Drug Delivery Systems Polymeric Nanocarriers in Cancer Therapy

Subjects: Oncology

Contributor: Nataša Avramović , Ana Savic-Radojevic

Conventional chemotherapy is the most common therapeutic method for treating cancer by the application of small toxic molecules that interact with DNA and cause cell death. Unfortunately, these chemotherapeutic agents are non-selective and can damage both cancer and healthy tissues, producing diverse side effects, and they can have a short circulation half-life and limited targeting. Many synthetic polymers have found application as nanocarriers of intelligent drug delivery systems (DDSs). Their unique physicochemical properties allow them to carry drugs with high efficiency, specifically target cancer tissue and control drug release. In recent years, considerable efforts have been made to design smart nanoplatforms, including amphiphilic block copolymers, polymer-drug conjugates and in particular pH- and redox-stimuli-responsive nanoparticles (NPs).

block copolymers polymer-drug conjugates polymeric nanocarriers cancer therapy

1. Introduction

After cardiovascular diseases, cancer is the second leading cause of death worldwide [1]. Conventional chemotherapy is the most commonly used approach in cancer treatment, along with surgery, irradiation and immunotherapy [2]. It is based on the application of small toxic chemotherapeutic molecules that interact with DNA molecules, modify them and induce cell death in cancer tissues [3][4]. Cancer cells have altered lipid and amino acid metabolic pathways, glycolysis, and redox homeostasis [1][5]. Indeed, altered energy metabolism with upregulated glucose transporter expression, disrupted redox homeostasis with upregulated glutathione transferase (GST) and high telomerase activityare responses that maintain DNA integrity, retaining replication, proliferation and cancer cell resistance [1][5][6]. Chemotherapy has many disadvantages, including drug toxicity, rapid degradation, low specificity and limited targeting. In the last few decades, nanomedicine has assumed an important role in cancer therapy based on diverse tailor-made drug delivery systems (DDSs) [7]. Nanomedicine produces materials with sizes ranging from 1–100 nm, which are used as drug nanocarriers with exceptional properties, such as their size, solubility, hydrophilicity, high specificity and a suitable drug-release profile. Nanocarriers also have an enhanced permeability and retention effect (EPR) due to their accumulation in cancer tissue with leaky vasculature [8].

Chemotherapeutics are mostly drugs that are poorly soluble in water with a limited delivery to the target tissue. Encapsulation or entrapment of drugs in nanocarriers facilitates their transport in the circulation to the cancer tissue, inhibiting their rapid biodegradation and improving their bioavailability [9]. Moreover, nanocarriers with incorporated drugs provide a longer circulation half-life of drugs, increasing their efficacy and enabling a lower dose

of application [2][9]. Compared with natural polymers, synthetic nanocarriers can be tailored to control the release of encapsulated drugs by modifying their structure [10].

2. Polymeric Nanoparticles (NPs)

Polymeric NPs are particles obtained from natural, semi-synthetic or synthetic polymers. Polymeric nanosystems are produced by a polymerization reaction of many monomer units, and under certain conditions, they can be organized and self-assemble with ananometric size (10–100 nm) [10][11][12]. Due to the high diversity of their properties, NPs attract great attention as multifunctional nanocarriers in DDSs [9][11]

Depending on the preparation method, drugs can be entrapped, encapsulated or bound to polymeric NPs in the form of a nanosphere, a nanocapsule or a drug conjugate (**Figure 1**) [7][9][10]. Nanospheres are colloidal particles that entrap the drug inside their matrix by physical dispersion or by adsorption on the particle surface, while nanocapsules are systems consisting of a core cavity with an encapsulated drug and polymeric shell surrounding it. Polymeric capsules can be designed by the conjugation of targeting ligands that increase selectivity for cancer cells and improve intracellular drug delivery, as well as reducing different side effects and drug toxicity. Targeting ligands of polymeric capsules are commonly monoclonal antibodies (mAbs) or antibody fragments, aptamers, peptides and small molecules, such as folic acid, which are conjugated to the shell-forming block [13][14][15][16][17][18][19]. These ligands are specifically bound to antigens or receptors that are overexpressed on the cancer cell [20] and they enable cellular selectivity and intracellular delivery of polymeric micelles [13]. Different designed polymeric capsules suitable for targeting the release of drugs are shown in **Figure 1**. The efficacy of polymeric carriers modified with targeting ligands depends on the ligand properties, such as their density and binding affinities to receptors, which can enhance receptor internalization and the biodistribution of drugs. Drug-conjugates have a drug that is chemically bonded to the polymer through a linker/spacer. The bond drug-linker/spacer is a common breakage-point when the drug is released at the target site (**Figure 1**).

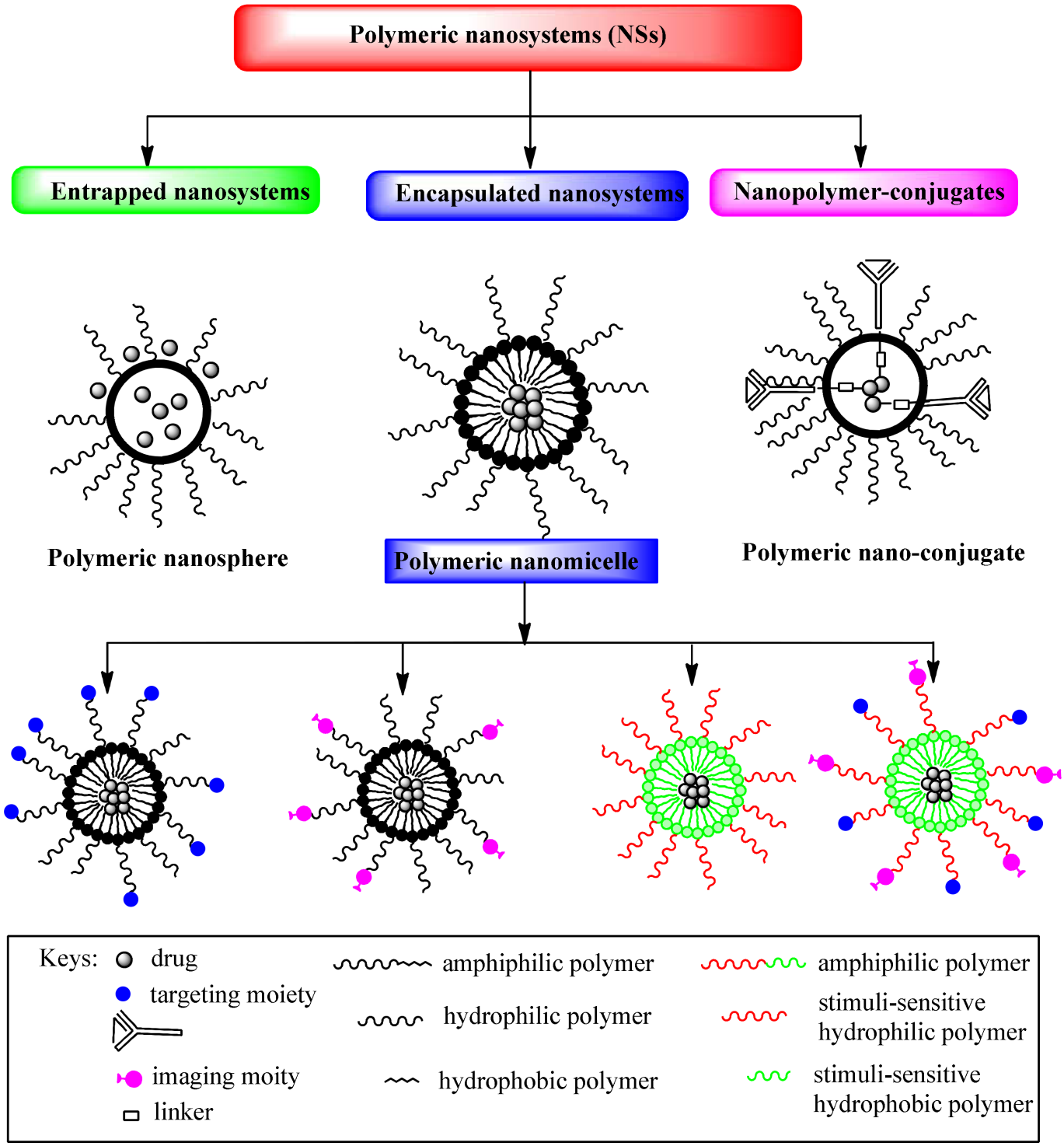

Figure 1. Schematic illustration of multifunctional drug delivery systems.

Natural polymers are biopolymers, including different classes of polysaccharides and proteins, which, due to their biocompatibility and biodegradability, are particularly suitable for medical applications, as in cell-based transplantation, tissue engineering and gene therapy [10] (**Figure 2**). Natural polymers can be combined with synthetic molecules through the chemical modification of their functional groups and so-called semi-synthetic polymers can mimic human tissue components. In formulations of controlled DDSs, synthetic polymers attract

more attention than biopolymers due to the considerable potential for the design of their structure and modifications of their physicochemical properties (**Figure 2**) [8]. Synthetic polymeric micelles exhibita high capacityto incorporate a broad range of bioactive molecules, such as antisense oligonucleotides [21], plasmid DNA [22], proteins [23], small interfering ribonucleic acids (siRNAs) [24], messenger RNAs (mRNAs) [25] and photosensitizers [26], by tailoring the core-forming segments of the block copolymers. In fact, several poly-ion complex (PIC) micelles have been designed that incorporate negatively charged biomolecules by electrostatic interaction with positively charged block copolymers [21][27]. In addition, they can be stabilized by the covalent crosslinking of their core through disulfide bonds [28], which can be cleaved under specific intracellular conditions, enabling the complexes to escape from endosomal compartments after endocytosis and to deliver the biomolecules to subcellular destinations [29] without drug degradation. By introducing hydrophobic molecules such as cholesterol to the core [30], PIC micelles become more stable, with a longer half-life in the bloodstream, allowing for the delivery of intact biomolecules to therapeutic targets. PIC micelles obtained from block copolymers with a core-forming polycation such as polyaspartamides, support enhanced delivery of biomacromolecules to the cytosol of cells, and the gene transfection in vitro and in vivo [25][29][30][31][32][33][34][35].

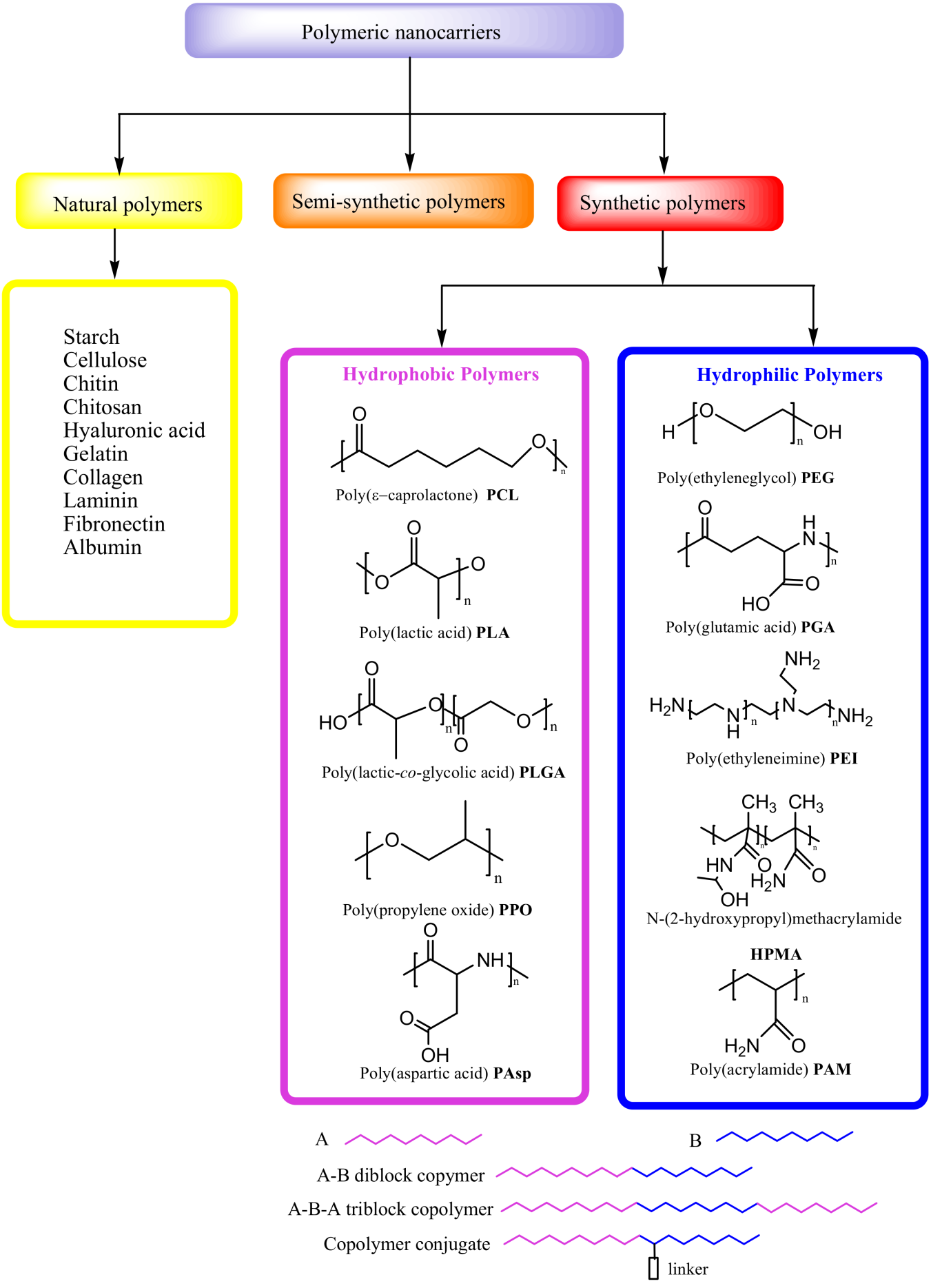
Polymeric nanocarriers
Natural polymers
Semi-synthetic polymers
Synthetic polymers
Starch
Cellulose
Chitin
Chitosan
Hyaluronic acid
Gelatin
Collagen
Laminin
Fibronectin
Albumin
Hydrophobic Polymers
Poly(ε–caprolactone) PCL
Poly(lactic acid) PLA
Poly(lactic-co-glycolic acid) PLGA
Poly(propylene oxide) PPO
Poly(aspartic acid) PAsp
Hydrophilic Polymers
Poly(ethyleneglycol) PEG
Poly(glutamic acid) PGA
Poly(ethyleneimine) PEI
N-(2-hydroxypropyl)methacrylamide
HPMA
Poly(acrylamide) PAM
A
B
A-B diblock copymer
A-B-A triblock copolymer
Copolymer conjugate
linker

Figure 2. Types of polymeric nanocarriers.

In recent years, the great potential of synthetic polymers as drug carriers has been highlighted, particularly because of the possibility to develop DDSs with a target sustained/controlled release of drugs [1]. The encapsulation of cancer drugs in polymeric micelles with modifications for cancer targeting and triggered release results inmore efficient drug delivery (**Figure 1**).

In addition to biocompatibility and biodegradability, synthetic polymers used in DDSs should be activated at the site of action, to be stable in blood circulation, to have low toxicity and immunogenicity, and to provide protection fromthe degradation of drugs before the target tissue is reached. Additionally, it is necessary that polymer nanocarriers of DDSscan be easily synthesized without impurities [8].

3. Amphiphilic Block Copolymers as Carriers in Drug Delivery Systems

3.1. Hydrophobic and Hydrophilic Polymeric Nanocarriers

Polymeric micelles are the most common nanocarriers of DDSs as regards the original core-shell structure [8]. They consist of amphiphilic block copolymers with hydrophilic and hydrophobic units that self-assemble in water solution at the critical micelle concentration (CMC). Micellar polymeric units can be formed in different ways, such as diblock copolymers (A-B), triblock copolymers (A-B-A) and copolymer conjugates (**Figure 2**) [9].

The hydrophobic core is suitable for encapsulating poorly water-soluble drugs, and the pharmacokinetics of drug release can be controlled by its modification. The most frequently used hydrophobic polymers for core formation of NPs are: poly(ε-caprolactone) (PCL), poly(lactic acid) (PLA), poly(lactic-*co*-glycolic acid) (PLGA), poly(propylene oxide) (PPO) and poly(aspartic acid) (PAsp) (**Figure 2**). The hydrophilic polymers that are most frequently considered for the hydrophilic shell of NPs in DDS include poly(ethylene glycol) (PEG), poly(glutamic acid) (PGA), poly(ethyleneimine) (PEI), N-(2-hydroxypropyl)methacrylamide (HPMA) and poly(acrylamide) (PAM) (**Figure 2**). A frequently used hydrophilic polymer of DDSs is PEG, which providesdistinctstability to NPs due to the reduction of nonspecific interactions with blood proteins, thus preventing their aggregation [36].

3.2. Block Copolymers of DDSs in Cancer Therapy

Poly(ethylene glycol)-b-poly(ε-caprolactone)(PEG-PCL) is a polyether-polyester diblock copolymer, synthesized by ring-opening polymerization of ε-caprolactone and PEG [37]. It is suitable for a variety of DDSs because ofits high biocompatibility, biodegradability and low toxicity. Many DDSs based on PEG-PCL with different hydrophilic/hydrophobic ratios (PEG/PCL) have been obtained, enablinghigher cellular internalization byincreasingPEGcontribution(PEG/PCL = 5/5) [38]. Çırpanlı et al. have recently developed PEG-PCL nanocarriers for the controlled delivery of camptothecin (CPT), whose active lactone form was maintained by drug entrapment to hydrophobic PCL, preventing drug hydrolysis in the carboxylate inactive form (**Table 1**) [39]. Furthermore, Hu et al.have designed a nanoplatform with paclitaxel (PTX) encapsulated in a triblock PCL-PEG-PCL copolymer that in

combination with circadian chrono-modulated chemotherapy confirmed sustained drug release and a lower cytotoxic effect compared with free PTX injection [40]. Hong et al. obtained image-guided polymeric micelles, including a folate-conjugated PEG-b-PCL copolymer loaded with doxorubicin (DOX) and superparamagnetic iron oxide nanoparticles (SPIONs) [41]. Active targeting was achieved by the conjugation of folic acid to the PEG-b-PCL shell-forming block, allowing micelles to specifically bind to receptors for folic acid that are overexpressed on the tumor cells. Drug-delivery efficiency and diagnostics were considerably improved by the combination of active tumor targeting and imaging in human hepatic carcinoma cells (Bel 7402 cells). Bel 7402 cells overexpress surface receptors for folic acid that bind these folate-conjugated polymeric micelles, providing targeted delivery of DOX to the cancer cells and exhibiting high inhibition of proliferation as compared to non-targeted micelles. The epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein with an intracellular tyrosine kinase domain, which is overexpressed on the cells of solid cancers [42]. Lee et al. developed EGF-receptor-targeted PEG-b-PCL micelles with incorporated DOX and labeled with ^{111}In. Images were taken with micro-SPECT/CT intratumoral distribution of both targeted and non-targeted micelles confirmedenhanced accumulation in tumor tissue with the targeted micelles (T-BCM) as compared to non-targeted micelles (NT-BCM) [43].

Table 1. Polymeric-anticancer drug nanoparticles (NPs), their loading mode and function.

Polymer	Drug	Loading Mode	Function	Reference
PEG-PCL	Camptothecin (CPT)	Entrapment	Colon, breast, ovarian, lung and brain cancers	[39]
PCL-PEG-PCL	Paclitaxel (PTX)	Encapsulation	Lung cancers in combination with chrono-modulated chemotherapy	[40]
PLGA-PEG	Paclitaxel (PTX)	Encapsulation	Breast, pancreatic and ovarian and brain cancers	[44]
PLGA-TPGS	Doxorubicin(DOX)- Metformin (Met)	Encapsulation	Multidrug resistance P388 cancer cell lines	[45]
PEG-PGlu	Cisplatin	Encapsulation	Solid cancers	[46][47][48]

Polymer	Drug	Loading Mode	Function	Reference
mPEG-PLGA-PGlu	Doxorubicin(DOX)	Encapsulation	Breast cancer	[49]
PEG-PAsp	Paclitaxel (PTX)	Entrapment	Advanced stomach cancer	[50][51][52]
PEO-b-PAsp	Doxorubicin	Entrapment	Pancreatic cancer	[53]
PEO-PPO-PEO	Doxorubicin.	Encapsulation	Metastatic adenocarcinoma of the esophagus and gastroesophageal junction	[54][55]
PCLLA-PEG-PCLLA	Doxorubicin (DOX)	Encapsulation	Breast cancer	[56]
PEI-PLA	Paclitaxel (PTX)	Entrapment	Lung cancer	[57]
PEG	Camptothecin (CPT)SN38 Irinotecan (C-11)	Copolymer-drug conjugation	Colorectal, metastatic breast cancer, platinum-resistant ovarian cancer and metastatic cervical cancer	[58][59][60] [61][62][63]
HPMA	Doxorubicin (DOX)	Copolymer-drug conjugation	Lung and breast cancer	[64][65]
HPMA	Paclitaxel (PTX)	Copolymer-drug conjugation	Solid cancers	[66]

References

Polymer	Drug	Loading Mode	Function	Reference
HPMA	Diaminocyclohexane(DACH)-platinum	Copolymer-drug conjugation	Solid cancer, ovarian cancer	[67][68][69][70]

3.3. Polymer-Drug Conjugates in Cancer Therapy

Some PEG- and HPMA-drug conjugates are approved by the FDA and have found clinical application due to their excellent properties, such as good solubility in water and many organic solvents, high hydrophilicity, low toxicity and immunogenicity [71][72]. Several important polymer-drug conjugates used in cancer therapy are summarized in **Table 1**.

PEG-based conjugates with the drugs camptothecin (CPT), camptothecin derivatives, SN38 and irinotecan (C-11), used as topoisomerase I inhibitors, have progressed to phases I and II of clinical studies [58][59][60]. These PEG-based conjugates carry the drugs in a lactone-active form bonded to PEG through a glycine spacer. The PEG-CPT conjugate known as prothecan displayed low toxicity and satisfactory tolerance in phase II studies in patients with adenocarcinoma of the stomach and the gastroesophageal (GE) junction, although it confirmed significantly lower drug loading (1.7%) than other polymer-drug conjugates [58]. PEG-SN38 (EZN-2208) and PEG-irinotecan (NKTR-102) conjugates were synthesized by coupling a 4 arm PEG of 40 kDa with SN38 and irinotecan, respectively [61][62]. Irinotecan is a derivative of SN38 containing an additional bis-piperidine group, which the PEG-irinotecan conjugate releases at the targeting site of action, forming the active metabolite SN-38. However, the PEG-SN38 conjugate provided a longer half-life of SN38 in the circulation and it is up to a 245-fold more efficient than PEG-irinotecan conjugate in human cancer cell lines [62]. The anticancer activity of PEG-SN38 was revealed in the therapy of breast, colorectal and pancreatic cancers. The PEG-irinotecan conjugate had a half-life of 15 days compared to 4 h for free irinotecan [70]. The PEG-irinotecan conjugate combined with cetuximab has entered into phase II study in the therapy of ovarian, breast, colorectal and cervical cancers [63].

4. Stimuli-Responsive Polymer-Drug Conjugates

In the last two decades, many small nanoplatforms have been designed by introducing stimuli and targeting moieties into polymers of DDSs [73][74][75][76][77]. Some pH- and redox-responsive polymeric NPs are described here as the most commonly used triggers in DDSs.

Due to increased aerobic glycolysis, cancer cells have an acidic environment (pH 6.5–7.2), in particular the intracellular organelles such as endosomes (pH 5–6) and lysosomes (pH 4–5) [78]. Therefore, many pH-responsive DDSs were designed by covalent attachment of the drug to the polymeric NPs via an acid-labile bond. Bae et al. created diblock PEG-b-Pasp copolymers conjugated with the drug adriamycin via a hydrazone bond, which can be easily cleaved under the acidic conditions found in cancer cells, followed by rapid release of the drug and break-up of copolymers [73]. The hydrazone bond of diverse nanoplatforms has been successfully applied to transport

ess in

l.;

ett.

2017, 190, 64–83.

3. Perez-Herrero, E.; Fernandez-Medarde, A. Advanced targeted therapies in cancer: Drug nanocarriers, the future of chemotherapy. Eur. J. Pharm. Biopharm. 2015, 93, 52–79.
4. Avramović, N.; Ignjatović, N.; Savić, A. Platinum and ruthenium complexes as promising molecules in cat[illegible] therapy. Srp. Arh. Celok. Lek. 2019, 147, 105–109.
5. Escobar, Q.M.; Maschietto, M.; Krepischi, A.C.V.; Avramovic, N.; Tasic, L. Insights into the Chemical Biology of Childhood Embryonal Solid Tumors by NMR-Based Metabolomics. Biomolecules 2019, 9, 843.
6. Radic, T.; Coric, V.; Bukumiric, Z.; Pljesa-Ercegovac, M.; Dinkic, T.; Avramovic, N.; Matic, M.; Mihailovic, S.; Dragicevic, D.; Dzamic, Z.; et al. GSTO1*CC Genotype (rs4925) Predicts Shorter Survival in Clear Cell Renal Cell Carcinoma Male Patients. Cancers 2019, 11, 2038.
7. Hossen, S.; Hossain, K.M.; Basher, M.K.; Mia, M.N.H.; Rahman, M.T.; Uddin, J.M. Smart nanocarrier-based drug delivery systems for cancer therapy and toxicity studies: A review. J. Adv. Res. 2019, 15, 1–18.
8. Guo, X.; Wang, L.; Wei, X.; Zhou, S. Polymer-Based Drug Delivery Systems for Cancer Treatment. J. Polym. Sci. A Polym. Chem. 2016, 54, 3525–3550.
9. Parveen, S.; Arjmand, F.; Tabassum, S. Clinical developments of antitumor polymertherapeutics: RSC Adv. 2019, 9, 24699–24721.
10. Fathi, M.; Barar, J. Perspective highlights on biodegradable polymeric nanosystems for targeted therapy of solid tumors. Bioimpacts 2017, 7, 49–57.
11. Calzoni, E.; Cesaretti, A.; Polchi, A.; Di Michele, A.; Tancini, B.; Emiliani, C. Biocompatible Polymer Nanoparticles for Drug Delivery Applications in Cancer and Neurodegenerative Disorder Therapies. J. Funct. Biomater. 2019, 10, 4.
12. Cabral, H.; Kataoka, K. Progress of drug-loaded polymeric micelles into clinical studies. J. Control. Release 2014, 190, 465–476.
13. Allen, T.M. Ligand-targeted therapeutics in anticancer therapy. Nat. Rev. Cancer 2002, 2, 750–763.
14. Torchilin, V. Antibody-modified liposomes for cancer chemotherapy. Expert Opin. Drug Deliv. 2008, 5, 1003–1025.

different anticancer drugs, such as DOX, cisplatin [8] as targeting agents for intratumoral polymeric-drug conjugate, FA-PEG-b-Poly-hydrazone-DOX, with anticancer PEG-PCL copolymer bound to DOX via a labile hydrazone bond, and decorated with folic acid (FA) [8]. This DDS exerts cancer targeting ability through the folate receptor (FR) interfering with endocytosis and pH-triggered drug release by the breaking of the hydrazine bond under acidic conditions (**Figure 3**).

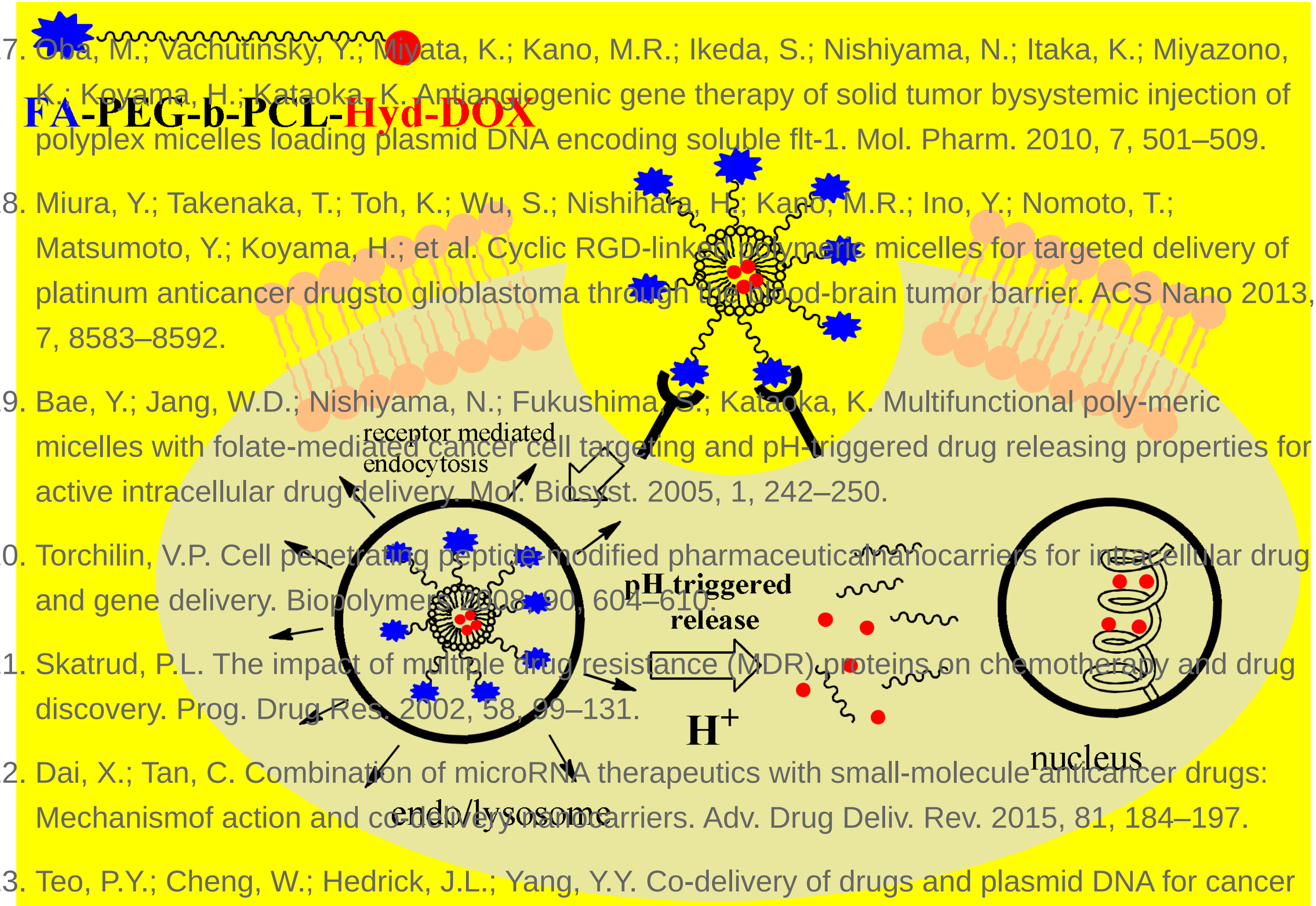

Figure 3. Mechanism of action of pH-responsive polymer nanoparticles (NPs) decorated with targeting ligand folic acid (FA) and with the drug doxorubicin(DOX)bound via a hydrazone bond to diblock copolymerPoly(ethylene glycol)-b-poly(ε-caprolactone)(PEG-PCL).

Due to the increased concentration of glutathione (GSH)in the cytosol and subcellular organelles, there is a redox potential difference between the intra- and extracellular micro environments of normal cellsthat is larger in cancer cells because of the 2- to 4-fold higher concentration of GSH [8]. The significant increase in the intracellular redox potential was used as an internal stimulus for creating intelligent DDSs by introducing a redox-sensitive functional group into the polymeric nanocarrier backbone. Similar to the previously described polymeric-drug conjugate, FA-PEG-b-PCL-hyd-DOX, Sun et al. designed a redox-responsive FA-PECL$_{SS}$-DOX nanocomplex by linking PEG and PCL polymers via a redox-sensitive disulfide bond [76]. Thus, as a result of stimulation by the acidic and reducing medium of cancer cells, GSH triggered DOX release by breaking the disulfide bond, with the

15. Cheng, W.W.; Allen, T.M. The use of single chain Fv as targeting agents for immunoliposomes: An update on immunoliposomal drugs for cancer treatment. Expert Opin. Drug Deliv. 2010, 7, 461–478.
16. Farokhzad, O.C.; Cheng, J.; Teply, B.A.; Sherifi, I.; Jon, S.; Kantoff, P.W.; Richie, J.P.; Langer, R. Targeted nanoparticle-aptamer bioconjugates for cancer chemotherapyin vivo. Proc. Natl. Acad. Sci. USA 2006, 103, 6315–6320.
17. Oba, M.; Vachutinsky, Y.; Miyata, K.; Kano, M.R.; Ikeda, S.; Nishiyama, N.; Itaka, K.; Miyazono, K.; Koyama, H.; Kataoka, K. Antiangiogenic gene therapy of solid tumor bysystemic injection of polyplex micelles loading plasmid DNA encoding soluble flt-1. Mol. Pharm. 2010, 7, 501–509.
18. Miura, Y.; Takenaka, T.; Toh, K.; Wu, S.; Nishihara, H.; Kano, M.R.; Ino, Y.; Nomoto, T.; Matsumoto, Y.; Koyama, H.; et al. Cyclic RGD-linked polymeric micelles for targeted delivery of platinum anticancer drugsto glioblastoma through the blood-brain tumor barrier. ACS Nano 2013, 7, 8583–8592.
19. Bae, Y.; Jang, W.D.; Nishiyama, N.; Fukushima, S.; Kataoka, K. Multifunctional poly-meric micelles with folate-mediated cancer cell targeting and pH-triggered drug releasing properties for active intracellular drug delivery. Mol. Biosyst. 2005, 1, 242–250.
20. Torchilin, V.P. Cell penetrating peptide-modified pharmaceuticalnanocarriers for intracellular drug and gene delivery. Biopolymers 2008, 90, 604–610.
21. Skatrud, P.L. The impact of multiple drug resistance (MDR) proteins on chemotherapy and drug discovery. Prog. Drug Res. 2002, 58, 99–131.
22. Dai, X.; Tan, C. Combination of microRNA therapeutics with small-molecule anticancer drugs: Mechanismof action and co-delivery nanocarriers. Adv. Drug Deliv. Rev. 2015, 81, 184–197.
23. Teo, P.Y.; Cheng, W.; Hedrick, J.L.; Yang, Y.Y. Co-delivery of drugs and plasmid DNA for cancer therapy. Adv. Drug Deliv. Rev. 2016, 98, 41–63.
24. Navarro, G.; Pan, J.; Torchilin, V.P. Micelle-like nanoparticles as carriers for DNA and siRNA. Mol. Pharm. 2015, 12, 301–313.
25. Alinejad, V.; Hossein Somi, M.; Baradaran, B.; Akbarzadeh, P.; Atyabi, F.; Kazerooni, H.; SamadiKafil, H.; AghebatiMaleki, L.; Siah Mansouri, H.; Yousefi, M. Co-delivery of IL17RB siRNA and doxorubicin bychitosan-based nanoparticles for enhanced anticancer efficacy in breast cancer cells. Biomed. Pharmacother. 2016, 83, 229–240.
26. Wei, W.; Lv, P.P.; Chen, X.M.; Yue, Z.G.; Fu, Q.; Liu, S.Y.; Yue, H.; Ma, G.H. Codelivery of mTERT siRNA and paclitaxel by chitosan-based nanoparticles promoted synergistic tumor suppression. Biomaterials 2013, 34, 3912–3923.

drug efficiently killing the cancer cells. Recent studies have also introduced a novel intracellular redox-responsive DDS based on the amphiphilic block copolymer PEG-b-PHEMA with covalently bonded PTX via a disulfide linker to poly(2-hydroxyethyl methacrylate)(PHEMA) in PEG-b-PHEMA (Figure 4)[77]. This biocompatible polymer-drug conjugate, PEG-b-P(HEMA-PTX),possessedglutathione-dependent cytotoxicity, providing higher proliferation inhibition in glutathione monoester-pretreated HeLa cells than in non-pretreated HeLa cells.

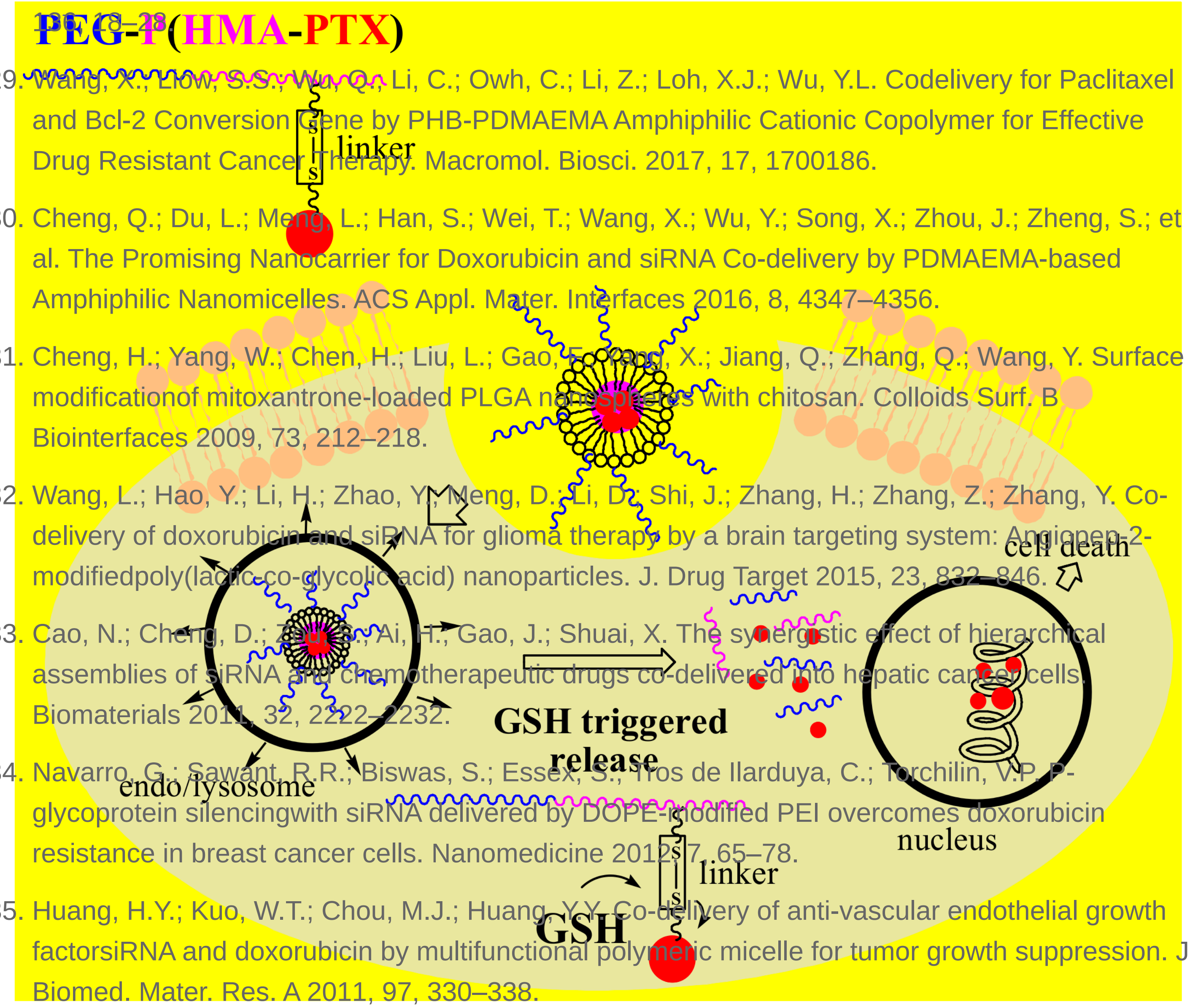

Figure 4. Mechanism of action of redox-responsive polymernanoparticles (NPs) with bonded drug PTX via a disulfide linker to diblock copolymerPoly(ethylene glycol)-b-poly(2-hydroxyethyl methacrylate)(PEG-b-PHEMA).

27. Li, N.; Huang, C.; Luan, Y.; Song, A.; Song, Y.; Garg, S. Active targeting co-delivery system based on pH-sensitive methoxy-poly(ethylene glycol)2K-poly(epsilon-caprolactone)4K-poly(glutamic acid)1K for enhanced cancer therapy. J. Colloid Interface Sci. 2016, 472, 90–98.

28. Pan, J.; Palmerston Mendes, L.; Yao, M.; Filipczak, N.; Garai, S.; Thakur, G.A.; Sarisozen, C.; Torchilin, V.P. Polyamidoamine dendrimers-based nanomedicine for combination therapy with siRNAand chemotherapeutics to overcome multidrug resistance. Eur. J. Pharm. Biopharm. 2019, 136, 18–28.

29. Wang, X.; Liow, S.S.; Wu, Q.; Li, C.; Owh, C.; Li, Z.; Loh, X.J.; Wu, Y.L. Codelivery for Paclitaxel and Bcl-2 Conversion Gene by PHB-PDMAEMA Amphiphilic Cationic Copolymer for Effective Drug Resistant Cancer Therapy. Macromol. Biosci. 2017, 17, 1700186.

30. Cheng, Q.; Du, L.; Meng, L.; Han, S.; Wei, T.; Wang, X.; Wu, Y.; Song, X.; Zhou, J.; Zheng, S.; et al. The Promising Nanocarrier for Doxorubicin and siRNA Co-delivery by PDMAEMA-based Amphiphilic Nanomicelles. ACS Appl. Mater. Interfaces 2016, 8, 4347–4356.

31. Cheng, H.; Yang, W.; Chen, H.; Liu, L.; Gao, F.; Yang, X.; Jiang, Q.; Zhang, Q.; Wang, Y. Surface modificationof mitoxantrone-loaded PLGA nanospheres with chitosan. Colloids Surf. B Biointerfaces 2009, 73, 212–218.

32. Wang, L.; Hao, Y.; Li, H.; Zhao, Y.; Meng, D.; Li, D.; Shi, J.; Zhang, H.; Zhang, Z.; Zhang, Y. Co-delivery of doxorubicin and siRNA for glioma therapy by a brain targeting system: Angiopep-2-modifiedpoly(lactic-co-glycolic acid) nanoparticles. J. Drug Target 2015, 23, 832–846.

33. Cao, N.; Cheng, D.; Zou, S.; Ai, H.; Gao, J.; Shuai, X. The synergistic effect of hierarchical assemblies of siRNA and chemotherapeutic drugs co-delivered into hepatic cancer cells. Biomaterials 2011, 32, 2222–2232.

34. Navarro, G.; Sawant, R.R.; Biswas, S.; Essex, S.; Tros de Ilarduya, C.; Torchilin, V.P. P-glycoprotein silencingwith siRNA delivered by DOPE-modified PEI overcomes doxorubicin resistance in breast cancer cells. Nanomedicine 2012, 7, 65–78.

35. Huang, H.Y.; Kuo, W.T.; Chou, M.J.; Huang, Y.Y. Co-delivery of anti-vascular endothelial growth factorsiRNA and doxorubicin by multifunctional polymeric micelle for tumor growth suppression. J. Biomed. Mater. Res. A 2011, 97, 330–338.

36. Knop, K.; Hoogenboom, R.; Fischer, D.; Schubert, U.S. Poly(ethylene glycol) in drug delivery: Pros and cons as well as potential alternatives. Angew. Chem. Int. Ed. 2010, 49, 6288–6308.

37. Zhou, S.; Deng, X.; Yang, H. Biodegradable poly(epsilon-caprolactone)-poly(ethylene glycol) block copolymers: Characterization and their use as drug carriers for a controlled delivery system. Biomaterials 2003, 24, 3563–3570.

38. Zhang, Z.; Qu, Q.; Li, J.; Zhou, S. The Effect of the Hydrophilic/Hydrophobic Ratio of Polymeric Micelles on their Endocytosis Pathways into Cells. Macromol. Biosci. 2013, 13, 789–798.

39. Çırpanlı, Y.; Allard, E.; Passirani, C.; Bilensoy, E.; Lemaire, L.; Çalış, S.; Benoit, J.P. Antitumoral activity ofcamptothecin-loaded nanoparticles in 9L rat glioma model. Int. J. Pharm. 2011, 403, 201–206.

40. Hu, J.; Fu, S.; Peng, Q.; Han, Y.; Xie, J.; Zan, N.; Chen, Y.; Fan, J. Paclitaxel-loaded polymeric nanoparticles combined with chronomodulated chemotherapy on lung cancer: In vitro and in vivo evaluation. Int. J.Pharm. 2017, 516, 313–322.

41. Hong, G.; Yuan, R.; Liang, B.; Shen, J.; Yang, X.; Shuai, X. Folate-functionalized polymeric micelle as hepatic carcinoma-targeted, MRI-ultrasensitive delivery system of antitumor drugs. Biomed. Microdevices 2008, 10, 693–700.

42. Wen, X.; Wu, Q.P.; Ke, S.; Ellis, L.; Charnsangavej, C.; Delpassand, A.S.; Wallace, S.; Li, C. Conjugation with (111)In-DTPA-poly(ethylene glycol)improves imaging of anti-EGF receptor antibody C225. J. Nucl. Med. 2001, 42, 1530–1537.

43. Lee, H.; Hoang, B.; Fonge, H.; Reilly, R.M.; Allen, C. In vivo distribution of polymeric nanoparticles at the whole-body, tumor, and cellular levels. Pharm. Res. 2010, 27, 2343–2355.

44. Guo, J.; Gao, X.; Su, L.; Xia, H.; Gu, G.; Pang, Z.; Jiang, X.; Yao, L.; Chen, J.; Chen, H. Aptamer-functionalized PEG–PLGA nanoparticles for enhance danti-glioma drug delivery. Biomaterials 2011, 32, 8010–8020.

45. Shafiei-Irannejad, V.; Samadi, N.; Salehi, R.; Yousefi, B.; Rahimi, M.; Akbarzadeh, A.; Zarghami, N. Reversion of Multidrug Resistance by Co-Encapsulation of Doxorubicin and Metformin in Poly(lactide-co-glycolide)-D-α-tocopheryl Polyethylene Glycol 1000 Succinate Nanoparticles. Pharm. Res. 2018, 35, 119.

46. Matsumura, Y. Polymeric Micellar Delivery Systems in Oncology. Jpn. J. Clin. Oncol. 2008, 38, 793–802.

47. Wilson, R.H.; Plummer, R.; Adam, J.; Eatock, M.; Boddy, A.V.; Griffin, M.; Miller, R.; Matsumura, Y.; Shimizu, T.; Calvert, H. Phase I and pharmacokinetic study of NC-6004, a new platinum entity of cisplatin-conjugated polymer forming micelles. Clin. Oncol. 2008, 26, 2573.

48. Plummer, R.; Wilson, R.H.; Calvert, H.; Boddy, A.V.; Griffin, M.; Sludden, J.; Tilby, M.J.; Eatock, M.; Pearson, D.G.; Ottley, C.J. A Phase I clinical study of cisplatin-incorporated polymeric micelles (NC-6004) in patients with solid tumours T. Br. J. Cancer 2011, 104, 593–598.

49. Yuan, J.D.; ZhuGe, D.L.; Tong, M.Q.; Lin, M.T.; Xu, X.F.; Tang, X.; Zhao, Y.Z.; Xu, H.L. pH-sensitive polymericnanoparticles of mPEG-PLGA-PGlu with hybrid core for simultaneous encapsulation of curcumin anddoxorubicin to kill the heterogeneous tumour cells in breast cancer. Artif. Cells Nanomed. Biotechnol. 2018, 46, 302–313.

50. Matsumura, Y. Poly (amino acid) micelle nanocarriers in preclinical and clinical studies. Adv. Drug Deliv. Rev. 2008, 60, 899–914.

51. Hamaguchi, T.; Matsumura, Y.; Suzuki, M.; Shimizu, K.; Goda, R.; Nakamura, I.; Nakatomi, I.; Yokoyama, M.; Kataoka, K.; Kakizoe, T. NK105, a paclitaxel-incorporating micellar nanoparticle formulation, can extend in vivo antitumour activity and reduce the neurotoxicity of paclitaxel. Br. J. Cancer 2005, 92, 1240–1246.

52. Hamaguchi, T.; Kato, K.; Yasui, H.; Morizane, C.; Ikeda, M.; Ueno, H.; Muro, K.; Yamada, Y.; Okusaka, T.; Shirao, K.; et al. A phase I and pharmacokinetic study of NK105, a paclitaxel-incorporating micellar nanoparticle formulation. Br. J. Cancer 2007, 97, 170–176.

53. Vilar, G.; Puche, J.T.; Albericio, F. Polymers and drug delivery systems. Curr. Drug Deliv. 2012, 9, 367–394.

54. Venne, A.; Li, S.; Mandeville, R.; Kabanov, A.; Alakhov, V. Hypersensitizing effect of pluronic L61 on cytotoxic activity, transport and subcellular distribution of doxorubicin in multiple drug-resistant cells. Cancer Res. 1996, 56, 3626–3629.

55. Valle, J.W.; Armstrong, A.; Newman, C.; Alakhov, V.; Pietrzynski, G.; Brewer, J.; Campbell, S.; Corrie, P.; Rowinsky, E.K.; Ranson, M. A phase 2 study of SP1049C, doxorubicin in P-glycoprotein-targeting pluronics, in patients with advanced adenocarcinoma of the esophagus and gastroesophageal junction. Investig. New Drugs 2010, 29, 1029–1037.

56. Hu, D.; Chen, L.; Qu, Y.; Peng, J.; Chu, B.; Shi, K.; Hao, Y.; Zhong, L.; Wang, M.; Qian, Z. Oxygen-generating Hybrid Polymeric Nanoparticles with Encapsulated Doxorubicin and Chlorin e6 for Trimodal Imaging-Guided Combined Chemo-Photodynamic Therapy. Theranostics 2018, 8, 1558–1574.

57. Jin, M.; Jin, G.; Kang, L.; Chen, L.; Gao, Z.; Huang, W. Smart polymeric nanoparticles with pH-responsive and PEG-detachable properties for co-delivering paclitaxel and survivin siRNA to enhance antitumor outcomes. Int. J. Nanomed. 2018, 13, 2405–2426.

58. Greenwald, R.B.; Pendri, A.; Conover, C.D.; Lee, C.; Choe, Y.H.; Gilbert, C.; Martinez, A.; Xia, Y.; Wu, D.; Hsue, M. Camptothecin-20-PEG ester transport forms: The effect of spacer groups on antitumor activity. Bioorg. Med. Chem. 1998, 6, 551–562.

59. Fraier, D.; Frigerio, E.; Brianceschi, G.; Casati, M.; Benecchi, A.; James, C. Determination of MAG-Camptothecin, a new polymer-bound Camptothecin derivative, and free Camptothecin in dog plasma by HPLC with fluorimetricdetection. J. Pharm. Biomed. Anal. 2000, 19, 505–514.

60. Singer, J.W.; Bhatt, R.; Tulinsky, J.; Buhler, K.R.; Heasley, E.; Klein, P.; James, C. Water-soluble poly-(l-glutamic acid)–Gly-camptothecin conjugates enhance camptothecin stability and efficacy in vivo. J. Control. Release 2001, 74, 243–247.

61. Pastorino, F.; Loi, M.; Sapra, P.; Becherini, P.; Cilli, M.; Emionite, L.; Ribatti, D.; Greenberger, L.M.; Horak, I.D.; Ponzoni, M. Tumor Regression and Curability of Preclinical Neuroblastoma

Models by PEGylated SN38 (EZN-2208), a Novel Topoisomerase I Inhibitor. Clin. Cancer Res. 2010, 16, 4809–4821.

62. Sapra, P.; Zhao, H.; Mehlig, M.; Malaby, J.; Kraft, P.; Longley, C.; Greenberger, L.M.; Horak, I.D. Novel Delivery of SN38 Markedly Inhibits Tumor Growth in Xenografts, Including a Camptothecin-11–Refractory Model. Clin. Cancer Res. 2008, 14, 1888–1896.
63. Crozier, J.A.; Advani, P.P.; Plant, B.L.; Anthony, T.H.; Jaslowski, J.; Moreno-Aspitia, A.; Perez, E.A. N0436 (Alliance): A phase II trial of irinotecan plus cetuximab in patients with metastatic breast cancer previously exposed to anthracycline and/or taxane-containing therapy. Clin. Breast Cancer 2016, 16, 23–30.
64. Duncan, R.; Vicent, M.J. Do HPMA copolymer conjugates have a future as clinically useful nanomedicines? A critical overview of current status and future opportunities. Adv. Drug Deliv. Rev. 2010, 62, 272–282.
65. Seymour, L.W.; Ferry, D.R.; Kerr, D.J.; Rea, D.; Whitlock, M.; Poyner, R.; Boivin, C.; Hesslewood, S.; Twelves, C.; Blackie, R.; et al. Phase II studies of polymer-doxorubicin (PK1, FCE28068) in the treatment of breast, lung and colorectal cancer. Int. J. Oncol. 2009, 34, 1629–1636.
66. Terwogt, J.M.M.; ten BokkelHuinink, W.W.; Schellens, J.H.M.; Schot, M.; Mandjes, I.; Zurlo, M.; Rocchetti, M.; Rosing, H.; Koopman, F.M.; Beijnen, J.H. Phase I clinical and pharmacokinetic study of PNU166945, a novel water-soluble polymer-conjugated prodrug of paclitaxel. Anticancer Drugs 2001, 12, 315–323.
67. Campone, M.; Rademaker-Lakhai, J.M.; Bennouna, J.; Howell, S.B.; Nowotnik, D.P.; Beijnen, J.H.; Schellens, J.H. Phase I and pharmacokinetic trial of AP5346, a DACH-platinum-polymer conjugate, administered weekly for three out of every 4 weeks to advanced solid tumor patients. Cancer Chemother. Pharmacol. 2007, 60, 523–533.
68. Rice, J.R.; Howell, S.B. AP-5346. Drugs Future 2004, 29, 561.
69. Kelland, L. Broadening the clinical use of platinum drug–based chemotherapy with new analogues. ExpertOpin. Investig. Drugs 2007, 16, 1009–1021.
70. Nowotnik, D.P.; Cvitkovic, E. ProLindac™(AP5346): A review of the development of an HPMA DACH platinum Polymer Therapeutic. Adv. Drug Deliv. Rev. 2009, 61, 1214–1219.
71. Pasut, G.; Veronese, F.M. PEG conjugates in clinical development or use as anticancer agents: An overview. Adv. Drug Deliv. Rev. 2009, 61, 1177–1188.
72. Kopecek, J.; Kopeckova, P. HPMA copolymers: Origins, early developments, present, and future. Adv. Drug Deliv. Rev. 2010, 62, 122–149.
73. Bae, Y.; Nishiyama, N.; Fukushima, S.; Koyama, H.; Yasuhiro, M.; Kataoka, K. Preparation and biological characterization of polymeric micelle drug carriers with intracellular pH-triggered drug

release property: Tumor permeability, controlled subcellular drug distribution, and enhanced invivo antitumor efficacy. Bioconjug.Chem. 2005, 16, 122–130.

74. Xiong, X.B.; Ma, Z.; Lai, R.; Lavasanifar, A. The therapeutic response to multifunctional polymeric nano-conjugates in the targeted cellular and subcellular delivery of doxorubicin. Biomaterials 2010, 31, 757–768.
75. Wu, P.; Opadele, A.E.; Onodera, Y.; Nam, J. Targeting Integrins in Cancer Nanomedicine: Applications in Cancer Diagnosis and Therapy. Cancers 2019, 11, 1783.
76. Shi, C.; Guo, X.; Qu, Q.; Tang, Z.; Wang, Y.; Zhou, S. Actively targeted delivery of anticancer drug to tumor cells by redox-responsive star-shaped micelles. Biomaterials 2014, 35, 8711–8722.
77. Chen, W.; Shah, L.A.; Yuan, L.; Siddiq, M.; Hu, J.; Yang, D. Polymer–paclitaxel conjugates based on disulfide linkers for controlled drug release. RSC Adv. 2015, 5, 7559–7566.