	
Metal-organic framework	70–80 nm −5 mV	-	PDT	Optimal adsorption and high stability for PDT of breast cancer	[238]
Heparin-coated metal organic framework	248, 250, and 260 nm	chloroquine phosphate	PDT	Enhanced cellular uptake	[239]
	−21.3 mV			Suppressing protective autophagy	
	21.7%			Improving therapeutic index in breast tumor ablation via providing PDT	
Phthalocyanine-conjugated glyconanoparticles	30.73 nm	Doxorubicin	PDT	Good colloidal stability and pH-sensitive release of DOX	[240]
	−20.50 mV			Generation of singlet oxygen under NIR irradiation	
				High cellular uptake in breast tumor cells	

doxorubicin release, was studied. Without applying the magnetic field, doxorubicin alone decreased the cell viability of cancer cells down to 30% %, whereas the drug-loaded carrier caused 40% cytotoxicity. Once the magnetic field was applied for 10 min, it was found that in the first 5 min, nearly 65% of cells were killed, and prolonging the procedure up to 10 min even killed 90% showing the high efficacy of hyperthermia treatment.[260] Along with hyperthermia treatment, some studies have added functionalized agents to the magnetic nanoparticles to selectively target specific receptors. A core-shell magnetic compound was designed, followed by encapsulation of camptothecin and conjugation of an EGFR antibody. The internalization of antibody-modified carrier was improved through treatment with MCF-7 cells. Up to 1 h, the drug release was around 18%, while in the presence of a magnetic field for 2 min, this value increased up to 40%.[261] Monoclonal antibody-modified magnetic nanoparticles were synthesized for doxorubicin delivery. The in vitro studies were performed on the HER2-positive SKBR3 cells, and as it was expected, the functionalization led to an enhancement in the internalization of nanoparticles and exhibited a sustained drug release inside the cells.[262] Besides spinel ferrite magnetic nanoparticles, there is another magnetic material with high potential in cancer therapy called liquid metals, which have a low melting temperature near or at room or body temperature, and this property endows this category with both fluidic and metallic properties.[263] Gallium-based eutectic alloys have sparked considerable attention in biomedicine with their desirable chemical stability, biocompatibility, environmental friendliness, etc. These alloys are reported to have melting points in the range of 10−30°C. A recent study combined doxorubicin-loaded mesoporous silica with PEGylated liquid metal to achieve a hybrid platform. In comparison with magnetic nanoparticles, it was observed that even a tiny drop of injectable liquid metal was enough to induce high temperatures inside the tumors into which it had been incorporated. Interestingly, through the use of polarizing microscopy, it was possible to observe the effect of a heat increase on the recrystallization of coated PEG all over the metal ions. The release of doxorubicin along with the hyperthermia provided a thermo-chemotherapy package for breast cancer therapy (Figure 9).[264] Some of the magnetic-responsive nanoparticles for breast cancer therapy are tabulated in Table 6.

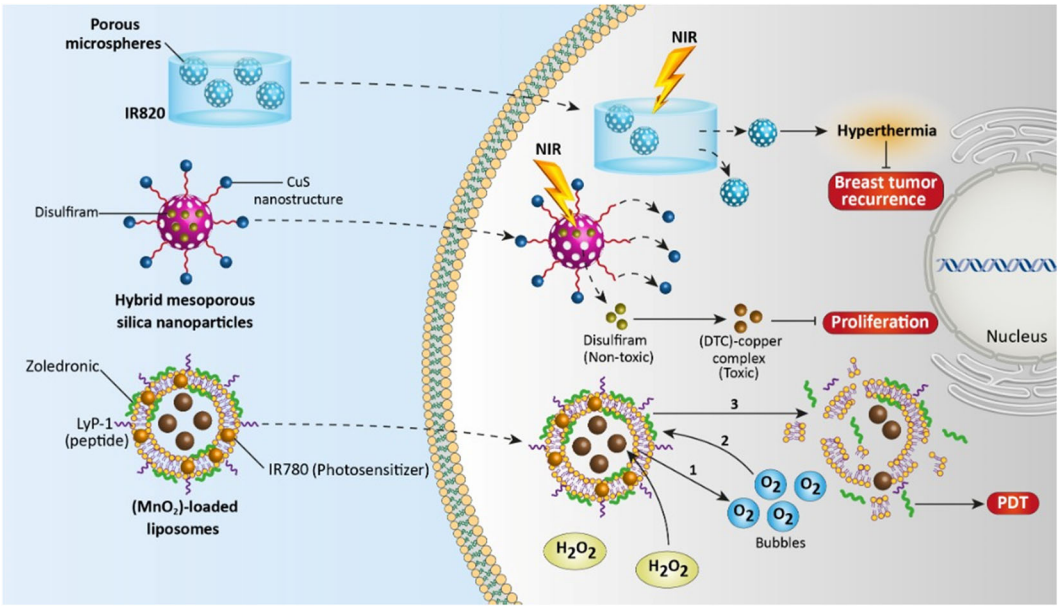

FIGURE 9 The nanomaterials for purpose of PTT and PDT in breast tumor therapy. PDT, photodynamic therapy; PTT, Photothermal therapy. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 6 Magnetic-responsive nanomaterials for breast cancer therapy.

Nano-vehicle	Cargo	Application	Remarks	References
Herceptin ligand-modified Fe_3O_4@PLGA–PVP	Tamoxifen	Drug delivery	The carrier was found with super-paramagnetic properties which reached the targeted tissue and induced toxicity to breast cancer cells.	
Fe_3O_4/SiO_2-graphene oxide quantom dots	Doxorubicin	Drug delivery-hyperthermia	The temperature increase led to an increase in the drug release The efficient cellular uptake of the carrier occurred through breast cancer 4T1 cells Combination of hyperthermia and chemotherapy together led to a higher efficacy in eradication of cancer cells	[265]
PEG-Chitosan-Fe_3O_4 hydrogel	Doxorubicin	Drug delivery-hyperthermia	Magnetic hyperthermia improved doxorubicin internalization and reduced the size of tumors.	[266]
Fe_3O_4-coated with calcium phosphate-PEG-polyanion block copolymers	siRNA	Gene delivery	The siRNA-loaded carrier was found to be directed to the targeted tissue by magnetic field followed by releasing the gene.	[267]
Progesterone-modified casein-calcium ferrite	soy-derived genistein	Drug delivery-hyperthermia	A high drug encapsulation of 88% % was obtained. Under applying an external magnetic field, the drug release reached 93% % in 4 h and the temperature raised up to 41°C.	[268]
Magnetic hydrogel nanozyme	-	Hyperthermia	The hyperthermia activated the enzymatic activity of iron oxide to generate hydroxide ions which simultaneously reinforce the efficacy of hyperthermia treatment.	[176]
PEG-based hyper saline hydrogel	Doxorubicin	Hyperthermia	Increasing in the local temperature rapidly once being exposed to an external magnetic field. In vivo observations showed that the hydrogel could suppress two kinds of breast cancer models.	[269]
Functionalized $MnFe_2O_4/Fe_3O_4$	-	Hyperthermia-imaging	The nanoparticles have been functionalized with a peptide culminating in a better accumulation in the tumor and more effective ablation of the tissue through magnetic hyperthermia.	[270]

(Continues)

TABLE 6 (Continued)

Nano-vehicle	Cargo	Application	Remarks	References
Gelatin-based magnetic hydrogel	Doxorubicin	Drug delivery-hyperthermia	The hydrogels were found to have a porous structure resulted in high amounts of drug loading. The combination of drug delivery and hyperthermia was observed to synergistically reduced the anticancer activity of breast cancer cells.	[271]

7 | IMMUNOTHERAPY

New hope has been opened in the treatment of hematological and solid tumors via immunotherapy, and in this case, various strategies such as immune checkpoint inhibitors and adoptive cell therapy have been introduced.[272] Anticancer immunity depends on using T cells and improving prognosis of cancer patients. The histopathological analysis reveals infiltration of inflammatory and lymphocytic cells in TME and their function in affecting tumor growth.[273] However, much impact has not been observed in breast cancer immunotherapy. Therefore, interdisciplinary research using nanoparticles for boosting immunotherapy in breast cancer has been suggested. An experiment has developed genetically edited nanostructures for breast cancer immunotherapy. The attachment of SIRPα on macrophages to CD47 inhibits activity of macrophages in phagocytosis of tumor cells. Besides, cancer cells have the capacity of secreting colony stimulating factors (CSFs) and polarizing macrophages to M2 phenotype. The cell membrane-coated magnetic nanostructures suppress SIRPα and CD47 interaction to maintain activity of macrophages in breast cancer phagocytosis, whereas magnetic core repolarizes M2 macrophages to M1 macrophages. These activities boost breast cancer immunity and improve survival and prognosis of breast cancer.[274] As it was mentioned, CSFs affect polarization of macrophages, and by binding to CSF 1 receptor (CSF1-R), mediate M2 polarization of macrophages. An experiment has developed self-assembled dual-inhibitor-loaded nanostructures for suppressing CSF1R and SHP2 pathways to induce M1 polarization of macrophages for phagocytosis of breast tumor cells and mediating cancer immunotherapy.[275]

Due to systemic toxicity after intravenous administration, it is preferred to use intratumoral administration for breast cancer therapy. In an effort, platelet-coated nanoparticles were loaded with resiquimod (R848) as a toll-like receptor agonist, and then they were administered via intratumoral route. The surface modification of nanoparticles with platelets promotes interactions of nanocarriers with TME and significantly enhances activity of R848 in breast cancer immunotherapy. Growth inhibition and the prevention of invasion of breast cancer cells to lung result from the application of R848-loaded platelet-coated nanostructures.[276] The coating of nanoparticles with immune and cancer cells is a promising strategy in tumor immunotherapy. The modification of PLGA nanostructures with macrophages and cancer cells was performed, and then metformin and siRNA-FGL1 were loaded. The guanidine group of metformin enabled the endo-lysosomal escape of siRNA in cytoplasm via providing a pH-triggered CO_2-generating nanostructure. The release of metformin by nanostructures results in stimulation of AMP-activated protein kinase (AMPK) to mediate PD-L1 degradation, resulting in PD-L1 inhibition. Furthermore, downregulation of FGL1 by siRNA induces a T cell response to promote antitumor immunity in suppressing breast cancer in vitro and in vivo.[277] Besides, to maximize anticancer activity, a combination of chemotherapy and immunotherapy is performed. The polymeric nanoparticles were synthesized from poly(L-histidine) (PHIS), and then PHIS was conjugated to R848 in the core of nanostructures. Then, DOX was conjugated to HA via hydrazone bond linkage.

These nanocarriers release DOX and R848 in response to pH due to cleavage of the hydrazone bond, and both chemotherapy and immunotherapy exert a synergistic impact in suppressing breast cancer progression.[278]

Immunotherapy and phototherapy can be co-utilized in synergistic breast cancer therapy. An effort has been made to develop ovalbumin-coated PEGylated $MnFe_2O_4$ nanoparticles for delivery of R837 as an immunoadjuvant. These nanoparticles decreased production of cytokines by M2 macrophages to prevent immunosuppression. These nanocarriers are also important for suppressing growth and lung metastasis of breast tumor cells in vitro and in vivo.[279] The TME remodeling by nanocarriers is a promising strategy for providing immunotherapy. The tumor-associated adipocytes in TME are responsible for secretion of CCL2 chemokine. Then, CCL2 recruits macrophages and monocytes that can differentiate into M2 macrophages and immunosuppressive myeloid-derived suppressor cells (MDSCs). An experiment has synthesized lipid-protamine nanostructures for delivery of plasmid trapping CCL2 to prevent its action in recruiting M2 macrophages and MDSCs, leading to immunotherapy and suppressing breast cancer progression.[280] The rhodamine B isothiocyanate (RITC) fluorescent MSNs were prepared and modified with PEG and TA. Finally, MSNs were loaded with cyclic diguanylate monophosphate (c-di-GMP or cdG). These nanostructures promoted secretion of IL-6, IL-1β, TNF-β and enhanced STING expression. Furthermore, MSNs significantly enhanced infiltration of immune cells such as leukocytes, dendritic cells (DCs), macrophages and CD4+ and CD8+ T cells in TME, reducing breast cancer progression.[53] These studies highlight the fact that nanoarchitectures can significantly enhance efficacy of immunotherapy in breast cancer suppression (Figure 10 and Table 7).[295–298]

Although most of the studies have focused on the regulation of macrophages in cancer immunotherapy, it is worth mentioning that other immune cells can be regulated by nanostructures in breast cancer immunotherapy. Fe-loaded organosilica nanostructures have been employed for the purpose of breast cancer immunotherapy. The modification of nanostructures was performed with hyaluronic acid was performed, and ICG was loaded in them. The nanostructures were spherical in shape, and they released Fe^{3+} in a pH-dependent manner by providing mild

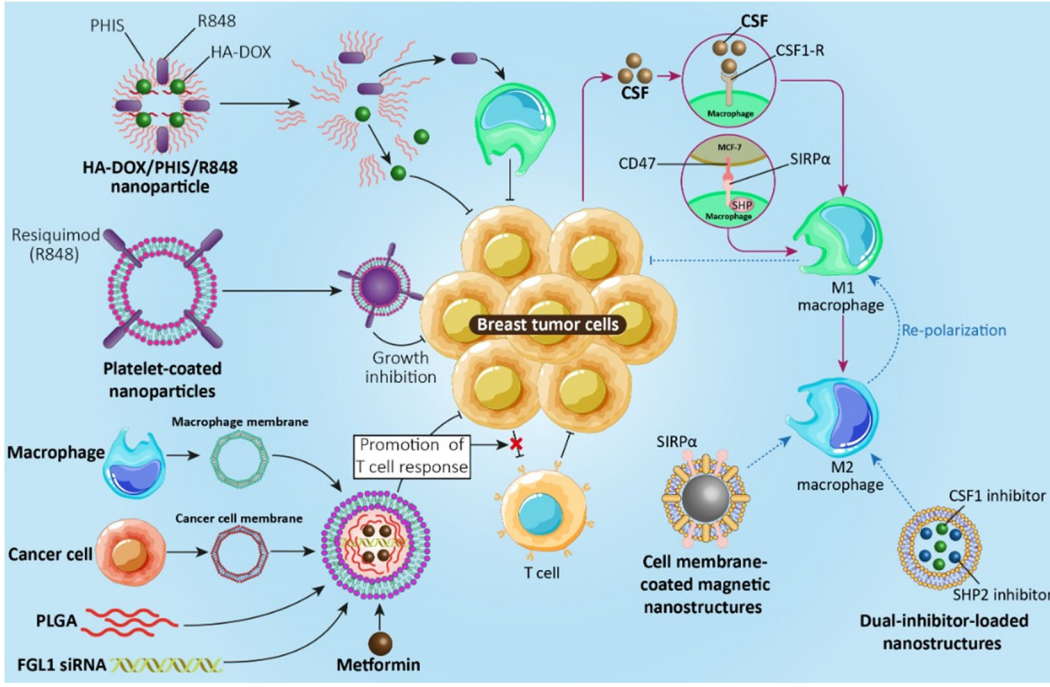

FIGURE 10 Nanostructures for purpose of immunotherapy in breast cancer. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 7 The efficacy of nanoparticles for immunotherapy in breast cancer.

Nanovehicle	Particle size (nm) Zeta potential (mV) Encapsulation efficiency (%)	Cargo	Remarks	References
Anti-CD3 and anti-HER2 exosomes	109 nm	-	Selective targeting of breast cancer cells overexpressing HER2 Stimulating T cell CD3 towards breast tumor cells High antitumor immunity in vitro and in vivo	[281]
PLGA nanoparticles	-	Indocyanine green (ICG) Decitabine (DCT)	Accumulation in tumor site with low immunogenicity Cancer cell membrane puncture to enhance Ca^{2+} in cytoplasm to induce cell death after NIR photo-activation Preventing DNA methylation Increasing antitumor immunity	[274]
Chitosan/γ-PGA nanoparticles	210.8 nm 18.7 mV	-	Decreasing immunosuppression and preventing lung metastasis of breast cancer Increasing number of CD4+ cells Decreasing levels of cytokines such as IL-3, IL-4, IL-10 and CCL4	[282]
PCL-glycol chitosan nanoparticles	100-220 nm +38 mV	-	ROS overgeneration, enhanced antitumor immunity and reducing viability of MCF-7 cells	[283]
Supramolecular nanoparticles	190.1 nm −17.1 mV	-	Suppressing MAPK and CSF1R signaling pathways by nanostructures results in polarization of M2 macrophages to M1 ones and promoting antitumor immunity	[284]
Polymeric nanoparticles	53.8 nm −3.2 mV 2.6% % (gemcitabine) 6.15% and 5.2% (imiquimod)	Gemcitabine Imiquimod	Targeting CD44-overexpressed breast tumor cells due to modification of nanoparticles with hyaluronic acid Activation of $CD11b^{+}$ immune cells Combination chemotherapy and immunotherapy	[285]

TABLE 7 (Continued)

Nanovehicle	Particle size (nm) Zeta potential (mV) Encapsulation efficiency (%)	Cargo	Remarks	References
Multifunctional polymeric nanoparticles	130 nm 14 mV	VEGF-siRNA PIGF-siRNA	Increased blood circulation time and release of drug in response to pH at tumor site Providing endosomal and lysosomal escape Internalization in M2 macrophages via mannose-mediated active targeting and passive targeting Downregulation of VEGF and PIGF and changing polarization of macrophages	[286]
MN-PLGA nanoparticles	155-254.3 nm −18 mV 73.77%	Poly I:C	Significant reduction in tumor growth and improving mice survival Increasing lymphocyte proliferation Promoting CD107a expression Overproduction of IL-2 and IFN-γ, and low production of IL-4 and IL-10 Enhanced immune cell infiltration and necrosis induction	[287]
Zn-pyrophosphate nanoparticles	45.4 nm −1.5 mV	-	The synergistic impact between PDL1 antibody as checkpoint inhibitor and nanoparticles for phototherapy in suppressing breast cancer progression	[288]
FA-PEG-PCL nanoparticles	90 nm −2.1 mV	MIP-3β plasmid	Overexpression of MIP-3β in tumor cells Inducing dendritic cell maturation Stimulating M1 polarization of macrophages Activation and promoting cytotoxicity of lymphocytes	[289]

(Continues)

TABLE 7 (Continued)

Nanovehicle	Particle size (nm) Zeta potential (mV) Encapsulation efficiency (%)	Cargo	Remarks	References
Chitosan-coated hollow copper sulfide nanostructures	-	immunoadjuvants oligodeoxynucleotides	The laser excitation breaks down structure of nanoparticles to mediate cell death and immunotherapy in impairing breast cancer progression and reducing tumor burden	[290]
Copper sulfide nanoparticles	10 and 13 nm 25.47 and 44.08 mV	-	These nanostructures possess antigen capturing capacity and are capable of inducing antitumor immunity for promoting efficacy of PD-L1 inhibitors in breast cancer therapy	[291]
Chitosan-conjugated green copper oxide nanoparticles	81.2 nm 9.58 mV	-	The nanostructures stimulate humoral immunity via IgG response, suppressing proliferation of breast cancer cells	[292]
Lipid-based immuno-nanoparticles	50 nm −0.019 mV	STING and TLR4 agonist	Increased production of interferon β The accumulation at perivascular space Preferential uptake by tumor-resident antigen-presenting cells Stimulation of CD8+ T cells and synergistic impact with checkpoint inhibitors	[293]
Mesoporous silica nanoparticles	72.5 nm	Doxorubicin Methylene blue	ROS overgeneration due to photodynamic therapy Inducing immunogenic cell death Synergistic impact between chemotherapy and immunotherapy	[294]

PTT, which induced cell death. One of the important results of using such nanostructures in breast cancer therapy is that they can mediate mild PTT that is important for inducing maturation of DCs and elevating infiltration of CD8+ T cells at tumor microenvironment for the purpose of breast cancer immunotherapy.[299] The T cells and natural killer (NK) cells mainly produce interferon-gamma for the purpose of breast cancer immunotherapy. The mitochondria-targeted nanoparticles containing photosensitizers that are responsive to light can stimulate maturation of DC cells for promoting generation and secretion of interferon-gamma in breast cancer immunotherapy.[300] It appears that regulation of immune cells by nanoparticles can affect both the growth and metastasis of breast tumor cells. Biomimetic nanostructures in combination with checkpoint blockade can stimulate CD4+, CD8+, and NK cells to elevate levels of TNF-α and IL-12, leading to tumor growth inhibition of 84.2% and suppression of metastasis.[301] When nanostructures increase infiltration of CD8+ T cells in TME,[302] it can lead to increased immune surveillance on breast tumor cells for the purpose of immunotherapy.[303]

8 | SURFACE MODIFICATION

The cell fate of nanoparticles is one of the most important aspects that has received much attention in recent years. Based on the studies, nanostructures mainly use endocytosis for internalization in cancer cells.[77] A recent experiment has shown overexpression of CD44 receptor on surface of breast tumor cells, and consequently, modification of nanoparticles with its ligand can provide receptor-mediated endocytosis. However, the design of the nanoparticle should be such that it mediates its endosomal escape; otherwise, it is degraded and undergoes unexpected alterations in structure. In this way, PEG-poly(β-amino ester) (PEG-PBAE) micelles were prepared, and PBAE provided protonation to mediate endosomal escape of nanoparticles after internalization (endocytosis) by breast tumor cells.[304] Designing a good nanocarrier depends on the selection of various kinds of polymers and agents that can enhance internalization, stability and endosomal escape of nanoparticles. A recent experiment utilized gold nanoparticles for pDNA delivery in breast tumor suppression. The chitosan was employed to increase stability of nanostructures; surface modification of gold nanostructures with folate to increase their internalization via endocytosis; and finally, modification with histidine provided endosomal escape to enhance potential of these nanocarriers for gene delivery. However, it should be noted that different modifications of nanomaterials with polymers can increase their particle size. For instance, in a previous study, modification of gold nanoparticles with histidine, folate and chitosan resulted in the preparation of nanostructures with a size of 135 nm and less, which may pose a problem for their internalization in breast tumor cells.[305] The advances in biology have resulted in identification of novel receptors with overexpression in breast cancer. For instance, neuropilin-1 (NRP-1) shows upregulation in breast tumor cells. The surface modification of polymeric nanostructures with iRGD results in its interaction with NRP-1 to mediate their cellular uptake via receptor-mediated endocytosis and transcytosis.[306] Another experiment examined internalization of transferrin (Tf)-modified PLGA nanostructures in 4T1 and MDA-MB-231 cells. These nanoparticles internalized into breast tumor cells via receptor-mediated endocytosis.[232] It is worth mentioning that endocytosis is an energy-dependent mechanism[304] and that modification of nanoparticles with ligands leads to receptor-mediated endocytosis.[307] Although surface modification of nanostructures is important for their endocytosis in breast tumor cells,[308] it should be noted that after the introduction of nanomaterials to biological medium, proteins are absorbed into surface of nanoparticles and form a biomolecular corona that can affect the fate of nanocarriers. However, studies related to protein corona are limited to in vitro, and a few experiments have focused on impact of protein corona on fate of nanostructures in vivo, but it is still a problem to reveal how protein corona can affect nanoparticle fate.[309–314] In addition, other kinds of endocytosis, including clathrin- and caveolae-mediated endocytosis, are involved in nanoparticle internalization. A recent experiment has shown that DOX-loaded sufactin-based nanostructures can internalize into MCF-7 cells via caveolin-mediated endocytosis and macropinocytosis.[315] Furthermore, PEGylated self-assembled nanoarchitecture internalizes into breast tumor cells via clathrin-mediated endocytosis.[316] Therefore, nanostructures mainly use

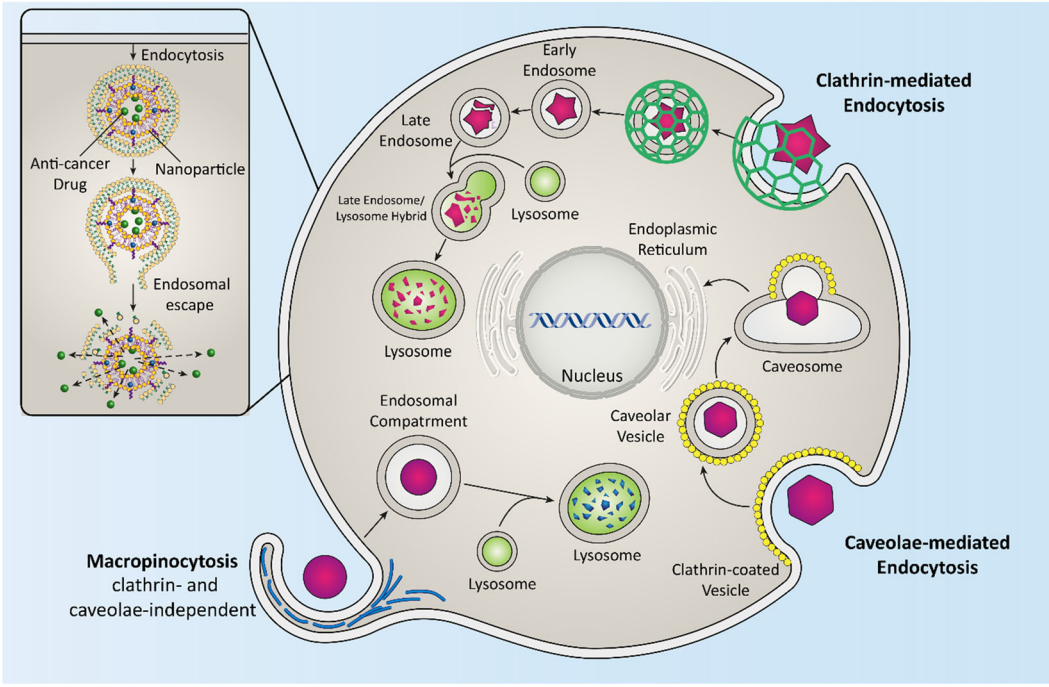

FIGURE 11 The endocytic pathway. The small molecules can enter into cells via diffusion, while large compounds enter into cells in an energy-deponent manner. For large compounds, two ways are utilized for internalization of cells by transporters on cell surface or membrane remodeling and formation of vesciels.[317] The cells, viruses and proteins are internalized into cells via endocytosis. The macropinocytosis, clathrin- and caveola-mediated endocytosis can be employed for nanoparticle internalization. Furthermore, clathrin- and caveolae-independent endocytosis results in nanoparticle internalization. After the incorporation of nanoparticles in endosomes, they can mediate protonation for endosomal escape and subsequent release in cytoplasm.[318–321] [Color figure can be viewed at wileyonlinelibrary.com]

endocytosis for entering breast tumor cells (Figure 11).[322–325] Table 8 provides a summary of nanoparticle internalization in breast tumor cells.

9 | CONCLUSION AND REMARKS

The present review focused on the application of nanomaterials for treatment of breast cancer. Although breast cancer treatment has been the focus of many experiments in recent years, it still causes high mortality rates among patients, and the prognosis for many of them is unfavorable. There are several reasons for the inability to treat breast cancer patients, including the development of drug resistance in patients that leads to chemotherapy failure and the lack of diagnostic agents for on time detection of breast cancer patients. Based on these drawbacks, it appears that breast cancer treatment requires an interdisciplinary approach. The aim of our review was to show how nanotechnology can help in treatment, management and diagnosis of breast cancer. The most important problem in the treatment of breast cancer is chemoresistance. The delivery of synthetic anticancer agents by nanostructures can significantly enhance their internalization in breast tumor cells to potentiate their tumor-suppressor activity and simultaneously prevent the development of drug resistance. Furthermore, targeted delivery of synthetic molecules reduces their side effects on normal cells. Noteworthy, nanocarriers can provide targeted

TABLE 8 The internalization of nanoparticles into breast tumor cells via endocytosis.

Nanostructure	Particle size (nm)	Zeta potential (mV)	Breast cancer cell line	Endocytic pathway	References
Decapeptide-conjugated mesoporous silica nanoparticles	159 nm	−17.94 mV	MCF-7 cells	Receptor-mediated endocytosis	[326]
ErbB2-targeting micelles	20.5 nm	−2 mV	SK-BR-3 and MCF-7 cells	Receptor-mediated endocytosis	[327]
Polydopamine (PD) and hyaluronic acid (HA) coated liquid perfluorocarbon nanoparticles	248 nm	−22.73 mV	4T1 cells	CD44 receptor-mediated endocytosis	[328]
Heptapeptide-conjugated nanostructures	Less than 200 nm	−20.7 mV	MDA-MB-468 cells	EGF receptor-mediated endocytosis	[329]
ERα antibody-functionalized gold nanoparticles	40–50 nm	−52 mV	MCF-7 cells	ERα receptor-mediated endocytosis	[330]
Lactoferrin-modified mesoporous silica nanoparticles	284.4 nm	+15.8 mV	MCF-7 cells	Lf-receptor mediated endocytosis	[331]
Platelet membrane (PM)-camouflaged antitumor nanoparticle	255 nm	−31 mV	4T1 cells	Irradiation enhances endocytosis of nanoparticles without negative impact on cell membrane	[332]
HER1 or HER2-targeted liposomes	80–94 nm and 180–220 nm	-	SKBR3 breast cancer cells	Receptor-mediated endocytosis	[333]
Lapatinib-incorporated lipoprotein-like nanoparticles	62.1 nm	22.80 mV	BT-474 cells	Energy-dependent endocytosis	[334]
Solid lipid nanoparticles	-	-	MCF-7 cells	Caveola-mediated endocytosis	[335]
Gelatin-oleic nanoparticles	300 nm	3.29 mV	MCF-7 cells	Clathrin-and energy-dependent pathway	[336]
TPGS-modified mesoporous silica nanoparticles	180 nm	-	MCF-7 cells	Clathrin-mediated endocytosis and energy-dependent cellular uptake	[337]

delivery of natural products with anticancer activity. Furthermore, codelivery of natural and synthetic drugs by nanomaterials promotes efficacy in breast tumor suppression and inhibits drug resistance development.

Although a great deal of effort has been put into passively targeting various types of nanocarriers for breast cancer therapy, their antitumor efficacy and accumulation in the targeted tissue are limited. To address these disadvantages, considerable attention has been devoted to stimuli-responsive nanocarriers. Based on the type of stimuli, which can be endogenous, exogenous, or a combination of both, different delivery systems have been developed. Single stimulus-sensitive systems like pH-, glutathione-, enzyme-responsive carriers, etc. have shown promising results, including better accumulation in the tumor's site and reducing the side-effects of free chemotherapeutic drugs. However, more attention goes to improving the potency of these carriers, so the research trend gradually steered towards synthesizing multi-responsive carriers with loading more than one drug in a single carrier. Nonetheless, external-responsive systems are of particular interest because their therapeutic approach is not dependent on the drug but instead uses hyperthermia through magnetic- and PTT-responsive agents and PDT therapy. On the upside, they can eradicate the cancerous cells by generating local heat at the tumor's site, which solves the problem of multidrug resistance. On the downside, there are still challenges revolving around these agents, like the depth of laser light penetration in the tissues in the case of PTT and PDT therapies or taking better control over the temperature increase induced by magnetic-responsive materials. Another family member of stimuli-sensitive delivery systems is nanocarriers, which have both internal and external stimuli simultaneously. Nowadays, there are more studies focusing on combining, for example, hyperthermia and chemotherapy into a single package. It is expected that the research trend in this field goes more towards these carriers modified with specific ligands to promote active-targeting, improved accumulation at the site of action, and finally inducing drug delivery and hyperthermia to efficaciously eliminate the tumor.

Another application of nanomaterials can be explored in delivery of genes for the purpose of breast cancer suppression. Although gene therapy has opened a new window in breast cancer therapy, their efficacy in vivo and in clinical trials appears to be limited due to poor accumulation at tumor site and risk of degradation by enzymes in blood circulation. The nanoparticles provide encapsulation of genetic tools to protect them against degradation and enhance their accumulation in tumor cells for improving efficacy in gene expression regulation and suppressing breast cancer progression. The codelivery of genes and drugs can potentiate breast cancer therapy. The regulation of TME components is of importance for cancer immunotherapy. The infiltration and cytotoxicity of T cells can be improved using nanomaterials, and they can provide delivery of checkpoint inhibitors such as PD-L1 inhibitors. Furthermore, nanomaterials can induce polarization of M2 macrophages to M1 phenotype, preventing immunosuppression. The most important and well-known mechanism followed in breast cancer therapy is cell death induction. The nanocarriers can provide both PTT and PDT in inducing cell death in breast tumor. The mechanism of PTT is to provide hyperthermia, which mediates cell death, while PDT promotes ROS generation to enhance apoptosis. Both PTT and PDT have demonstrated high potential in suppressing breast cancer progression and reducing cell viability. Significant emphasis was put on the role of nanocarriers for enhancing internalization in breast tumor, and the mechanism utilized is endocytosis. The clinical application of nanoparticles depends on different aspects that should be considered. First of all, biocompatibility of nanoparticles should be considered, and for this purpose, modification and green synthesis of nanomaterials should be performed.[243,338–343] Another aspect is large-scale production and its affordability. For instance, hyaluronic acid is used for nanomaterial modification, but it is an expensive agent and cannot be employed for clinical course. The majority of breast cancer patients are diagnosed in advanced stages. The reason is the lack of specific symptoms for breast cancer at early stages, and when cancer cells are malignant and have the capacity to develop therapy resistance, they are diagnosed and it is difficult to treat. The developed nanoplatforms have the capacity to diagnose of biomarkers related to breast cancer such as miRNAs and HER2, and the introduction of such nanomaterials into clinical course can lead to a milestone progress in diagnosis of breast cancer patients.

In recent years, the field of inorganic nanomaterials, especially metal-organic frameworks (MOFs), has rapidly grown as a promising platform for drug and gene delivery applications. However, in this article, the focus was not

about categorizing the nanoparticles/nanomaterials, we can make a clear future perspective about inorganic nanomaterials in breast cancer therapy here. MOFs are highly porous materials, consisting of metal ions or clusters coordinated to organic ligands. These materials have tunable pore sizes, high surface area, and can be engineered to have specific chemical and physical properties, making them highly attractive for a wide range of biomedical applications. In particular, the development of MOFs for breast cancer therapy has shown significant promise due to their ability to improve drug delivery and overcome challenges related to drug resistance. However, challenges related to the stability, biocompatibility, and targeting of MOFs must be overcome to enable their use in clinical settings. Surface engineering approaches have been proposed to address these challenges and enhance the performance of MOFs in drug and gene delivery applications for breast cancer therapy. The first step in the development of MOFs for drug and gene delivery applications is the synthesis of MOFs with suitable chemical and physical properties for biomedical applications. The chemical structure of MOFs can be engineered to provide different surface functionalities and to enable the encapsulation and release of various drugs and genetic materials. Surface functionalization can be achieved through the introduction of various functional groups, such as carboxyl, amine, and hydroxyl groups, onto the organic ligands or through the use of post-synthesis modifications. Furthermore, MOFs can be engineered to have specific physical properties, such as pore size, surface area, and stability, through the choice of metal ions and organic ligands. One of the major challenges in the development of MOFs for biomedical applications is their stability and biocompatibility. MOFs are typically synthesized in nonaqueous solvents, which can result in the incorporation of residual solvents or ligands that can be toxic to cells. Additionally, the presence of metal ions in MOFs can induce toxicity and induce immune responses in vivo. To address these challenges, various surface engineering approaches have been proposed to improve the biocompatibility and stability of MOFs. One approach is the use of biocompatible coatings, such as PEG, to shield the MOFs from the biological environment and reduce toxicity. Another approach is the incorporation of biocompatible and biodegradable organic ligands, such as amino acids, into the MOF structure. Furthermore, the use of metal ions that are less toxic or biocompatible, such as zinc or magnesium, has been proposed to reduce toxicity and improve biocompatibility. Another challenge in the development of MOFs for drug and gene delivery applications is the targeting of specific tissues and cells. MOFs can be functionalized with various ligands, such as antibodies or peptides, to enable targeted delivery to specific cells or tissues. This can be achieved through the use of bioconjugation techniques, such as click chemistry or thiol-ene chemistry, to attach targeting ligands to the MOF surface. Furthermore, the incorporation of stimuli-responsive components, such as pH-sensitive or temperature-sensitive moieties, can enable targeted drug release in response to specific physiological conditions. The use of magnetic nanoparticles as external triggers for MOF drug release has also been explored. In the field of breast cancer therapy, MOFs have shown significant promise as drug delivery vehicles due to their ability to enhance drug efficacy and overcome challenges related to drug resistance. MOFs can be engineered to have specific physical and chemical properties that enable efficient drug loading, controlled release, and targeted delivery. Furthermore, MOFs can overcome challenges related to drug resistance by delivering multiple drugs simultaneously or by delivering drugs in a synergistic manner to enhance their efficacy. The use of MOFs in combination with other therapeutic approaches, such as PDT or immunotherapy, has also been explored to enhance their therapeutic potential. The promising strategy for improving the performance of MOFs in drug/gene delivery and breast cancer therapy is the use of smart surface engineering techniques. These techniques involve the functionalization of MOF surfaces with stimuli-responsive molecules, such as pH-responsive polymers or temperature-sensitive hydrogels. These smart coatings can be designed to respond to specific stimuli in the tumor microenvironment, such as low pH or high temperature, and release their cargo selectively in the tumor cells. Another strategy for improving the performance of MOFs in drug/gene delivery and breast cancer therapy is the use of surface engineering techniques to enhance the biocompatibility and reduce the immunogenicity of MOFs. One approach is to functionalize MOFs with biocompatible polymers, such as PEG, to form a “stealth” coating that can prevent recognition and clearance by the immune system. This can improve the pharmacokinetics and biodistribution of MOFs, leading to better therapeutic outcomes. Moreover, surface engineering techniques can be used to enhance the specificity and

selectivity of MOFs for breast cancer cells. One approach is to functionalize MOFs with targeting ligands, such as antibodies or peptides, that can selectively bind to receptors overexpressed on breast cancer cells, such as HER2 or EGFR. This can improve the cellular uptake of MOFs in breast cancer cells and reduce their uptake in healthy cells, leading to improved therapeutic efficacy and reduced side effects. In addition to surface engineering techniques, the use of MOFs in combination with other therapeutic modalities, such as chemotherapy or radiation therapy, is another promising strategy for improving the treatment of breast cancer. One approach is to use MOFs as carriers for chemotherapy drugs, such as doxorubicin or paclitaxel, to improve their delivery and reduce their side effects. Another approach is to use MOFs as radiosensitizers, which can enhance the sensitivity of cancer cells to radiation therapy and improve its therapeutic efficacy. Furthermore, the development of personalized medicine approaches, such as the use of patient-derived organoids or xenograft models, can enable the evaluation of the efficacy and safety of MOFs in a patient-specific manner. This can help identify the optimal MOF formulation and treatment regimen for individual patients, leading to improved therapeutic outcomes and reduced treatment-related toxicities. In conclusion, the role of surface engineering in the world of MOFs for drug/gene delivery and breast cancer therapy is rapidly evolving, and holds great promise for improving the efficacy and safety of cancer treatment. Future research in this field should focus on the development of smart surface engineering techniques, the enhancement of biocompatibility and specificity of MOFs, and the use of MOFs in combination with other therapeutic modalities. With continued advancements in surface engineering and the increasing understanding of the complex tumor microenvironment, MOFs are poised to revolutionize the treatment of breast cancer and other cancers in the near future.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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