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Review

Nanoparticle-mediated targeted drug delivery for breast cancer treatment

Piumi Y. Liyanage[a,1], Sajini D. Hettiarachchi[a,1], Yiqun Zhou[a,1], Allal Ouhtit[b], Elif S. Seven[a], Cagri Y. Oztan[c], Emrah Celik[c], Roger M. Leblanc[a,*]

[a] Department of Chemistry, University of Miami, Coral Gables, FL 33146, USA
[b] Department of Biological & Environmental Sciences, College of Arts & Sciences, Qatar University, Doha, Qatar
[c] Department of Aerospace and Mechanical Engineering, University of Miami, Coral Gables, FL 33146, USA

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ABSTRACT

Breast cancer (BC) is the most common malignancy in women worldwide, and one of the deadliest after lung cancer. Currently, standard methods for cancer therapy including BC are surgery followed by chemotherapy or radiotherapy. However, both chemotherapy and radiotherapy often fail to treat BC due to the side effects that these therapies incur in normal tissues and organs. In recent years, various nanoparticles (NPs) have been discovered and synthesized to be able to selectively target tumor cells without causing any harm to the healthy cells or organs. Therefore, NPs-mediated targeted drug delivery systems (DDS) have become a promising technique to treat BC. In addition to their selectivity to target tumor cells and reduce side effects, NPs have other unique properties which make them desirable for cancer treatment such as low toxicity, good compatibility, ease of preparation, high photoluminescence (PL) for bioimaging *in vivo*, and high loadability of drugs due to their tunable surface functionalities. In this study, we summarize with a critical analysis of the most recent therapeutic studies involving various NPs-mediated DDS as alternatives for the traditional treatment approaches for BC. It will shed light on the significance of NPs-mediated DDS and serve as a guide to seeking for the ideal methodology for future targeted drug delivery for an efficient BC treatment.

1. Introduction

Cancer is a class of diseases resulting from unregulated cell growth and these abnormal cells are able to spread or invade other parts of the body. Based on the presumed origin of the tumor cells, cancers are classified into carcinoma, sarcoma, lymphoma, leukemia, germ cell tumor and blastoma. Among them, carcinoma indicates cancer that derive from the epithelial cells and it includes nearly all cancers in breast, prostate, lung, pancreas and colon [1]. Considering the damage various cancers incur, skin and lung cancers are the most common malignancies worldwide. In addition, breast cancer (BC) is the most common cancer type among women accounting for nearly 30% of all cancers [2]. In 2018, about 266,120 new cases of invasive BC have been diagnosed that will potentially cause 40,920 cases of death according to the statistics of the American Cancer Society [2]. In contrast, BC in men accounts only for 1% of all malignant breast neoplasms [3]. Also compared to women, men tend to be diagnosed for BC at an older age as 67 years [4]. Although it is the most common cancer type in women, it is considered as treatable if diagnosed at an early stage [5,6]. However, if metastasis is achieved, it can spread through blood and lymph systems to distant organs, increasing treatment difficulties and the fatality rates rapidly.

Similar to other cancers, the traditional treatment approaches for BC include surgery, chemotherapy and radiotherapy. The primary goal of these therapies is to eradicate tumors while prolonging the survival of patients. Nonetheless, these standard methods are challenged by the advanced and metastatic tumors in terms of tumor recurrence and drug resistance. For instance, surgery is not effective in case of tumor recurrence and metastases to distant organs including bone, lung and liver. In contrast, the goal of chemotherapy is to use cytotoxic chemotherapeutic drugs either after or without surgery to interfere with tumor cell division and growth. Radiotherapy involves delivering powerful waves of energy to disrupt the tumor cell division, which results in the shrinkage or eradication of tumors. Although chemotherapy and radiotherapy are powerful cancer treatment techniques to increase the survival rate, these techniques could lead to acute and long-term adverse effects on the patients' healthy organs [7,8]. For instance, the chemotherapeutic agent; trastuzumab, a monoclonal antibody used to treat BC, has shown toxicity assisted with cardiac dysfunction in long-term use [9]. Furthermore, multidrug resistance is also

* Corresponding author.
E-mail address: rml@miami.edu (R.M. Leblanc).
[1] All authors contributed equally to the work

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a challenging issue caused by over-expression of certain proteins in the tumor cells. The effect of chemotherapy is often drastically reduced in this case. Radiation therapy is a local treatment that only affects the area of the tumor location. But side effects can occur due to the damages caused on the neighboring healthy tissues. Considering these adverse effects present in the classic cancer treatment approaches, novel effective alternatives need to be well sought.

Alternatively, the use of nanomaterials as an effective drug delivery method for the cancer treatment has recently gained specific interest, and ongoing investigations are aiming to optimize this method to ultimately reduce the adverse effects caused by the conventional approaches. To date, such NPs commonly used in research for drug delivery to treat BC include liposomes, mesoporous silica NPs, viral NPs, polymer-, metal- or carbon-based NPs and different drug loading techniques are used depending on the NPs such as encapsulation, covalent or electrostatic binding and adsorption. There are numerous advantages of using NPs for drug delivery: i) it solves issues related to the poor solubility and bioavailability of the drug; ii) it enhances targeted drug permeability to cancer cells and administer slow release of the drug; and iii) NPs are small (1–100 nm), nontoxic, biodegradable and highly photoluminescent particles on to which the cancer drugs can be easily loaded. The PL could endow the *in vivo* drug tracking ability to determine drug delivery efficacy during treatment. For the studies of targeted DDS, different types of breast tumor cell lines have been used *in vitro* including MDA-MB-231, MDA-MB-453, SkBr3 and MCF-7 [5,7,10–14]. Besides, doxorubicin (Dox) is the most popular chemotherapeutic agent for NPs mediated delivery for BC and it has also been used together with siRNAs and miRNAs in co-delivery systems. Other chemotherapeutic agents, namely paclitaxel (PTX), cisplatin, trastuzumab, fulvestrant, anastrozole, and carboplatin are also often used for phase II and III clinical trials [14–17]. Furthermore, several combinations among these therapeutics have shown synergistic effects against BC [14].

Administering drugs using a targeted DDS can help reduce the doses because the pharmacologically effective concentrations can be achieved at lower concentrations compared to untargeted administering of drugs. Side effects resulting from toxicity and damages to healthy cells and tissues could also be significantly reduced through a targeted delivery method compared to the standard chemotherapy approach. Therefore, the development of new treatment methods such as NPs-based targeted DDS as well as combination therapy has the potential to alleviate the side effects. Usage of a DDS is also of crucial importance in treatments using drug combinations or oligonucleotides, due to the needs such as delivery without premature decay and simultaneous drug administration.

2. Drugs and breast cancer biomarkers

2.1. Chemotherapy drugs and side effects

Chemotherapeutic agent, Dox which is a member of the anthracycline class is heavily used in the clinical treatments for many human cancers. It is one of the most commonly used chemotherapeutic drugs for the treatment of BC either alone or in combinations with other drugs. Various studies have been conducted to understand the side effects of Dox both *in vivo* and clinically [18,19]. It is well known for its high possibility in hematopoiesis and gastrointestinal or cardiac toxicity [20]. Therefore, targeted delivery can be utterly important in Dox treatments [21].

Paclitaxel (PTX) has emerged as another important and popular chemotherapeutic agent in the BC treatments. Unlike other anti-microtubulin agents, PTX promotes tubulin dimerization and inhibits microtubule depolymerization to achieve antitumor effect [22]. The lack of cross-resistance with anthracyclines is one of the major reasons for the drastic increase of intensive clinical investigation on PTX worldwide [23]. Commonly known PTX side effects are neutropenia and peripheral neuropathy [22]. Thus, PTX dose optimization and evaluation of PTX in combination therapy regimens have become a central focus in research.

Few other commonly used regimens for chemotherapy are tamoxifen, trastuzumab, cisplatin and docetaxel. Also, for adjuvant chemotherapy treatments which are used to increase the effectiveness and lower the reoccurrence, cyclophosphamide and fluorouracil are commonly administered combined with methotrexate, Dox or mitoxantrone (MTX) [24]. The mostly reported side effects on patients are fatigue, weight loss, peripheral neuropathy and nausea [25]. But several severe after effects that have been identified are heart problems, osteoporosis, lymphedema and concerns about cognitive functions [24,26].

2.2. Biomarkers

A biomarker can be described as a measurable indicator to understand biological processes or diseases from outside the patient. Currently, the clinical use of biomarkers has become inevitable in disease identification and treatments. The key aspect of the targeted nanodrug delivery in BC treatment is to target the molecular recognition markers using nanocarriers. Biomarkers targeted drug delivery improves the target specificity of drugs only towards cancer cells and less toxic to the healthy cells. Due to the overexpression of various oncogenes, biomarkers have been associated with the development and progression of resistant breast tumors. The most common BC biomarkers include estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER2/ERBB2). The majority of breast tumors have ER overexpression while only approximately 25% of breast tumors have HER2 overexpression [2]. About 15% of breast tumors do not express ER, PR or HER2, classified as triple negative BC (TNBC), and are considered as the most challenging type of breast tumors [27–29]. Hence, these biomarker proteins have been used in BC classification as well as target ligands for developing novel therapeutics. Both monoclonal antibodies and anticancer drugs have been extensively tested in the treatment of BC, targeting biomarkers.

2.2.1. ER

ERs are located on the BC cell membrane as well as intracellularly. As is mentioned previously, the majority of the breast tumors are ER+ and both pre- and post-menopausal women can be affected by the ER+ type BC. Tamoxifen is the most popular antagonist for ER+ breast tumors. However, since tamoxifen does not specifically target adipose tissues, the use of NPs as nanocarrier for targeted drug delivery seems to be of significant [30]. Li et al. reported a tamoxifen delivery system based on polymer-based NPs to ER+ BC cells with a remarkably reduced cytotoxicity towards healthy cells [31]. In addition, El-Sayed and coworkers have also successfully delivered tamoxifen-conjugated NPs to ERs [32]. The system was uptaken into cancer cells mediated by the receptor, which induced the efficacy of tamoxifen up to 2.7-fold higher than the free drug.

2.2.2. PR

Similar to ER, PR is also a steroid hormone receptor and it mediates progesterone in its target tissues. It also exists in two forms, namely PR-A and PR-B [33]. PR also plays an important role in lobuloalveolar differentiation [34]. The clinical use of these is to identify the patients with invasive BC for different categories of endocrine therapy. It is used as a prediction marker for all stages of treatment such as adjuvant and neoadjuvant [35].

2.2.3. HER2

HER2 is a type of transmembrane glycogen protein that has three different regions. It has an N-terminal extracellular domain (ECD), a single α-helix transmembrane domain (TM) and an intracellular tyrosine kinase domain. HER family includes four proteins named as HER1, HER2, HER3 and HER4. HER2 is the only receptor which does

not have any identified ligands, but it contributes to dimerization with the other three proteins in the family during cell growth [28]. The largest part of HER2 is the ECD which further divides into subdomains (I-IV). Cysteine rich subdomain II and IV are responsible for homodimerization and heterodimerization [28]. Subdomain II has the dimerization arm that propagates the dimerization. The monoclonal antibodies pertuzmab and trastuzumab have been identified as dimerization inhibitors. These bind to the dimerization arm of HER2 and block the signal to inhibit the dimerization with other family members retarding the cell propagation [36]. Rathinaraj et al. mentioned a covalent conjugation of trastuzumab with mercaptosuccinic acid immobilized-gold NPs which was tested with SK-BR3 BC cells [13].

2.2.4. TNBC

15% of breast tumors do not express ER, PR or HER2, which makes the targeted drug delivery more challenging. Also TNBC grow fast and aggressively making it more lethal [27]. Only 85% of TNBC are basal type but not all basal type tumors are triple negative. Basal-type tumors are similar to TNBC and they do not have ER, PR or HER2 expressions either [37]. However, some protein changes may happen to basal-type tumors, which is not common to TNBC. In many solid basal-type tumors such as BC, receptors including transferrin, folic acid, arginylglycylaspartic acid (RGD) and the epidermal growth factor receptors (EGFR) are expressed. Wu et al. introduced a NPs-mediated drug delivery system (DDS) conjugated with RGD ligand, which shows a higher cellular uptake in MDA-MB-231 BCE cells than the non-targeted system [38]. Also, the simultaneous delivery of a combination of therapeutic agents has shown higher success in the treatment of TNBC. The system has shown efficacy in reducing cell proliferation both *in vitro* and *in vivo* [39,40].

2.3. Nanoparticles for targeted drug delivery

Nanoparticles (NPs) are defined as particles (1–100 nm) with a surrounding outer layer of various organic or inorganic coatings that determine the properties of NPs. Although not frequently used in clinical treatments yet, numerous research studies are currently conducted to leverage the potential benefits of NPs in DDS for cancer therapy. NPs have been popular as nanocarriers mainly due to their characteristics such as water dispersity, biocompatibility and biodegradability. Use of NPs in cancer treatment increases the solubility and half-life of drugs thus, increasing the bioavailability of many chemotherapeutic drugs [41–43]. Also, NPs can increase the drug accumulation in the cancer tissues *via* the enhanced permeability and retention (EPR) [44]. Ultimately, NPs-anti-cancer drug combination can improve the efficiency of the therapy by reducing the side effects through targeting specific cancer sites using target ligands [45–47]. There are various types of NPs that have been used for BC targeted DDS. These NPs can be categorized into liposomal, polymer-, metal-, carbon-, protein-based and mesoporous silica NPs as shown in Fig. 1. In addition, Table 1 summarizes some properties of these NPs in BC treatment.

2.4. Liposomal NPs

Liposomal NPs (LNPs) are spherical vesicles which are formulated through incorporating one or more phospholipid bilayers and their size can reach up to a few hundred nanometers. The LNPs contain a hydrophilic inner core which is surrounded by the hydrophobic lipid bilayer. Because of this unique morphology, usually hydrophobic therapeutic agents are encapsulated in the phospholipid bilayer for delivery. LNPs are also popular therapeutic carriers for hydrophilic agents by encapsulating in the inner core. Drug encapsulation also helps to drastically reduce the toxicity of drugs due to non-target distribution. Furthermore, amphiphilic agents can also be encapsulated into the aqueous inner core of the LNPs, such as vincristine and Dox [48], which specifically has been found to lower the cardio-cytotoxicity of Dox than its unencapsulated form [49]. In a study of PTX encapsulation and biological response using LNPs, Marcial et al. demonstrated that PTX encapsulated in nanostructured lipid carriers (size-75 nm) were significantly effective against MCF-7 (half maximal inhibitory concentration, IC50, −25.33 ± 3.17 nm) and MDA-MB-231 (IC50–2.13 ± 0.21 nM) BC cells whereas the IC50 of free drug exceeded 500 nM [50].

LNPs tend to accumulate in tumor cells by incorporating the bilayer through the cell membrane. It has been reported that by surface modification of LNPs using PEG, longer half-lives could be achieved, and the targeting efficacy also increases [51]. PEGylated LNPs showed effective targeting through passive strategies both *in vitro* and *in vivo*. LNPs have also been used to deliver combinations of drugs to achieve synergic effects by encapsulating more than one therapeutic agent in the LNPs. Wong and Chiu introduced a co-encapsulation method of both vincristine and quercetin in a PEGlyated liposome for the treatment of hormone- and trastuzumab-insensitive BC. This study showed that the co-encapsulation achieved higher synergism, prolonged drug circulation in plasma and controlled release *in vivo* for JIMT-1 cells. Moreover, the liposomal encapsulation has proved to be the most effective approach for the growth inhibition of JIMT-1 cells in comparison to the two individual drugs [52]. A non-PEGlyated LNPs system has also been fabricated to deliver a combination of Dox and cyclophosphamide for the treatment of metastatic BC [53].

LNPs have been identified as an effective delivery model for oligonucleotides, peptides and siRNA-based gene therapy for BC. The use of LNPs to encapsulate these peptides and nucleotides prevents their degradation in vasculature environment and allow targeted delivery by using target ligands [54,55]. Cao et al. showed a design of surface modified LNPs with A7R-cystein peptide for PTX delivery to MDA-MB-231 cells *in vitro* and *in vivo* [56]. The study showed that A7R-cystein peptide enhanced the vesicle uptake thus increasing the cytotoxicity and accumulation in the BC xenografts, which confirmed the importance of peptide as targeting ligand in the PTX targeted delivery. Another study introduced a co-delivery system of siRNA *in vitro* using chitosan-coated LNPs. In this study siHIF1-α (hypoxia inducible factors) and siVEGF (vascular endothelial growth factors) were co-delivered to achieve lower cytotoxicity and higher silencing efficiency. The expressions of respective mRNAs significantly suppressed the growth of MCF-7 and MDA-MB-435 BC cells. They also explained that the chitosan-coated LNPs enhanced the stability of siRNAs by protecting them from serum degradation even after 24 h of incubation [57]. A carrier combination of bio-nanocapsule that derived from the antigen on the surface of hepatitis B virus and liposomes has also been reported for the delivery of siRNA to HER2-expressing BC. The gene silencing and protein knockdown were achieved through this system [58]. Chen et al.

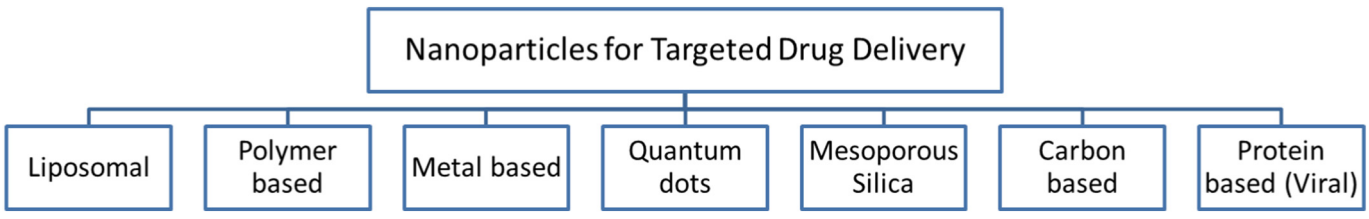

Fig. 1. A diagram of different types of NPs used in BC research for targeted DDS.

Table 1
Some of the NPs and their properties used for BC treatment.

NPs Type	Solubility	Particle size (nm)	Synthesis	Popular drugs /genes	Cell lines	Targeted biomarkers/ receptors	Reference
Liposomal NPs	Amphiphilic	100–300	Hydrophilic inner core and hydrophobic lipid bilayer	DOX, PTX, siRNA, mRNA, siHIF1-α, siVEGF	MDA-MB-231 MDA-MB-435 MCF-7 JIMT-1	HER2	48–59
Polymer-based NPs	Highly hydrophilic and permeable	100–300	Natural polymers including cellulose and chitosan; Synthetic polymers including PVA, PEG, PLGA	DOX, PTX, Trastuzumab,Cis-platin, siRNA	MDA-MB-231	HER2 TNBC	15, 63–69
Gold NPs	Hydrophilic	10–20	Mostly made up of Au^{3+} reduction by citrate and organic surface coating is useful for target the biomarkers	Dox, MTX, SMTX	MDA-MB-231 MCF-7 MCF-10	EGFR, VEGFR2	85–89
Superparamagnetic Iron Oxide NPs	N/A	1–100	Magnetic inner core which is made up of magnetite, Fe_3O_4, or maghemite, γ-Fe_2O_3	DOX	MDA-MB-231 MCF7	HER2	97–102
Quantum Dots	Resuspend able	2–10	Made up of heavy metals such as Cd,In, Se,Te	Monoclonal antibodies	MDA-MB-231 MCF7 BT474	ER, PR, HER2, EGFR	106–111
Mesoporous silica NPs	N/A	N/A	Inorganic nanomaterial which has large surface area and variable pore sizes	DOX, siRNA	MCF7 BT474	HER2	117, 119, 120
Carbon nanotubes	Low solubility	1–100	Cylindrical shape single wall or Multi wall nanomaterials which are allotropes of fullerenes.	DOX PTX	SK-BR-3 MCF7	HER2	126–143
Carbon dots	Resuspendable	1–10	Spherical shape nanoparticles with variable surface functionality	N/A	MCF-7 MDA-MB-231	N/A	11, 158–162
Protein based viral NPs	N/A	N/A	Protein envelops or capsids of viruses	DOX Trastuzumab	MCF7 MDA-MB-231	HER2	163–172

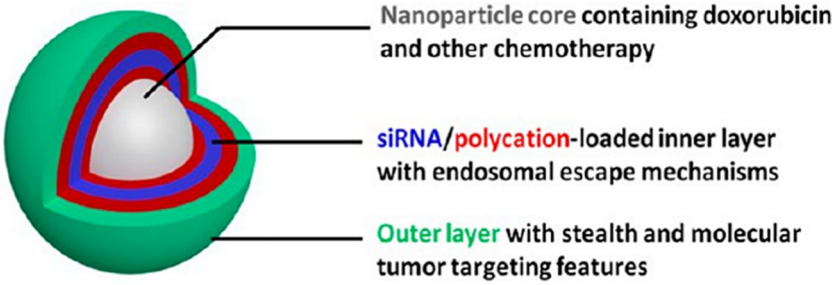

Fig. 2. The schematic illustration of the layer-by-layer drug delivery platform of poly-L-arginine NPs. The figure is adapted with permission from ref. [15].

reported a cationic and anionic liposomal technique to overcome multidrug resistance (MDR) of BC by using Dox along with siRNA [59]. This study exhibited the fabrication of liposome-polycation-DNA (LPD) NPs using a guanidinium-containing cationic lipid which induces reactive oxygen species (ROS) and downregulates the MDR expression. Increased Dox cell uptake was observed when combined with siVEGF and targeted passive metastatic BC. Higher entrapment efficiency of Dox was observed in anionic-LPD NPs, which was modified to overcome Pgp-mediated drug efflux. Therefore, LNPs have been very popular as a nanocarrier for easily biodegradable therapeutic agents since these therapeutics can be encapsulated and protected until they reach the target cells, which is especially important for peptides and siRNAs. Although amphiphilic therapeutics can be encapsulated in LNPs the size of the LNPs is considerably larger (< 50 nm), which could pose a disadvantage for nanodelivery. Moreover, to achieve better biocompatibility LNPs are often coated with polymers which increases the size further. The drug release process by opening the phospholipid bilayer could also be further discussed.

2.5. Polymer-based NPs

Polymer-based NPs (PNPs) are colloidal particles in the size order of a few hundred nanometers. These NPs are usually formulated by binding a copolymer to another polymer matrix. Polymers used in this regard can be natural products such as cellulose and chitosan [60]. On the other hand, synthetic polymers can also be used to prepare PNPs to achieve specific chemical and biological functions which make these PNPs highly demanding for biomedical applications [61]. Nanoprecipitation, emulsification and salting-out are common methodologies for chemical synthesis of PNPs [62]. These chemical syntheses of PNPs can be designed to have the required lipophilicity, charge and biocompatibility to suit a certain drug to be carried to the specific target [63]. The anti-cancer drug can be loaded onto the surface of PNPs by surface adsorption, chemical conjugation or by encapsulating into the PNPs-based DDS to be delivered to the target site [64]. Most PNPs have high solubility and permeability enabling them to be stable with slow drug release over a long period of time making these PNPs efficient nanocarriers for less hydrophilic anti-cancer agents. Moreover, it has been found that PNPs have high drug loadability and low toxicity especially when they were coated with a PEG-phospholipid copolymer [65]. Numerous clinically used chemotherapeutic agents such as Dox, PTX, trastuzumab and cis-platin have been tested for PNPs-drug conjugation. Various PNPs including polyhydroxyalkanoates, PLGA, cyclodextrins-derived PNPs have been studied as nanocarriers for various cancer treatments [63]. PEG-modified poly(ε-caprolactone) PNPs were reported for targeted delivery of tamoxifen in BC [66]. This study showed significant increase of drug accumulation in target BC cells by using the PEG-modified NPs than the unmodified NPs. A combination of N-(2-hydroxypropyl) methacrylamide with a tyrosine kinase inhibitor was also studied as a HER2-targeted DDS for HER2-overexpressing metastatic BC [67].

Moreover, different approaches of cancer inhibition have been researched apart from the use of traditional chemotherapeutic agents. Jin et al. recently reported a photodynamic therapy based on conjugated PNPs for TNBC treatment [68]. Their study showed that the luminescent conjugated PNPs could produce ROS upon light irradiation. Their synthesis of a cyclic arginine-glycine-aspartic acid peptide-decorated conjugated PNPs with poly [2-methoxy-5-(2-ethyl-hexyloxy)-1,4-phenylenevinylene] as photosensitizer had negligible cytotoxicity and could selectively kill the αvβ3 integrin-overexpressing MDA-MB-231 cells, a subtype of TNBC cells. Another study exhibited an enhanced cleavage of DNA of tumor cells, which was achieved through a tamoxifen-embedded PLGA-derived PNPs system [69]. The PLGA-tamoxifen NPs were synthesized using an emulsified nanoprecipitation technique. These PLGA-tamoxifen NPs showed higher nuclear fragmentation, cytotoxicity and greater bioavailability compared to pure tamoxifen *via* receptor-mediated endocytosis in both Dalton's lymphoma ascites and MDA-MB-231 BC cells. Another different synthesis approach, a controlled layer-by-layer NPs fabrication process was developed by Deng et al. for the co-delivery of siRNA and Dox for a TNBC treatment [15] (Fig. 2). They have synthesized the PNPs using poly-L-arginine (PLA) and have noticed the size of PNPs increased up to 140 nm with the increment of layers. They concluded that the layer-by-layer technique could have high loading capability of chemotherapeutic agents. And the combination of siRNA and Dox, which targeted the multidrug resistance protein 1 (MRP1) drug efflux pump and TNBC in animal models, respectively, has shown a significantly high drug efficacy. Thus, PNPs-based DDS is another approach besides the use of LNPs. Although, the different synthetic approaches allow the PNPs to achieve certain desired characteristics, the sizes of these PNPs still are in range of about few hundred nanometers, which renders particles larger than even the LNPs, thus affecting the biodistribution [70]. Furthermore, the enhanced stability of PNPs could be disadvantages in terms of biodegradability and accumulation in the reticular-endothelial system.

In addition, nanofibers are another group of polymeric NPs as potential candidate for drug delivery applications as well as numerous others such as cosmetics, filtration, sensors, nanoelectronics. Nanofibers manifest excellent surface area to volume ratio (approximately 100 times larger than that of microfibers), flexibility and mechanical properties such as tensile strength. As for the starting materials, polymers including polyvinylalanine (PVA), PLA, PEG and chitosan have all been used for the production of nanofibers for drug delivery applications [71]. Regarding synthetic approaches, such materials can be fabricated through drawing, template synthesis, self-assembly, phase separation and electrospinning [72]. For instance, Jayakumar et al. utilized electrospinning, which was based on the deposition of a polymer compound onto a collector under the presence of an electric field, to fabricate chitin and chitosan nanofibers [73]. On the other hand, Marty et al. fabricated nanofiber DDS to assess the cell movement in patients with metastatic BC cells [74]. Although nanofibers could provide a new approach for DDS, the toxicity and the drug loadability are concerns for major drawbacks [75].

2.6. Metal-based NPs

The metal-based NPs can be categorized also as inorganic NPs. The capabilities of these inorganic NPs have also been extensively investigated over the past decade owing to their therapeutic and imaging properties. Most of these NPs share the same type of structure containing a core which is responsible for the electronic, magnetic and optical properties and a shell which is mainly an organic surface coating. Among them, most widely used metal-based NPs for BC treatment are gold NPs, superparamagnetic iron oxide NPs (SPIONs) and quantum dots (QDs).

2.6.1. Gold NPs

Gold NPs (AuNPs) have been synthesized during the past few decades for various applications by tailoring their size [76], shape [77] and surface functionalities [78]. The most common synthesis of AuNPs involves the Au^{3+} reduction by citrate in aqueous media. These AuNPs have been used extensively in DDS due to the controllable unique properties and significantly low cytotoxicity as reported [79–83]. The organic surface coating is important for the DDS for targeting specific receptors/biomarkers. Thiolates and disulfides are widely used for these surface coatings mainly due to their affinity to bind onto the surface of Au. Afterwards, the drugs or therapeutic agents can be loaded on AuNPs by binding onto the surface through covalent or non-covalent bonds. The drug release could be administered at the target site depending on the loading method [79,84]. Fig. 3 is a graphic illustration of the potential Dox release triggered by pH considering the Dox conjugation with AuNPs *via* a pH-sensitive hydrazine band. Jafarizad et al. introduced the use of reduced graphene oxide-gold NPs for the drug delivery of covalently bonded drugs to the BC cells [85]. In this study, anticancer drug, MTX was used. The MTX was first covalently linked to 3-mercaptopropionic acid to synthesize MTX terminated thiol molecules, which were then used to functionalize the AuNPs. The formation of nanocomposite was achieved by mixing the functionalized AuNPs in a reduced graphene oxide (RGO) dispersion. It showed a DLS hydrodynamic size of the AuNPs before thiol group functionalization was with a mean diameter of 7.1 nm while, on the other hand, the hydrodynamic size after the thiol MTX (SMTX) functionalization onto the AuNPs increased up to a mean diameter of 14.9 nm confirming the functionalization. A comparison of drug release ability triggered by pH changes between the SMTX-AuNPs and SMTX-AuNPs/RGO shows that the drug release from the nanocomposite of AuNPs/RGO is significantly lower than the AuNPs. This effect could be from the slow hydrolysis of the amide bond or due to the π-stacking barrier of the reduced graphene oxide sheets. The *in vitro* studies have been conducted on MCF-7 BCE cells.

Receptor targeting using transferrin has been used in several different cancer studies owing to the fact that cancer cell membranes contain high amount of transferrin receptors compared to that of healthy cells. Simultaneously, several studies on BC have also been performed to target transferrin receptors on BC cells. By conjugating transferrin to AuNPs, the cellular uptake of AuNPs by BC cells can be increased for the targeted therapy [86]. Another study showed a significant inhibition of BC cells by targeting EGFR/VEGFR-2 that plays a major role in metastasis BC by increasing cell proliferation and angiogenesis. This study reported that AuNPs loaded with quercetin could inhibit the epithelial-mesenchymal transition which contributes to BC malignancies in both MCF-7 and MDA-MB-231 cells. It has shown significant decreases in several protein expressions in response to this DDS such as vimentin, N-cadherin, MMP-9, p-EGFR, VEGFR-2, p-PI3K, Akt and p-GSK3β while the DDS helped in the enhancement of E-cadherin protein expression [87]. The functionalization of AuNPs with various

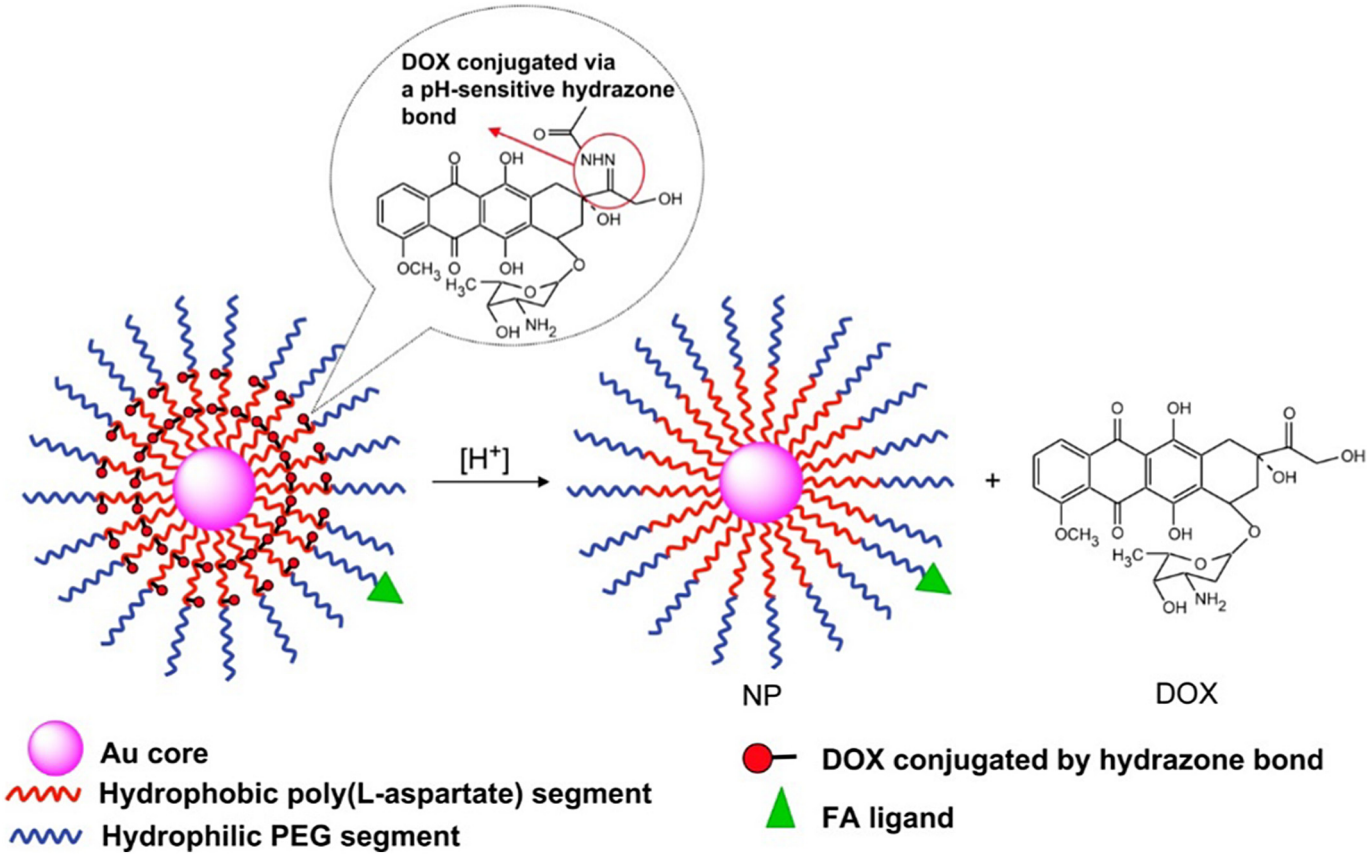

Fig. 3. Schematic illustration of the Au-Poly(L-aspartate-DOX)-b-PEG-OH/*FA NP and its pH-triggered drug release (*FA – Folic acid). The figure is adapted with permission from ref. [84].

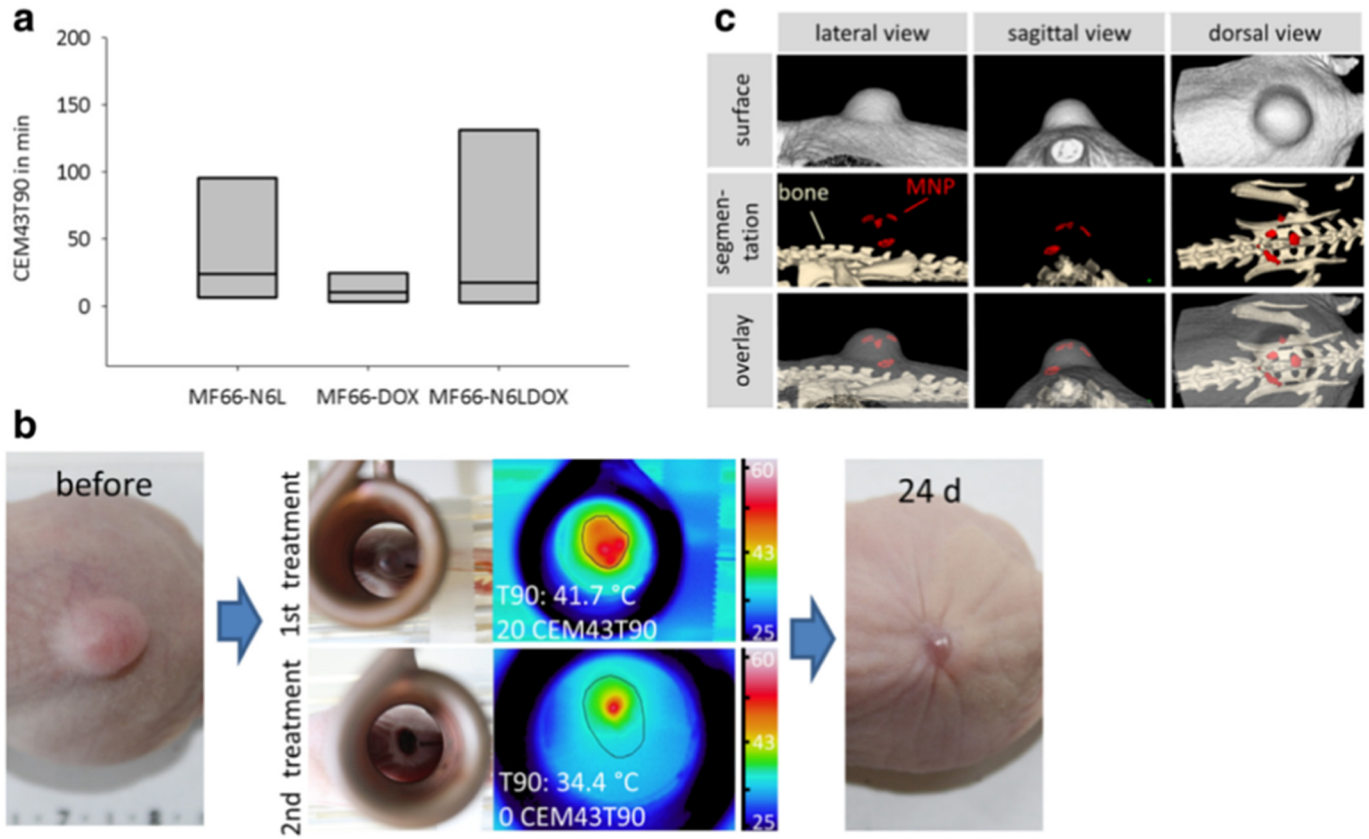

Fig. 4. Individual temperature dosages over tumor areas. (a). By using tumor surface temperature during hyperthermia treatment, median temperature dosages were calculated as cumulative equivalent minutes (CEM43T90) and displayed as box plots. (b). Example of a treatment sequence within the alternating magnetic field (AMF), the corresponding temperature distribution over the tumor surface and the effect on tumor volume. (c). Intratumoral distribution of SPIONs (MF66-N6LDOX) was determined using micro computed tomography 24 h prior to the first hyperthermia treatment. The figure is adapted with permission from ref. [102].

ligands or functional molecules helps stabilize the AuNPs significantly compared to the naked AuNPs and also enhances the cancer killing or protein expression inhibitions. In another study, AuNPs have been used to enhance the radiotherapy activity to kill BC cells. This study involved both MCF-7 and non-malignant MCF-10A cell lines. AuNPs decorated with two different functionalization molecules, cysteamine and thioglucose, have been used for the treatment. And they illustrated that although the cytoplasm distribution of these two functionalized AuNPs differed from each other, both molecules enhanced the effectiveness of the radiotherapy treatment in cancer killing compared to the non-AuNPs treated cells [88]. Another investigation showed that the Dox loaded AuNPs were able to overcome the MDR in MCF-7/ADR cancer cells [89]. AuNPs have been used in drug carrier studies extensively due to their unique characteristics especially including easy imaging through microscopic techniques such as transition electron microscopy (TEM) and controllable functionalization. One major drawback of the AuNPs could be their increased stability against the biodegradability in a biological system despite the reported low cytotoxicity.

2.6.2. Superparamagnetic iron oxide NPs

Superparamagnetic Iron Oxide NPs (SPIONs) are NPs of size in between 1 and 100 nm. These NPs have a magnetic inner core which is comprised of magnetite, Fe_3O_4, or maghemite, γ-Fe_2O_3. Maghemite is considered as one of the most suitable inner core materials for SPIONs due to its least likely toxicity from Fe(III) in the body unlike Fe(II) released from magnetite [90–93]. Direct use of SPIONs in therapeutic and biomedical applications can result in biofouling and agglomeration of these NPs in blood plasma, which is a huge drawback of direct use [94]. Thus, this magnetic core is covered by a hydrophilic coating for stabilization such as polymers which allow targeted delivery of biomolecules to specific sites. Most commonly used stabilization biopolymers include polysaccharides, PEG, dextran, alginate and polyacrylic acid [95,96]. SPIONs have received increased popularity for immunoassays, tissue repairs, chemotherapy and magnetic resonance imaging (MRI) as contrast agents due to the inherent properties such as great biocompatibility and magnetism through which therapeutics can be guided to target site using external magnetic fields and magnetic visualization can be achieved. Marcu et al. reported a SPIONs synthesis through laser pyrolysis with uniform size of about 8–10 nm in diameter [97]. They observed an effective antitumor activity of SPIONs on MCF-7 cells after further coating the NPs with antracyclinic antibiotic violamycine B1. Poller et al. also compared the impact on BC cells of three different types of SPIONs that varied in size, shape, zeta potential and surface coating. Their effects on cellular uptake, magnetic properties and cytotoxicity of SPIONs were studied in comparison [98]. From the three types of SPIONs that were used for BC treatment including dextran-coated ($SPION^{DEX}$), lauric acid coated ($SPION^{LA}$) and $SPION^{LA}$ with the addition of human serum albumin ($SPION^{LA\text{-}HSA}$), $SPION^{LA}$ showed the highest cellular uptake and the cell cytotoxicity towards the BC cells.

MRI is one of the frontier noninvasive visualization methods to identify tumors and other relevant targets in biomedical imaging and clinical diagnosis. An MRI measurement of tyrosine kinase HER2/neu receptor in BC cells using SPIONs was reported. Streptavidin-conjugated SPIONs were used as the targeted MRI contrast agent in this study. These NPs were directed to a panel of MCF-7 BC cells containing different amounts of the receptors which were pre-labeled with a biotinylated monoclonal antibody. The contrast of the observed imaging was illustrated to be proportional to the expression level of HER2/neu receptors. Also, an interesting observation was that the SPIONs were able to only attach to the surface of the BC cells without entering

intracellularly, which is an advantage in the *in vivo* imaging [99]. Thus, SPIONs are capable of potentially enhancing the contrast in imaging compared to the conventional techniques [100].

Another interesting technique of reducing the size of cancers is by involving heat. Tumor cells are susceptible to heat and can be killed *via* treatments such as magnetic hyperthermia. But hypothermia alone is not an effective method of tumor reduction. It is often used in combination with other techniques as radiotherapy or chemotherapy for clinical use [101]. However, SPIONs functionalized electrostatically with either Nucant multivalent pseudopeptide (N6L) (MF66-N6L), Dox (MF66-DOX) or both (MF66-N6L-DOX) act as potential antitumor therapeutics on MDA-MB-231 BC bearing female athymic nude mice exposed to an altered magnetic field. The therapeutic cytotoxicity effect of magnetic hypothermia has been reported to increase while the tumor volume decreased in the combination functionalization of both N6L and DOX [102] (Fig. 4). Thus, SPIONs can be synthesized with control in size, shape and mainly surface functionalization to suit different applications.

2.6.3. Quantum dots

Imaging of cancer cells is essential to track cancer progression and drug efficacy during treatment. Thus, quantum dots (QDs) play an important role owing to its excellent optical properties in the long-run of tumors imaging [103,104]. QDs are semiconductor nanocrystals with particle size ranging between 2 and 10 nm. These NPs usually are comprised of a metal inner core which exhibits a narrow emission spectrum with a size-dependent emission ranging from visible to infrared (IR) light. The shell could comprise of doped metals or semiconductor layers varying according to the applications. Conjugation of QDs with surface modifing ligands and peptides allows them to be used in target-specific cancer studies. Compared with most NPs mentioned previously, significantly, QDs enabled *in vivo* cellular imaging due to their excellent tunable optical properties, large surface to volume ratio, high brightness and resistance towards photobleaching. However, one drawback of these QDs is their high hydrophobicity. Thus, they require surface coating with polymers or by multilayer ligand shells to gain certain water solubility [105]. Conjugation with PEG reduces the potential toxic deposition of QDs in the reticular-endothelial system and allows better surface decoration [106–108]. QDs-based multiplexed imaging has been performed for *in situ* better than conventional methods which obtain biomarker information at a time such as immunofluorescence and western blot [109] (Fig. 5).

In a study of MCF-7 and BT-474 cell lines, QDs that could emit at multiple wavelengths were introduced. These two cell lines were found to express different levels of the following five biomarkers, ER, PR, EGFR, mTOR and HER2. Thus, the QDs were conjugated with the primary antibodies of these protein biomarkers and used for simultaneous quantitative and multicolor detection of those biomarkers [110]. Sun et al. mentioned a type of $CuInS_2$/ZnS QDs-based water-soluble imaging agent for the detection of BC cells after conjugating with anti-Ki-67 monoclonal antibody, a nuclear protein associated with the cell cycle, Ki-67 [111]. The hydrophobic QDs were coated with octadecylamine and then encapsulated in an amphiphilic polymer before conjugating with the monoclonal antibody. They revealed that the optical properties of the naked QDs remained unchanged in the decorated probe and no distinct toxicity was observed *in vitro* in MDA-MB-231 BC cells. But slight changes were observed in the cell shapes and the overall viability of the cells. The major drawback of QDs is that its inner core is commonly comprised of heavy metals which could be toxic to human body in the long-run through accumulation in organs as liver. And the excellent stability of QDs makes them less biodegradable and thus less biocompatible. Therefore, recently, more researches have been focused on non-metal NPs as alternatives to these conventional metal-based QDs.

2.7. Mesoporous silica NPs

Mesoporous silica NPs (MSNs) have attracted much attention as another inorganic nanomaterial in targeted therapeutic delivery and imaging due to their unique properties such as large surface area, pore volume (shown in Fig. 6) and the capability to vary the pore size other than having an easily modifiable surface [112–117]. MSNs have a high and controllable drug loading capacity due to the characteristic porous surface and are also able to deliver drugs without premature release before reaching the target site, which makes MSNs a good carrier for the easily degradable molecules such as genes and proteins. Tsai et al. have reported a NPs-based DDS of anti-HER2/neu monoclonal antibody using green fluorescent MSNs as drug carrier for the selective targeting of BC cells [118]. To facilitate imaging, the MSNs had been first loaded with a green fluorescent dye using a PEG spacer. They examined the targeting ability of the MSNs using both HER2-overexpressing cells (BT474 BC cells) and HER2 negative cells (MCF7 BC cells and NIH3T3 mouse fibroblast cells) and the green fluorescence was exhibited evidently in BT474 cells. Furthermore, they were also able to show that an MSN conjugate with the lowest Trastuzumab content nonspecifically bounded with all the three types of cells. Also, some MSNs have been observed to escape the endosomal vesicles in the intracellular environment and were able to image in the cytosol, which is an important discovery for drug delivery.

In another report, Meng et al. have developed an MSNs DDS to deliver siRNA to overcome Dox resistance in MDR BC cells in nude mice [119]. They have selected the Pgp drug exporter siRNA through a screening of the MCF-7/MDR cell line. Polyethyleneimine (PEI) and PEG copolymer functionalized MSNs have been applied for the stability and protection purposes for the Dox and Pgp siRNA system. They have observed an increasing retention and permeability at the tumor sites as well as the reduced reticuloendothelial aggregation from this nanocarrier synthesis. They also observed a synergistic inhibition of tumor growth which resulted from the co-delivery system, significant knockdown of Pgp and apoptosis induced by Dox intracellularly in the xenografts (Fig. 7). The study also revealed that much lower Dox limits can be administered through this system, and an encapsulation would open possibilities of lower risks to cardiovascular toxicity, resulting from Dox. Furthermore, the combined DDS exhibited higher drug efficacy compared to either single treatment administered. The research on MSNs possibly can be more reliable compared to metal-based NPs in terms of toxicity and biocompatibility whereas the latter mostly contain heavy metal elements that are harmful for human's health. Moreover, the facts that these porous NPs can deliver a cocktail of drugs to a target site simultaneously and silica being an abundant material could be advantages. Nonetheless, one major limitation of MSNs is that their poor penetration ability in to a tumor mass [120]. Therefore, vast surface modifications need to be conducted for *in vivo* use.

2.8. Carbon-based NPs

Carbon-based NPs including fullerene, graphene, carbon nanotubes and dots are all promising tools for the treatment of BC due to their unique physicochemical, optical and biological properties [121]. Specifically, carbon-based NPs research were developed in hope to replace the toxic, heavy-metal containing QDs and other metal NPs with a non-metallic NPs system. These carbon-based NPs own numerous favorable characteristics such as small size, high specific surface area, versatile surface functional groups, benign biocompatibility, low-toxicity, unique optical and thermal properties [122]. Thus, carbon-based NPs can be considered as a better and promising DDS to be applied in cancer theranostics compared to the metal-based NPs. Based on the discovery and application history, carbon nanotubes (CNTs) will be introduced followed by carbon dots (CDs) regarding their application in BC treatment.

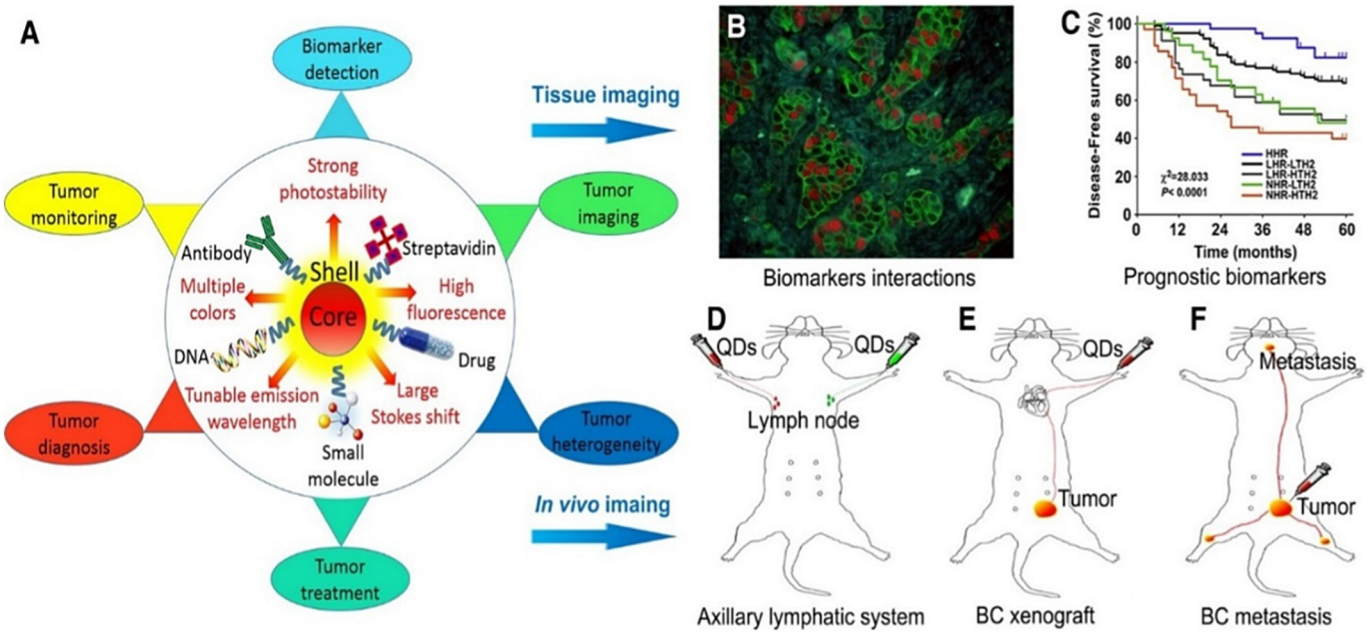

Fig. 5. Optical properties and potential applications of QDs in BC research studies. Commonly used QDs are core–shell structure encapsulated with amphiphilic polymers carrying chemically active groups. Compared with traditional organic dyes, QDs show excellent optical properties (A). After being coupled with active molecules, QDs can be adapted for tissues imaging, such as studying biomarker interactions (B) and evaluating prognostic biomarkers (C), and for *in vivo* imaging such as mapping auxiliary lymphatic system (D), showing BC (BC) xenograft (E) and detecting BC metastasis (F) in BC research studies. The figure is adapted with permission from ref. [109].

2.8.1. Carbon nanotubes

CNTs are allotropes of fullerene with a cylindrical shape of long, hollow structures with a wall composed of graphene sheet rolled at a specific angle. According to single or multiple graphene sheet, CNTs are categorized as single-walled (SWNTs) or multi-walled nanotubes (MWNTs). The ongoing development of CNTs exhibits many extraordinary properties including thermal conductivity, optical and electrical properties [123]. In addition, CNTs have become a versatile tool for nanomedicine application, particularly in the cancer targeting [124]. Due to the tunable surface and unique thermal properties, CNTs can serve as excellent optical absorber in near IR (NIR) light where biological systems prove to be highly transparent [125]. And the process to treat cancer cells by laser-irradiation mediated with biofunctionalized CNTs is called nanophotothermolysis [126].

He and coworkers observed that SWNTs showed two unique optical properties. They reported on a cancer cell detecting strong Raman signal and NIR absorbance for selective photothermal ablation of tumors [127]. After conjugation with HER2 IgY, the composite demonstrated dual functionality for both functions of detection and selective destruction of cancer cells in an *in vitro* model with HER2-expressing SK-BR-3 cells and HER2-negative MCF-7 cells. Another similar case was reported by Neves et al. [128]. As is known that the human protein annexin V (AV) binds specifically to anionic phospholipids expressed externally on the surface of tumor and endothelial cells that line the tumor vasculature [128,129], Harrison et al. adopted the conjugate of SWNTs and AV to realize the targeting treatment of BC by the photothermal therapy with the help of a laser of 980 nm wavelength.

Since CNTs are pre-formed supramolecular nanotubes, the drug loading to CNTs could be very challenging. There are two drug-loading patterns including the filament and direct loading to the surface. CNTs can be filled with both organic and inorganic chemotherapeutic drugs through simple capillarity-induced filling [130–132]. However, the loadable amount is as low as 5% (*w*/w) of drugs [132]. On the other hand, pre-functionalized CNTs allow some small hydrophobic drugs to directly attach on the coating-polymers, which can greatly improve the loading capacity. For example, one investigation demonstrated that the loading capacity of Dox can reach 400% (w/w) by using the coating-polymer technique [133]. However, for drugs with bulky structures, the lack of space on the surface of polymer will limit further conjugation of other ligands, which results in difficulties in the multifunctional DDS [134]. To solve this problem, Shao et al. first conjugated PTX with a long chain lipid docosanol molecules, and the lipid chain was bonded to the surface of CNTs *via* hydrophobic interactions [135]. Then with the aid of folic acid, the new conjugate of SWNTs-lipid-PTX achieved high cell penetration and much improved drug efficacy *in vitro* (78.5 *vs.* 31.6 and 59.1% in cytotoxicity respectively, $p < 0.01$) and *in vivo* using a human BC xenograft mice model compared to free drug and non-targeted SWNTs-lipid-PTX.

Faraj et al. provided a novel DDS consisting of antibody conjugated-SWNTs, Dox as well as SPIONs [136]. By the specific antibody-antigen interaction and magnetic force from an externally applied magnet to the SPIONs, the conjugate composite showed efficient drug delivery. Further, the superiority of apparent diffusion coefficient measurements using diffusion-weighted MRI was found to be a sensitive imaging biomarker for assessment of treatment-induced changes.

Based on the challenges of the treatment and effectiveness of PTX, Wang et al. found CNTs with abundant oxygen-containing functional groups on surface could enhance the inhibitory effect of PTX on the proliferation of BC cells by downregulation of HIF-1α under hypoxia [137]. This study did not mention any side effects of PTX. Hypoxia is an important factor that downregulates the efficacy of the treatment of BC. It will stimulate the tumor resistance to the chemotherapy or radiotherapy. In addition, it can improve the invasiveness of tumor [138]. Hypoxia-inducible factor 1 alpha (HIF-1α) plays a key role in the effects of hypoxia on cancer cells. Indeed, HIF-1α expression is associated with the survival of BC patients after surgery. Therefore, overcoming the effects of hypoxia might improve the efficiency of BC treatments.

Another type of CNTs widely investigated for the treatment of BC is MWNTs. In 2005, Jia and coworkers compared the cytotoxicity of SWCNTs and MWCNTs in the alveolar macrophages and observed an impaired phagocytosis at a low dose of SWCNT, while MWCNT resulted in the identical outcomes at a higher dose, which reveals a higher

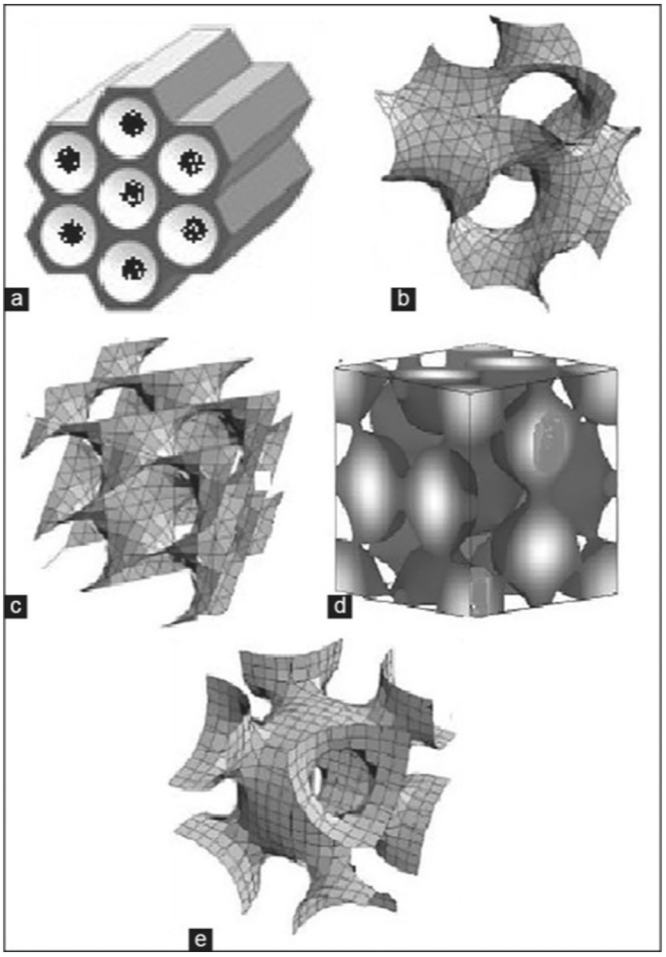

Fig. 6. Various pore geometrics of mesoporous structure (a) 2D hexagonal p6 mm, (b) bicontinuous cubic Ia3d, (c) bicontinuous cubic pn3 m, (d) cage type pm3n, (e) cage type Im3 m. The figure is adapted with permission from ref. [117].

toxicity of SWCNT than MWCNT [139]. Therefore, in recent years, more MWCNTs have been studied for the BC treatments [140]. For example, Risi et al. performed a series of studies including the cytotoxicity, internalization and loading of MTX in MDA-MB-231 [141]. The internalization of MWCNTs was evidenced by TEM. MTX release from MWCNTs showed linear kinetics over a 24 h period and MWCNT–MTX cytotoxic effects were time- and dose-dependent. However, the MWCNT–MTX DDS lacked the specific targeting effect showing no distinction between cancer and non-neoplastic cells.

Thus, functionalization of MWCNTs could enhance the drug loading and targeted drug delivery. Singh and coworkers functionalized MWCNTs with glucosamine in two patterns as covalently linked glucosamine and non-covalent phospholipid-glucosamine coated MWCNTs [142]. The binding of MWCNTs was mediated by the specific interaction with the glucose transporters. Glyco-MWCNTs prepared by non-covalent coating of MWCNTs with phospholipid-glucosamine displayed an extended blood circulation time, delayed urinary clearance, low tissue retention and increased BC tumor accumulation *in vivo*.

Therefore, CNTs are a good drug delivery carrier. However, the preparation of CNTs cannot be easily achieved. CNTs are also known to have certain limitations in terms of solubility and biodegradability [143]. In addition, the loading of drugs could be challenging in several different ways.

2.8.2. Carbon dots

As a new family member of carbon-based NPs, CDs were discovered in 2004 [144]. In the early beginning of their discovery, the primary research was mainly related to the photoluminescence (PL) using various synthetic approaches, starting materials and surface modifications [145]. As a measurement of PL, fluorescence quantum yield (QY) has been improved up to 93.3% by surface doping [146]. Besides the enhancement of QY, the PL mechanism of CDs draws wide investigation in different viewpoints [147,148] to obtain optimizable PL properties especially in regard to imaging *in vivo*. Due to the unique properties including water-dispersion, ease of produce, high PL and bio-compatibility, large surface area and abundance of functional groups on the surface, CDs have been widely used in printing [149,150], sensing [151], imaging [152], photocatalysis [153,154], thermoelectricity [155], and are considered to be excellent drug nanocarriers for *in vitro* and *in vivo* studies [156,157]. Despite of these attractive properties, the application of CDs in the treatments of BC was first introduced in 2013.

In 2013, Hsu et al. reported a type of CDs prepared from green tea, which exhibited inhibition activity of cancer cells [158]. Three cancer cell lines have been employed including MCF-7, MDA-MB-231, and HeLa (human cervical carcinoma) cells. The cell viability decreased with the increasing concentration of CDs. The cell viability percentages for MCF-7, MDA-MB-231, and HeLa cells for CDs were 20, 18, and 68%, respectively, which demonstrated their great inhibition effect on BC cell lines. As for the mechanism of the reduced viability, they ascribed it to the generation of H_2O_2 and ROS. Li and coworkers illustrated a green emitting CDs synthesized from urea and citric acid *via* a microwave-mediated method as a trackable nanocarrier for Dox [159]. It is noteworthy that the as-prepared CDs showed low or even no toxicity by comparing human liver carcinoma HepG2 cells, and human normal liver HL-7702 cells. The viability of both cell lines remained constant 100% even when the incubation time was extended up to 96 h and the CDs concentration increased from 1.5625 to 100 $mg{\cdot}ml^{-1}$. This was a remarkable achievement which was hardly achieved by any other reported CDs [160,161]. Then CDs were conjugated with Dox through basic electrostatic force or hydrogen bonds, which established a foundation for the pH-dependent release of Dox in the cancer cells. To test the universality of the conjugate composite to cancer cells, two other cancer cell lines, namely HeLa, MCF-7 and two other healthy cell lines, namely H9C2 (cardiomyocytes) and HUVEC cells (human umbilical vascular endothelial) were also employed for the same set of evaluations. As a result, the CDs-Dox conjugate showed a selective therapeutic effect on the cancer cells, which was clearly revealed by the decline of cell viability. In addition, Zhao and coworkers have investigated MCF-7 in contrast to MDA-MB-231 cells to explore the tumor extracellular acidic condition triggered targeting ability of CDs [11]. In their work, owing to the interaction between RGD and overexpressed integrin $\alpha_v\beta_3$, higher cellular uptake of CDs conjugate (CDs-RGD-Pt(IV)-PEG) was achieved by MDA-MB-231 compared to MCF-7 cells due to the exposure of RGD peptide after the hydrolysis of the benzoic-imine bond at pH 6.8 rather than 7.4. The result was confirmed by confocal laser scanning microscopy, flow cytometry, and cytotoxicity studies. In general, BC cell lines in many ongoing cancer research are only used as a cancer model to study the cytotoxicity and internalization of CDs alone or CD-drug conjugate, which suggests the lack of the systematic study of BC treatments using CDs.

Later in 2018, another study was reported on the BC treatment using CDs as the nanocarrier where Kong et al. conjugated CDs with Dox through electrostatic interaction and the conjugate achieved a higher cellular uptake and anti-tumor efficacy on MCF-7 cells in contrast to free Dox [162] (Fig. 8). In this pioneering study, however, the confirmation of successful conjugation was not convincing by the fluorescence spectroscopy. To be specific, even though there was no obvious shift of the fluorescence emission after conjugation with Dox, the PL emission spectra of both CDs and Dox are not apparently different.

Thus, provided the favorable properties of CDs such as non-toxicity, excellent water dispersity, good biocompatibility and the excellent PL that allow the imaging and tracking to be possible, it will be a very

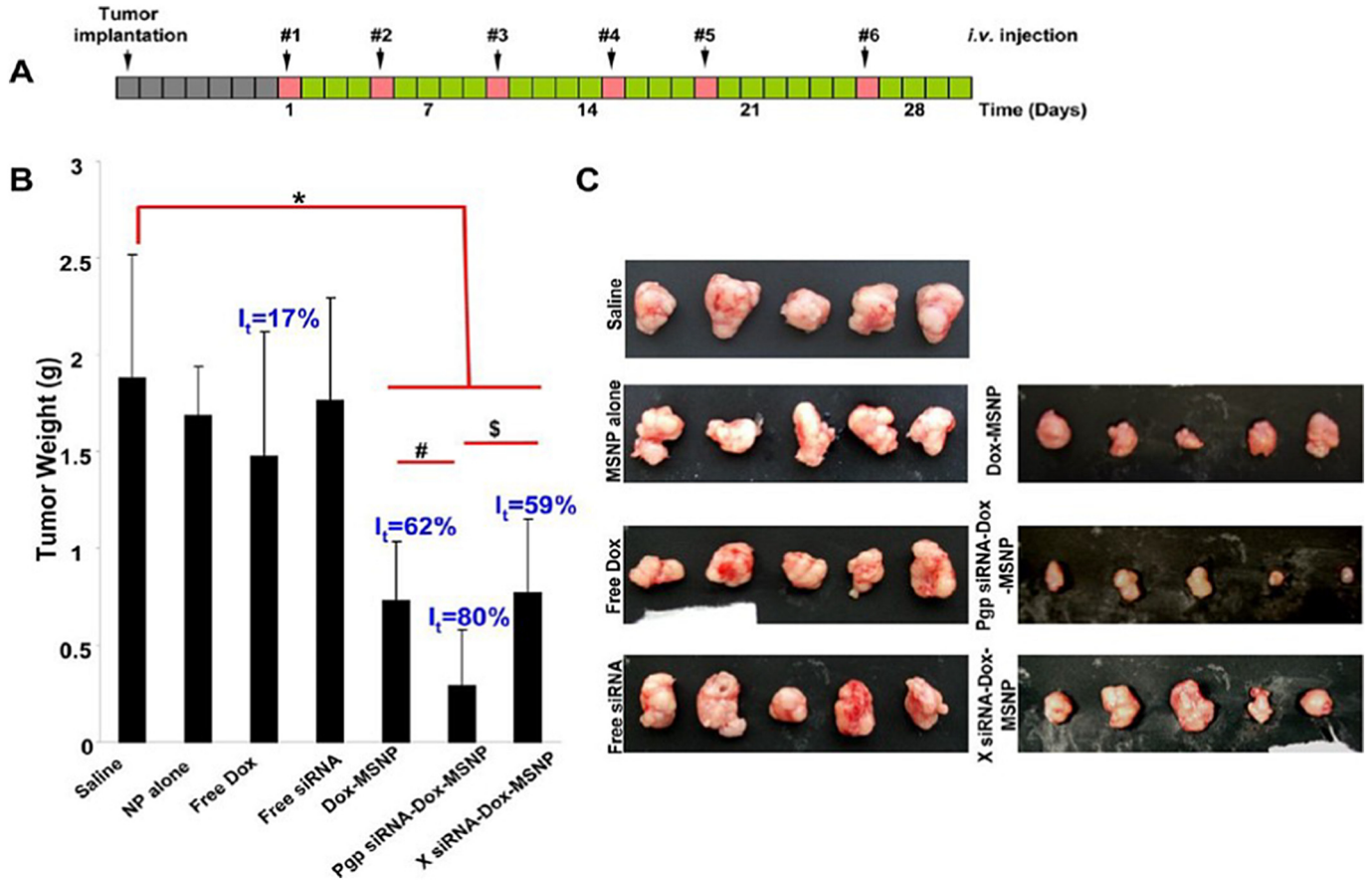

Fig. 7. Tumor growth inhibition of xenografts established from MCF-7/MDR cells in nude mice. (A) MCF-7/MDR cancer cells were subcutaneously injected into mice 7 days before treatment with MSNs (gray boxes). These animals received six i.v. injections (red boxes) every 3–6 days (green boxes) for 30 days as shown. (B) Comparison of the tumor inhibition effect of Dox-loaded MSNs containing Pgp siRNA *versus* other treatment groups: saline, empty MSNs, free Dox, free siRNA, Dox-loaded MSNs without siRNA, and Dox-loaded MSNs containing scrambled siRNA. Following sacrifice of the animals, tumor tissues were collected and weighed to determine the tumor inhibition rate. (/) $p < .05$, compared to saline; (#) $p < .05$, compared to Dox-loaded MSNs without siRNA; ($) $p < .05$, compared to Dox-loaded MSNs with scramble (X) siRNA. (C) Photograph of the collected tumor tissues for each treatment group. The figure is adapted with permission from ref. [119].

promising nanocarrier in BC drug delivery. Nonetheless, only few studies have been conducted. Therefore, elaborate studies are needed on CDs capability to be used in DDS for BC to enlighten these new possibilities.

2.9. Protein-based NPs (viral NPs)

Viral NPs are a group of NPs resembling the protein envelopes or capsids of viruses, which determines the targeting of viral NPs. However, in absence of genome of viruses, these viral NPs are not infectious. The synthesis of viral NPs undergoes the expression and recombination of viral envelope and capsid proteins, and the process can take a short period especially in plant. For example, since transient transformation of plant tissues is very rapid, it can produce recombinant proteins or the products within days of their activity and can then be scaled up to commercially relevant production levels [163]. Also, the highly ordered repetitive structures on the surface of viral NPs provide a good platform for the conjugation with various drugs [164]. Therefore, viral NPs are emerging as a versatile tool for targeted drug delivery.

In terms of drugs species that have been delivered by viral NPs to treat BC, trastuzumab is currently in use as a targeted therapy for HER2+ BC patients. It was carried by potato virus X (PVX), which was reported by Esfandiari et al. in 2015 to cause the increasing death of BC cells [165]. Based on this work, Esfandiari and his team furthermore conjugated PVX with trastuzumab monoclonal antibody, which can prevent the proliferation of BC cells and inhibit transducing the signals [166], as a new option in specific targeting of BC. Later, as was presented by Le *el al.* in 2017, Dox was also conjugated and delivered by PVX to athymic mice bearing human MDA-MB-231 BC xenografts and PVX-Dox treatment resulted in reduced tumor growth [167]. Therefore, PVX, as one type of plant-derived viral NPs, opens the door of viral NPs for the cancer therapy applications.

In addition to PVX, influenza viral NPs modified *via* protein transfer by anchoring glycophosphatidylinositol (GPI) and HER2 antigen led to enhanced protection against HER2-expressing tumor growth in a murine BC model. And GPI-HER2 modified influenza viral NPs led to HER2-specific IgG production and enhanced HER2-specific Th1-type immunity compared to vaccination with GPI-HER2 alone [168].

Viral NPs are biocompatible and biodegradable, which is the best advantage of such DDS. Moreover, those viral NPs that originated from plant viruses and bacteriophages are particularly advantageous since they are less likely to be pathogenic in human body, and thus less likely to cause unwanted side effects [169]. To the best of our knowledge, no studies have been reported regarding the potential shortcoming of this method. It seems viral NPs come of age and it is predicted not too long before viral NPs play a prominent role in the clinic [170]. However, the synthesis of viral NPs that resemble certain virus is still more complicated and costly than other NPs preparation [171], which needs to be simplified and accessible for a wider application.

3. Conclusion

BC is one of the deadliest cancers in contemporary. Alongside this,

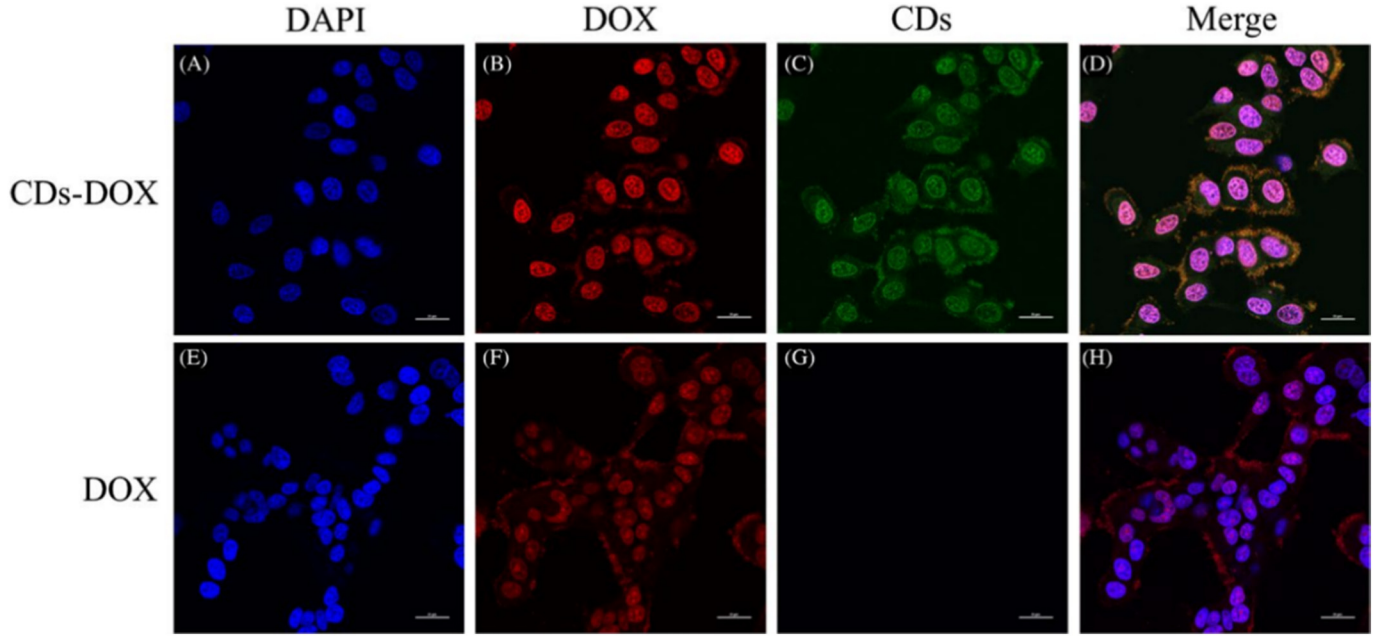

Fig. 8. Confocal microscopy images of MCF-7 cells incubated with CDs- Dox (A, B, C and D) and free delivery of Dox (E, F, G and H) for 4 h, respectively. The cell nuclei were stained with DAPI and the concentration of Dox was 1 μg mL^{-1}. The cell nuclei, Dox and CDs exhibited blue, red and green fluorescence, respectively. The scale bars are 25 μm in all the images. The figure is adapted with permission from ref. [162]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

studies focusing on cancer treatments are increasing prominently. To this aspect nanoparticles could serve as a powerful tool in cancer therapy. Also given the fact that the traditional techniques of surgery, radiotherapy and chemotherapy have found to bear numerous side effects and shortcomings in the long-run of the treatment, NPs-mediated DDS is a promising candidate for replacement as a recently emerging methodology. Several different types of NPs have been investigated as possible nanocarrier candidates. These NPs can be modified through controlled syntheses, functionalization or decorating by polymers such as PEG to enhance the carrier requirements to suit certain DDS.

In terms of synthesis, CNTs, viral, and several metal-based NPs turned out to be difficult. Ease of production can be advantages in possible new NPs. CDs alongside other carbon-based NPs have proved to be non-toxic unlike several heavy metal-based NPs. Liposomal NPs show better drug loadability towards hydrophobic/lipophilic therapeutics due to the phospholipid bilayer structure. However, CDs also display interesting characteristics such as good water dispersity, ease of production and biocompatibility apart from the excellent PL properties, which allow the easy imaging and also allow administration of the drugs without incurring any toxic effects as QDs. CDs can also be easily functionalized for specific targeting through the abundantly available functional groups on the particle surface. Nevertheless, to this date, the ability of CDs in specific targeting for BC has not been extensively studied. Thus, the understanding on this aspect is very lacking unlike the other NPs such as liposomal and polymer-based NPs. Continuous research on these new emerging NPs could open fruitful pathways in efficient DDS development.

The most common chemotherapeutic agent used in BC studies in conjunction with NPs is Dox, which was approved for medicinal use in 1974 [172]. Considering the high possible toxicity of Dox, it is most likely to be replaced by new chemotherapeutics. Further studies have proved drug combinations to be more effective for cancer inhibition compared to single drug treatment in terms of MDR and synergism. Thus, with new information on BC, possibility for novel therapeutics can still increase. Researches on novel anti-cancer agents such as siRNA and miRNA have also proved to be effective in BC treatment and are being investigated for the possibility for use as dual systems in combination with other drugs. These combined systems although still not very popular, will possibly lead to increasing needs of NPs as drug carriers. By incorporating target-specific DDS, the pharmacologically effective drug dosage can be lowered and drug efficacy on target site is improved, which reduces the harmful side effects incurred through non-specific drug administration. Although not all these NPs have shown excellent activity in clinical trials, continues development of DDS especially using carbon-based NPs in conjunction with novel combined therapeutics can be promising and will be of great importance for BC research.

Author contributions

Piumi Y. Liyanage, Sajini D. Hettiarachchi and Yiqun Zhou were mainly responsible for researching and compiling the data from the literature and drafted a first draft of the manuscript, and they contribute equally. In addition, Cagri Y. Oztan contributed to the manuscript with the data and discussion regarding nanofibers. Elif S. Seven made the graphical abstract. Allal Ouhtit, Emrah Celik, and Roger M. Leblanc edited and revised the manuscript.

Competing interests

The authors declare no competing interests.

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