



## Reduction-sensitive polymeric nanomedicines: An emerging multifunctional platform for targeted cancer therapy

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### ABSTRACT

The development of smart delivery systems that are robust in circulation and quickly release drugs following selective internalization into target cancer cells is a key to precision cancer therapy. Interestingly, reduction-sensitive polymeric nanomedicines showing high plasma stability and triggered cytoplasmic drug release behavior have recently emerged as one of the most exciting platforms for targeted delivery of various anticancer drugs including small chemical drugs, proteins, and nucleic acids. *In vivo* studies in varying tumor models reveal that these reduction-sensitive multifunctional nanomedicines outperform the currently used clinical formulations and reduction-insensitive counterparts, bringing about not only significantly enhanced tumor selectivity, accumulation and inhibition efficacy but also markedly reduced systemic toxicity and improved therapeutic index. In this review, we will highlight the cutting-edge advancement with a focus on *in vivo* performances as well as future perspectives on reduction-sensitive polymeric nanomedicines for targeted cancer therapy.

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### Contents

1. Introduction . . . . .	17
1.1. Reduction-sensitive polymeric nanoparticles . . . . .	17
1.2. Reduction-sensitive reversibly crosslinked polymeric nanoparticles . . . . .	17
2. Reduction-sensitive polymeric nanomedicines for breast cancer treatment . . . . .	18
2.1. 4T1 murine breast tumor . . . . .	18
2.2. MCF-7 human breast tumor . . . . .	19
2.3. Triple-negative human breast tumor . . . . .	21
3. Reduction-sensitive polymeric nanomedicines for liver cancer treatment . . . . .	22
3.1. Murine hepatoma . . . . .	22
3.2. Human hepatoma . . . . .	23

*Abbreviations:* GSH, glutathione tripeptide; DOX, doxorubicin; DTX, docetaxel; DTT, dithiothreitol; PEG, poly(ethylene glycol); P(TMC-co-DTC), poly(trimethylene carbonate-co-dithiolane trimethylene carbonate); LA, lipoic acid; EAT, Ehrlich's ascites tumor; TNBC, triple-negative breast cancer; PCL, poly( $\epsilon$ -caprolactone); Cur, curcumin; SSPAA, multi-disulfide containing poly(amido amine); FA, folic acid; R8, octa-arginine; POEGMA, poly(oligo(ethylene glycol) methacrylate); Das, dasatinib; DA, 2,3-dimethylmaleic anhydride; PLA, poly(D,L-lactide); PEI, polyethylenimine; sPLys, star shaped polylysine; CPT, camptothecin; PTX, paclitaxel; PPDSEMA, poly(pyridyldisulfide ethylmethacrylate); HA, hyaluronic acid; IPEI-SS, hyperbranched disulfide-crosslinked linear PEI; siRNA<sup>sur</sup>, survivin-targeted siRNA; Ator, atorvastatin calcium; VES, vitamin E succinate; Ce6, chlorin e6; DM1, mertansine; MTD, maximum tolerated dose; PLGA, poly(D,L-lactide-co-glycolide); TPP, triphenylphosphonium; DLPE, 1,2-dilauroyl-sn-glycero-3-phosphoethanolamine; UA, urocanic acid; CC, cytochrome C; OEG-Tet, oligo(ethylene glycol)-tetrazole; MA-Cys-MA, L-cystine dimethacrylamide; DOX-LPs, pegylated liposomal doxorubicin hydrochloride; hyd, hydrazone; PPLG, poly( $\gamma$ -propargyl-L-glutamate); IC<sub>50</sub>, half-maximal inhibitory concentration; MCF-7/ADR, drug resistant MCF-7; SSPAE, multi-disulfide containing poly( $\beta$ -amino esters); SSMA, cystamine methacrylamide; GrB, Granzyme B; CSCs, cancer stem cells; PBA, phenylboronic acid; PCBM, polycarboxybetaine methacrylate; HCPT, 10-Hydroxycamptothecin; PSSHCTP, poly(dithiodioethanol-alt-10-Hydroxycamptothecin); TPGS, D- $\alpha$ -Tocopherol polyethylene glycol;  $\beta$ CD,  $\beta$ -cyclodextrins; Bcl-2, B-cell lymphoma 2; pDNA, plasmid DNA; PSSAm-g-Arg, arginine-grafted poly(disulfide amine); TAMs, tumor associated macrophages; PAMAM<sub>ss</sub>, reducible hyperbranched poly(amido amine); pDNA-shRNA, short hairpin RNA-encoding pDNA; NSCLC, non-small cell lung cancer; cNQG/RCCPs, cNQG-decorated chimeric PEG-*b*-P(TMC-co-DTC)-*b*-PEI polymersomes; siPLK1, Polo-like kinase1 specific siRNA; AG, aminoglucose; PHPMA, poly(N-2-hydroxypropyl methacrylamide); MTX·2Na, methotrexate sodium; PAA, poly(acrylic acid); BBB, blood brain barrier; DOCA, deoxycholic acid; TRAIL, TNF-related apoptosis-inducing ligand; Dex, dexamethasone; OEI, oligoethylenimine; BODIPY, boron dipyrromethene; PpIX, protoporphyrin IX; SSBPEI, disulfide-crosslinked branched PEI.

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4. Reduction-sensitive polymeric nanomedicines for melanoma treatment . . . . .	23
5. Reduction-sensitive polymeric nanomedicines for lung cancer treatment . . . . .	24
6. Reduction-sensitive polymeric nanomedicines for malignant glioma treatment . . . . .	25
7. Reduction-sensitive polymeric nanomedicines for ovarian cancer treatment . . . . .	26
8. Reduction-sensitive polymeric nanomedicines for cervical cancer treatment . . . . .	27
9. Reduction-sensitive polymeric nanomedicines for treatment of other cancers. . . . .	28
10. Conclusions and perspectives . . . . .	28
Acknowledgements . . . . .	29
References . . . . .	29

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## 1. Introduction

The past decades have witnessed the fast development of polymeric nanosystems including polymeric prodrugs, micelles, vesicles and nanogels for targeted delivery of small chemical drugs, proteins and nucleic acids to treat malignant tumors [1–4]. Polymeric nanomedicines with prolonged circulation time, reduced adverse effects, enhanced accumulation *via* passive targeting and better drug availability have demonstrated superiorities over traditional chemotherapeutic approaches, in both preclinical and clinical studies [5–8]. Despite these advantages, the performance of current polymeric nanomedicines remains far from reaching the clinical expectations [9,10]. As a matter of fact, most reported nanomedicines expose poor *in vivo* stability, low tumor accumulation (typically less than 1% of injected dose), poor tumor penetration, inefficient tumor cell uptake, and/or slow intracellular drug release [11–13]. Poor *in vivo* stability after *i.v.* administration, as the first critical issue of polymeric nanomedicines, generally results in premature drug release and low tumor targeting ability [14]. To overcome this issue, crosslinking strategies were widely utilized and led to enhanced stability during circulation [15,16]. It should be noted, however, that overly stable nanomedicines face the challenge of inadequate drug release in the target tumor cells [17].

In order to solve the extracellular stability *versus* intracellular drug release dilemma of nanomedicines, researchers have engineered various bio-responsive polymeric nanomedicines that are sufficiently stable under circulation and extracellular environment, while release drugs quickly and efficiently in the tumor site or inside cancer cells [18–21]. In particular, reduction-sensitive polymeric nanomedicines have come into a booming development era in the past decade, due to presence of a highly reducing condition inside the tumor cells while oxidative environment in the body fluids [22,23]. Glutathione tripeptide ( $\gamma$ -glutamyl-cysteinyl-glycine, GSH), maintained by NADPH and glutathione reductase, is the main biological reducing agent that induces a high reducing potential in the cytosol and cell nucleus (2–3 orders higher than that in the body fluids) [24]. High reducing potential has also been reported for the acidic endo/lysosomal compartment which is modulated by excess cysteine co-existence with  $\gamma$ -interferon-inducible lysosomal thiol reductase (GLTR) redox enzyme [25,26]. It should further be noted that GSH concentration in the tumor tissues is at least 4-fold higher compared to normal tissues [27]. Therefore, reduction has emerged as a promising biological stimulus for controlled drug release and offers polymeric nanomedicines with several merits, including high stability during workup and under extracellular milieus, fast response to intracellular reductive condition at a time scale of minutes to hours, and triggering release of drugs right into cytosol and cell nucleus where most anticancer drugs take effects [28].

### 1.1. Reduction-sensitive polymeric nanoparticles

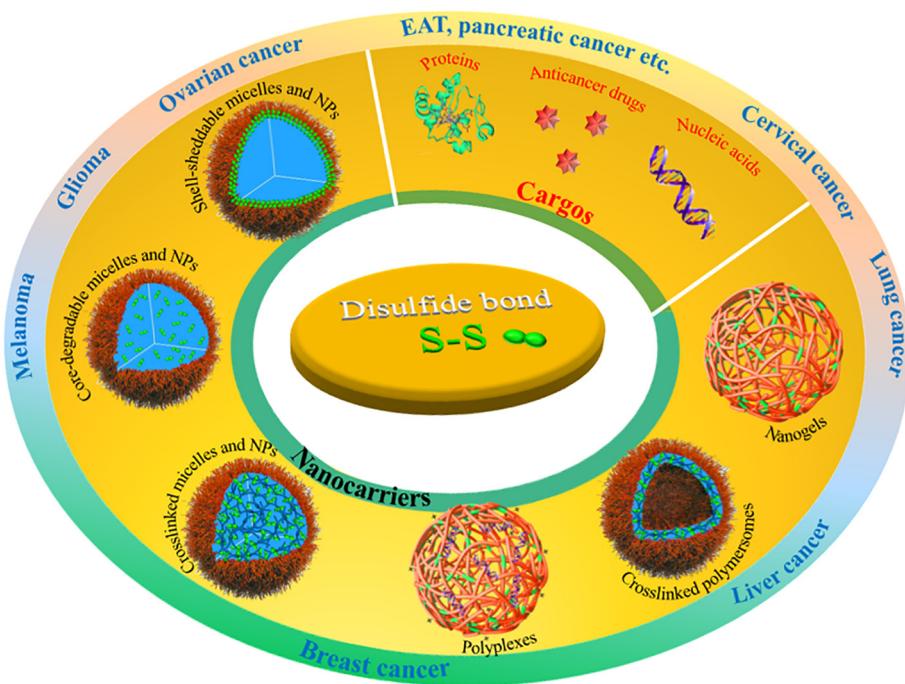
Reduction-sensitive polymeric nanoparticles are usually self-assembled from amphiphilic copolymers containing disulfide units that are cleavable under reductive condition while stable under oxidative environment. The disulfide bond has been widely employed as a unique linkage between hydrophilic and hydrophobic segments

in block [29–31], star [32,33] and graft copolymers [34–37], which give micelles, polymersomes, nanoparticles or polyplexes that shed off hydrophilic shells in response to intracellular reducing potential. In addition, amphiphilic block [38–42], graft [36,43] and hyperbranched copolymers [44] containing single or multi-disulfide bonds in the hydrophobic regime have been utilized to afford core reductively degradable micelles and nanoparticles, which quickly release anticancer payloads such as doxorubicin (DOX) and docetaxel (DTX) inside cancer cells. Linear [45,46], star [47], graft [48,49] and hyperbranched polymers [50–52] with multi-disulfide bonds positioned in the hydrophilic and cationic regime have mainly been used to deliver siRNA, mRNA and DNA. Furthermore, diselenide and ditelluride bonds have also been introduced into the hydrophobic part of amphiphilic triblock [53–55] or hyperbranched copolymers [56] to engineer reduction-sensitive micelles for drug delivery.

### 1.2. Reduction-sensitive reversibly crosslinked polymeric nanoparticles

Reversible disulfide-crosslinking is an attractive and key strategy to endow polymeric nanomedicines with simultaneous high *in vivo* stability and rapid intracellular drug release. Up to now, disulfide-crosslinking is usually achieved *via* three approaches, *i.e.* ring-opening polymerization of dithiolane rings in the prepolymer, oxidizing thiolated polymers, and crosslinking with disulfide containing crosslinkers. Dithiolane containing polymeric nanomedicines have been demonstrated to form disulfide-crosslinking either spontaneously or catalyzed by dithiothreitol (DTT). For example, our group recently developed self-crosslinkable and intracellular de-crosslinkable polymersomes and micelles based on poly(ethylene glycol)-*b*-poly(trimethylene carbonate-co-dithiolane trimethylene carbonate) (PEG-*b*-P(TMC-*co*-DTC)) and poly(ethylene glycol)-*b*-poly(dithiolane trimethylene carbonate) (PEG-*b*-PDTC) copolymers [57–61]. Disulfide-crosslinked micelles, nanoparticles and nanogels were also fabricated from lipoic acid (LA) conjugated polymers followed by DTT catalyzed crosslinking [62–64]. Another green strategy enabling disulfide-crosslinking lies in direct oxidation of thiol groups in the polymers or polymeric nanomedicines in the air or oxygen atmosphere, which is free of both catalyst and crosslinker [65–67]. Moreover, various disulfide containing small molecules, such as cystamine, cystamine bisacrylamide and dithiol bis(propanoic dihydrazide) have been used to crosslink polymeric nanosystems, leading to high circulation stability while fast response to GSH [68–72]. Diselenide-crosslinked polymeric nanosystems were developed either by visible light induced diselenide exchange [73] or by adding sodium diselenide to react with 4-methylbenzenesulfonate enriched polymers [74].

With the burgeoning of reduction-sensitive and reversibly crosslinked polymeric nanomedicines in the past several years, a series of systems have demonstrated significantly enhanced anti-tumor activity to diverse malignant tumors as compared to their reduction-insensitive counterparts. There are several excellent reviews on reduction-responsive polymeric nanosystems for drug delivery [75–77], including two early review papers published in 2009 and 2011 by our group. This review aims to provide an overview of up-to-date advances of reduction-sensitive polymeric nanomedicines for targeted tumor therapy,



**Scheme 1.** Emerging reduction-sensitive polymeric nanomedicines ranging from prodrugs, micelles, polymersomes, nanoparticles, nanogels, to polyplexes for the treatment of various tumors including triple-negative breast cancer, liver cancer, melanoma, non-small cell lung tumor, glioblastoma, ovarian tumor, and pancreatic cancer.

with a focus on *in vivo* studies and work reported in the past five years. The rational design and construction of reduction-sensitive polymeric nanomedicines as well as their *in vivo* anti-tumor performances in various tumor models such as triple-negative breast cancer, liver cancer, melanoma, non-small cell lung tumor, glioblastoma, ovarian tumor, Ehrlich's ascites tumor (EAT), cervical cancer, pancreatic cancer, squamous cell carcinoma, colon cancer, gastric and prostate tumor are discussed ([Scheme 1](#)).

## 2. Reduction-sensitive polymeric nanomedicines for breast cancer treatment

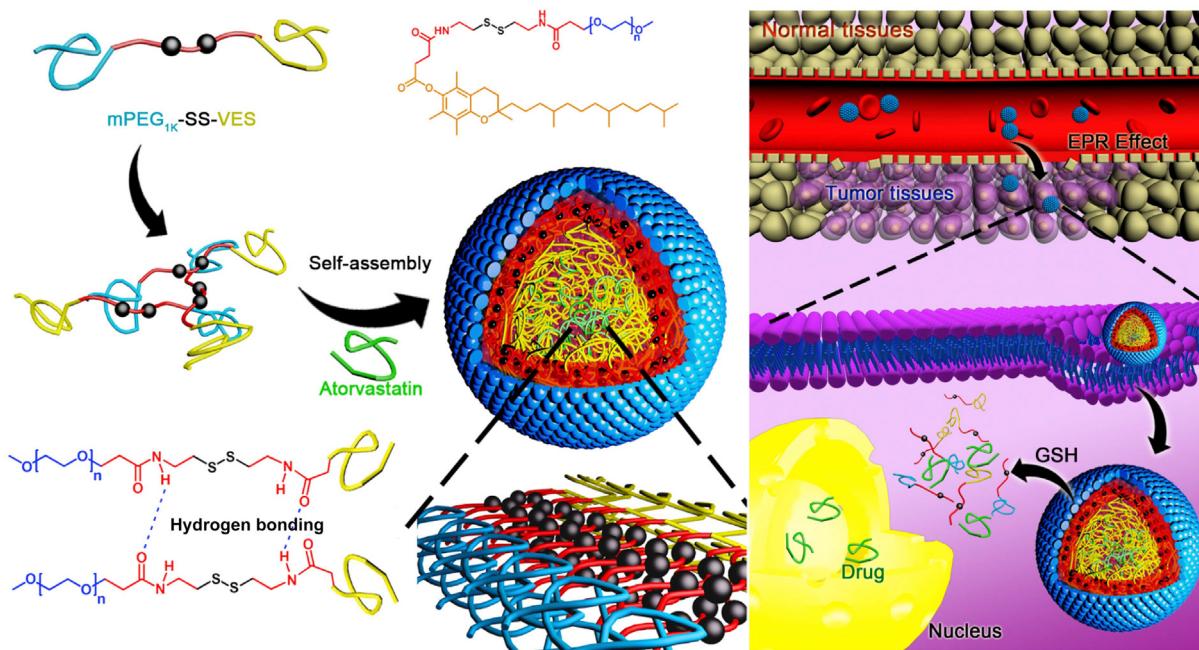
Breast cancer, the most common cancer amongst women with incidence and mortality continuously increasing over the past 50 years, is one of the leading causes of cancer related death in female patients. Particularly, triple-negative breast cancer (TNBC) that does not express or express only low levels of estrogen receptor, progesterone receptor and human epidermal growth factor receptor, represents the most formidable challenge for current clinical practices in breast cancer therapy [[78,79](#)]. In the past 5 years, various reduction-sensitive polymeric nanomedicines with either anticancer drugs, proteins, DNA or RNA as effective warheads have been developed for targeted therapy of breast cancer including TNBC, which accounts for one third of the *in vivo* tumor related therapy with reduction-responsive polymeric systems.

### 2.1. 4T1 murine breast tumor

4T1 tumor has been used as an experimental animal model of human breast cancer due to its ease of transplantation into the mammary gland and similar metastasis characteristics with human breast cancer. Reduction-sensitive polymeric micelles and polyplexes have been employed to efficiently deliver anticancer drugs, DNA or siRNA to subcutaneous, orthotopic and metastatic 4T1 tumor-bearing mice. For example, Shi et al. developed reduction-sensitive shell-shedding micelles based on 4-arm-poly( $\epsilon$ -caprolactone)-SS-poly(ethylene glycol) (4-arm-PCL-SS-PEG) star shaped copolymers [[32](#)]. These micelles while showing sufficient stability at pH 7.4 with a DOX leakage of about 10% in 72 h, rapidly released DOX upon adding 10 mM GSH,

mimicking the intracellular reductive environment, with *ca.* 60% of DOX release in 12 h. As a result of the fast DOX release under reductive condition, DOX-loaded 4-arm-PCL-SS-PEG micelles induced smaller tumor volume, *ca.* 2-fold higher apoptotic rate of tumor sections and longer survival time of subcutaneous 4T1 tumor-bearing mice than their reduction-insensitive control. Similarly, curcumin (Cur)-loaded PEG-SS-polyanhydride micelles although showing similar tumor accumulation to their reduction-insensitive counterpart, produced a 2.3-fold higher inhibition efficiency of 4T1 tumor growth due to the fast intracellular drug release [[80](#)]. Reduction-sensitive core-degradable micellar DOX assembled from multi-disulfide containing poly(amido amine)-g-PEG (SSPA-g-PEG) amphiphilic copolymer demonstrated a high drug loading content of over 50 wt% and significantly promoted tumor accumulation as well as tumor growth inhibition in subcutaneous 4T1 tumor-bearing mice as compared to free DOX-HCl (median survival time: 38.3 versus 28.5 days) [[43](#)]. The median survival time was further prolonged to 45 and 49.5 days after functionalizing micellar DOX with folic acid (FA) and octa-arginine (R8), respectively [[81,82](#)]. Nanoparticulate DOX based on multi-ditelluride containing PEG-*b*-polyurethane-*b*-PEG triblock copolymer also exhibited GSH triggered fast DOX release and effectively suppressed 4T1 tumor growth with a tumor volume of *ca.* 2.2-fold smaller than its reduction-insensitive counterpart [[55](#)]. Sun et al. prepared reduction-sensitive prodrug polymers (POEGMA-PSSDAs) by conjugating dasatinib, an oncogenic tyrosine kinases inhibitor, to the side chain of poly(oligo(ethylene glycol) methacrylate)-*b*-poly(N-methacryloyl cystamine) for co-delivery of Das and DOX [[83](#)]. Compared to the reduction-insensitive POEGMA-PCCDAs control, POEGMA-PSSDAs micelles either with or without DOX were more active against 4T1 tumor cell growth both *in vitro* and *in vivo*, due to accelerated intracellular drug release.

Further taking advantages of the slightly acidic pH (~6.8) at tumor tissue, pH-sensitive charge conversion was combined with reduction-sensitivity to afford reduction and pH dual-sensitive polymeric nanomedicines with enhanced cellular uptake and fast intracellular drug release. For instance, Guo et al. designed a reduction and pH dual-sensitive micellar DOX based on 2,3-dimethylmaleic anhydride (DA) modified PEG-*b*-poly(D,L-lactide)-SS-polyethylenimine-FA (PEG-*b*-PLA-SS-PEI-DA/FA) for targeted treatment of subcutaneous 4T1



**Fig. 1.** Construction of Ator-loaded PEG-SS-VES polymeric micelles with intermolecular hydrogen-bonding and bioreducible disulfide linker for enhancing intracellular release and tumor targeting efficacy to overcome breast cancer metastasis.  
Adapted from [89] with the permission of Elsevier.

tumor-bearing mice [84]. This micellar DOX enabled charge reversal upon arriving at the tumor site, thus promoting cellular uptake, facilitating endosome escape *via* a proton sponge effect, deshielding the PEI shells in the cytosol and finally shipping the therapeutic agent to the nucleus to efficiently inhibit tumor growth and increase survival rate. Cheng et al. prepared a reduction and pH dual-sensitive supramolecular prodrug complex from star shaped polylysine-g-SS-camptothecin (sPLys-g-SS-CPT) and PEG-*b*-P(Lys-DA) copolymers that resulted in about 2-fold better inhibition of 4T1 tumor-bearing mice than free CPT [85]. Ke et al. introduced imidazole and paclitaxel (PTX) to PEG-*b*-poly(pyridyl disulfide ethylmethacrylate) (PEG-*b*-PPDSEMA) block copolymer *via* thiolactone chemistry [86]. The resulting reduction and pH dual-sensitive prodrug micelles, with a PTX loading content of over 50 wt%, showed enhanced cellular internalization as a result of protonation of imidazole groups under tumor pH and rapid intracellular PTX release in response to GSH, leading to almost complete ablation of 4T1 tumor *in vivo*.

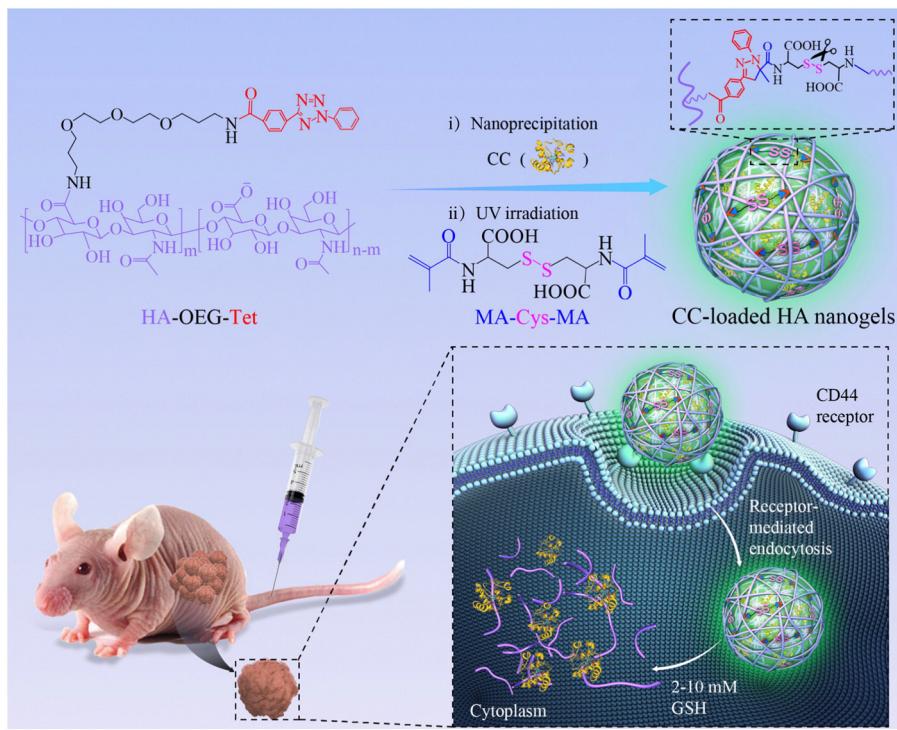
Metastasis is one of the major challenges for successful breast tumor therapy. To further evaluate their potency, reduction-sensitive polymeric nanomedicines were investigated in orthotopic and metastatic 4T1 tumor models. Chen et al. developed a CD44-targeted CPT micellar prodrug, based on hyaluronic acid with pendent disulfide-linked CPT (HA-g-SS-CPT), to treat orthotopic 4T1 tumor [87]. The results indicated that HA-g-SS-CPT micelles improved the tumor accumulation of CPT (4.9% of injected dose) at 24 h following *i.v.* administration, which combining with intracellular GSH triggered rapid CPT release led to strong inhibition of tumor growth and metastasis to lung and liver. Hyperbranched disulfide-crosslinked linear PEI (IPEI-SS) complexed with survivin-targeted siRNA (siRNA<sup>sur</sup>) was reported more efficient in inhibiting the proliferation of 4T1 cells than IPEI-siRNA<sup>sur</sup> and naked siRNA<sup>sur</sup> (cell viabilities: 33.7% versus 68.8% and 80.6%, respectively) [88]. Moreover, *in vivo* antitumor studies revealed that IPEI-SS-siRNA<sup>sur</sup> polyplexes treated group had *ca.* 2-fold lower tumor weight than that of naked siRNA<sup>sur</sup> and were free of lung and liver metastasis. Atorvastatin calcium (Ator)-loaded reduction-sensitive micelles based on PEG-SS-vitamin E succinate (PEG-SS-VES) amphiphilic copolymer were shown to rapidly release Ator into cytosol, leading to efficient inhibition of migration and invasion of 4T1 cells (Fig. 1) [89]. *In vivo*

studies demonstrated that PEG-SS-VES micellar Ator almost completely blocked the lung metastasis of orthotopic 4T1 tumor with an inhibition rate of 84.8%, significantly higher than its reduction-insensitive control (53.3%). DTX-loaded PEG-SS-VES micelles were later encapsulated into matrix metalloproteinase-sensitive PEG-pp-VES liposomes [90]. The resulting shrapnel structure had an average size of ~113 nm and revealed increased tumor accumulation and significantly inhibited tumor growth and lung metastasis.

Diselenide-crosslinked micelles were constructed from PEG-*b*-poly(diselenide methacrylate) for co-delivery of CPT and DOX to subcutaneous murine EMT-6 breast tumor-bearing mice [73]. These diselenide-crosslinked micelles showed extraordinary stability against 50% fetal bovine serum, SDS or organic solvent, and low drug leakage under physiological condition. However, quantitative drug release was achieved in the presence of 10 mM GSH, mimicking the intracellular reductive environment. Compared with the non-crosslinked counterpart, crosslinked micellar CPT/DOX exhibited *ca.* 3-fold longer circulation time, 2-fold higher tumor accumulation at 24 h post-injection and 4-fold better tumor growth inhibition after 24 days treatment.

## 2.2. MCF-7 human breast tumor

There are extensive studies on reduction-sensitive polymeric nanomedicines for treatment of MCF-7 human breast tumors including subcutaneous, orthotopic and drug resistant models. For instance, Liu et al. developed self-quenched dextran-g-SS-chlorin e6 (Dextran-g-SS-Ce6) nanoparticles with intracellular GSH triggered “OFF/ON” switch, which greatly enhanced the *in vitro* photo-toxicity, *in vivo* tumor accumulation and photodynamic therapeutic efficacy of Ce6 in subcutaneous MCF-7 tumor, resulting in complete tumor ablation without recurrence [91]. We conjugated mertansine (DM1) toxin to 2-(2-pyridylthio)-ethylamine modified HA *via* thiol-disulfide exchange reaction, yielding reduction-sensitive HA-g-SS-DM1 prodrug with a high DM1 content of 20 wt% for CD44-targeted therapy of subcutaneous MCF-7 tumor-bearing mice [92]. HA-g-SS-DM1 presented low drug leakage under physiological condition while fast GSH triggered drug release behavior (over 90% in 24 h). *In vivo* studies revealed that HA-g-SS-DM1 improved the maximum tolerated dose (MTD) of DM1 by 4-fold



**Fig. 2.** Disulfide-crosslinked and intrinsically fluorescent photoclick HA nanogels for breast tumor-targeted delivery of CC. HA nanogels are prepared from HA-g-OEG-Tet and MA-Cys-MA via combining inverse nanoprecipitation and “tetrazole-alkene” photoclick chemistry. These photoclick nanogels show superb loading, CD44-targeted delivery and GSH-triggered intracellular release of CC.

Adapted from [96] with the permission of American Chemical Society.

and effectively suppressed tumor growth with an inhibition rate of 87.6% while causing little side effects. Zhou et al. reported that nanoparticles consisting of poly(D,L-lactide-co-glycolide) (PLGA), TPP-PEG<sub>1k</sub>-C18 and PEG<sub>4k</sub>-SS-DLPE (TPP: triphenylphosphonium, DLPE: 1,2-dilauroyl-sn-glycero-3-phosphoethanolamine) would shed off longer PEG shell in the cytosol, leading to exposure of positively charged TPP and subsequently rapid and precise localization into mitochondria [93]. PTX-loaded shell-detachable and mitochondria-targeted nanoparticles showed much higher antitumor efficacy in MCF-7 tumor-bearing mice than their reduction-insensitive counterparts (tumor inhibition rate: 90.5% versus 47.1%) albeit with similar tumor accumulation. VEGF-siRNA nanocomplexes based on reduction-sensitive SSPAA with pendent dimethyl amino and cholesterol groups exhibited specific VEGF gene silencing effect *in vitro* and growth inhibition of MCF-7 tumor *in vivo* [94]. Zhu et al. reported that reduction and pH dual-sensitive low-density lipoprotein-decorated chitosan-g-SS-UA (UA: urocanic acid) micelles co-loaded with PTX and siRNA against breast cancer resistance protein achieved potent inhibition of subcutaneous MCF-7 tumor in mice [95].

To target cytochrome C (CC) protein to MCF-7 xenografts, disulfide-crosslinked fluorescent HA nanogels were fabricated via nanoprecipitation and photoclick crosslinking from oligo(ethylene glycol)-tetrazole grafted HA (HA-g-OEG-Tet) and L-cystine dimethacrylamide (MA-Cys-MA) (Fig. 2) [96]. HA nanogels displayed a high CC loading of 40.6 wt% while quickly released CC in its active form in the presence of 10 mM GSH, significantly boosting antitumor efficacy of CC *in vitro* and *in vivo*. These multifunctional HA nanogels appear to be a unique delivery system for cancer protein therapy in that they are easy to fabricate, have excellent protein compatibility, are able to specifically recognize CD44 overexpressing tumors, and can rapidly release protein drugs into cancer cells. The absence of safe and efficient protein delivery vehicles is a major challenge for clinical translation of protein therapeutics. Disulfide-crosslinked DOX nanotherapeutics based on HA-g-poly( $\gamma$ -benzyl-L-glutamate-LA)

copolymer exhibited a 5-fold higher MTD than clinically used pegylated liposomal doxorubicin hydrochloride (DOX-LPs), high tumor accumulation of 8.6%ID/g and significantly improved survival rate over DOX-LPs (median survival time: 52 versus 13 days) in subcutaneous MCF-7 tumor-bearing mice [97]. Interestingly, reduction, pH and enzyme triple-sensitive disulfide-crosslinked protein nanoparticles were obtained via electrostatic assembly of human serum albumin and Plgs with intermolecular disulfide-crosslinking and surface pegylation [57]. Ce6-loaded multi-responsive nanoparticles showed enhanced photodynamic ablation of MCF-7 tumor *in vivo*.

The work from different groups shows that reduction-sensitive nanomedicines can also effectively inhibit orthotopic and drug resistant MCF-7 breast tumors. Orthotopic MCF-7 tumor-bearing mice treated with Cur-loaded reduction-sensitive chitosan-g-PEG/SS-C16 micelles revealed a 4-fold lower tumor weight than those with free Cur [98]. Yang et al. reported that a reduction and pH dual-sensitive disulfide-crosslinked micellar DOX based on L-phenylalanine ethyl ester and L-cysteine ethyl ester co-modified succinyl-dextran showed lower systemic toxicity and similar antitumor efficacy against orthotopic MCF-7 tumor compared with free DOX-HCl [99]. Zhang et al. prepared reduction and pH dual-sensitive PEG-b-P(PLG-hyd-DOX) prodrug nanogels via one step “click chemistry” of pH-sensitive hydrazone bond containing azide-DOX, 2-azidoethyl disulfide crosslinker, and PEG-b-PPLG copolymer (PPLG: poly( $\gamma$ -propargyl-L-glutamate)) [100]. These prodrug nanogels had only 7.8% of DOX release in 5 days under physiological condition while released 85.5% of DOX under 5 mM GSH at pH 5.5. *In vivo* studies indicated that disulfide-crosslinked prodrug nanogels had significantly higher antitumor efficacy in orthotopic MCF-7 tumor-bearing mice than the non-crosslinked counterpart. DOX-loaded disulfide-crosslinked HA-g-(Lys-LA) nanoparticles were shown to mediate efficient treatment of DOX resistant MCF-7 (MCF-7/ADR) breast tumor *in vivo* [101]. Notably, these CD44 targeted DOX nanotherapeutics exhibited superior anti-proliferative effect toward MCF-7/ADR tumor cells with an half-maximal inhibitory concentration ( $IC_{50}$ ) of 2.8  $\mu$ g/mL,

about 10-fold lower than that of free DOX, and significantly improved tumor accumulation reaching 12.71%ID/g, leading to potent inhibition of MCF-7/ADR breast tumor. Yin et al. reported that multi-disulfide containing cationic poly( $\beta$ -amino esters) (SSPAE) complexed with iMdr-1-shRNA and isurvivin-shRNA, which down-regulated the expression of P-gp and survivin, respectively, obviously increased the sensitivity of MCF-7/ADR tumor cells to free DOX, leading to effective inhibition of MCF-7/ADR tumor growth *in vivo* [102]. Drug resistance represents a major issue for the clinical treatment of various malignancies. It's known that continuous exposure to a sublethal dose of chemical drugs is a leading cause for drug resistance. Reduction-sensitive nanomedicines would dump a large amount of drugs into cancer cells, thereby effectively reversing drug resistance. It is interesting to note that they can also be modified with a targeting ligand and/or co-loaded with different drugs to further overcome drug resistance and improve cancer therapy.

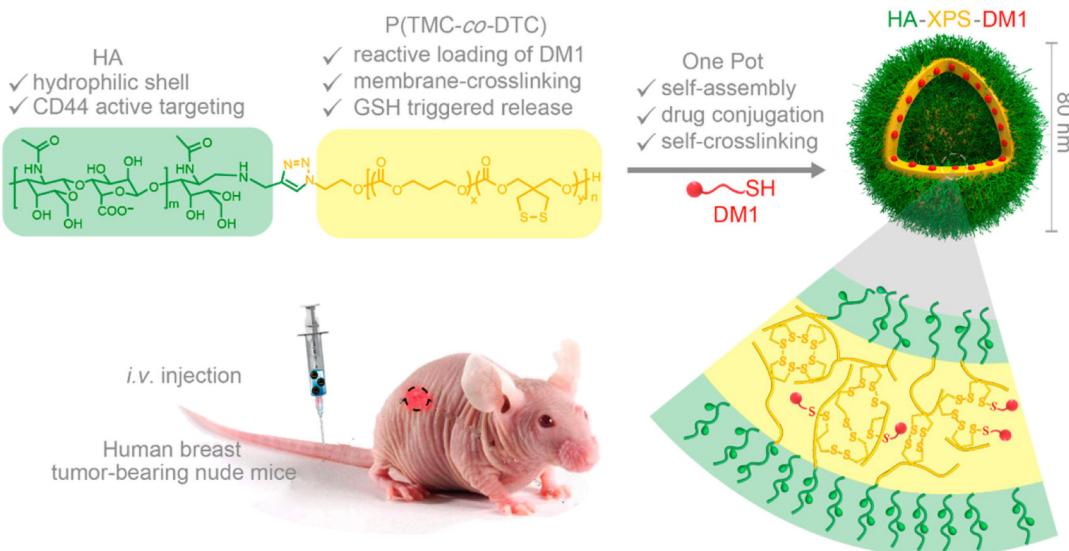
### 2.3. Triple-negative human breast tumor

TNBC, accounts for 12–17% of breast cancer globally, has the highest mortality and worst prognosis amongst all breast cancer subtypes. In the past several years, various reduction-sensitive polymeric nanomedicines have been engineered for efficient treatment of TNBC. Huo et al. reported that reduction-sensitive micellar PTX based on O, N-hydroxyethyl chitosan-*g*-SS-octylamine induced significantly enhanced antitumor efficacy and lower systemic toxicity in subcutaneous MDA-MB-231 tumor-bearing mice compared to the reduction-insensitive micellar PTX and free PTX [103]. Reduction-sensitive magnetic micellar DOX based on SSPAA-*g*-PEG/C12 and iron oxide ( $Fe_3O_4$ ) nanoparticles exhibited *ca.* 4-fold better inhibition of MDA-MB-231 tumor xenografts than free DOX [36]. Koo et al. reported that disulfide-crosslinked micellar DTX prepared from PEG-*b*-PLys-*b*-poly( $\alpha$ -phenylalanine) using 3,3'-dithiobis(sulfosuccinimidylpropionate) as a crosslinker led to about 2-fold enhanced tumor accumulation and therapeutic efficacy in MDA-MB-231 tumor-bearing mice compared with the non-crosslinked control [104]. Ruttala et al. developed disulfide-crosslinked polypeptide micelles based on PEG-*b*-poly(aspartic acid)-*b*-poly(tyrosine) using cystamine as a crosslinker [105]. DTX and lonidamine co-loaded micelles showed more efficacious tumor growth inhibition and better safety than non-crosslinked micelles and free drug cocktail in MDA-MB-231 tumor-bearing mice. Dextran nanogels

with reduction-cleavable junctions prepared via one step self-assembly assisted graft polymerization of acrylic acid and diallyl disulfide from dextran were further conjugated with DOX via a pH-sensitive hydrazone bond, which exhibited stronger therapeutic effect against MDA-MB-231 tumor *in vivo* than the irreversibly crosslinked counterpart [106]. Xiao et al. found that reducible PEI-(SS-Tween 85)<sub>2</sub> could efficiently condense p65 shRNA into polyplexes with an average size of *ca.* 130 nm [107]. These polyplexes down-regulated p65 expression in MDA-MB-435 cells by over 90% and almost completely inhibited the growth as well as lung and lymph node metastasis of orthotopic MDA-MB-435 breast tumor in nude mice.

Actively targeted reduction-sensitive polymeric nanomedicines have recently been explored for chemotherapy of TNBC. For instance, cRGD-decorated GSH-activatable micellar DM1 prodrug (cRGD-PEG-*b*-P(TMC-*g*-SSDM1)) showed efficient delivery of DM1 to  $\alpha_v\beta_3$  integrin overexpressing MDA-MB-231 tumor cells, leading to potent tumor growth inhibition and reduced side effects *in vivo* [108]. Wu et al. reported that cRGD targeted and disulfide-crosslinked micellar nanoforumulation of lipophilized bortezomib based on PEG-*b*-P(TMC-*co*-DTC) amphiphilic copolymer exhibited 3.6-fold lower IC<sub>50</sub> in MDA-MB-231 cells than the non-targeted control, 20-fold improvement in circulation half-life and MTD over free bortezomib, and nearly complete inhibition of MDA-MB-231 tumor in nude mice [109].

HA-shelled disulfide-crosslinked nano-polymersomes self-assembled from HA-*b*-(PTMC-*co*-DTC) exhibited an ultrahigh-efficiency conjugation of DM1 *via* thiol-disulfide exchange reaction (Fig. 3) [110]. The resulting polymersomal DM1 showed less than 10% of DM1 release in 24 h under physiological condition, while over 80% of DM1 release in response to 10 mM GSH. *In vivo* studies showed improved toleration, pronounced targeting ability and significantly more potent inhibition of MDA-MB-231 tumor compared with free DM1. Yin et al. reported that CD44-targeted and reduction-sensitive HA-*g*-SS-PTX micelles revealed about 5-fold lower IC<sub>50</sub>, 2.1-fold higher tumor accumulation and about 2.5-fold smaller tumor volume compared to the reduction-insensitive counterpart [83]. EGFR and CD44 dual-targeted disulfide-crosslinked fluorescent HA nanogels were prepared from HA-*g*-Tet/GE11 and HA-*g*-SSMA (SSMA: cystamine methacrylamide) *via* combining nanoprecipitation and photoclick chemistry. Granzyme B (GrB)-loaded dual-targeted nanogels showed efficient growth inhibition of MDA-MB-231 tumor with a tumor inhibition rate of 82% [111]. Hu et al. designed reduction-sensitive HA-SS-PLGA nanoparticles for co-



**Fig. 3.** Engineering disulfide-crosslinked HA-shelled HA-*b*-(PTMC-*co*-DTC) polymersomes for high-efficiency reactive encapsulation and CD44-targeted delivery of DM1 in MDA-MB-231 human breast tumor-bearing nude mice.

Adapted from [110] with the permission of American Chemical Society.

delivery of DOX and cyclopamine (a specific inhibitor of cancer stem cells) to eradicate orthotopic MDA-MB-231 breast tumor and cancer stem cells (CSCs) [34]. *In vivo* studies demonstrated that dual drug-loaded HA-SS-PLGA nanoparticles completely eliminated tumor after 40 days treatment, which was significantly better than either free drugs or dual drug-loaded PLGA nanoparticles. Notably, mice treated with dual drug-loaded nanoparticles maintained tumor free in 75 days, signifying the complete ablation of CSCs during therapy. CSCs, with the ability to self-renewal and differentiation, are responsible for the development of drug resistance as well as tumor recurrence and metastasis, leading to treatment failure. Reduction-sensitive polymeric nanosystems might help to kill drug-resistant CSCs by rapidly releasing cytotoxic drugs into their cytosols. It should further be noted that reduction-sensitive polymeric nanosystems also allow co-delivery of both cytotoxic drugs and CSC inhibitors, which might efficiently eliminate normal tumor cells and CSCs, resulting in complete tumor ablation.

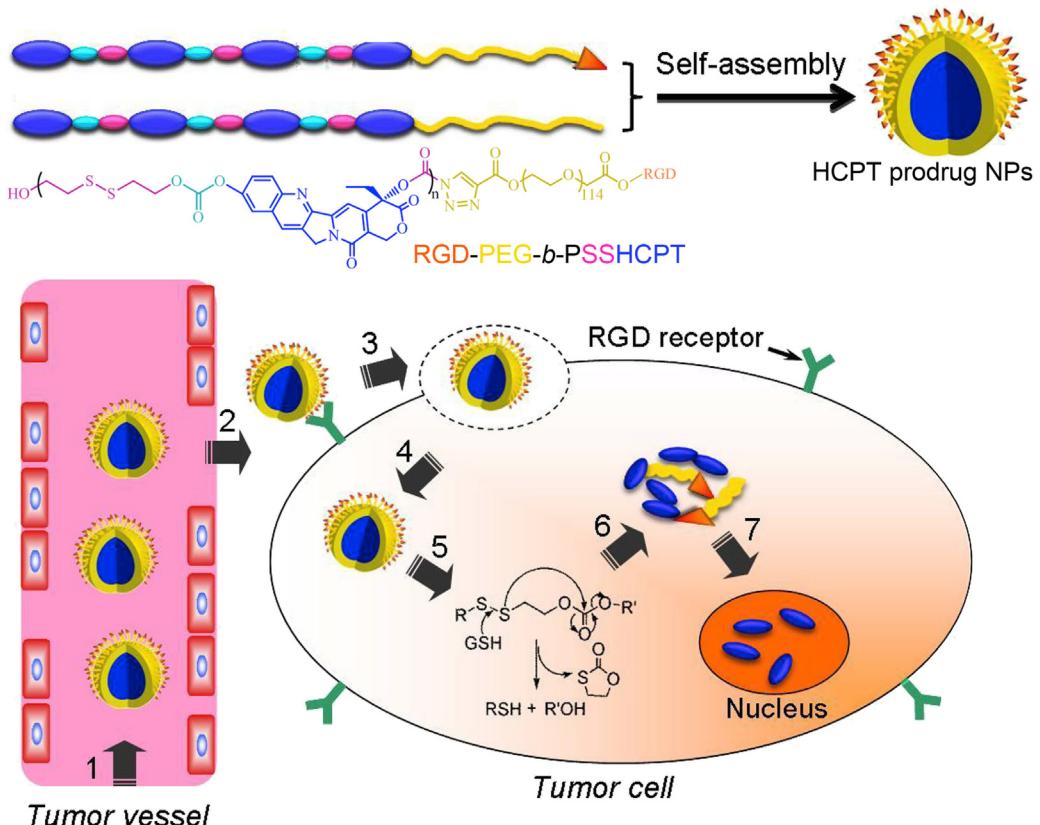
### 3. Reduction-sensitive polymeric nanomedicines for liver cancer treatment

Liver cancer is one of the top five globally leading causes of cancer death. The conventional chemotherapy and biotherapy generally resulted in a low therapeutic efficacy likely due to fast clearance and low cellular uptake *in vivo*. In recent years, various reduction-sensitive polymeric nanomedicines have been explored for enhanced treatment of hepatoma, which accounts for up to 75% of liver cancers.

#### 3.1. Murine hepatoma

Reduction-sensitive polymeric nanomedicines have been actively investigated for treatment of subcutaneous H22 tumor, a main

murine hepatoma model. Qian et al. reported that DOX-loaded bioreducible cellulose nanogels showed comparable cytotoxicity to free DOX against H22 cells and ca. 1.7-fold better suppression of H22 tumor than their reduction-insensitive counterparts [112]. DOX-loaded, actively targeted, and reduction-responsive magnetic micelles based on star shaped 4-arm-PCL-SS-PEG-PBA (PBA: phenylboronic acid, targeting to salic acid) copolymer resulted in a high tumor inhibition rate of 91.6% in H22 tumor-bearing mice with little side effects [33]. Reduction-sensitive photo-crosslinked micellar DOX based on 6-arm-PEG-*b*-PCL-cinnamate and PBA-PEG-SS-PCL induced around 2-fold better inhibition of H22 tumor than free DOX [113]. Reduction and pH dual-sensitive micellar DOX prodrug based on PBA-PEG-SS-PCL-hyd-DOX copolymer, wherein DOX was conjugated to the PCL end via a pH-sensitive hydrazone bond, showed about 3 and 4-fold better inhibition of subcutaneous H22 tumor than free DOX and DOX-loaded insensitive PBA-PEG-*b*-PCL micelles, respectively [114]. Wu et al. synthesized a reduction and pH dual-sensitive charge conversional DMC prodrug, PEG-*b*-poly(disulfide-*alt*-demethylcantharidin)-*b*-PEG, via click chemistry [115]. DOX-loaded prodrug nanoparticles underwent a negative to positive charge transition and accelerated dual drug release in the presence of 10 mM GSH at pH 6.5. *In vivo* results revealed 9-fold better tumor growth inhibition of H22 tumor-bearing mice than free DOX. KLAK peptide drug based tumor targeted reducible polypeptide (poly(R8(FA)-KLAK(TPP))) complexed with p53 plasmid and coated with pH-sensitive charge switchable PEG-*b*-P(Lys-DA) copolymer exhibited high tumor accumulation, reduced systemic toxicity, and almost complete growth inhibition of H22 tumor in mice [116]. HA-g-SS-PTX micellar prodrug displayed more efficacious growth inhibition of subcutaneous Heps murine hepatoma in mice, resulting in around 9-fold smaller tumor volume than taxol [117].



**Fig. 4.** GSH-activatable HCPT prodrug nanoparticles based on RGD-PEG-*b*-PSSHCPT and PEG-*b*-PSSHCPT copolymers for targeted hepatoma therapy. RGD-decorated HCPT prodrug nanoparticles show enhanced accumulation in HepG2 tumor and fast uptake by HepG2 tumor cells (1–3). GSH in the cytoplasm rapidly breaks the disulfide bonds releasing intact HCPT molecules and inducing tumor cell apoptosis (4–7). Adapted from [123] with the permission of Elsevier.

### 3.2. Human hepatoma

Reduction-sensitive polymeric nanomedicines can also effectively treat human hepatoma xenografts including HepG2, LM3 and SMMC-7721 tumors. Zhang et al. reported that DOX-loaded reduction-sensitive lipid-polymer hybrid nanoparticles co-assembled from PEG-SS-DLPE and PCL polymers exhibited significantly enhanced suppression of HepG2 tumor than their reduction-insensitive control [118]. Reduction and pH dual-sensitive shell-sheddable micellar DOX based on PEG-SS-poly[2-(dibutylamino)ethylamine-l-glutamate] diblock copolymer demonstrated ca. 1.8-fold higher tumor inhibition efficiency against HepG2 tumor compared to free DOX [119]. Glycyrhetic acid, a targeting ligand to hepatocellular carcinoma cells, was introduced to the surface of shell-sheddable PEG-SS-PLGA micelles for targeted delivery of Tanshinone IIA [120]. Thus obtained formulation showed enhanced cytotoxicity against HepG2 cells *in vitro* and improved tumor inhibition rate *in vivo* as compared to reduction-insensitive PEG-*b*-PLGA formulation. Reduction-sensitive and actively targeted Pullulan-g-SS-cholesterol nanoparticles showing high DOX loading content of 26.3 wt% effectively suppressed the growth of subcutaneous HepG2 tumor *in vivo* and led to prolonged median survival time of ~80 days, about 70 days longer than PBS treated group [121]. Huang et al. reported that  $\alpha_1\beta_3$  integrin targeted reduction-responsive shell-detachable nanoparticles based on cRGD-PCBM-SS-PCL (PCBM: polycarboxybetaine methacrylate) block copolymer mediated efficient delivery of DOX to HepG2 tumor cells, leading to ca. 4-fold lower IC<sub>50</sub> *in vitro* and about 1.5-fold better inhibition of HepG2 tumor *in vivo* compared to the reduction-insensitive PCBM-*b*-PCL control [122].

RGD-decorated reduction-sensitive HCPT prodrug nanoparticles were prepared *via* co-self-assembly of PEG-*b*-poly(dithiodiethanol-*alt*-10-Hydroxycamptothecin) (PEG-*b*-PSSHCTP) and RGD-PEG-*b*-PSSHCTP (Fig. 4) [123]. The prodrug nanoparticles showed fast and almost quantitative HCPT release after 5 h incubation at pH 7.4 with 10 mM GSH, whereas drug release was negligible under non-reductive condition even after 24 h. These prodrug nanoparticles induced over 28-fold better inhibitory effect to HepG2 cells *in vitro* and 3-fold enhanced inhibition of HepG2 tumor *in vivo* than their reduction-insensitive control. Reduction and pH dual-sensitive nanoparticles based on SSPAE-g-TPGS (TPGS: D- $\alpha$ -Tocopheryl polyethylene glycol) copolymer significantly improved the antitumor effect of DTX toward HepG2 hepatoma in mice [124]. Enhanced treatment of HepG2 tumor *in vivo* with reduced side effects was also reported for DOX-loaded disulfide-crosslinked PEG-*b*-P(Ph-co-Cys) nanogels [125], micellar DOX based on PEG-*b*-poly(disulfide carbamate amine) copolymer [126], and DOX-loaded reduction and pH dual-sensitive HA nanocapsules based on HA-g-SH/(acetyl protected galactopyranose) copolymer [127].

Hu et al. developed redox-responsive SP94 peptide decorated PEG-PEI supramolecular complexes from PEI-crosslinked  $\beta$ -cyclodextrins (PEI- $\beta$ CD), adamantly-SS-PEG and adamantly-PEG-SP94 for targeted delivery of tumor suppressor miR-34a to subcutaneous LM3 hepatoma-bearing mice [128]. Interestingly, miR-34a complexes significantly increased the miR-34a expression level in the tumor and almost completely inhibited the tumor growth following 21 days treatment. Wang et al. prepared a redox-responsive co-delivery vector by conjugating PAMAM dendrimer of two generations to 8-arm PEG through disulfide linkages (8-arm-PEG-SS-PAMAM) for simultaneous delivery of DOX and B-cell lymphoma 2 (Bcl-2) siRNA to subcutaneous SMMC-7721 tumor-bearing mice [129]. Co-delivery of DOX and Bcl-2 siRNA *via* intratumoral administration led to at least 5-fold better tumor suppression than either Bcl-2 siRNA or DOX-loaded nanoparticles. Very recently, GE11-decorated disulfide-crosslinked polymersomal DOX was prepared with a high drug loading content of 15.4 wt% and small size of 78 nm from PEG-*b*-P(TMC-co-DTC) copolymer [61]. *In vivo* studies indicated that GE11-functionalized polymersomal DOX presented an extraordinary tumor accumulation of 13.3%ID/g and significantly improved survival rate in orthotopic

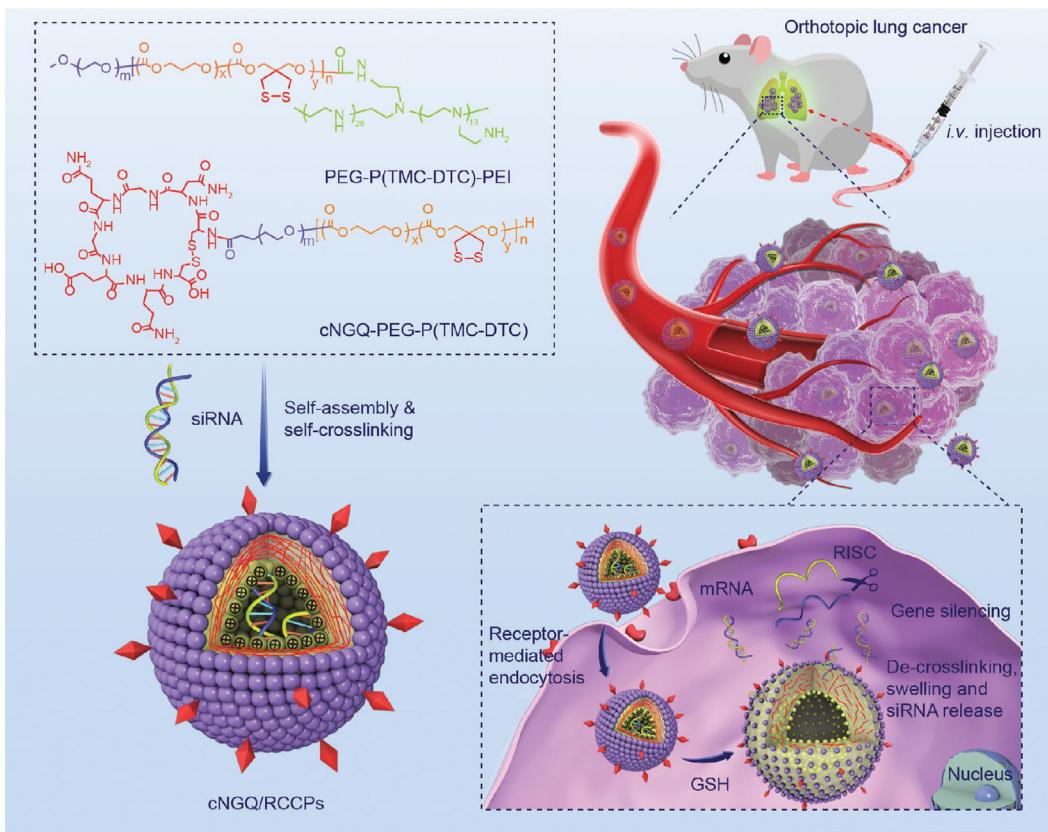
SMMC-7721 tumor-bearing mice, with 3.4-fold longer median survival time than that with DOX-LPs and 50% of mice becoming tumor-free.

### 4. Reduction-sensitive polymeric nanomedicines for melanoma treatment

Melanoma is a main cause of death amongst skin cancers. Researchers have put great efforts in exploring efficient therapeutic strategies to treat melanoma. Hu et al. reported that DOX-loaded reduction and pH dual-sensitive PAMAM-SS-PEG dendrimer released DOX in a GSH and acid triggered manner and exhibited significantly higher anti-tumor effect against B16 melanoma *in vivo* compared to its reduction-insensitive control [130]. Zhang et al. prepared DOX-loaded alginate-g-SS-PheoA (PheoA: pheophorbide A, a hydrophobic photosensitizer) nanoparticles for combinational chemo- and photodynamic therapy of B16 melanoma-bearing mice [131]. These DOX-loaded nanoparticles provoked intracellular ROS generation upon light irradiation, leading to 2-fold enhancement of anti-proliferative effect to B16 cells and substantial tumor growth inhibition *in vivo* [131].

cRGD-installed self-crosslinkable and intracellular decrosslinkable micellar DOX was obtained with superior stability, minimum drug leakage and GSH triggered DOX release from PEG-*b*-PDTC diblock copolymer [58]. This micellar DOX showed at least 10-fold improvement on MTD over free DOX and high tumor accumulation of 6.13% ID/g at 6 h post i.v. injection (3-fold higher than DOX-LPs), leading to effective tumor growth inhibition and a survival rate of 100% in an experimental period of 43 days. ATN-161 peptide functionalized disulfide-crosslinked polymersomal DOX based on PEG-*b*-P(TMC-co-DTC) demonstrated 4-fold higher tumor accumulation in B16F10 tumor-bearing mice than DOX-LPs and effective suppression of tumor growth in an experimental period of 12 days [132]. cRGD-decorated polymersomal DM1 obtained from PEG-*b*-P(TMC-co-DTC) *via* simultaneous conjugation of DM1 through thiol-disulfide exchange reaction during fabrication displayed a tumor inhibition rate of 93% without obvious systemic toxicity in mouse B16F10 melanoma model [133]. Micellar DM1 prodrug based on cRGD-PEG-*b*-P(TMC-g-SSDM1) showed also a high potency in suppressing the growth of subcutaneous B16F10 melanoma in mice with a high tumor inhibition rate of 97.5% at a dosage of 2.4 mg DM1 equiv./kg [134]. This micellar DM1 prodrug could further be loaded with DTX, achieving redox-triggered ratiometric dual drug release and targeted synergistic treatment of B16F10 melanoma [135]. Notably, these dual drug formulation almost completely inhibited tumor growth *in vivo* with a superior inhibition rate of 98.2% at 1.2 mg DM1 equiv./kg plus 0.7 mg DTX equiv./kg. Lv et al. found that reduction and pH dual-responsive PEG-*b*-P(Lys-SS-PTX) micellar prodrug effectively inhibited the growth of mouse B16F1 tumor, resulting in 5-fold smaller tumor volume than its insensitive control [136]. Zhao et al. reported that mixed micelle based on reduction-activatable PEG-SS-PTX and PEG-SS-DOX conjugates revealed reduced side effects and similar antitumor efficacy to free PTX and DOX in B16 melanoma [137]. PTX-loaded cRGD-functionalized reduction-sensitive shell-sheddable polymeric nanoparticles based on TPGS-SS-PLA also showed a high potency in inhibiting the growth of subcutaneous B16 melanoma (inhibition rate: 76.6%) [138].

In addition to small anticancer drugs, reduction-sensitive polymeric nanosystems can also be engineered to deliver therapeutic siRNA, mRNA and plasmid DNA (pDNA) to eradicate the subcutaneous or metastatic B16F10 melanoma. For example, Chen et al. reported that reducible fluorinated and cationic SSPAA complexed with siLuc could silence the luciferase of luc-B16F10 melanoma *in vivo* by 88%, which was over 3-fold higher than reduction-insensitive PAA/siLuc polyplexes [45]. Beloork et al. synthesized an arginine-grafted reducible poly(disulfide amine) (PSSAm-g-Arg) polymer to deliver a siRNA cocktail targeting Bcl-2, VEGF and Myc to B16F10 tumor in mice, resulting in 35–50% of tumor regression [46]. Liu et al. constructed a reduction and pH dual-sensitive charge conversional and self-crosslinked nanoparticles



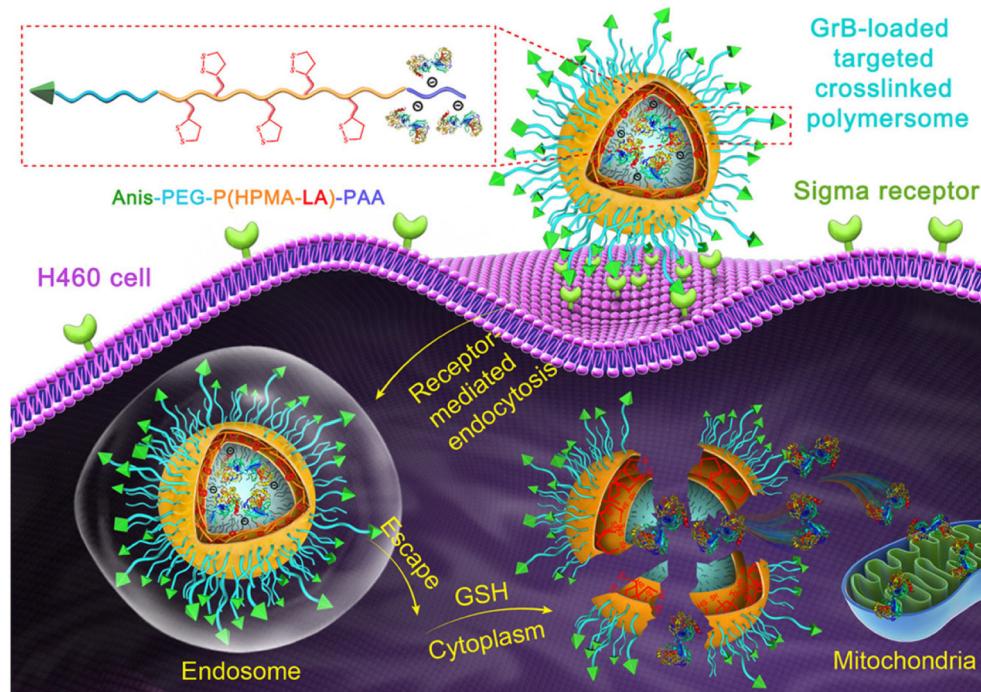
**Fig. 5.** cNGQ-decorated reversibly crosslinked chimeric polymersomes (cNGQ/RCCPs) for high-efficiency targeted delivery of siPLK1 to orthotopic A549 lung cancer bearing nude mice. cNGQ/RCCPs are co-assembled from PEG-*b*-P(TM-co-DTC)-PEI asymmetric triblock copolymer and cNGQ-PEG-*b*-P(TM-co-DTC) diblock copolymer. cNGQ/RCCPs achieve high loading of siRNA into their lumen by charge interactions with short PEI. siPLK1-loaded cNGQ/RCCPs exhibit high tumor accumulation, efficient uptake by  $\alpha_3\beta_1$ -overexpressing A549 lung cancer cells, and fast cytoplasmic release of siPLK1, resulting in effective treatment of orthotopic A549 human lung tumor-bearing nude mice. Reproduced from [60] with the permission of Wiley.

consisting of galactose-PLys-*b*-PCys and PEG-*b*-P(Lys-DCA) for targeted delivery of miR155 to tumor associated macrophages (TAMs) [139]. Thus obtained nanocomplexes induced about 100 to 400-fold increase of miR155 expression in TAMs both *in vitro* and *in vivo*, promoted repolarization of TAMs to anti-tumor M1 macrophages, and increased active T lymphocytes and NK cells in tumors, resulting in robust regression of B16F10 tumor. Moreover, RIF7 peptide modified HA-coated reducible hyperbranched poly(amido amine)/pDNA (RIF7-HA/PAMAM<sub>ss</sub>/pDNA) nanoparticles was designed for annexin 1 and CD44 dual-targeted delivery of short hairpin RNA-encoding pDNA (pDNA-shRNA) to treat pulmonary metastatic B16F10 melanoma in mice [140]. The results pointed out that pDNA-shRNA containing dual-targeted nanoparticles significantly prolonged the median survival time of tumor-bearing mice from 9 days (PBS group) to 22 days and produced much better gene silencing effect with less B16F10 melanoma cells deposited in lungs than single or non-targeted controls.

## 5. Reduction-sensitive polymeric nanomedicines for lung cancer treatment

Lung cancer is the leading cause of cancer death in men and second leading cause of cancer death in women worldwide [141]. Non-small cell lung cancer (NSCLC), accounting for about 85% of lung cancers, has gained particular attention in evaluating the lung cancer related antitumor performance of reduction-sensitive polymeric nanosystems. Human A549 and H460 serve as the mostly studied types of NSCLC tumors. Wu et al. synthesized a cysteine based hydrophobic poly(disulfide amide) polymer to form reduction-sensitive nanoparticles in the presence of lipid PEG to deliver DTX to subcutaneous A549 lung tumor in mice [142]. The resulting

nanoparticles with a high DTX loading capacity up to 25 wt% significantly improved the tumor inhibition *in vivo* as compared to free DTX or DTX-loaded PLGA nanoparticles. To improve the performance of PLGA nanoparticles, a reductively cleavable vitamin E-SS-oligo (methyl diglycol L-glutamate) was used as a surfactant and further coated with HA to achieve CD44-targeted delivery and fast intracellular release of DTX [143]. Thus obtained DTX-loaded multifunctional PLGA nanoparticles with sizes of about 60 nm showed specific and potent cytotoxicity to A549 cells with an IC<sub>50</sub> of 0.52  $\mu$ g/mL, lower than that of free DTX (0.87  $\mu$ g/mL). *In vivo* studies demonstrated that these nanoparticles completely suppressed the growth of orthotopic A549-Luc tumor in mice and led to 100% mice survival over an experimental period of 50 days, which was significantly longer than free DTX treated group (median survival time: 32 days). cNGQ peptide decorated disulfide-crosslinked polymersomal DOX based on PEG-*b*-P(TM-co-DTC) showed superior treatment of both orthotopic and subcutaneous A549 tumor-bearing mice to DOX-LPs, leading to 3.1-fold higher tumor accumulation, effective tumor inhibition, significantly prolonged survival time and reduced side effects. Moreover, cNGQ-decorated chimeric PEG-*b*-P(TM-co-DTC)-*b*-PEI polymersomes (cNGQ/RCCPs) were employed for high-efficiency targeted delivery of Polo-like kinase1 specific siRNA (siPLK1) to orthotopic A549 lung cancer bearing nude mice (Fig. 5) [60]. *In vitro* and *in vivo* studies showed that siPLK1-cNGQ/RCCPs substantially down-regulated PLK1 mRNA level in A549-luc cells and effectively inhibited tumor growth. Aminoglucose (AG)-functionalized reduction-sensitive shell-sheddable micellar PTX based on AG-PEG-SS-PLA showed ca. 3.4-fold lower IC<sub>50</sub> to drug resistant A549 lung tumor cells (A549/ADR) *in vitro* and about 4-fold better inhibition of A549/ADR tumor in



**Fig. 6.** Anisamide-functionalized reversibly crosslinked chimeric polymersomes based on PEG-*b*-P(HPMA-LA)-*b*-PAA asymmetric triblock copolymer show high loading of GrB protein into their lumen, selective internalization by sigma receptor-overexpressing H460 lung cancer cells, and triggered intracellular release of GrB, leading to potent inhibition of H460 lung cancer cells *in vitro* and *in vivo*.

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vivo compared to the reduction-insensitive PEG-*b*-PLA micellar PTX [144].

Wadhwa et al. conjugated D-penicillamine and Idarubicin anti-cancer drugs to the side chain of poly(L-glutamic acid) via disulfide and pH-sensitive hydrazone bonds, respectively [145]. The resulting dual-sensitive dual drug conjugate enhanced the drug exposure by 7-fold and induced a 2 to 3-fold higher therapeutic index than free drugs in H460 tumor-bearing mice. Yang et al. reported that anisamide-functionalized disulfide-crosslinked chimeric polymersomes based on PEG-*b*-poly(N-2-hydroxypropyl methacrylamide-*g*-LA)-*b*-poly(2-(dimethylamino)ethyl methacrylate) (PEG-*b*-P(HPMA-LA)-*b*-PDMA) triblock copolymer had a high loading content of 22 wt% for hydrophilic methotrexate sodium (MTX·2Na) [146]. MTX·2Na-loaded polymersomes showed a 10-fold lower IC<sub>50</sub> against H460 cells than free MTX·2Na, 9-fold enhanced tumor accumulation, and ca. 8-fold better tumor inhibition in H460 tumor model than Trexall, clinically used MTX·2Na injection. Anisamide modified disulfide-crosslinked chimeric polymersomes based on PEG-*b*-P(HPMA-LA)-*b*-PAA (PAA: poly(acrylic acid)) were developed for efficient loading and targeted delivery of GrB to H460 lung tumor (Fig. 6) [147]. GrB-loaded polymersomes displayed a remarkably low IC<sub>50</sub> of 7.8 nM *in vitro* and complete tumor growth inhibition *in vivo* at a low dosage of 6.24 nmol GrB equiv./kg, suggesting its remarkable antitumor efficacy.

Octreotide(Phe)-functionalized PEG-SS-PTX was investigated for targeted therapy of human H446 small cell lung cancer *in vivo* [148]. The results showed substantial tumor growth inhibition compared to reduction-insensitive control (tumor inhibition rate: 79.4% versus 66.3%). Lee et al. reported that disulfide-crosslinked PEG-(Cys)<sub>4</sub>-PDLLA micellar DOX had 7 and 19-fold enhanced DOX accumulation in subcutaneous murine M109 lung tumor than the non-crosslinked control and free DOX·HCl, respectively [149]. Interestingly, disulfide-crosslinked micellar DOX led to almost complete inhibition of tumor growth at a low DOX dosage of 2 mg/kg.

## 6. Reduction-sensitive polymeric nanomedicines for malignant glioma treatment

Glioblastoma is one of the most aggressive human malignancies with poor prognosis. The presence of blood brain barrier (BBB) hinders the penetration of therapeutics into the tumor site. In recent years, reduction-sensitive polymeric nanomedicines have been decorated with brain-targeting ligands to enhance anti-glioblastoma effect. Jiang et al. reported that RNAi nanoparticles based on iNGR-modified reduction-sensitive poly(disulfide branched oligoethylenimine)-PEG polycations exhibited significantly more accumulation in orthotopic U87 glioma than the non-targeting control, leading to remarkable down-regulation of tumor luciferase [150]. Morales-Cruz et al. disclosed that reduction-activatable protein conjugate, FA-PEG-*b*-PLGA-SS-CC, was able to inhibit growth of orthotopic murine GL261 tumor by 40% [151].

Giving the fact that cRGD peptide is able to cross the BBB and target to human U87MG glioma cells [152,153], cRGD-decorated reduction-sensitive polymeric nanomedicines have been investigated for anti-glioma therapy. cRGD-functionalized reduction-sensitive shell-sheddable micellar DOX based on PEG-SS-PCL exhibited 4-fold stronger cellular uptake and 5.3-fold lower IC<sub>50</sub> in U87MG cells than cRGD-decorated reduction-insensitive control as a result of fast intracellular drug release [154]. *In vivo* studies in subcutaneous U87MG tumor model revealed significantly more effective tumor inhibition than cRGD-decorated reduction-insensitive control. cRGD-decorated disulfide-crosslinked micelles based on PEG-*b*-P(CL-co-DTC) enhanced the DOX exposure by 2.6 and 8.5-fold compared to the non-crosslinked counterpart and free DOX·HCl, respectively, leading to significantly reduced systemic toxicity and comparable tumor suppression to DOX-LPs [59]. To further improve their delivery efficacy, TAT was introduced into cRGD-PEG-*b*-P(CL-co-DTC) micelles [155]. These dual-ligand disulfide-crosslinked micelles showed 8.3 and 18.3-fold higher uptake in U87MG cells than cRGD single-ligand and non-targeted controls, respectively. Interestingly,

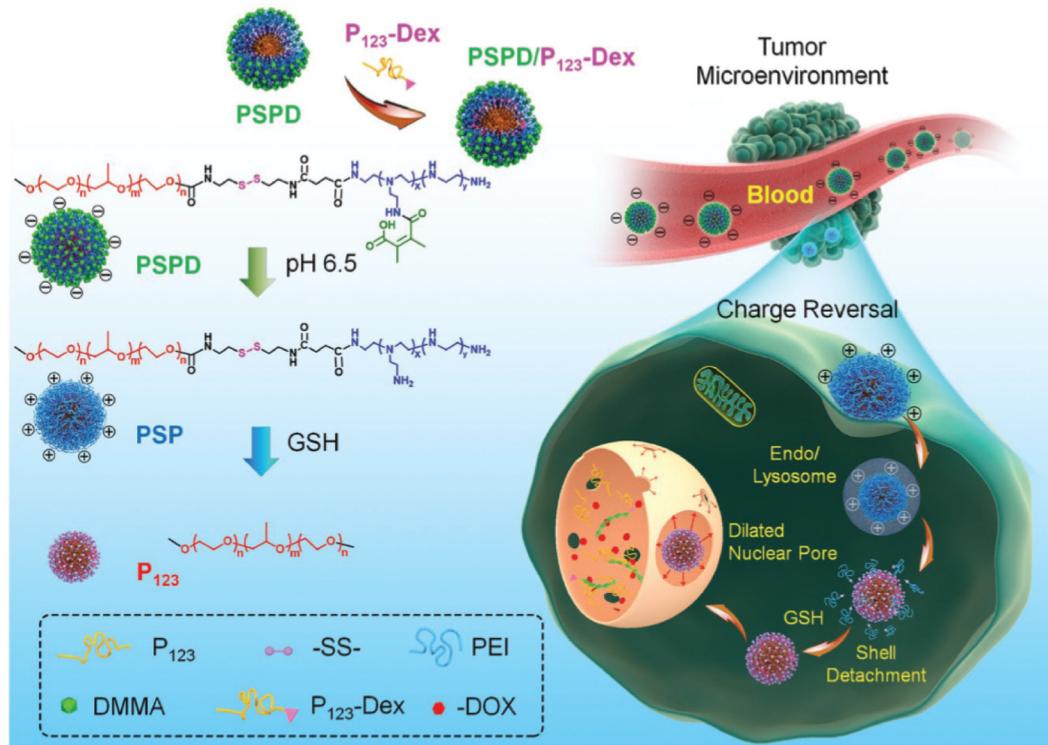
DTX-loaded dual-ligand micelles displayed significantly improved accumulation and deep penetration in U87MG tumor tissue, leading to nearly complete inhibition of tumor growth in 21 days. In a further work, PEG-*b*-P(CL-*co*-DTC) micelles were decorated with 20 mol% Angiopep-2 and 10 mol% TAT [156]. DTX-loaded brain tumor-targeting and cell-penetrating micelles showed markedly enhanced BBB permeation, and accumulation and penetration in orthotopic U87MG human glioma model, leading to significantly better glioma inhibition and survival rate than the corresponding Angiopep-2 single peptide-functionalized control. Chen et al. reported that DOX-loaded cRGD-decorated reduction-sensitive poly(vinyl alcohol) nanogels effectively inhibited growth of subcutaneous U87MG tumor *in vivo*, with relative tumor volumes about 4.5 and 7.1-fold smaller than non-targeting and reduction-insensitive controls, respectively [157]. Huang et al. reported that intratumoral injection of p53 gene complexes with reduction-responsive hyperbranched polyaminoglycosides showed efficient transfection in C6 tumor in mice, leading to about 2-fold better tumor inhibition than the reduction-insensitive counterpart [158].

The high stability of disulfide-crosslinked polymeric nanomedicines offers a unique possibility to co-functionalize them with two different ligands that not only significantly enhance BBB-crossing ability but also boost glioma accumulation, penetration and selectivity, resulting in superior brain tumor inhibition with reduced systemic toxicity. These dual-targeting disulfide-crosslinked nanomedicines have opened a new avenue to anti-glioma therapy.

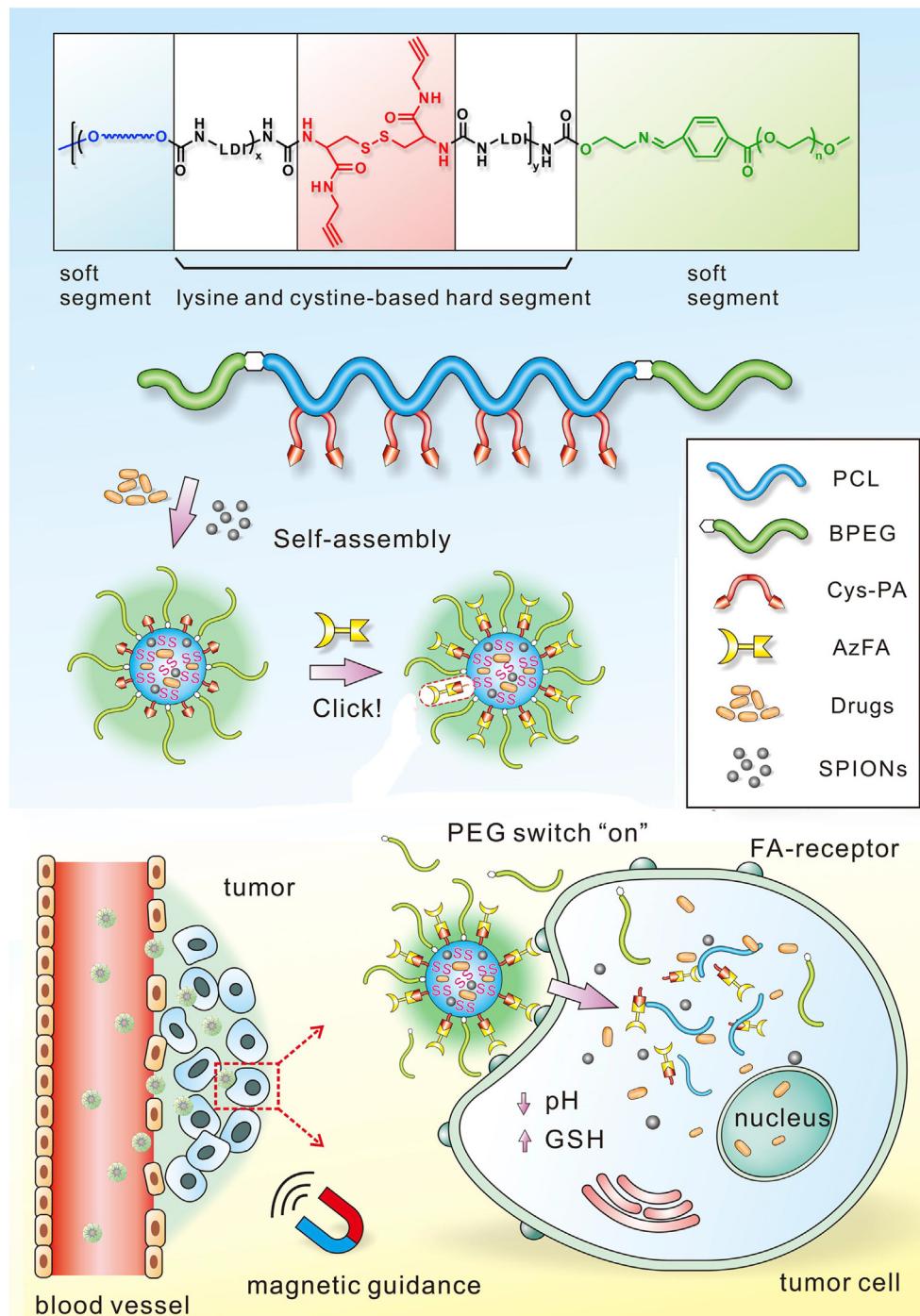
## 7. Reduction-sensitive polymeric nanomedicines for ovarian cancer treatment

Several reduction-sensitive polymeric nanotherapeutics have been investigated for treatment of subcutaneous human SKOV-3 and A2780 ovarian tumor in mice. Song et al. reported that DOX-loaded reducible

micelles based on Dextran-g-SS-DOCA (DOCA: deoxycholic acid) polymer could slow growth of SKOV-3 tumor *in vivo* (tumor inhibition rate: *ca.* 50%) [159]. PTX-loaded disulfide-crosslinked micelles based on PEG-(vitamin E)<sub>4</sub>-LA<sub>4</sub> polymer showed over 2.4-fold better tumor accumulation and significantly higher antitumor efficacy in SKOV-3 tumor-bearing mice than the non-crosslinked counterpart [160]. GrB-loaded, GE11 modified and reduction-sensitive HA nanogels based on HA-g-Tet/GE11 and HA-g-SSMA showed effective growth inhibition of EGFR and CD44 overexpressed SKOV-3 tumor in mice at a low dosage of 3.85 nmol GrB equiv./kg, resulting in a tumor inhibition rate of 87% without causing obvious side effects [111]. Cheng et al. synthesized a reducible cationic polyurethane, SSPUBAP-g-DOCA/PEG-FA (SSPUBAP: 1,4-bis(3-aminopropyl)piperazine and multi-disulfide containing polyurethane), for targeted delivery of TNF-related apoptosis-inducing ligand (TRAIL) therapeutic gene to SKOV-3 ovarian tumor [161]. The resulting polyplexes showed comparable TRAIL expression in SKOV-3 cells to that of branched PEI and significant inhibition of tumor growth *in vivo* (2.9-fold smaller tumor volume compared to PBS group). Chen et al. constructed reduction and pH dual-sensitive micelles based on PEG-*b*-poly(N-(2,2'-dithiobis(ethylamine))-aspartamide)-*b*-poly(2-(diisopropyl amino)ethyl methacrylate) for co-delivery of DOX and Bcl-2 siRNA [162]. These dual-sensitive micelles efficiently delivered and released Bcl-2 siRNA into SKOV-3 cells, resulting in down-regulation of Bcl-2 protein and improved sensitivity to DOX treatment. DOX and Bcl-2 siRNA dual drug-loaded micelles showed a two orders of magnitude lower IC<sub>50</sub> *in vitro* and *ca.* 3.4-fold better tumor inhibition *in vivo* than scrambled siRNA and DOX co-loaded micelles. To achieve ultrasound assisted siRNA delivery to subcutaneous human A2870 ovarian tumor-bearing mice, VEGF siRNA complexes based on PSSAm-g-Arg were integrated with microbubbles [163]. The results showed that ultrasound-assisted siRNA formulation led to 45% of VEGF protein knockdown in A2870 cells and intratumoral injection gave 3 to 4-fold reduced tumor size compared to the scrambled siRNA loaded control.



**Fig. 7.** Reduction and pH dual-sensitive charge reversal micelles (PSPD/P123-Dex) for efficient delivery of DOX into the nucleus of cervical tumor cells. PSPD/P123-Dex micelles undergo charge conversion from negative to positive at the tumor site, enhancing HeLa cell uptake. Cytoplasmic GSH rapidly cleaves disulfide bonds, triggering detachment of PEI shell and size reduction of micelles, which in cooperation with Dex-mediated pore dilation significantly improves the nuclear delivery of DOX, augmenting therapeutic efficacy. Reproduced from [164] with the permission of Wiley.



**Fig. 8.** Illustration of the formation of DOX-loaded, FA-targeted, reduction and pH dual-sensitive multiblock polyurethane micelles for magnetic-guided and PEG-switched targeting of HeLa cervical tumor as well as intracellular stimuli-triggered release of DOX.  
Adapted from [165] with the permission of Elsevier.

### 8. Reduction-sensitive polymeric nanomedicines for cervical cancer treatment

Cervical cancer is one of the most common malignancies in women. Wang et al. developed reduction and pH dual-sensitive charge reversal micelles (PSPD/P123-Dex) based on Pluronic P123-SS-PEI-DA and dexamethasone modified Pluronic P123 polymer for nuclear-targeted delivery of DOX to subcutaneous human HeLa cervical tumor in mice (Fig. 7) [164]. The resulting micellar DOX reversed charge from negative to positive and reduced size from ca. 120 to 95 nm at the slightly acidic pH mimicking that of the tumor site, hence enhancing cellular uptake. In

the cytosol, cleavage of disulfide bonds led to detachment of PEI shell, further size reduction to about 30 nm and exposure of Dex moieties for nuclear targeting and nuclear pore dilating. The cooperative strategy of nuclear targeted and dual-sensitive micellar DOX significantly improved the delivery of DOX to cell nuclei and induced over 2-fold more efficient tumor inhibition *in vivo* than its reduction-insensitive control. Wei et al. reported that DOX-loaded, FA-targeted, reduction and pH dual-sensitive multiblock polyurethane micelles with PEG-switched targeting ability exhibited a tumor growth inhibition rate of 87% against HeLa cervical tumor (Fig. 8) [165]. Notably, a high tumor growth inhibition rate of 98.6% was achieved by incorporating Fe<sub>3</sub>O<sub>4</sub>

nanoparticles for magnetic guidance. Liu et al. developed a GSH-activatable light-up micelle consisting of PEG-SS-oligoethylenimine-boron dipyrromethene (PEG-SS-OEI-BODIPY) for precise image guided DTX delivery and real-time monitoring the pharmacokinetics in subcutaneous HeLa tumor-bearing mice [166]. The fluorescence of micelles is quenched during circulation while activated in the tumoral and intracellular reductive environment as a result of detaching PEG shell, DTX release and BODIPY exposure, providing a robust way to monitor the temporal and spatial pharmacokinetic. Moreover, DTX-loaded light-up micelles revealed *ca.* 3.7-fold lower IC<sub>50</sub> *in vitro* and *ca.* 2-fold better tumor inhibition *in vivo* than free DTX. A star shaped βCD-OEI-SS-FA was designed to co-deliver PTX and Nur77 gene to efficiently treat the Bcl-2 high expression drug resistant HeLa tumor in mice, wherein Nur77 gene is capable of conversing the function of Bcl-2 from anti-apoptosis to apoptosis inducer [167]. *In vivo* studies showed that PTX and Nur77 co-loaded polyplexes obviously inhibited the tumor growth with a final volume of about 46 mm<sup>3</sup>, whereas PTX-loaded control and free PTX caused much lower tumor growth inhibition efficiency with the final tumor sizes reaching over 600 mm<sup>3</sup>, highlighting the enhanced therapeutic efficacy of this co-delivery system. Lin et al. synthesized reducible poly(ester amide)s with pendent iodinated BODIPY that formed nanoparticles with a size of about 200 nm [168]. Under green light irradiation, these nanoparticles would generate ROS, leading to growth suppression of murine U14 cervical tumor *in vivo*.

## 9. Reduction-sensitive polymeric nanomedicines for treatment of other cancers

Reduction-sensitive polymeric systems have also been explored for treatment of subcutaneous EAT, pancreatic, squamous cell carcinoma, colon and gastric tumor as well as peritoneal prostate tumor. Koul's group reported that FA and trastuzumab dual-ligand functionalized reduction-sensitive polymersomal DOX based on POEGMA-*b*-PCL-SS-PCL-*b*-POEGMA or PEG-SS-PLA-SS-PLA-SS-PEG triblock copolymer showed low systemic toxicity while nearly complete ablation of subcutaneous EAT tumor in mice [169,170]. DOX-loaded, FA and trastuzumab dual-targeted, reductively degradable nanoparticles based on multi-disulfide containing poly(ester urethane) multiblock copolymers consist of PEG-*b*-PLA-*b*-PEG or PEG-*b*-PLA-*b*-PEG showed a tumor inhibition rate of 99% in subcutaneous EAT tumor-bearing mice [171,172]. DOX and siPLK1 co-loaded reduction-sensitive P(OEGMA-PEI)-SS-PCL nanoparticles induced almost complete elimination of EAT tumor *in vivo*, with tumor volume about 29 and 8.4-fold smaller compared to PBS and siPLK1-loaded controls, respectively [173]. DOX and siPLK1 co-loaded reduction and pH dual-sensitive micelles based on poly(styrene-*alt*-maleic anhydride)-g-PEG/SS-arginine-histidine also induced a 15-fold smaller tumor volume than PBS treated group [174].

Li et al. conjugated a plectin-1 targeted PTP peptide to the surface of reduction-sensitive 8-arm-PEG-SS-PAMAM dendrimer nanoparticles for targeted co-delivery of PTX and TR3 siRNA to treat subcutaneous PANC-1 pancreatic tumor in mice [175]. Thus obtained systems were demonstrated to knockdown TR3 and simultaneously decrease the expression of Bcl-2 and survivin antiapoptotic proteins, leading to synergistic antitumor effects both *in vitro* and *in vivo* with complete tumor ablation after 24 days treatment. A reduction and pH dual-sensitive photosensitizer and CPT prodrug (Dextran-g-PpIX/PBA-SS-CPT) was synthesized *via* conjugation of protoporphyrin IX (PpIX) and CPT to dextran through ester bond and disulfide containing pH-sensitive linker, respectively [176]. These prodrug micelles showed enhanced cellular uptake and photodynamic efficiency under short-time and long-time light irradiation as well as fast release of CPT to the cytosol, resulting in 43-fold higher tumor inhibition effect than free CPT in PANC-1 pancreatic tumor xenografts. cRGD-decorated disulfide-crosslinked rod shaped polyion complex micelles based on cRGD-PEG-*b*-P(Lys-SH) and pDNA encoding soluble fms-like tyrosine kinase-1

were reported to significantly inhibit the growth of subcutaneous BxPC-3 pancreatic tumor in mice [177].

Pyridine disulfide, lithocholic acid and DA co-modified branched PEI provides a disulfide-crosslinked and pH-sensitive charge conversional nanoparticles for efficient delivery of DOX to subcutaneous SCC7 squamous cell carcinoma in mice [178]. DOX level in the tumor was 2.9 and 8.8-fold higher than the non-crosslinked control and free DOX, respectively, resulting in more than 2-fold better tumor inhibition. Disulfide-crosslinked micellar DOX based on HA-*b*-PPDSEMA diblock copolymer was also reported to afford 2-fold higher accumulation and significantly increased tumor growth inhibition in SCC7 tumor-bearing mice than the non-crosslinked control [179].

Reduction-sensitive glycol chitosan-g-SS-PheoA photosensitizer nanoparticles were designed for photodynamic therapy of subcutaneous human HT-29 colon tumor in mice [180]. The results showed significantly improved antitumor efficacy upon laser irradiation, leading to reduction of tumor volume from *ca.* 60 to 20 mm<sup>3</sup> after 8 days treatment. Recently, reduction-responsive adenosine triphosphate (ATP)-depleting micelles were developed based on 8-arm-PEG-SS-P123-PEI for PTX and siPLK1 co-delivery [181]. Interestingly, PTX and siPLK1-co-loaded micelles exhibited about 2-fold better inhibition of drug resistant human colon tumor (HCT-8/ADR) than free PTX. DOX-loaded reduction and pH dual-sensitive micelles based on poly(L-histidine)-SS-polyurethane-SS-poly(L-histidine) triblock copolymer showed over 2-fold enhanced antitumor efficiency while reduced systemic toxicity in subcutaneous murine CT-26 colon tumor-bearing mice than free DOX [182].

Anti-miR-21 formulated with reduction-sensitive PEG-SS-PLA-SS-PEI micelles were reported to down-regulate miR-21 and induce apoptosis of SGC7901 gastric cells [183]. *In vivo* studies showed effective growth inhibition of SGC7901 gastric tumor. Interestingly, miR-145 complexes based on arginine oligomer (R11) modified disulfide-crosslinked branched PEI (R11-SSbPEI) showed over 3-fold improved tumor accumulation than their SSbPEI counterpart and completely inhibited growth of peritoneal PC3 prostate tumor *in vivo* [184].

## 10. Conclusions and perspectives

The past several years have witnessed an explosive advancement of diverse reduction-sensitive polymeric nanomedicines for efficient treatment of various tumor models. These reduction-sensitive nanosystems, in particular prodrugs and disulfide-crosslinked nanoparticles, have demonstrated high stability under physiological condition as well as GSH-triggered fast cytoplasmic drug release inside the cancer cells, leading to multi-fold enhancement of tumor accumulation and tumor inhibition rate compared to reduction-insensitive counterparts. Notably, reduction-sensitive polymeric nanosystems have been applied for active intracellular delivery of hydrophilic or hydrophobic small chemical drugs as well as varying biotherapeutics such as therapeutic proteins and siRNA. The simultaneous intracellular delivery of dual drugs, either chemical drug cocktails or combination of chemical drugs and biotherapeutics, endows synergistic treatment effect, leading to further improved tumor inhibition rate *in vivo*. Moreover, the high stability of reduction-sensitive polymeric nanomedicines allows versatile functionalization with diverse targeting ligands, to attain single or dual-targeted treatment of various solid tumors. Many preclinical studies corroborate that active targeting reduction-sensitive polymeric nanomedicines are highly potent in suppressing the growth of varying malignancies including triple-negative breast tumor, non-small cell lung cancer, hepatoma, melanoma, glioblastoma and pancreatic tumor, outperforming currently used clinical formulations. Furthermore, several preliminary studies have shown that reduction-sensitive polymeric nanomedicines with fast cytoplasmic drug release can also effectively inhibit cancer metastasis, kill cancer stem cells and reverse multi-drug resistance *in vivo*.

It should be noted, however, that given their tremendous progress, reduction-sensitive nanomedicines have shown to improve the tumor inhibition rate to varying degrees and none of these systems have reached the stage of clinical translation to date. It is found that many reported reduction-sensitive nanomedicines have a complicate design and involve multi-step fabrication and/or exotic materials that pose potential toxicity concerns. Low cancer cell specificity and uptake is another problem for reduction-sensitive polymeric nanomedicines. Even for targeted systems, though enhanced tumor accumulation is observed, uptake by major organs like liver and off-target healthy cells remains an issue. It will be interesting to develop more specific systems utilizing antibody or antibody fragments as targeting ligands, as for antibody drug conjugates. It should further be noted that we do not know exactly how much reduction-sensitive polymeric nanomedicines, likely only a low percentage, can effectively escape from the endo/lysosomal compartments and transport to the cytosols. Moreover, disulfide cleavage kinetics and extent in the cytosol, which heavily depends on the accessibility of glutathione to nanosystems, is also largely unknown. To unveil the intracellular trafficking kinetics, intracellular reductive degradation and drug release profiles of reduction-sensitive polymeric nanomedicines, in-depth biophysical characterization needs to be undertaken in the future. It would be interesting to further develop strategies to promote endosomal escape of reduction-sensitive polymeric nanomedicines. Nevertheless, aiming at clinical translation, we have to balance the complexity and added multi-functionalities of nanosystems. Very recently, we have developed a robust, versatile and fast glutathione-responsive reversibly crosslinked nano-platform including polymersomes and micelles based on the proprietary dithiolane trimethylene carbonate (DTC) technology for active loading and targeted delivery of varying drugs such as therapeutic proteins, siRNA, and small chemical drugs to different tumor models including orthotopic lung tumor, glioblastoma and melanoma. Encouraged by the preclinical results, we in collaboration with a local pharmaceutical company in Suzhou are endeavored to bring tumor-targeting reversibly crosslinked nanosystems to clinical translation. We are convinced that reduction-sensitive polymeric nanomedicines provide an emerging platform for targeted cancer therapy.

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