Graphical Abstract: Text

Multidrug resistance in tumor involves multiple mechanisms, which mainly includes lowered extracellular pH, hypoxic region, and irregular vasculature in physiological level, and the alteration of apoptotic machineries, over-expression of efflux transporters, and enhanced repair mechanism of drug induced DNA damage in cellular level. With the increasing role of tumor microenvironment in multidrug resistance, cell proliferation and metastasis, this review will focus on the characteristics of tumor microenvironment and their targeting mechanisms with PEG-based amphiphilic nanoparticles to overcome chemoresistance.

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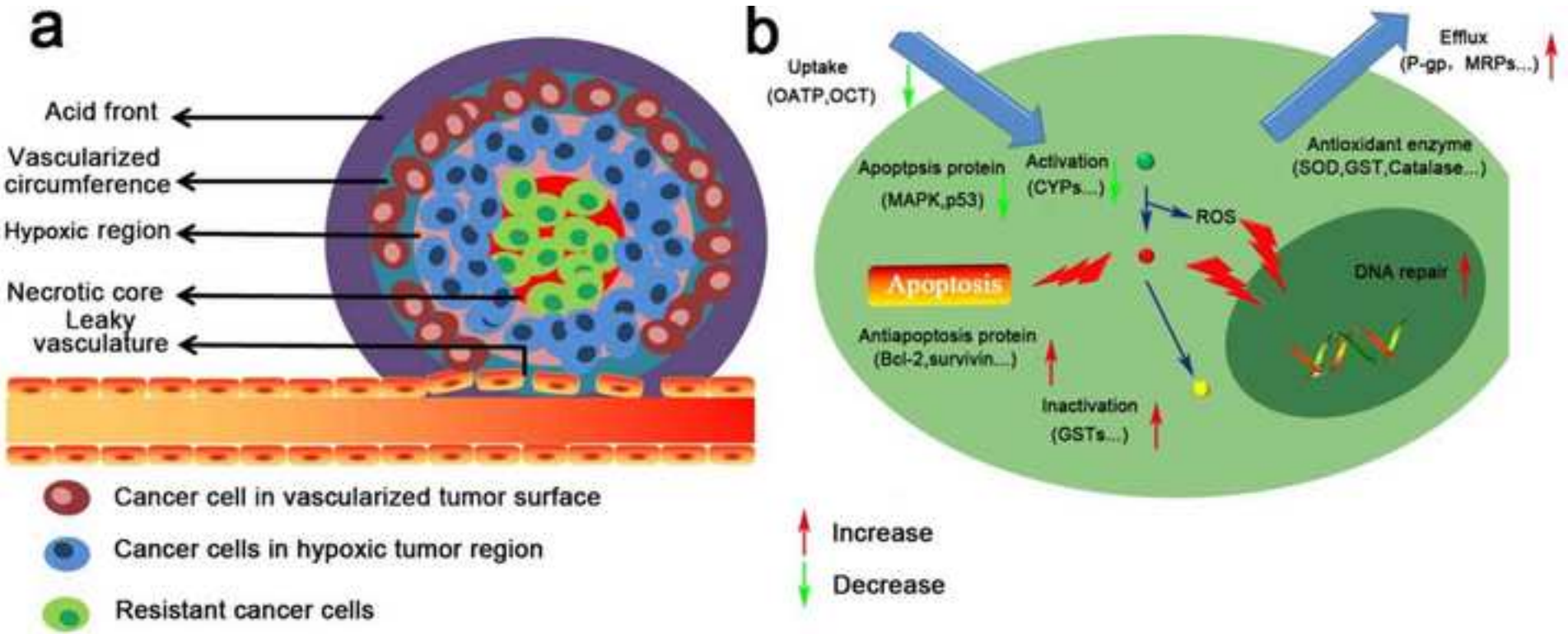

Targeting tumor microenvironment with PEG-based amphiphilic nanoparticles to overcome chemoresistance

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We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

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Abstract

Multidrug resistance is one of the biggest obstacles in the treatment of cancer. Several factors involves in drug resistance including enhanced repair mechanisms of drug induced DNA damage, lowered tumor extracellular pH, alteration of cell cycle check points, blockage of apoptosis pathway, poor tumor vasculature and over expression of drug efflux pumps. Recent research studies highlight that tumor microenvironment plays a predominant role in tumor cell proliferation and metastasis. Hence, targeting the tumor microenvironment provides a novel strategy for the evolution of cancer nanomedicine. The blooming knowledge about the tumor microenvironment merging with the design of PEG-based amphiphilic nanoparticles can provide an effective and promising platform to address the multidrug resistant tumor cells. This review describes the characteristic features of tumor microenvironment and their targeting mechanisms with the aid of PEG-based amphiphilic nanoparticles for the development of newer drug delivery systems to overcome multidrug resistance in cancer cells.

Keywords: Poly(ethylene glycol), amphiphilic nanomaterials, tumor targeting, cancer microenvironment, multidrug resistance

Abbreviations

ABCs: ATP-binding cassette superfamily

AUC: Area under the curve

BBB; Blood brain barrier

BCRP: Breast cancer resistance protein

CMC: critical micellar concentration

CT: Computer Tomography

CUR: Curcumin

DOX: Doxorubicin

DSPE-PEG:

1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)]

EGF: Epidermal growth factor

EGFR: Epidermal growth factor receptor

EPR: Enhanced permeability and retention

FA: Folic acid

FDA: Food and Drug Administration

IVCLSM: Intravital confocal laser scanning microscopy

Lf: Lactoferrin

MDR: Multidrug resistance

MRP: Multidrug resistance-associated proteins

NIR: Near infrared reflection

OCT: Octreotide

PDMAPMA : poly(N,N-dimethylamino-propyl methacrylamide)

PAE: poly(β-amino ester)

PCL: poly(ε-caprolactone)

PEG: polyethylene glycol

PEG-CPT: poly(ethylene glycol)-camptothecin

P-gp: P-glycoprotein

PTX: Paclitaxel

RES: Reticuloendothelial System

Tf: Transferrin

TfR: Transferrin receptor

TPGS: D-α-tocopheryl polyethylene glycol succinate

VEGF: vascular endothelial growth factor

1. Introduction

Cancer is among the most serious diseases faced by the humanity. Following cardiovascular diseases, malignant tumor occupies the second place for the cause of death. According to the statistical data from the American Cancer Society, 1658370 cancer cases have been registered and 589430 cancer deaths are projected to occur in 2015 only in the United States[1]. In the past few decades, with the progress of medical technologies various treatments for cancer have been developed, which include surgery, chemotherapy, radiation therapy, immunotherapy, hormone therapy, targeted therapy et al (Table 1). Depending on different conditions of cancers, each type of treatment can be given alone or associated with other forms of cancer therapy.

Table.1

Among the various treatments, chemotherapy is one of the most common types of cancer treatment. Compared to other therapies, chemotherapy with the advantages of easy operation, good patients' compliance and better treatment effects, remains the first-line treatment of choice for clinic[2,3]. Though chemotherapy plays an important role in cancer treatment, there are still many problems during clinical application. The major drawback is side effect as chemotherapeutic agents would kill cells in both healthy and tumor tissue[4-6]. What's more, the surrounding environment of tumors is another obstacle for chemotherapeutic efficiency. Some special pathophysiology changes such as growth-induced solid stress, abnormal blood vessel networks, elevated interstitial fluid pressure and dense interstitial structure can form the transport barriers that limit the rate and extent of the chemotherapeutic drugs delivery

to both primary and metastatic tumors[7-13]. In addition, the other limitation of chemotherapy is the multi-drug resistance. Tumor cells can develop drug resistance which leads to reduced or complete absence of antitumor effect[14]. Drug resistance mechanisms could appear at the tumor level such as low pH or high interstitial pressure, and at the cellular level including certain overexpressed enzyme systems, increased drug efflux and reduced uptake[15-17]. It is worth mentioning that the tumor microenvironment also play an important role on the multi-drug resistance. All of those have limited the effect of chemotherapy treatment.

In order to solve these issues in chemotherapy, various approaches had been applied. One of the most promising methods is applying nanomedicines for delivering anticancer drugs to their action site. Nanomedicine is nanoscale complex system which is fabricated from different materials and applicable to various drugs, proteins, nucleic acids. They comply with the requirements of stability, safety, biocompatibility and biodegradability[18]. Application of nanomedicine will be able to overcome many problems such as poor water solubility of therapeutic agents, short blood circulation time, non-specific distribution, toxicity, tumor resistance (both at the tissue and cellular levels), low therapeutic index, which not only help to decrease systemic toxicity of chemotherapy but also enhance the efficacy of anticancer drugs. During the last few decades many types of nanomedicine for cancer treatment have been fabricated[19]. Among them amphiphilic polymers is one of the most promising nanomaterials with desirable properties, which can self-assemble above critical micellar concentration (CMC) and form micelles with an average size 20-100nm[18].

Structural units of the micelles are hydrophilic and hydrophobic moieties. The hydrophilic part is usually presented by polyethylene glycol (PEG) which forms the hydrophilic outer layer (corona) that can enhance the circulation time by evading plasma protein adsorption[20]. The hydrophobic part forms the core of the system capability to incorporate the anticancer substances that solve water-insolubility issue[21]. Micelles are dynamic systems and undergo rapid modification when compared to solid stable structures. In addition, amphiphilic polymers represent better kinetic and thermodynamic properties with high biocompatibility and degradation rate[18, 21].

In this review, we will focus on the PEG-based amphiphilic nano structures which were developed to target tumor microenvironment and overcome multi drug resistance.

2. Use PEG-based amphiphilic nanostructure for targeting tumor therapies

Since Paul Ehrlich, the founder of chemotherapy who won the Nobel Prize for Physiology or Medicine in 1908, proposed the concept of 'magic bullets' that drugs go directly to their intended cell-structural targets while remain harmless in normal tissues[22]. Generations of researchers have been inspired to design powerful therapeutics for cancers[23-26]. With the development of nanotechnology and nanomedicine over the past few decades, nanoparticles show greater potentials to realize the Paul's postulate and present higher efficacy in targeting cancer treatment compared to other anticancer therapies[27,28]. This is owing to the size and surface properties of nanoparticles which contribute to the improvement of pharmacokinetics and pharmacodynamics and active intracellular delivery of anti-cancer drugs[29-31]. What's more, among various nanoparticles, PEG-based amphiphilic nanomaterial is one of the most promising candidates for targeting tumor therapies because of their high anticancer drug payload[32,33], prolonged circulation half-life[33,34], and flexibility[35] and ease of functionalization with specific ligands[36,37]. This part will focus on the roles and applications of PEG-based amphiphilic materials as nanocarriers in targeting tumor therapies.

2.1. Passive targeting of cancer via PEG-based amphiphilic nanomaterials

The growth of human tumors is always accompanied with angiogenesis to conquer diffusion limitation[38,39]. The major characteristics of angiogenesis are abnormalities in the basement membrane and deficiency of pericytes lining endothelial cells[40]. The incomplete tumor vasculature leads to leaky vessels with gap

sizes from 100 nm to 780 nm relying on tumor types[41], while normal vessels possess tight endothelial junctions of 5 nm to 10 nm[42]. Additionally, since tumor interstitium is made up of collagen networks and gel-like fluid and tumors lack a well-defined lymphatic system, the interstitial pressure in the center of tumors is higher than that at the periphery[43]. Therefore, the combination of incompact vasculature and poor lymphatic drainage account for the enhanced permeability and retention (EPR) effect[44].

The discovery of the EPR effect is an important step forward for targeting tumor therapy[45]. Nanoparticles with smaller sizes can enter the interstitium and accumulate in tumor while restricted from exiting normal vasculature[28], which allows for passive tumor targeting. However, injected nanoparticles are generally cleared by reticuloendothelial system (RES) fast after administration due to the binding of plasma proteins and accumulate in the liver and spleen[33]. The amount of nanoparticles in blood circulation through tumors is far less than that entrapped in RES organs. Only the nanoparticles that don't bond with plasma macromolecules and then are not fast eliminated from circulation will have chances to encounter the leaky vasculature of tumors[46].

PEG-based amphiphilic materials can self-assemble into nanoparticles in aqueous media, and provide a stealth surface that would reduce RES recognition of nanoparticles and prolong circulation half-life[47]. Theoretically, amphipathic PEG assembled nanoparticles would not be opsonized at all and stay in blood circulation until they run into and penetrates leaky vasculatures in tumor[34], thus increasing

opportunity to reach their action site. Therefore, PEG-based amphiphilic nanomaterials play an important role in passive targeting therapies. In 1995, DOXIL, the doxorubicin (DOX) loaded liposome formulation containing a PEG derived phospholipid, hit the market as the first therapeutic nanomedicine with the Food and Drug Administration (FDA) approval[48]. The inclusion of a small fraction of PEG-based amphiphilic material increases surface hydrophilicity, reduces opsonization and RES uptake, and prolongs liposome circulation time, which contributes to the enhancement of drug concentration in malignant effusion via passive targeting when DOXIL is compared to free DOX[49]. In 2007, Genexol-PM, the paclitaxel-loaded poly(lactic acid)-*block*-poly(ethylene glycol) micelles, came into the market. The PEG-based amphiphilic formulation permits the delivery of a higher paclitaxel dose without Cremophor EL and shows favorable biodistribution and greater antitumor efficacy[50].

In addition, many formulations based on PEG-derived amphiphilic nanometrials are developed in preclinical studies to realize passive targeting and treatments of cancers. Liang *et al.*[51] fabricated a unique nanoprobe via co-loading fluorescence molecule and gold nanoparticles into the micelles made up of the FDA approved 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (DSPE-PEG2000) copolymer. The chemical structures of DSPE-PEG_{2000} and NPAPF and the scheme of micelle preparation have been showed in Figure 1a. Thanks to the excellent properties of DSPE-PEG_{2000}, the nanoprobe exhibited good biocompatibility (Figure 1b), long blood circulation half-life (Figure

1e), superior tumor targeting ability (Figure 1d and h), and excellent fluorescence and computer tomography (CT) imaging (Figure 1c and g), which indicated the significantly potential application of NPAPF and gold nanoparticles loaded PEG-based micelle as a dual-modal non-invasively fluorescent/X-ray CT nanoprobe for tumor-targeted imaging and diagnosis *in vivo*. Yu *et al.*[52] designed poly(ethylene glycol)-camptothecin conjugate (PEG-CPT) and studied their antitumor effect in the nude mouse model of human colon xenografts. The results demonstrated that PEG-CPT provided passive tumor targeting of drug, improved biodistribution and increased the drug stability during circulation. Compared to native drug, the conjugate offered better uptake by targeted tumor cells and adequately enhanced apoptosis and antitumor stability of camptothecin and reduced side-effects in normal tissues.

Figure 1

2.2. Active targeting of cancer via PEG-based amphiphilic nanomaterials

Despite the fact that EPR effect provides the opportunity for tumor targeting, it is not applicable in low vascular permeability cancers such as pancreatic cancer[53]. Besides, passive targeting is often not enough for drug accumulation in tumors and PEGylation hinders the uptake of nanoparticles by tumor cells once they extravasate. Therefore, it is desirable to develop active targeting systems that are able to selectively recognize specific cells or tissues[34]. Active targeting involves the use of a biologically active ligand conjugating at the periphery of the nanostructures, and will be achieved by molecular recognition of targeted cells or tissues via specific signature molecules overexpressed in tumors[53]. Recently, various ligands have been employed

to develop active tumor targeting nanoformulations based on amphiphilic derivatives, ranging from proteins, peptides, polysaccharides to small biomolecules.

2.2.1 Protein-directed active targeting

In the past decades, PEG-based amphiphilic nanomaterials have been modified a range of proteins, including antibodies, antibody fragment, growth factors, transferrin and lactoferrin, to develop active targeting systems.

Antibodies, the large Y-shaped proteins, perhaps stand for the most efficient ligands owing to their high specificity and affinity to the corresponding antigens. They typically consist of basic structural units with two large heavy chains and two light chains. In some cases, a region of antibodies can be applied as targeting ligands, which dramatically reduce the total molecular weight and adverse immune reactions[24]. Thus the monoclonal antibodies and their fragments are widely employed in active targeting schemes[53]. Two receptor tyrosine kinases, Her2 and epidermal growth factor receptor (EGFR) that are overexpressed in tumors, have been extensively studied for cancer treatments. Feng *et al.*[54] developed herceptin-conjugated nanoparticles of poly(lactide)-$_D$-α-tocopheryl polyethylene glycol succinate (PLA-TPGS) and carboxyl group-terminated TPGS (TPGS-COOH) copolymer blend for multimodality treatment for cancer (Figure 2a). In this system, herceptin serves as a targeting ligand to bind with Her2 receptors overexpressed on SK-BR-3 breast cancer cells and enhances nanoparticles internalization and therapeutic efficacy (Figure 2b, c and d). In a similar way, Feng *et al.*[55] also fabricated DTX-loaded PEG-PLGA/PLGA nanoparticles with varying Herceptin surface densities, which demonstrated an obvious targeting effect

to SK-BR-3 cells and the Herceptin density on nanoparticle surface positively affected their *in vitro* performance. Kim *et al.*[56] prepared EGFR antibody conjugated block copolymer micelle based on PEG and poly(ε-caprolactone) (PCL) for active targeting to EGFR overexpressed cancer cells. Results displayed that the presence of anti-EGFR antibody on the DOX-micelle surface increased the uptake of DOX-micelle and the nuclear accumulation of DOX, and subsequently enhanced the DOX-induced cell death. In addition to anti-EGFR antibodies, several other receptor-specific antibodies have been applied for targeted tumor therapies such as DOX-PLGAPEG micelles modified with bivalent fragment HAb18 $F(ab')_2$[57].

Figure 2

Unlike antibody-antigen interactions, Epidermal Growth Factor (EGF) also can act as a targeting ligand against EGFR overexpressed cancer via ligand-receptor interaction. Wagner *et al.*[58] coupled EGF ligand to PEG-PAMAM-PEHA copolymer, and the EGF decorated copolymer showed a 10-folds higher gene transfection efficiency in HuH-7 hepatocellular carcinoma cells as compared to the ligand-free copolymer. Allen *et al.*[59] reported a EGF-conjugated PEG-PCL micelle, which was 13-folds more potent than free EGF against EGFR-overexpressed MDA-MB-468 cells.

Transferrin (Tf) and Lactoferrin (Lf) belong to transferrin family with the primary function of binding and transport of iron[60]. Transferrin receptor (TfR) is expressed at levels up to 100-fold higher on highly proliferative cells (e.g. cancer cells) than those on normal cells[61], whose increased expression is generally correlated with

cancer progression an tumor stage. Pei at al.[62] prepared Tf decorated stealth nanoparticles (Tf-PEG-NP) comprised by PEG-hydroxycamptothecin conjugate (PEG-HCPT) and exploited the possibility of the combination of passively and actively targeting with Tf-PEG-NP. The investigation of pharmacokinetic and biodistribution showed that Tf-PEG-NP exhibited the longest retention time in blood, the highest accumulation in tumor and the most powerful anti-tumor effect with the inhibition rate of 93% against S180 tumor in mice. In addition, TfR was reported to exist on the blood brain barrier (BBB) in different species and involved in Tf transport across the BBB *in vitro* and *in vivo*[63, 64]. Jiang *et al.*[65] developed DOX-loaded Tf-conjugated biodegradable PEG-PCL polymersomes for glioma chemotherapy (Figure 3), which increased both the BBB permeability and intracellular drug delivery to C6 cells. They also linked Lf to PEG-poly(lactide) nanoparticles to construct a biodegradable brain drug delivery system[66].

Figure 3

Though PEG-based amphiphilic nanomaterials conjugated with targeting proteins achieve enhanced accumulation in tumor, they still suffer from many disadvantages including large size to shield effect of PEG layer[67], low stability, expensive and time-consuming produce, and potential immunogenicity.

2.2.2 Peptide-directed active targeting

Compared to proteins, peptides possess several desirable features such as easy manipulation, low cost, good stability, and reduced immune reaction. Furthermore, with the flexibly reactive groups and relatively small sizes, peptides can be precisely

controlled during conjugating process and have little influence on physicochemical properties[68].

Among various (poly)peptides, the tri-peptide Arg-Gly-Asp (RGD) and its derivatives appeared greatly attractive as tumor and vascular targeting ligands, as they are demonstrated to bind to $\alpha_v\beta_3/\alpha_v\beta_5$ inegrin receptor highly expressed on the surface of malignant cells and endothelial cells[69,70]. Kataoka *et al.*[71] fabricated cyclic RGD-conjugated PEG-b-poly($_L$-glutamic acid) micelles (cRGD/m) for targeted delivery of platinum anticancer drugs to glioblastoma (Figure 4a). Intravital confocal laser scanning microscopy (IVCLSM) demonstrated that cRGD/m accumulated quickly and permeate deeply from vessels into tumor parenchyma (Figure 4b and c) when compared to cRAD/m (negative control). Furthermore, the *in vivo* experimental results showed that cRGD/m selectively and rapidly accumulated in tumor (Figure 4d) and produced significant antitumor effects in an orthotopic mouse model of U87MG human glioblastoma. Besides, Gao *et al.*[72] attached cRGDfK to the surface of DOX-loaded PEG-PCL micelles that can selectively deliver drugs to angiogenic tumor endothelial cells. In a following study, a multifunctional micelle of poly(ethylene glycol)-block-poly($_{D,L}$-lactide) with cRGDfK decorated on the surface while DOX and superaramagnetic iron oxide nanoparticles loaded inside the micelle core were developed for cancer targeting and MRI-ultrasensitive drug delivery[73].

Figure 4

In addition to RGD, several other peptides have been employed in targeting tumor treatment based on PEG derived amphiphilic nanomaterials. For instance,

Liang *et al.*[74] exploited a tumor-penetrating peptide, CRGDK, to link to the surface of DOX encapsulated DSPE-PEG2000 micelles (Figure 4e). The CRGDK peptide binds specifically to neuropilin-1, contributing to enhanced internalization of nanoparticles and cytotoxicity of DOX *in vitro* and high accumulation and penetration in tumors *in vivo*. Zhang *et al.*[75] developed octreotide (Oct)-modified paclitaxel-loaded PEG-b-PCL polymeric micelles (Oct-M-PTX) to target somatostatin receptor overexpressed tumors and increase cytotoxicity.

2.2.3 Small molecule-directed targeting

Small molecules as targeting ligands are easily obtained, inexpensive, low cytotoxic, non-immunogenic, and easy to be manipulated and modified. Among several small molecules with bioactivity, vitamins such as folic acid (FA, vitamin B9)[76] and biotin (vitamin B7)[77] have been extensively used to decorate PEG-based amphiphilic nanomaterials for the development of drug delivery systems. FA binds with a high affinity (nanomololar range) to Glycosyl-phosphatidylinositol-linked folate receptor that is overexpressed on many types of tumors, of which the expression levels are 100 to 300 times higher than those observed in normal tissues[78]. Shuai *et al.*[79] constructed a tumor-targeted, pH-responsive and fluorescence-imaging delivery system by conjugating FA to the paclitaxel (PTX) and quantum dot loaded copolymer micelles (PEG-PAsp(DIP)-CA) (Figure 5a). The multifunctional micelle realized low pH-response drug release, effective tumor targeting when the Bel-7402 tumor bearing mice were treated with micelles (Figure 5b), and finally the stop of tumor growth and the extension of animal survival time (Figure 5c). Park *et al.*[80]

conjugated FA and DOX separately at α- and ω-terminal end of a PEG chain to DOX nano-aggregates, which could stabilize hydrophobic DOX and showed a greater extent of intracellular uptake against FA-receptor-positive cancer cells via a FA-receptor-mediated endocytosis mechanism. In a human tumor xenograft nude mouse model, FA-targeted DOX nanoaggregates significantly reduced the tumor volume. Similarly, Schiavon prepared a FA modified PEG-gemcitabine prodrug as a targeted antitumoral delivery system[81].

Figure 5

In terms of biotin, it is a cell growth promoter, which is needed with a greater quantity for tumors than normal tissues because of the rapid proliferation of cancer cells, thus its receptors being overexpressed in tumors. Lee *at el.*[82] fabricated a tumor-targeted drug delivery system by conjugating biotin to PEG-PCL copolymer. The copolymer can self-assemble into micelles to load paclitaxel and showed higher cytotoxicity for cancer cells. Sinko *et al.* synthesized a PEG-camptothecin conjugate which included biotin as a moiety to enhance targeted uptake and increase anti-cancer activity[83].

Other small molecules such as curcumin[84] and selectin[85] have also been used targeting ligands in PEG-based delivery systems. Though small molecules as biologically active ligands are convenient to be modified on nanocarriers, they still suffer from the drawbacks of relatively non-specific interaction[86]. This is mainly due to the bond between non-targeted issues and targeting molecules and the competition of binding between freely small molecules from daily diets and the one modified on

nanocarrier surface.

2.2.4 Other active ligands for tumor targeted therapies

Other active ligands for tumor targeted therapy based on amphiphilic PEG-derivation mainly include aptamer and saccharide. Aptamers are short single-stranded DNA or RNA oligonuleotides that can bind selectively to small or large molecular targets. Chen *et al.*[87] decorated AS1411 (Ap), a DNA aptamer specifically binding to nucleolin highly expressed in angiogenic blood vessels, to paclitaxel loaded PEG-PLGA micelles for anti-glioma delivery system. Dhar *et al.*[88] also fabricated aptamer functionalized Pt (IV) prodrug-PLGA-PEG nanoparticles for targeted delivery of cisplatin.

In tumor tissues, various glycans are often expressed compared to normal tissues, which renders saccharides as an active ligand for targeted tumor therapy. For example, Agrawal *et al.*[89] conjugated hyaluronic acid, a naturally occurring glycosaminoglycan that can target to CD44 overexpressed in tumor, to DOX loaded PEG-PLGA micelles to develop a targeting drug delivery system. Zhong *et al.*[90] reported galactose-directed reduction-sensitive shell-sheddable biodegradable micelles based on PEG-PCL copolymer effectively delivering DOX into targeted cancer cells (Figure 6), showing superb *in vitro* antitumor effects.

Figure 6

2.3 Tumor microenvironment targeted via PEG-based amphiphilic nanomaterials

In addition to the use of targeting ligands, engineering carries to release drugs

only in tumor environments can realize targeted nanomedicine[91,92]. As mentioned above, tumor environments possess lowered intercellular/intracellular pH, higher redox potential and increased level of certain enzymes[93,94]. Thus, 'smart' nanocarriers based on amphiphilic PEG derivatives, which response to the tumor microenvironment and release drug specifically in tumor with the modulation of the microenvironment, have been developed extensively. Min et al.[95] fabricated a pH-responsive micelles by copolymerizing methyl ether PEG (MPEG) and pH-biodegradable poly(β-amino ester) (PAE). The amphiphilic MPEG-PAE showed a pH-dependent micelliaztion/demicellization transition in the acidic environment of tumor. Thus, camptothecin encapsulated micelles could release drug in a targeting manner and exhibited higher therapeutic efficiency when compared to free drug and non-responsive micelles. Koo et al.[96] reported a redox-responsive micelle of PEG-*b*-poly(L-lysine)-*b*-poly(L-phenylalanine) (PEG-PLys-PPhe), in which the PLys middle shell provided disulfide cross-links. The docetaxel-loaded micelle can release drug at an intracellular level, thus meeting the requirement of targeting nanomedicine with low toxicity.

3. Use PEG-based amphiphilic nanostructures to overcome chemoresistance

As mentioned above, cancer is a group of diseases involving abnormal cell growth, which is the major disease of morbidity and mortality in worldwide. Nowadays, different anticancer strategies including surgery, radiotherapy and chemotherapy etc. have made a big difference in improving the survival rate of cancer patients. Among those approaches, chemotherapy is one of the beneficial therapeutic

options for the cancer treatment. However, when chemotherapy is used during cancer treatment, clinician are often are confronted with a big challenge, which is so called multidrug resistance (MDR). Existing research shows that the development of MDR is one of the major factors leading to the failure of many traditional chemotherapeutic agents. Moreover, MDR plays a critical role in promoting tumor progression, metastasis, infiltration and thus makes the cancer as an unbeatable disease[97-100]. In general, MDR is a term to describe the broad spectrum resistance to chemotherapy in human cancer, which often can be defined as a phenomenon of resilience against large number of chemically, structurally or/and functionally unrelated drugs[101]. There are two main causes for the MDR: physiological level and cellular level. Physiological level describes about the changes happening outside the each individual cells such as low extracellular, hypoxia region, acid micro environment and formation of irregular tumor vasculature. In cellar level the over-expression of efflux transporters, modification apoptotic machineries, and altered molecular targets are also responsible for multidrug resistance[102] (Figure 7).

Figure 7

Recently, multifunctional and multiplex nanoparticles are now being actively investigated and they are on the horizon as the next generation of nanomedicine for the cancer treatment including overcoming the MDR. Among clinically advanced nano-delivery systems, PEG-based amphiphilic nanoparticles constitute a broad variety of self-assembled drug delivery systems may provide an effective way for the chemotherapy[103,104]. Followed by these, we will mainly state how to use PEG-based

amphiphilic nanostructures to overcome chemoresistance.

3.1 Increase the drugs concentration in tumor tissue and cells to overcome MDR

Considering the various mechanisms which attribute to the MDR, the minimal concentration of drug in tumor tissues and cells is one of the main causes of the multidrug resistance[105-107]. In general, the microenvironment of the tumor region is very different from the normal tissues. It mainly shows that as cancer cells grow aggressively there will be deficient in oxygen concentration in the blood supply, forming a hypoxia condition. To offset this situation, the tumor cells outgrow new blood vessels for the nutrient supplement. The formation of new vessels in tumor region is poorly formed with disorganized vascular cells and can't deliver an adequate blood supply to all areas rather than a tumor[106, 107-109]. Besides that, the dense extracellular matrix and absence of lymphatic drainage system of solid tumor could synergistically induce a reduced transcapillary pressure gradient and an elevated interstitial fluid pressure[27, 109, 110]. In fact in the clinical treatment of cancer, most of chemotherapeutics are delivered to the tumor site by circulatory system thus, alteration in tumor micro-environment will restrict the chemotherapeutics in the perivascular areas of the tumor tissue and result in a low concentration of drugs in the tumor cells. Hence, this is considered to be the primary reasons to induce the MDR. Recently, applying the nanomaterials for drug delivery has provided an alternative route for tumor treatment. Among of the various nanomaterials, PEG-based amphiphilic nanostructures occupied the leading position. Firstly, these special nanostructures can co-delivery hydrophilic and hydrophobic drug simultaneously.

Furthermore, the hydrophilic corona formed by PEG provides a stabilizing interface between the aqueous environment and the hydrophobic inner core, which help drugs to continue to maintain longer blood circulation time and bypass the rapid RES clearance [111]. Moreover, the PEGylation also can enhance the EPR and as a result improving the therapeutic efficacy of the enveloped drugs. For instance, one mixed nano-micelles was developed by mPEG-PLA and Pluronic copolymers for enhancing the drug's bioavailability and ability to overcome MDR. *In vivo* pharmacokinetics studies showed that this system could induce a high plasma concentration of Taxotere and provided significantly higher area under the curve (AUC) compared to the commercial formulation result in a higher tumor accumulation of drugs as well as the efficacy of cancer treatment[112].

In recent years, more and more studies have shown that the over-expression of pumps of the ATP-binding cassette superfamily (ABCs) (such as P-glycoprotein (P-gp), multidrug resistance-associated proteins (MRP), breast cancer resistance protein (BCRP) etc.) presented within the cancer cell membrane is associate with MDR[113-115]. In many cancer types, nearly 40–50% of the patients diagnosed with cancer have ABCs overexpression in the malignant tissue [116, 117]. These proteins can recognize and remove the substrate that is partitioned into the lipid bilayer or the near-bilayer cytoplasm from the intracellular compartment by efflux, which leading to dramatically reduced drug uptake and drugs efflux result in reducing intracellular drug concentration and thus limit the cytotoxic effects of drugs in tumors[118]. To overcome the ABCs based MDR, usage of nanocarrier to deliver drugs has made an enormous

contribution. Nanocarriers are taken up by non-specific endocytosis to cross the cellular membrane in an invisible form to transporter pump and prevent the drugs efflux out of the cells[105,119,120]. The carriers are internalized by the endosome and burst release the loaded drugs. In this way the released drugs were near to the nuclear region or deep inside the cytoplasm and thus, they could escape the pump out by the transporter protein, it results in a higher intracellular accumulation[27,121]. Another strategy to circumvent ABCs protein based MDR in cancer chemotherapy is utilized ABCs protein blocking agent (MDR modulators or reversals) to inhibit the drug efflux from the cells. A broad range of compounds (such as quinidine, cyclosporineA, verapamil, PSC833, VX-710, tariquidar, elacridar etc.) that interact with multidrug resistance protein and block drug efflux has been used to reverse the MDR phenotype[122-128]. However, often associated with unacceptable toxicity of those compounds and unpredictable pharmacokinetics interactions with the anticancer drug or other transport proteins limited their utility[129,130]. Some studies suggest that deliver multidrug resistance transporter modulator and anticancer drug together is a very promising approach to overcome tumor drug resistance. In one such study, a PEG-PE based micelles were developed and co-loaded with elacridar and paclitaxel, which demonstrated the higher cytotoxicity than free PTX in resistance cell line and achieved a promising option to overcome MDR[128].

Recently, various amphiphilic copolymers, such as PEG-PCL, PEG-PE, TPGS and pluronics have been identified to be the most promising ABCs transporter inhibitors due to less concern on safety issues than the small molecular

inhibitors[131-135]. Xiao *et al.* have constructed a drug delivery system based on PEG-PLA and the drug delivery mechanism was studied in depth. They concluded that the PEG-PLA micelles could affect the membrane microenvironment and inhibit the P-gp function and P-gp ATPase activity without effect on the protein expression to achieve the MDR reversal[136]. In a similar study, Wang et al. make a systematic and comprehensive study of the uptake mechanism of amphiphilic nanostructure (PEG-PE) uptake into cells. They found that this system could penetrate through the cell membrane and internalized by non-specific endocytosis and get burst release into the cytosol. Further the released agents are accelerated to enter cells due to the increased membrane fluidity caused by PEG–PE insertion without affecting cellular ATP and viability to increase their cellular accumulation to overcome MDR[137].

3.2 Modulation of apoptotic threshold to overcome MDR

It is well-known, that the increased expression of anti-apoptotic factors and/or decreased expression of pro-apoptotic factors are another characteristics reason for the development of MDR in cancer cells. The consequence is an enhanced cell survival and a higher threshold for the induction of apoptosis when exposed to chemotherapeutic agents[138]. Numerous approach attempts to utilize this specific characteristic of MDR cancer via co-administration of pro-apoptotic agents or anti-apoptotic inhibitors with chemotherapeutic drugs. The rationale of this strategy is to decrease the apoptotic threshold of resistant cells to render chemotherapeutic agents more effective during the clinical treatment of MDR cancer.

The ability of small interfering RNA to disrupt the cellular signal pathway can be utilized for re-sensitizing the tumor cells apoptotic procedure which have acquired resistance to chemotherapeutic agents via knock-down the anti-apoptotic protein expression[139,140]. For instance, survivin is an inhibitor of apoptosis that has been shown to be over-expressed in the majority cancer cells especially in the MDR cancer cells, many strategies are devoted to knocking-down or silencing the survivin expression[141]. V.P. Torchulin's group has developed a multifunctional micelle platform constructed by a copolymer (PEG-pp-PEI-PE) via self-assembly for tumor-targeted siRNA and drug co-delivery. This platform was used to co-deliver anti-survivin siRNA and chemotherapy agent DOX, which can effectively down-regulation of the survivin in PTX-resistant NSCLC cells and emerge the synergistic antitumor activity of DOX[142]. Bcl-2 is another anti-apoptotic protein which is also over-expressed in the MDR cells and decreased the sensitivity of cancer cells to chemotherapeutic drugs[143]. In the same way with V.P. Torchulin, a novel star-like nanostructure, composed of polypeptide poly(L -glutamic acid c-hydrazide) (PGAH) core, a cationic -poly(N,N-dimethylamino-propyl methacrylamide) (PDMAPMA) inner shell and a PEG outer shell had been designed. The PGAH core can conjugate DOX via hydrazine linkages and the inner shell of PDMAPMA allows the complexation of siRNA against Bcl-2 through electrostatic interaction, resulting in a "two-in-one" micelleplex nanocarrier. The cells studies shows that this micelleplex nanocarrier can effectively deliver Bcl-2 siRNA and DOX into the same cancer cells and induce high toxicity in a synergistic fashion[144]. In a latest studies by He *et al.* show that they have

structured a new structure based on cisplatin prodrug and self-assembled nanoscale coordination polymers. More interesting is that this nanostructure can adsorption of pooled siRNAs targeting three different MDR genes including survivin, Bcl-2 and P-gp synchronously. The cells studies results demonstrated that this new structure could mediate effective gene silencing in cisplatin-resistance cancer cells to re-sensitize the cells to cisplatin treatment and overcome the MDR[145].

Several evidences have indicated that chemosensitizer also can modulate cells apoptosis mechanism and decrease the apoptotic threshold in MDR cells. Thus, co-administration of chemotherapeutic drugs and chemosensitizer provide a new prospect to overcome MDR in cancer. Take curcumin (CUR) as an example, which is a polyphenol known as diferuloylmethane extracted from curcuma longa. Previous reports show that CUR have multiple pharmacological effects including anti-bacterial, antiviral, antioxidant and hypolipodemic activities[146,147]. Recent studies revealed that CUR has an anti-tumor activity by inhibition of angiogenesis, induction of apoptosis and reduction of invasion and metastasis[147-150]. Moreover, CUR also can act as a chemosensitizer that augments the cytotoxic effect of other chemotherapeutic drugs such as PTX, DOX and cisplatin[149-152]. Although modulation of apoptotic threshold seems to be a successful approach to overcome MDR, still more studies are needed to discover the benefits of using this approach in multifunctional formulation.

3.3 Combination of different drugs in one delivery system to overcome MDR

As outlined in the previous section, MDR is often defined by resistance to two or more chemically unrelated drugs. Thereby, the use of single chemotherapeutic drugs

has shown some limitations in the treatment of cancer. In order to improve the treatment efficacy, combination chemotherapy can be applied against many cancer types. Its universal accepted concept that if there is a proper drug combination, the treatment can promote synergistic actions, improve the ability of antitumor activity and overcome the cancer drug resistance[153]. Inspired by the excellent therapeutic efficacy from the sequential combinatorial chemotherapy treatment used in clinical treatment, treating cancer by the delivery two or more chemotherapy agents in a single nanocarrier to form a co-delivery system is considered to be an effective and reliable method due to their synergistic anticancer effect[154,155]. The reason for using this design is that single co-delivery systems loaded with different anti-cancer drugs with different physiochemical properties can deliver all the loaded chemotherapeutic agents to the same cells have been proven to minimizing the amount of drug to achieve the synergistic therapeutic effect in cancer treatment[156,157]. The success of these combinations is thought to hinge largely on the biological complexity and redundancy of cancer cells. Through administration of multiple agents, each with its own biochemical target and accompanying toxicities, thus cancer cells are subjected to a multipurpose attack which is much more difficult to tolerate[158]. Recently, various nanostructures have been designed for co-delivery of different guests, including liposomes[109, 159], inorganic nanoparticles[159-161], and micelles[149,162,163]. Due to the unique physicochemical property of nanostructures with a hydrophobic core and a hydrophilic shell, make them as a good candidate for the delivery of different anti-cancer drug, gene or protein simultaneously.

Most drug combinations were discovered empirically by the clinicians'. Therefore, intracellular effects of certain drug classes and their systemic toxicity are maintained by them. Hence, each drug within a combination is chosen upon avoiding overlapping toxicities with the other agents, and allowing dosing to the highest tolerable level of each agent[157]. In one such study, Wang *et al.* have created a core-shell nanostructure based on amphiphilic copolymer mPEG-PLA to deliver the hydrophilic doxorubicin and hydrophobic paclitaxel at the same time. This nanostructure with a small size and a better polydispersity offered advantages over other nanocarriers, as they are easy to fabricate, biocompatible and showed high loading efficacy. Studies on the drug release behavior and cellular uptake of this co-delivery system demonstrated that both the drugs were could uptake up by the cells and released simultaneously. The cell experiment results showed that this system is more efficient and had a synergistic effect than the administration of either DOX or TAX individually at the same concentrations[162]. In a similar study, a drug delivery system based on PEG-PLGA was designed to co-delivery DOX and TAX. This system was conjugated with a targeting ligand (folate) to promote the targeting delivery and with a cell penetrate peptide to enhance the uptake. The results also show that the dual encapsulation system has a lower IC50 than a single drug loaded micelles and would be a promising technology for cancer treatment[163].

Even though use of nanotechnology to achieve the combination treatment of cancer shows a huge advantage, but formulation of multiple drugs within a carrier also presents significant challenges. On the one hand, pharmaceutical development

activities must also demonstrate safety and biocompatibility of novel carrier compositions. On the other hand, after the co-delivery systems are formed, the clinician could not alter the precise ratio between the different drugs. This feature limits potential dose alteration of either agent on a case-by-case basis. It remains to be determined whether this limitation will hinder the use and acceptance of multidrug carrier systems in the clinical setting.

3.4 Stimuli response nanostructure to overcome drug resistance

Using nanotechnology, especially nano drug carrier can enhance the drug targeting to the tumor region and to achieve higher cancer cell uptake. Every coin has two sides, using nanocarrier to deliver drug is no exception. If the delivery systems are designed with a weaker structure, it will degrade during the treatment procedure and couldn't achieve longer circulating time in the body. But, when the systems are designed as a robust system, the insufficient intracellular drug release can be a rete-limiting steps in reaching the optimum therapeutic promptly[164]. In order to address this obstacle, the drug delivery systems with a trigged release behavior were developed which enable the carriers to release drugs in response to specific stimuli. Due to the specific micro environment of the tumor, some of the unique factors such as low pH, hypoxia, and rich in detoxicating enzyme (such as GSH,GST) can be used as a trigger to overcome MDR.

As it is well known to us, the measured tumor extracellular pH value of most solid tumors is lower than normal blood and tissue due to the anaerobic respiration and subsequent glycolysis[165,166], and accumulated evidences indicated that cancer

cells contain more of lysosomes with a higher acid environment[167, 168]. All of those characteristics can be exploited to specifically deliver drugs to tumor cells by pH-responsive drug delivery systems[111,169-171]. In such a study, Wu and coworkers have developed a mixed micelles based on DSPE-PEG2000, DSPE-PEG3400 and a pH-rensitive polymer PHIS-PEG2000. This mixed micelles showed pH-dependent drug release property with much faster release at pH around 5.5 than micelles without PHIS-PEG2000. Their results indicated that this systems could releasing anticancer drug paclitaxel quickly and resulting in the improved anti-cancer efficacy[172]. In another study, Liu et al reported a liposomal cocktail constructed by doping pH-responsive molecule (malachite green carbinol base) within a liposome nanocarrier for co-delivery of DOX and verapamil to suppress drug resistance breast cancer. When this system are exposed to a weak acid condition the neutral malachite green carbinol base was transformed to carbocationic form and dynamic disordering of the liposome result in fast release of DOX. Combination of the relative high intracellular drug concentration and P-gp inhibitor, this system reveal a high anti-cancer and multi-drug resistance reversal effect both *in vivo* and *in vitro*[173]. There have some other internal simulation responsive such as reactive oxygen species triggered[174], glutathione-responsive[175] and redox-sensitivity[176,177] nanocarriers which have been well documented, but not explained here.

In the last few years, amphiphilic nanocarrier which are responsive to specific external stimuli such as light, temperature[178,179], near infrared reflection (NIR)[180,181] and ultrasound also have been designed and developed. Most of them have achieved a

good effect on killing tumor cells and overcoming the MDR (Figure 8). Using the stimuli responsive nanocarrier will be the new trend of future development of drug delivery systems [182-184].

Figure 8

3.5 Hybrid nanostructure to overcome the MDR

Though amphiphilic macromolecule as a nano-delivery system have made a big difference in the drug delivery field, but there still have some drawbacks in the context of the current use, such as low bioavailability and *in vivo* stability, premature or slow drug release etc[185-187].

Recently, combination of amphiphilic molecules with inorganic nanomaterials to develop a hybrid nanostructure has been paid a great attention. This hybrid nanostructure can take the benefits from each of the component and achieved a multifunctional drug delivery system. Recently, Zhong *et al.* use gold nanorod and a copolymer PEG-PLA to form an organic-inorganic hybrid nanodelivery. The gold nanorod coated by micelles can get a robust system to enhance the stability in the blood circulation. Besides that, when this system was exposed under the NIR radiation, the photothermally effect induced the phase transition of PCL regime and resulting in rapid drug release. Both the *in vitro* and *in vivo* studies indicated that usage of photo-triggered nanostructure can have an effective reversal of MDR[188]. In the further studies, they added a targeting moiety (cRGD) on the surface of gold nanorod coated by mixed micelles. The results indicating that the innovative delivery system can overcome the MDR via enhancing the drug tumor penetration[181].Due to

the unique and different physicochemical properties, the hybrid nanostructure were endowed the ability of combining many function in one system. In such studies, TPGS was used as a surface modifier to functionalize upconversion nanoparticles NaYF4:Er. This hybrid nanodelivery showed that it can decrease the P-gp expression and facilitate the intracellular drug accumulation, thus achieving MDR reversal. Take the advantages of the upconversion nanoparticles, this system could serve as a dual-modal probe for upconverion luminescence imaging and X-ray computed tomography imaging. Making them promising for image-guided cancer therapy[189].

In addition to organic-inorganic hybrid nanostructure, different amphiphilic copolymer also can create a hybrid nano delivery system. For example, a hybrid micelles were formed by pluronic copolymer conjugated DOX prodrug and cypate-conjugated poly(ethylene glycol)-block-poly (diisopropanolamino ethyl methacrylate). These hybrid micelles were designed to combine the pH- and NIR light-responsive into one single nanocomposite. At physiological condition it will maintain stable structure to prolong the blood circulation time and achiever the passive tumor targeting. But at the tumor acid region the micelles are quickly dissociation and release DOX prodrug. In combination with localized NIR laser radiation, the hybrid micelles may cause significant tumor penetration and cytosolic release of DOX payload leads to a significantly inhibition of the growth of DOX-resistant breast cancer in a tumor bearing mouse model[180].

4. Summary and future perspective

Advancement in the field of nanotechnology has rendered the great opportunity for the design of PEG-based amphiphilic nanoparticles to overcome the multidrug resistance mechanism and resensitizing the anticancer drug to the cancer cells to achieve the enhanced chemotherapeutic efficacy in cancer treatment. However, the current nanomaterial provides the information only about the macroscopic phenomenon of the tumor, but they cannot supply microscopic clues regarding the tumor tissues at the cellular level. In-order to have an accurate, efficient and low-cost therapeutic treatment, we are expecting more advanced therapeutic technology has to be continue to grow over the next upcoming decades. Currently, many multifunctional nano-platforms are still at initial stage of development and much more research studies has to be carried out before they enter into the clinical trials. Most importantly, a number of safety issues and therapeutic efficacy of the nanomaterials should also be addressed. Additionally, reliable and reproducible synthetic protocols are necessary for scale-up manufacturing.

Acknowledgement

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Figure captions

Figure 1 (a) Molecular structures of DSPE-PEG_{2000} and NPAPF and scheme for preparation of M-NPAPF-Au. (b) Viability of CT26, HepG2, L02 cells incubated with different concentrations of M-NPAPF-Au for 24 h. (c) Non-invasive fluorescence image of CT26 tumor-bearing mice and their dissected tumors and organs 6, 12 and 24 h after intravenous injection. The white arrows indicate tumor sites and the red circles indicate dissected tumors. 1-Liver, 2-Spleen, 3-Kidney, 4-Heart, 5-Lung, 6-Tumor, 7-Brain, 8-Intestine. (d) Semi-quantitative biodistribution of M-NPAPF-Au in mice determined by the averaged fluorescence intensity of each tumor and organ. Error bars are based on three mice per group. (e) Blood circulation curved of free NPAPF (black) and M-NPAPF-Au (red) determined by measuring the fluorescence intensity of NPAPF in blood at different time points post-injection. (f) CT images of CT26 tumor-bearing mice before and after intravenous injection M-NPAPF-Au (6, 12 and 24 h). The white circles indicate tumor regions, the upper row shows stereo images and the bottom row shows sectional images. (g) Biodistribution of Au by ICP-MS in tumor tissues and major organs. Reprinted from Liang et al.[51] with permission of Elsevier.

Figure 2 (a) Schematic illustration of the structure of multimodality treatment nanoparticles (MMNPs). (b) and (c) CLSM images of MMNPs without Herceptin and MMNPs for 2 h incubation in SK-BR-3 cells respectively. (d) SK-BR-3 cell viability of different treatment methods at various concentrations of nanoparticles after 24 h

incubation and recovered in fresh medium for 12 h. Reprinted from Feng et al.[54] with permission of Elsevier.

Figure 3 The scheme of DOX-loaded Tf-conjugated biodegradable PEG-PCL polymersomes for glioma chemotherapy. Reprinted from Jiang et al.[65] with permission of American Chemical Society.

Figure 4 (a) Scheme of cRGD/m for for targeted delivery of platinum anticancer drugs to glioblastoma. IVCLSM observations of 20% cRAD/m (green) and 20% cRGD/m (red) in blood vessels and tumors at (b) 5 min and (c) 5 h after intravenous coadministration. Their colocalization is shown in yellow. Scale bars represent 100 μm in all images. (d) Comparison of tumor growth inhibition with 20% cRGD/m and 20% cRAD/m. Five days after tumor cell transplantation, the mice were injected intravenously with micelles. Data represent mean ± SEM (n=12). Two-way ANOVA was used to analyze differences in the tumor mass volume, and $^{**}p < 0.001$ and $^{*}p < 0.01$ were considered significant. Reprinted from Kataoka et al.[71] with permission of American Chemical Society. (e) Scheme of CRGDK modified micelles for drug delivery of cancer therapy in vitro and in vivo. Reprinted from Liang et al.[74] with permission of American Chemical Society.

Figure 5 (a) Illustrative preparation of FA-targeted and PTX and QD loaded micelle and pH-tunable drug release. (b) In vivo QD fluorescent images showing FA-enhanced tumor targeting of the QD-loaded targeted micelles after tail vein injection into nude mice bearing Bel-7402 subcutaneous xenograft. (c) Tumor growth

inhibition in nude mice (n=20) bearing Bel-7402 tumor after tail vein injection of different formulation. Reprinted from Shuai et al.[79] with permission of John Wiley and Sons.

Figure 6 Illustration of ligand-directed, reduction-sensitive, shell-sheddable, biodegradable micelles based on PEG-SS-PCL and Gal-PEG-PCL copolymers actively delivering DOX into the nuclei of asialoglycoprotein receptor-overexpressing hepatocellular carcinoma cells. Reprinted from Zhong et al.[90] with permission of American Chemical Society.

Figure 7 (a) The schematic drawing shows solid tumor organization with the characteristic acidic front, vascularized circumference, hypoxic region and necrotic core. (b) Representation of different mechanisms involved in MDR.

Figure 8 Schematic illustration of stimuli-response drug delivery systems based on amphiphilic nanostructure. (a) pH responsive, (b) Photo irradiation-responsive, (c) Redox-responsive, (d) Rox-responsive. Reprinted from Wang et al.[173] with permission of Elsevier, Li et al.[180] with permission of John Wiley and Sons, Zhang et al.[177] with permission of American Chemical Society, and Zhang et al.[174] with permission of Elsevier.

Table

Table 1. Advantages and disadvantages of different types of cancer treatment.

Type of cancer treatment	Advantages	Disadvantages
Surgery	Is used to cure many types of cancer, especially those that have not spread to other tissues.	In some cases surgery might be the cause of cancer spread; the possibility of damage nearby healthy tissues; postoperative side effects (sometimes long-term side effects) such as pain, bleeding, infections, blood clots, slow recovery etc.
Chemotherapy	Can destroy cancer cells anywhere in the body including metastases; more than 100 anticancer drugs are used alone or in combination to achieve better treatment efficiency; various pathways of drug administration; the ability to receive treatment remotely.	Damage healthy tissues and may cause side effects such as nausea, vomiting, hair loss, fatigue etc. Some drugs can damage cells in the lungs, heart, kidneys, bladder, nervous system and might be a reason of severe side effects. Chemoresistance.
Radiation therapy	Local treatment with a minimum harm of nearby healthy tissue even when using radioactive substances.	Side effects caused by damaging of normal cells: fatigue, skin problems, hair loss, changes in blood count, risk of another cancer.
Immunotherapy	Triggers own immune system or provides with what it needs to kill tumor cells throughout the whole body.	Can cause a variety of side effects the most common of which are fatigue, nausea, diarrhea, mouth sores, low or high blood pressure, risk of infection. Even sometimes causes severe or fatal allergic conditions to the patient.
Hormone therapy	Selective site of action; prevention of early cancers.	Useful only for limited number of cancer types. Blocks ability to produce hormones or alters the hormones behavior thereby, causing undesirable side effects.
Targeted therapy	Drugs target the specific changes in cancer cells thereby less affect the normal tissues.	Some drugs interact with the substrates which are mostly located on neoplastic tissues. Sometimes they also found in healthy tissues. Thereby, affecting the healthy cells may cause side effects. Cancer cells may become resistant to targeted drugs.

Figures

Figure 1

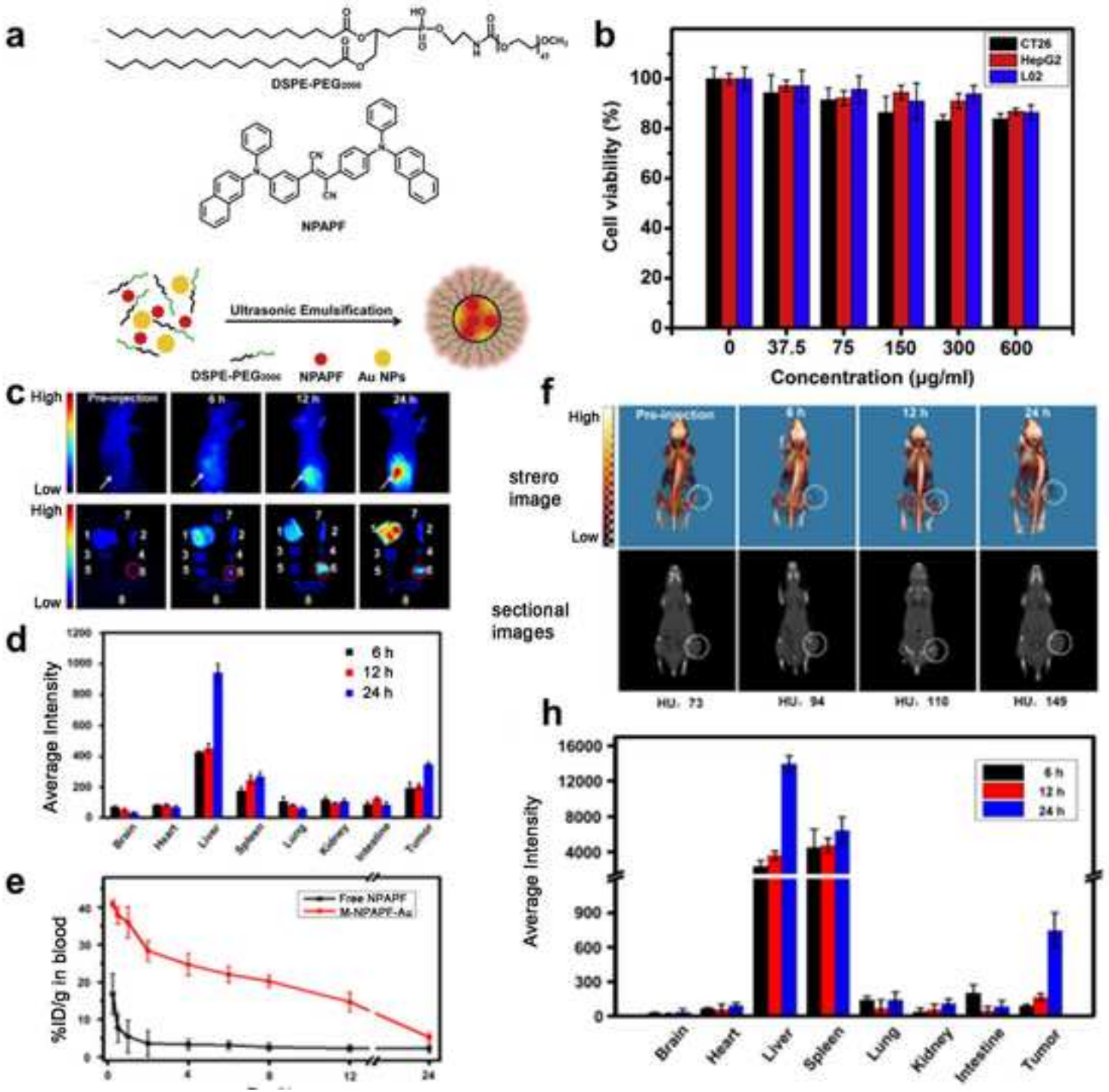


Figure 2

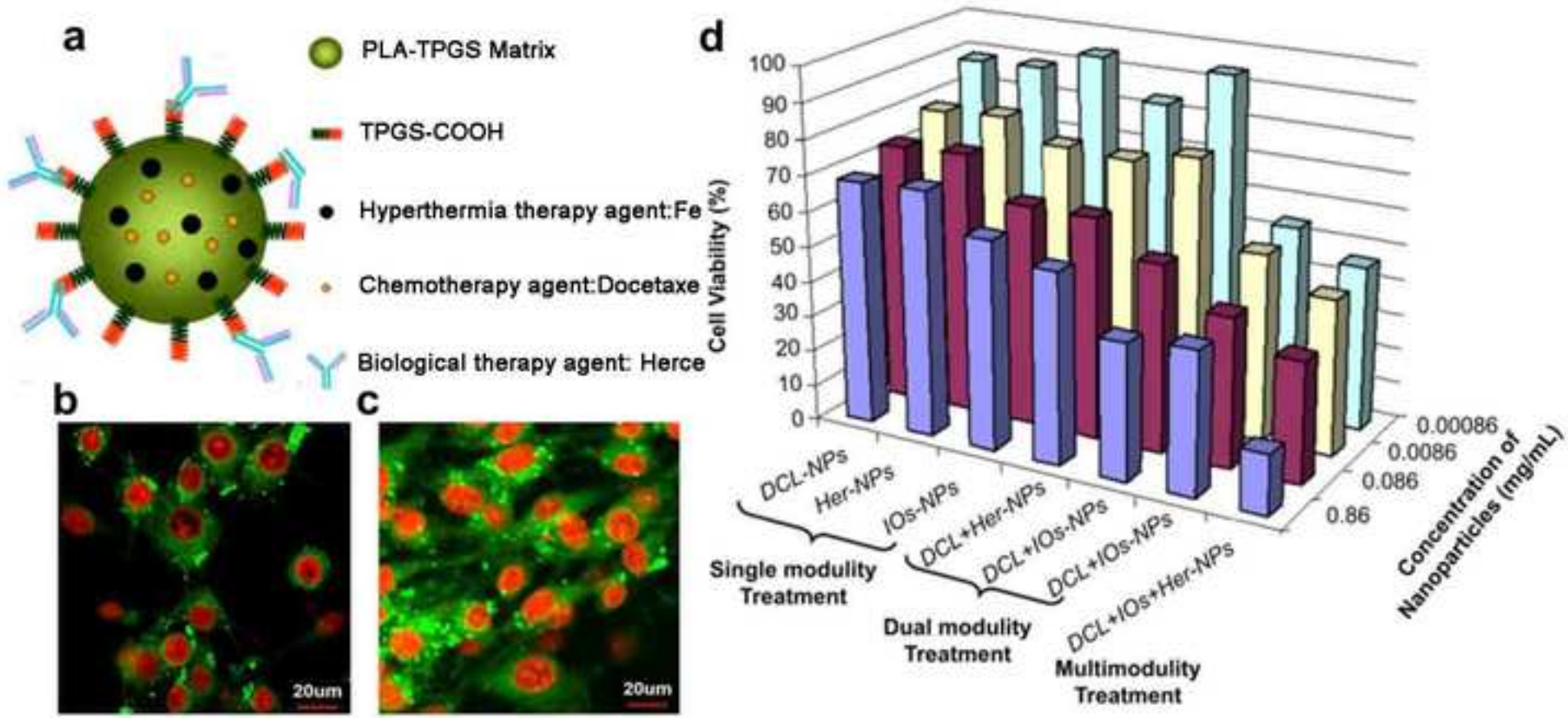

a
PLA-TPGS Matrix
TPGS-COOH
Hyperthermia therapy agent:Fe
Chemotherapy agent:Docetaxe
Biological therapy agent: Herce
b
20um
c
20um
d
Cell Viability (%)
100
90
80
70
60
50
40
30
20
10
0
DCL-NPs
Her-NPs
IOs-NPs
DCL+Her-NPs
DCL+IOs-NPs
DCL+IOs-NPs
DCL+IOs+Her-NPs
Single modality Treatment
Dual modality Treatment
Multimodality Treatment
0.00086
0.0086
0.086
0.86
Concentration of Nanoparticles (mg/mL)

Figure 3

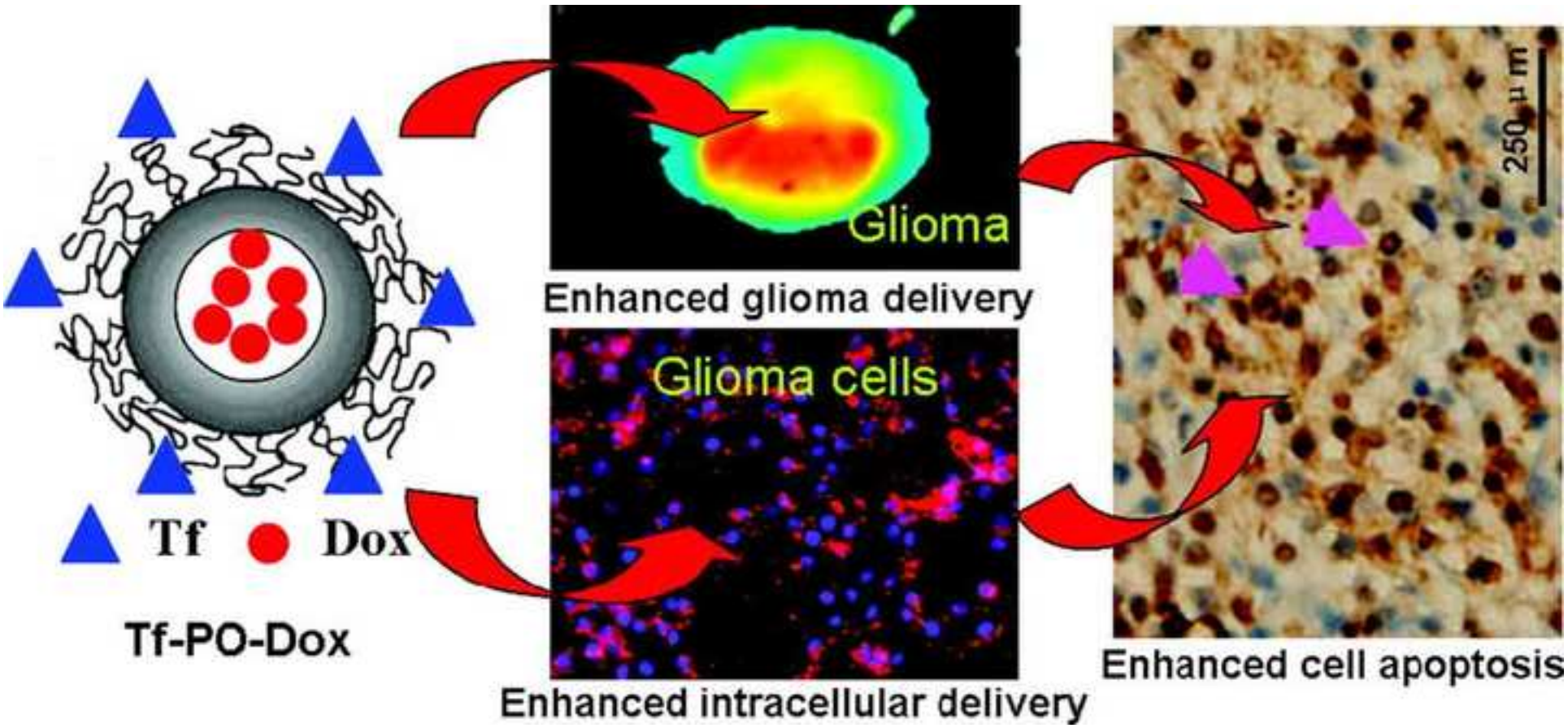

Tf
Dox
Tf-PO-Dox
Glioma
Enhanced glioma delivery
Glioma cells
Enhanced intracellular delivery
250 μm
Enhanced cell apoptosis

Figure 4

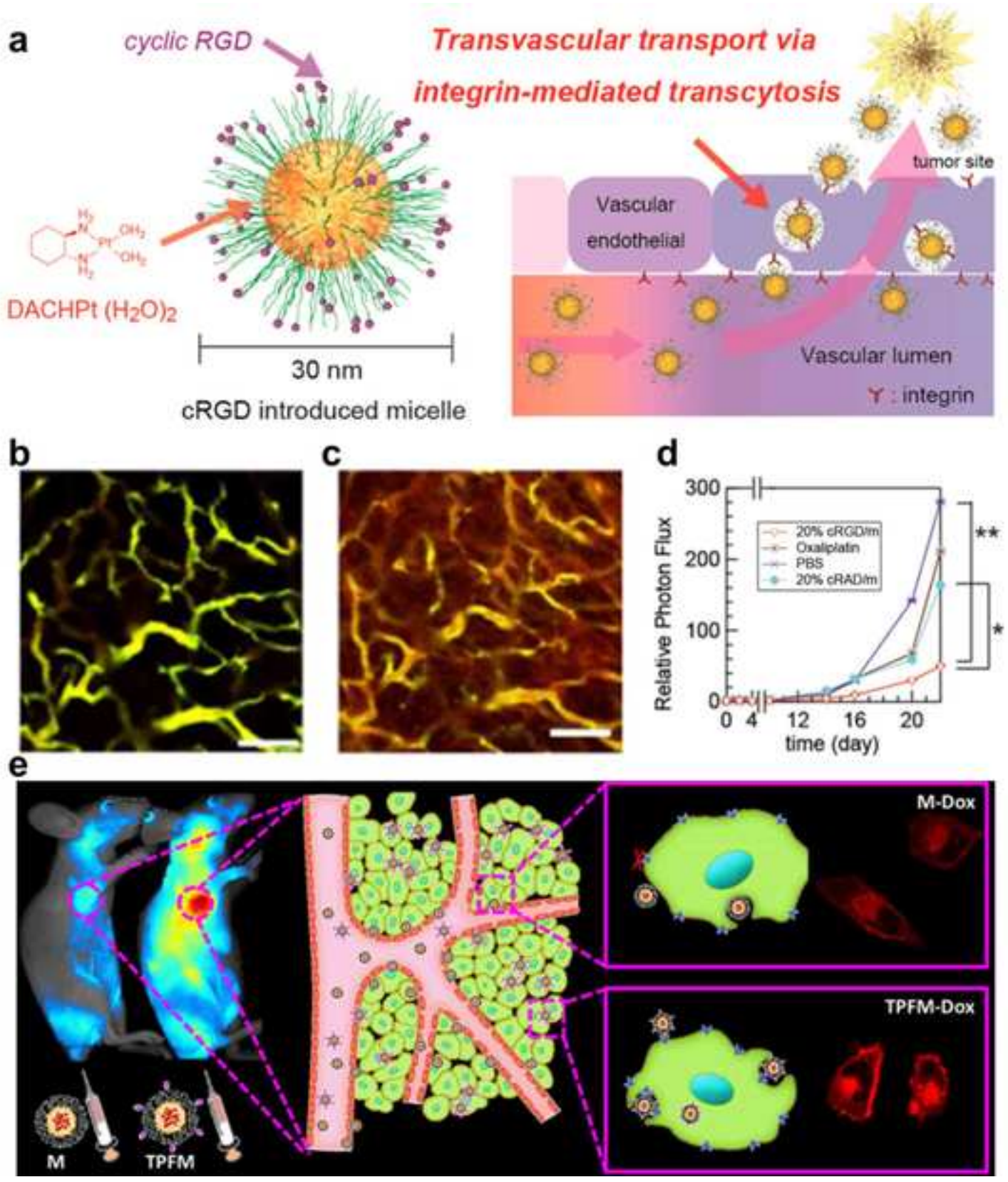

a
cyclic RGD
Transvascular transport via
integrin-mediated transcytosis
tumor site
Vascular
endothelial
Vascular lumen
: integrin
DACHPt (H2O)2
30 nm
cRGD introduced micelle
b
c
d
Relative Photon Flux
300
200
100
0
0 4 12 16 20
time (day)
20% cRGD/m
Oxaliplatin
PBS
20% cRAD/m
**
*
e
M-Dox
TPFM-Dox
M
TPFM

Figure 5

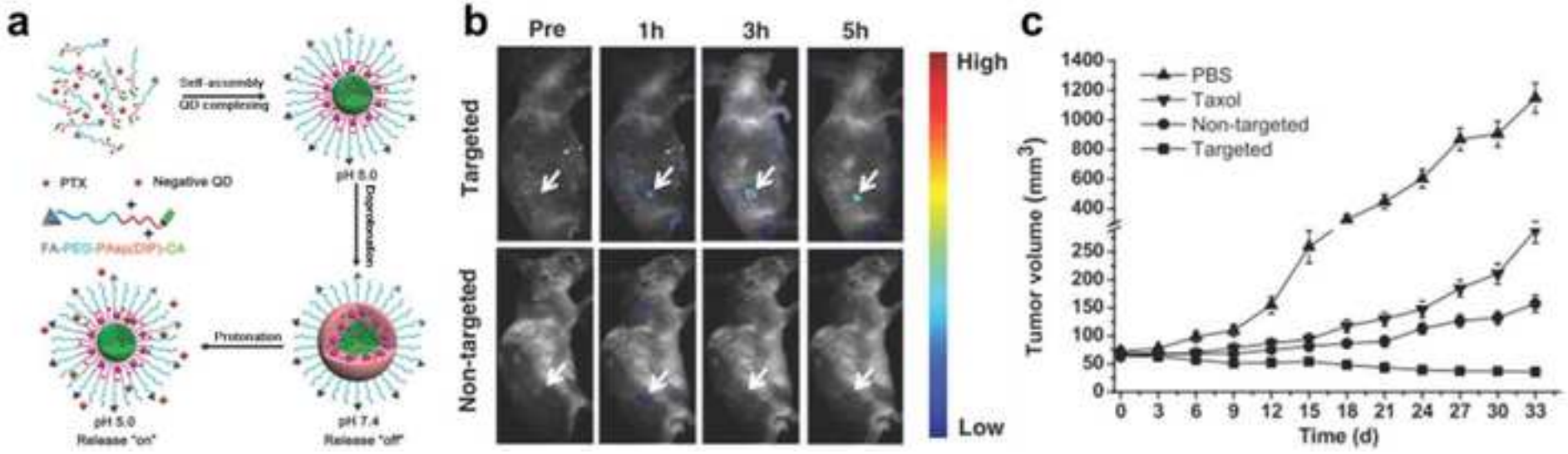

a
Self-assembly
QD complexing
PTX
Negative QD
FA-PEG-PAsp(DIP)-CA
pH 5.0
Deprotonation
pH 5.0
Release "on"
Protonation
pH 7.4
Release "off"
b
Pre
1h
3h
5h
Targeted
Non-targeted
High
Low
c
PBS
Taxol
Non-targeted
Targeted
Tumor volume (mm3)
Time (d)
0
50
100
150
200
250
400
600
800
1000
1200
1400
0
3
6
9
12
15
18
21
24
27
30
33

Figure 6

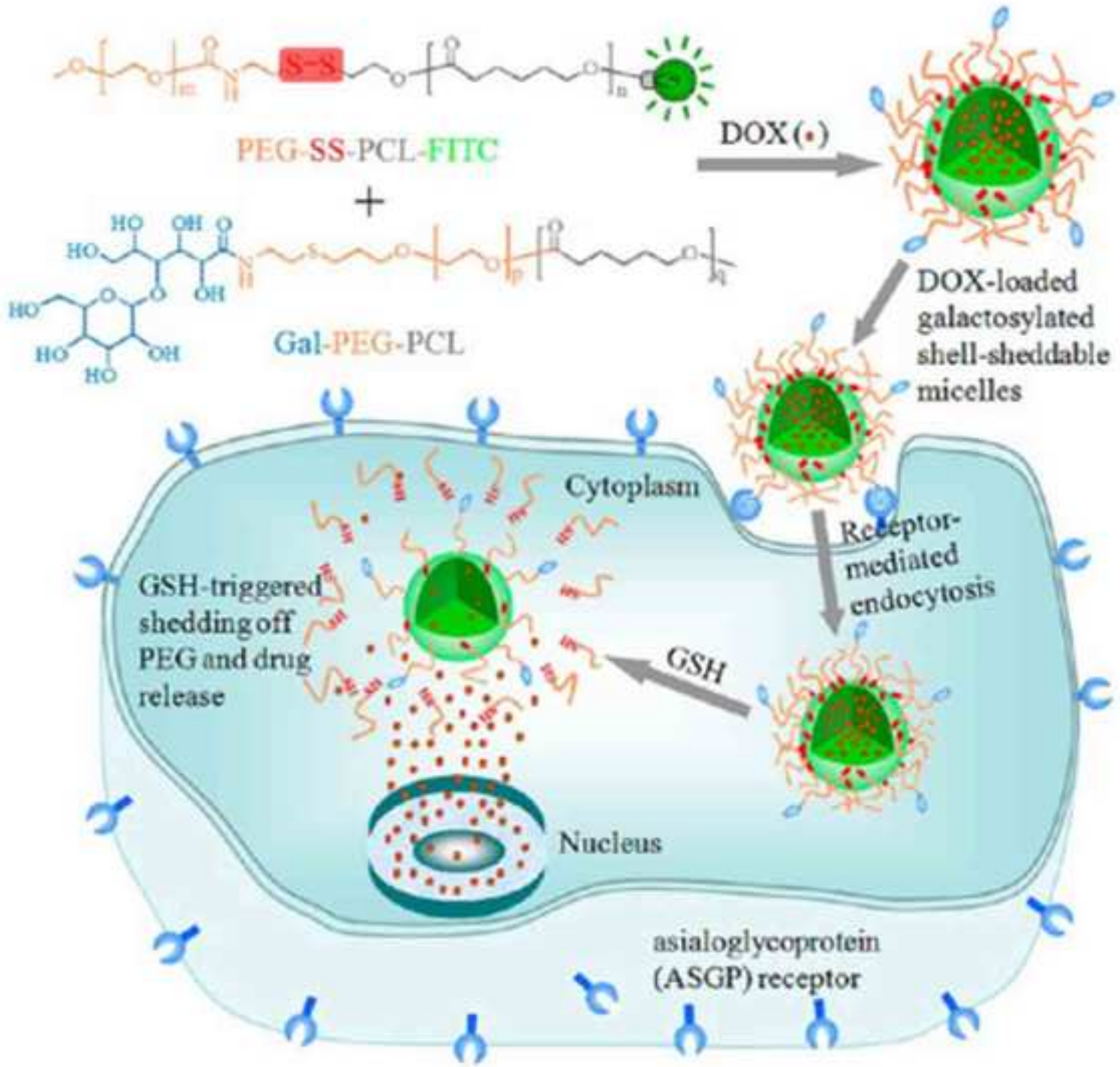

S-S
PEG-SS-PCL-FITC
+
Gal-PEG-PCL
DOX(•)
DOX-loaded galactosylated shell-sheddable micelles
Cytoplasm
Receptor-mediated endocytosis
GSH-triggered shedding off PEG and drug release
GSH
Nucleus
asialoglycoprotein (ASGP) receptor

Figure 7

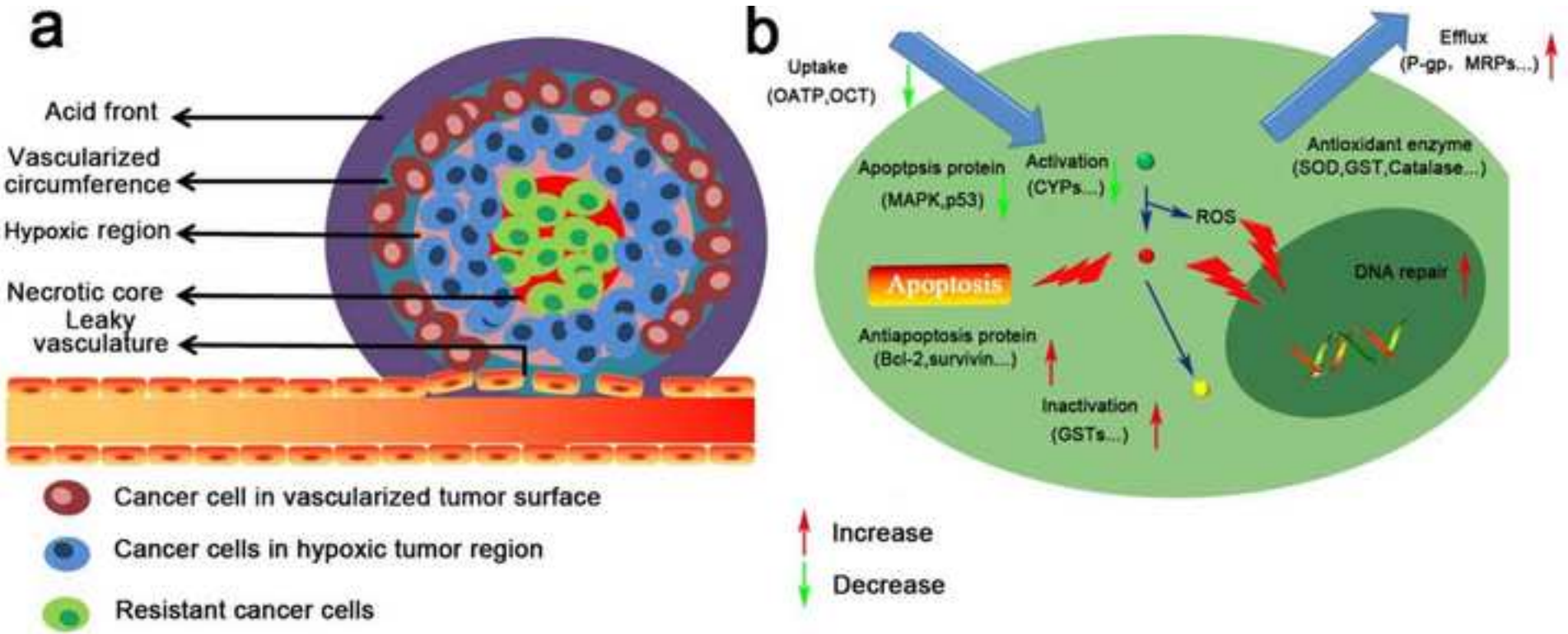
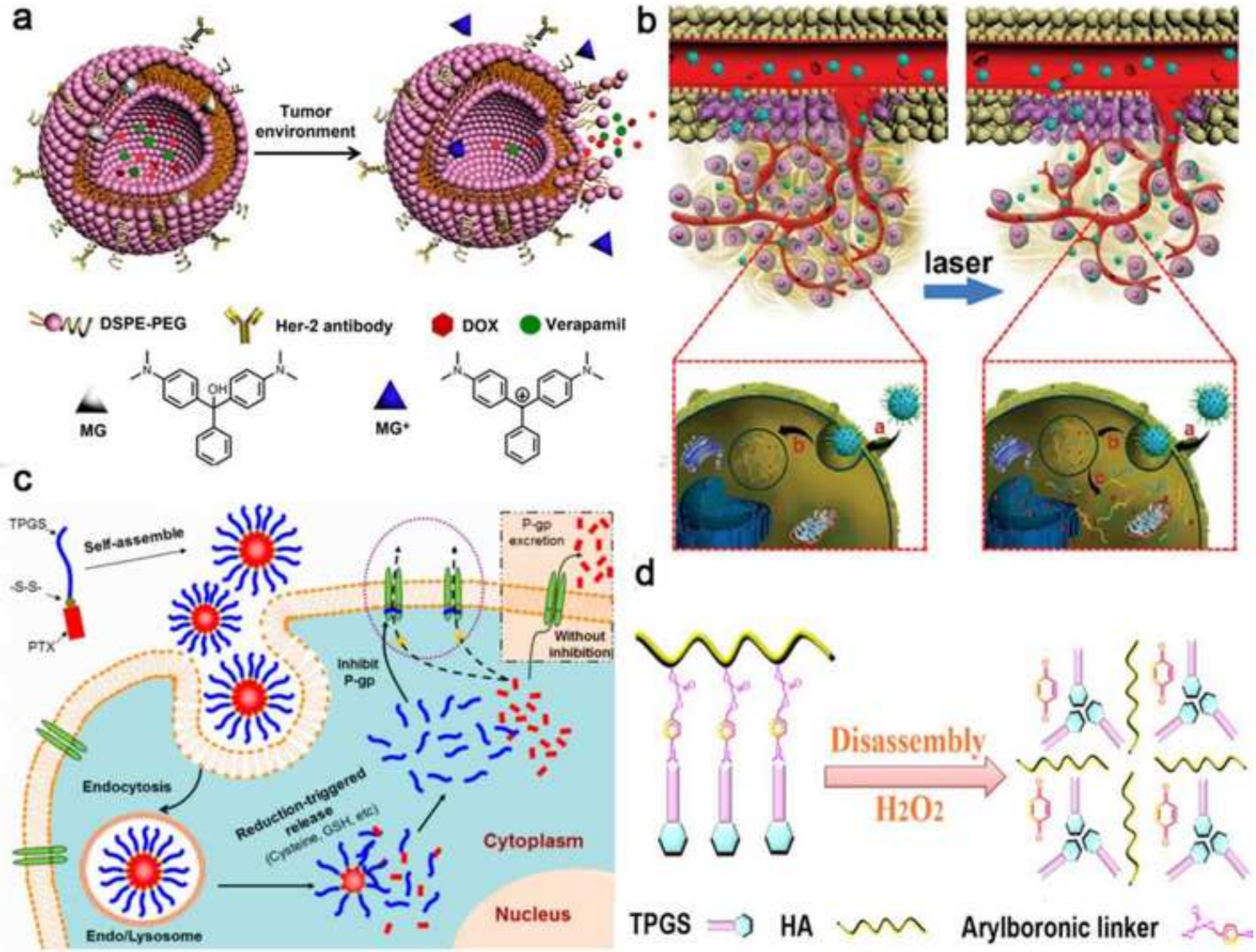

a
Acid front
Vascularized circumference
Hypoxic region
Necrotic core
Leaky vasculature
Cancer cell in vascularized tumor surface
Cancer cells in hypoxic tumor region
Resistant cancer cells
b
Uptake
(OATP,OCT)
Efflux
(P-gp, MRPs...)
Apoptpsis protein
(MAPK,p53)
Activation
(CYPs...)
Antioxidant enzyme
(SOD,GST,Catalase...)
ROS
Apoptosis
DNA repair
Antiapoptosis protein
(Bcl-2,survivin...)
Inactivation
(GSTs...)
Increase
Decrease

Figure 8


a
Tumor environment
DSPE-PEG
Her-2 antibody
DOX
Verapamil
MG
MG+
b
laser
c
TPGS
Self-assemble
-S-S-
PTX
P-gp excretion
Without inhibition
Inhibit P-gp
Endocytosis
Reduction-triggered release
(Cysteine, GSH, etc)
Cytoplasm
Nucleus
Endo/Lysosome
d
Disassembly
H2O2
TPGS
HA
Arylboronic linker