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Anticancer Polymeric Nanomedicines

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Polymers play important roles in the design of delivery nanocarriers for cancer therapies. Polymeric nanocarriers with anticancer drugs conjugated or encapsulated, also known as polymeric nanomedicines, form a variety of different architectures including polymer-drug conjugates, micelles, nanospheres, nanogels, vesicles, and dendrimers. This review focuses on the current state of the preclinical and clinical investigations of polymer-drug conjugates and polymeric micelles. Recent progress achieved in some promising fields, such as site-specific protein conjugation, pH-sensitive polymer-drug conjugates, polymer nanoparticles for targeted cancer therapy, stimuli-responsive polymeric micelles, polymeric vesicles, and dendrimer-based anticancer nanomedicines, will be highlighted.

Keywords nanomedicine, polymer-drug conjugate, polymeric micelle, polymeric nanoparticle, drug delivery, anticancer

An Introduction to Polymeric Nanomedicines in Cancer Drug Delivery

Nanotechnology is making a significant impact on drug delivery. There is a growing interest in integrating nanotechnology with medicine, creating so-called nanomedicine aiming for disease diagnosis and treatment with unprecedented precision and efficacy.[1] In the past few years, resources allocated to the development of nanomedicine increased dramatically, highlighting the importance of this evolving field. In drug delivery, nanomedicine is a recently developed term to describe nanometer sized (1–1000 nm), multi-component drug or drug delivery systems for disease treatment.[2]

The existing challenge of drug delivery is to design vehicles that can carry sufficient drugs, efficiently cross various physiological barriers to reach disease sites, and cure diseases in a less toxic and sustained manner. As most physiological barriers prohibit the permeation or internalization of particles or drug molecules with large sizes and undesired surface properties, the main input of nanotechnology on nanomedicine is to miniaturize and multi-functionalize drug carriers for improved drug delivery in a time- and disease-specific manner.

Although nanomedicine was conceptualized only recently,[1–5] nanotechnology has been employed in drug delivery for decades.[6,7] For example, nanoparticulate liposomes were first

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introduced more than 40 years ago.[7] Today, a handful of liposome based, nanoparticulate delivery vehicles have been approved by the FDA for clinical applications.[2,8] The use of colloidal nanoparticles in drug delivery can date back to almost 30 years.[2,6] They became clinically promising when long circulating, stealth polymeric nanoparticles were developed.[9] Both micelles and polymer-drug conjugates have been investigated for more than two decades for the treatment of various diseases including cancer.[4,10] The support from both government and industry, the breakthroughs in fundamental nanoscale science and engineering, and the progress of translational science that integrates medicine and nanotechnology has impacted and will continue to impact the development of nanomedicine.

The application of nanotechnology to clinical cancer therapy, also known as cancer nanotechnology, was recently detailed by Ferrari et al.[3] Cancer is the second leading cause of death in the United States, accounting for 22.7% of total mortality in 2003.[11] Although significant efforts have been devoted to cancer diagnosis and therapy, cancer induced mortality continues to rise.[11] In cancer drug delivery, delivery strategies can be categorized as either lipid-based or polymer-based. Lipid-based nanomedicines, mainly in the form of liposomes, have been extensively reviewed.[8,12–15] This review will only focus on various polymer-based nanocarriers that have been developed for cancer therapy. Polymeric-drug nanomedicines to be discussed in details are polymer-drug conjugates[16–19] and polymeric micelles,[10,20–26] some of which have either been approved for clinic use or currently under clinical investigations.[2,18,27] Other newer delivery systems, such as dendrimers[28–32] and polymeric vesicles[33–39] that have been developed and employed in cancer drug delivery (Fig. 1), will also be discussed.

Development of Polymer-Drug Nanomedicines: Conjugation Versus Encapsulation

One of the central themes of drug delivery is to improve the pharmacological and pharmacokinetic profiles of therapeutic molecules. Drug molecules (small molecule or macromolecules) can be either released through the cleavage of a covalent linkage between drug molecules and polymers (conjugation) or through the diffusion from a drug and polymer blended matrix (physical encapsulation).

The covalent conjugation approach was first introduced by Ringsdorf in 1975.[40,41] In his postulated model of a polymer-drug conjugate, multiple drug molecules are bound to polymer side chains through covalent, cleavable bonds. The cleavage of the polymer-drug linker results in the release of the attached drug molecules. This concept received immediate attention since it was introduced. In the late 1970s, Kopecek, Duncan and others started to develop N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer and designed the first synthetic polymer-drug conjugate.[42] Their efforts led to a handful of HPMA-drug conjugates that later entered several clinical trials.[2,43] Using the same strategy, Maeda and colleagues developed SMANCS conjugate by covalently linking the anticancer drug neocarzinostatin (NCS) to two styrene maleic anhydride (SMA) polymer chains.[44] They successfully brought this antitumor protein conjugate to the Japanese market in 1994 as the first polymer-protein conjugate approved for human cancer treatment.[2] Since these early studies, many different polymers have been developed and evaluated as delivery vehicles for both protein and small molecules.[2,17,18,43,45] However, only a limited number of polymeric carriers have reached clinical trials (Fig. 2).[43]

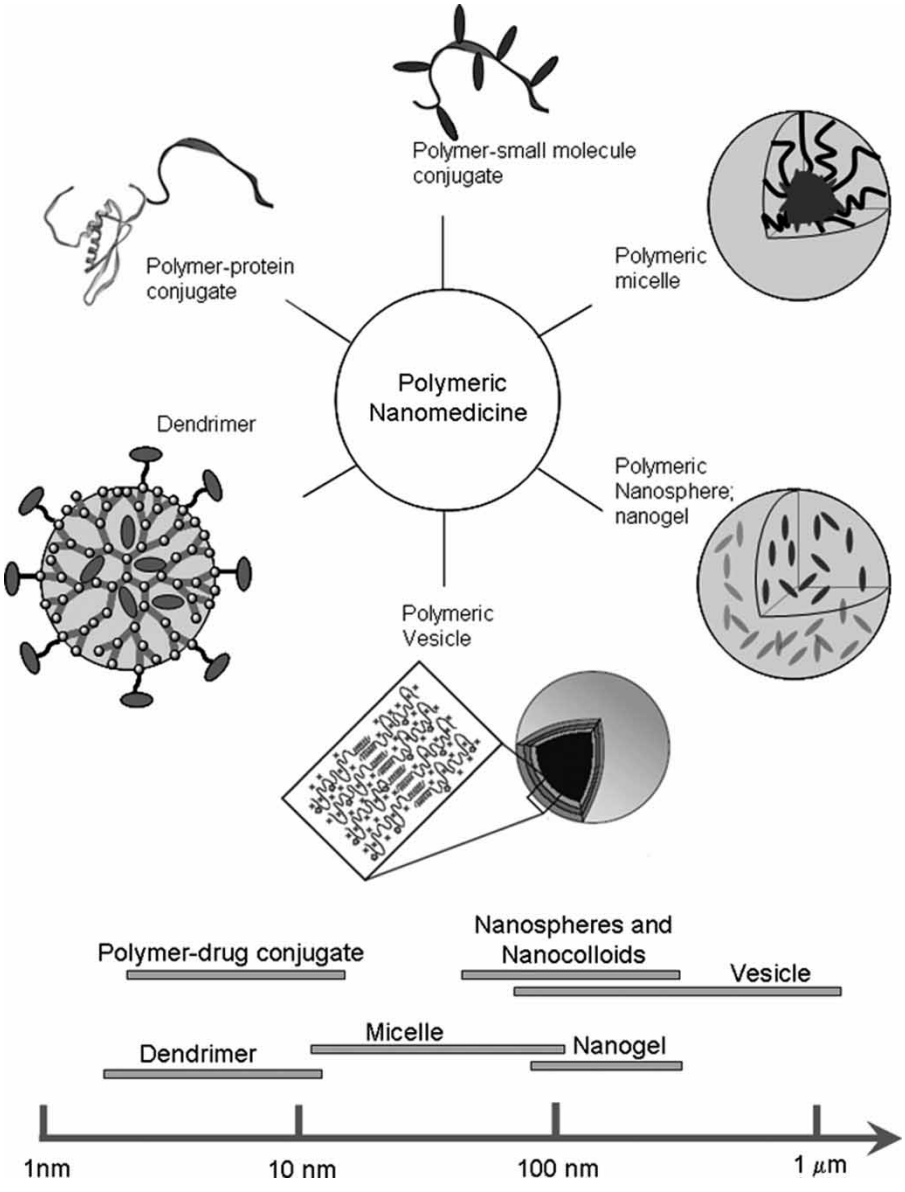

Figure 1. Schematic illustration of various polymeric nanomedicine drug delivery systems.

Nano-sized polymer-drug conjugates based on these polymers as well as the other promising candidates will be discussed in section on polymer-drug conjugates.

The physical encapsulation approach controlling drug release from a polymer matrix was originated from the seminal work by Folkman and Long in 1964.[46] They reported that hydrophobic small molecules could diffuse through the wall of silicone tubing at a controlled rate. Later, Langer and Folkman developed the first polymer-based slow-release system.[47] They found that a soybean trypsin inhibitor could be encapsulated and released from an ethylene-vinyl acetate copolymer matrix over a 100-day period. This

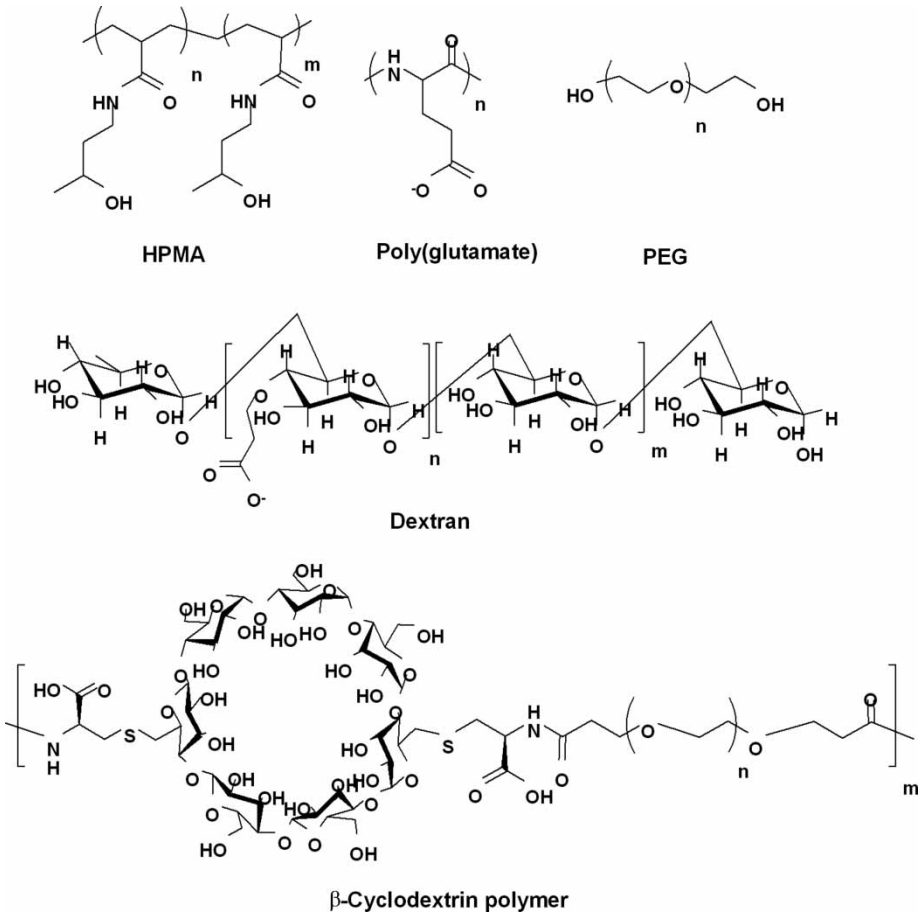

Figure 2. Polymers in clinical trials as vehicles for conjugated therapeutics.

is the first report of sustained release of protein and other macromolecules from polymer matrix. This concept was extended to the development of Gliadel, an implantable wafer that can slowly release 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) from a degradable poly[bis(*p*-carboxyphenoxy) propane-sebacic acid] matrix for brain tumor treatment. Through the efforts of Langer, Brem and others,[48–50] Gliadel was approved by the FDA in 1996 as the first treatment to deliver chemotherapeutics directly to the tumor site using controlled release techniques.

The physical encapsulation approach was also applied to the development of a variety of nanometer sized delivery vehicles, many of which are based on the aggregation of hydrophobic polymers (polymeric nanoparticles)[51] or the self-assembly of the hydrophobic polymer domain of an amphiphilic block-copolymers (polymeric micelles and vesicles).[10,33,34,52,53] Compared to polymer-drug conjugates with sizes generally around 10 nm or less, nano-aggregates formed through phase-separation are larger, typically in a range of 20–100 nm for micelles[24] and 100 nm to a few micrometers for polymer vesicles.[35,36,54] Nanocarriers based primarily on physical encapsulation will be covered in section on polymeric micelles.

Polymer-Drug Conjugates

Polymer-Protein Conjugates

The application of proteins and peptides as anticancer therapeutics has expanded rapidly in recent years. It is estimated that more than 500 biopharmaceuticals have been developed.[55] Protein and peptide biopharmaceuticals commonly suffer from their pharmacokinetic and pharmacological drawbacks such as short circulating half-lives, immunogenicity, instability against proteolytic degradation, and low solubilities. In addition to the manipulation of amino acid sequence to reduce immunogenicity and improve stability, the conjugation of hydrophilic polymers to proteins is frequently employed to overcome these drawbacks. A covalent link of hydrophilic polymers and protein therapeutics to form polymer-protein conjugates is the most widely adopted strategy. Research on protein modification with polymers started in the late 1960s and early 1970s with dextran as the modifying polymer. However, significant progress in this field was achieved after poly(ethylene glycol) (PEG) was introduced by Frank Davis for protein modification (so-called protein pegylation).[56,57]

PEG is a linear polyether terminated with 1-2 hydroxyl groups (Fig. 2). It is highly flexible, highly water soluble, non-degradable, non-toxic, and non-immunogenic.[58] The conjugation of PEG to a protein or peptide can shield antigenic epitopes of the polypeptide, resulting in significant reduction of the recognition by reticuloendothelial system (RES). Because of the steric effect, pegylation also reduces protein degradation by proteolytic enzymes. In addition, PEG conjugation increases the molecular weight (MW) and the hydrodynamic volume of proteins, resulting in decreased blood clearance by renal filtration.

Protein pegylation involves labile biopharmaceutical molecules, therefore coupling reactions are usually carried out under mild conditions. The amino functional groups (or other groups such as thiol and hydroxyl) in proteins are frequently used as the nucleophiles to attack an activated ester of PEG. PEGs are then bound to the ε-amino groups of lysine residues or the N-terminal amino group of the protein. In addition to the amino function groups on lysine, other conjugation sites include the side chain of cysteine, histidine, tyrosine, and serine.[58] Uncontrollable, multi-site pegylation is one of the major drawbacks of pegylation, which leads to pharmaceutical products with heterogeneous structures and reduced activities.[58] For instance, interferon-α2b (IFN-α2b) coupled with an activated 12 kDa mPEG forms as many as 15 different PEG-IFN-α2b products.[58] Less than 10% of bioactivity (relative to the original IFN-α_{2b}) remains after the conjugation of PEG on Lys-83 and Lys-121 of IFN-α2b.[58] Bioactivities of these pegylated IFN-α2b vary dramatically, presumably due to the blocking of certain active sites by PEG. Despite these difficulties, several pegylated systems have received regulatory approvals for clinical applications, such as Oncaspar (pegylated asparaginase) for the treatment of acute leukemia and Neulasta (pegfilgrastim) for stimulating neutrophil production that are depleted during chemotherapy.[18] The powerful pegylation techniques have been extended to the delivery of other macromolecules. A branched PEG-anti-VEGF aptamer (Pegaptanib sodium injection, Macugen) was approved recently by the FDA for the treatment of neovascular age-related macular degeneration,[59] which demonstrated the utility of PEG for the systemic delivery of nucleic acids.

The reduction of protein activities of pegylated IFN-α2b is due primarily to uncontrollable PEG conjugation, which suggests the necessity of developing site-specific pegylation. The design of newer generation pegylated proteins have mainly focused on the use of branched or heterodifunctional linear PEG that are capable of controlling site-specific, stepwise conjugation. Recently, a unique site-specific pegylation

through the formation of a three-carbon bridge was reported by Brocchini, Shaunak, and coworkers.[60] They exploited the chemical reactivity of both thiols in an accessible disulfide bond in a protein molecule for pegylation. An exterior S-S bond in the protein was reduced to a pair of SH groups, both of which subsequently reacted with one PEG monosulfone, a molecule that is specifically designed for interactive bisalkylation with the two SH groups. The "insertion" of PEG to the disulfide bond showed minimum disturbance to the protein structures. This technique can be potentially applied for site-specific pegylation of numerous proteins containing disulfide bonds.

The further development of site-specific conjugation relies on the advancement of new conjugation chemistry. In 2001, click chemistry was introduced by Sharpless and coworkers, which received immediate recognition for its potential in site-specific biological conjugation.[61,62] Click chemistry usually gives very high yields, and proceeds in very mild condition. Ligand conjugation induced by click chemistry has been successfully carried out both in situ[63] and in vitro.[64,65] One type of click chemistry, the Azide-Alkyne Huisgen cycloaddition, is particularly important to site-specific protein conjugation through the formation of 1,2,3-triazole between an azide and an alkyne.[66] In this reaction, a 1,3-dipolar cycloaddition between an azide and an alkyne gives a 1,2,3-triazole.[62] The conjugation of cellular glycans with fluorescent tags through click chemistry, for example, resulted in rapid, versatile, and site-specific covalent labelings.[66]

Tirrell and coworkers demonstrated that click chemistry can be used for site-specific conjugation of the fluorescent tag to genetically engineered proteins containing non-natural homopropargylglycine or ethynylphenylalanine.[67,68] The introduced alkynyl groups on these non-natural amino acids provide sites for the attachment of fluorescent dyes containing azide groups (shown in Fig. 3). Recent advance in protein engineering makes it possible to incorporate many non-natural amino acids to any specific position in a protein. Therefore, this technique may potentially be applied to the site-specific pegylation that gives minimum disturbance to the structure and activity of proteins.

Polymer-Small Molecule Drug Conjugates

The conjugation of hydrophobic small molecule drugs to hydrophilic polymers has been actively pursued for improved pharmacological and pharmacokinetic properties of the

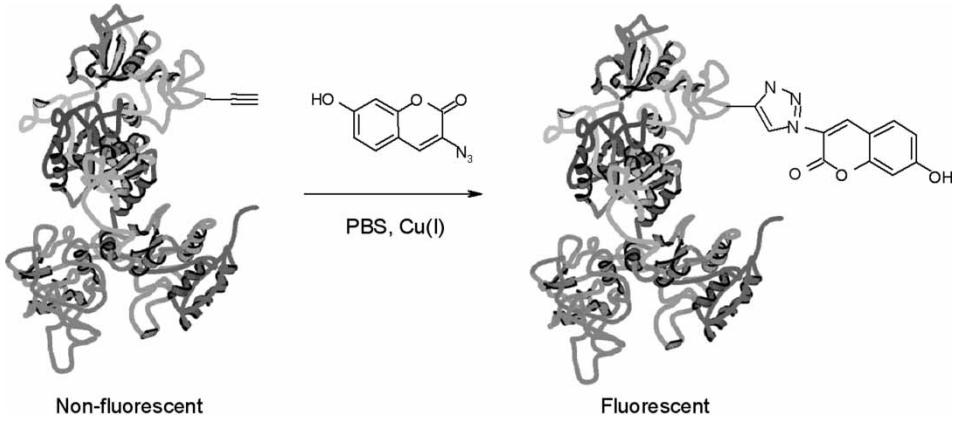

Figure 3. Schematic illustration of site-specific labeling of protein through click chemistry.

therapeutic molecules. In general, polymer-drug conjugates have increased aqueous solubility, reduced toxicity, and prolonged plasma circulation half-life compared to free drugs. Polymer-drug conjugation may also change the internalization pathway of small molecules by bypassing P-glycoprotein associated multi-drug resistance.[69] Polymers that are particularly important and have track records of preclinical success for small molecule conjugation include N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer,[70–73] PEG,[74–78] poly(glutamic acid) (pGlu),[79–82] dextran,[83–86] and cyclodextrin-based polymer (Fig 2).[87–90] Conjugates of various anticancer drugs with these polymers are currently in clinical trials (Table 1). Other polymers that have been successfully developed and are currently in clinical trails include polymannopyranose,[91] albumin,[92] and antibody.[93–95]

PEG has been used for the conjugation and delivery of paclitaxel (PTXL),[75] doxorubicin (DOXO)[96] and camptotehcin (CPT).[76,77,97–99] Linear PEG only has two terminal hydroxyl groups for conjugation, which limits its drug-carrying capacity. A PEG-CPT conjugate (Prothecan),[100] for example, only has about 2 wt% CPT linked to PEG.[101] PEG-CPT conjugates showed antitumor efficacy in various preclinical studies,[76,98,102,103] and have also been tested clinically.[100] In a biodistribution study, the plasma half-life of a 20 kDa PEG-DOXO conjugate was found to be less than 10 hours.[96] Protracted antitumor activity was observed with prolonged circulation and improved tumor accumulation due to the Enhanced Permeability and Retention (EPR) effect (Fig. 4).[104] In a phase-I clinical study, PEG-CPT showed a 77-hour plasma clearance half-life,[100] which is much greater than that of a similar system in mice.[96] A recent study showed that coupling of PEG and CPT through an alanine ester linker can induce apoptosis in tumor and decrease apoptosis in liver and kidney as compared to free CPT.[103] Extended circulation and slow release of CPT may also contribute to the observed neutropaenia and thrombocytopaenia.[100]

HPMA-drug conjugates are another type of conjugates that have been extensively evaluated in clinic.[42,105,106] HPMA is very water soluble, biocompatible, and non-degradable, which resembles PEG to some degree. To ensure complete clearance of non-degradable polymers from circulation, polymer MWs have to be maintained at or below 45–50 kDa.[107] Most HPMA copolymers tested in vivo are 30 kDa or shorter.[70,108–110] However, the HPMA-drug conjugates with such low MWs showed fast renal clearance, which may adversely affect their antitumor efficacy. Enhanced accumulation through EPR effect for polymer-drug conjugates with MWs at or around its renal clearance threshold (40–45 kDa) is as effective as their higher MW analogues.[104,111] Compared to PEG, HPMA has a large number of pendent functional groups that allow the conjugation of many hydrophobic small molecules on each HPMA polymer. The drug loading capacity of HPMA is thus significantly larger than that of PEG and is comparable to that of pGlu. The HPMA copolymer conjugates with PTXL,[109] CPT,[110,112,113] DOXO,[70,108,114] and the platinate[115] have all been evaluated in various clinical trials.

pGlu, a biodegradable polypeptide, has also been used for small molecule drug delivery. pGlu has a large number of pendant carboxyl groups, which makes pGlu extremely water soluble. As much as 30 wt% of PTXL[116,117] or CPT[79] can be conjugated to pGlu, which is much higher than that in PEG conjugates. The resulting pGlu-CPT or pGlu-PTXL still showed sufficiently high water solubility. PTXL molecules linked to pGlu through a degradable ester bond can be released at a controlled hydrolysis rate. The release rate is usually significantly enhanced when the pGlu-PTXL is internalized to cell and exposed to a harsh endolysosomal environment. PTXL and CPT conjugated to pGlu showed enhanced preclinical antitumor efficacy in several preclinical tumor

Table 1
Polymer-drug conjugates in clinical trials

Name	Polymer	Drug	Linker	Company	Target	Status	Ref.
Prothecan	PEG (40 kDa)	CPT	Ester	Enzon	SCLC	Phase II	99, 220
PK1	HPMA (30 kDa)	DOXO	Gly-Phe- Leu-Gly	CRC/Pharmacia	Various cancers	Phase II	70, 108
PK2	HPMA (30 kDa)	DOXO	Gly-Phe- Leu-Gly	CRC/Pharmacia	Various cancers	Phase I discontinued	114
PNU-166945	HPMA (40 kDa)	PTXL	Ester	Pharmacia	Various cancers	Phase I completed	109
MAG-CPT	HPMA (30 kDa)	CPT	Gly-6-aminohexanoylgly	Pharmacia	Various cancers	Phase I completed	110, 113
AP5280 AP5286	HPMA (25 kDa)	Diamine-platinum(II)	Gly-Phe- Leu-Gly	Access Pharmaceuticals	Various cancers	Phase I completed	221–224
AP5346	HPMA (25 kDa)	Oxaliplatin	Gly-Gly-Gly	Access Pharmaceuticals	Head and neck cancer	IND approved	225

CT-2103 (XYOTAX)	PG (40 kDa)	PTXL	Ester	Cell Therapeutics	Various cancers	Phase III	116–119 226–228
CT-2106	PG (50 kDa)	CPT, 5-Fu	Gly-ester	Cell Therapeutics	Various cancers	Phase I	79
MTX-HSA	Albumin (67 kDa)	MTX	—	AK St. Georg	Advanced cancers	Phase II	92, 229–232
DOXO-EMCH	Albumin (67 kDa)	DOXO	Hydrazone	Tumor Biology Center	Various cancers	Phase I	143
IT-101	CD polymer	CPT	Gly ester	Insert Therapeutics	Various cancers	Phase I	87–90
DAVANAT	Polymanno-pyranose	5-Fu, AV and LV	—	Pro-Pharmaceuticals	Colorectal cancer	Phase II	91
AD-70	Dextran (70 kDa)	DOXO	Schiff base	Alpha Therap. GmbH	—	Phase I	129
HuC242-DM4	humAb huC242	MTS-DM4	—	ImmunoGen	Various cancer	Phase I	—
BB-10901	humAb N901	MTS-DM1	—	ImmunoGen	SCLC and CD56-SC	Phase II	93–95, 144

5-Fu = 5-Fluorouracil; LV = Leucovorin; CPT = Camptothecin; PTXL = Paclitaxel; AV = Avastin; MTS = maytansinoid; SCLC = small-cell lung cancer; DOXO = doxorubicin; MTX = methotrexate; humAb = humanized monoclonal antibody; CD56-SC = CD56-positive SC carcinoma.

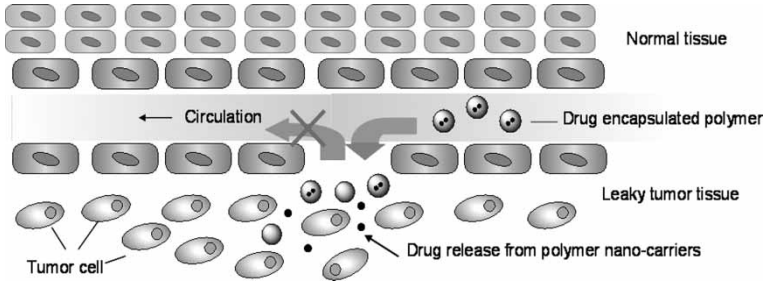

Figure 4. Schematic illustration of enhanced permeability and retention (EPR) effect.

models presumably due to the EPR-mediated passive tumor targeting.[81,116,118] Interestingly, pGlu-PTXL also showed a positive response in taxane-resistant patients in several Phase I and II studies of various cancers.[119] A recently completed Phase III trial of pGlu-PTXL in combination with standard chemotherapy against ovarian cancer and non-small-cell lung cancer (NSCLC) suggests that estrogen may participate in regulating the in vivo efficacy of pGlu-PTXL. pGlu-PTXL was found efficacious only in a certain group of patients, such as pre-menopausal female NSCLC patients. A pGlu-CPT conjugate (CT-2106) with CPT linked to pGlu through a glycine linker with 33–35 wt% loading is currently in phase I/II trials.[79]

Cyclodextrin (CD)-containing polymer is a new class of hydrophilic biomaterials that has recently been developed for drug delivery. CDs are cyclic oligomers of glucose that can form water-soluble inclusion complexes with numerous hydrophobic molecules with compatible sizes. CDs are biocompatible, non-immunogenic and non-toxic, therefore they have been extensively used in many pharmaceutical applications to improve the bioavailability and solubility of drugs.[120] CD-containing polymers have also been developed and used for decades.[121,122] Because CD has many hydroxyl groups, CD-containing polymers are usually heavily crosslinked with uncontrollable compositions and limited applications. In 1999, Davis and coworkers developed the first linear, β-cyclodextrin polymer (β-CDP)[123] bearing cationic pendant groups for gene delivery.[123–128] CDPs were further modified to introduce pendant carboxyl groups (Fig. 2) for CPT conjugation (IT-101, Fig 5). CDPs are very water-soluble (over 200 mg/mL), and can increase the solubility of CPT by three orders of magnitude after conjugation.[88]

A pharmacokinetic study in rats showed a half-life of bound CPT in IT-101 is 17–19 h, which is significantly longer than CPT alone.[90] The half-life is also longer than those of PEG-CPT and HPMA-CPT, which may be due in part to the high MW of the β-CDP tested (85 kDa).[90] IT-101 forms large particles ($\approx$50–80 nm) in solution presumably through the interchain interaction between CPT and CD. This unusual nano-aggregation is in sharp contrast to most polymer-drug conjugates reported so far whose sizes are typically ranged from 5 to 15 nm. The increase in particle size of IT-101 likely reduces its clearance through glomerular filtration, thus enhancing its in vivo antitumor efficacy.[89] Protracted antitumor activity was observed in LS174T colon carcinoma tumor-bearing mice[87] as well as in a number of other irinotecan-resistant tumors (MDA-MB-231, Panc-1, and HT29),[89] which is consistent with the hypothesis that polymer-drug conjugates may overcome multi-drug resistance. An open-label, dose-escalation Phase I study using IT-101 in patients with inoperable or metastatic solid tumors has recently been initiated.

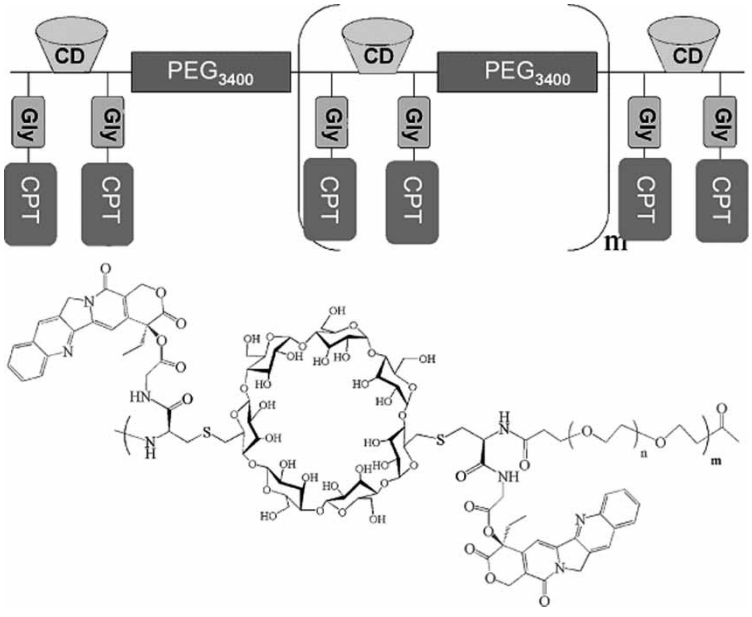

Figure 5. Schematic illustration of IT-101, a conjugate between 20(S)-camptothecin and a linear, β-cyclodextrin-based polymer through a glycine ester linker.

Polysaccharides were also developed for the delivery of small molecule therapeutics. DAVANAT, a (1–4)-linked-β-D-mannopyranose]-[(1–6)-linked-α-D-galactopyranose] polymer, is currently in phase-II trial for colorectal cancer treatment with a combination of 5-fluorouracil (5-FU), avastin and leucovorin.[91] DAVANAT binds to surface lectins, proteins that are overexpressed in metastatic tumor cells and mediate cell association, apoptosis, and metastasis. The interaction of DAVANAT with lectin may promote transport of 5-FU into the tumor cells. A Phase I open-label study showed that DAVANAT alone or in combination with 5-FU were well tolerated in patients, which facilitated its Phase II clinical trials.[91]

Besides polymannopyranose, other polysaccharides such as dextran and dextran derivatives have also been used for the delivery of small molecule drugs (Fig 2). Dextran is biocompatible to some extent, and has been approved for certain clinical application (e.g., as plasma expander). An oxidized form of dextran (70 kDa) was conjugated with DOXO through a Schiff base linker, and the resulting conjugate (AT-70) was subsequently evaluated preclinically and clinically. Severe hepatotoxicity was observed, presumably due to the uptake of dextran by the reticulendothelial systems (RES).[129] DE-310, another dextran-based conjugate with a 340 kDa carboxymethyldextran polyalcohol conjugated with CPT analogue DX-8951 through an Gly-Gly-Phe-Gly linker, was also tested in clinic.[84,130–132] The formation of amide, instead of ester linkages, reduced drug release from DE-310 during systemic circulation. As the peptidyl linker is enzymatically degradable, DX-8951 can presumably only be released after DE-310 is taken up by cells to endolysosomal compartments with active proteinases. Thus drug release can be specifically controlled inside cells.[84] A Phase I study showed dose-limiting toxicities due to thrombocytopaenia and neutropaenia.[131]

As polymer accumulation in tumor through EPR effect is usually enhanced with increased polymer MW,[104] it has been actively pursued to develop degradable, high MW polymers using biocompatible building blocks. Duncan and coworkers developed water-soluble and biocompatible polyacetals through the condensation of PEG and tri(ethylene glycol) divinyl ether (Fig. 6).[111,133,134] The acetal moiety was chosen because it can undergo faster hydrolysis under mildly acidic conditions but is stable at physiological pH. As the main-chain of the polyacetals can be hydrolyzed to small, renal-clearable fragments, the polymer can be made significantly larger than 45 kDa for prolonged circulation in blood. One drawback is that the polyacetals were prepared through step-growth polymerization that gave polymers with fairly broad MW distributions (in a range of 1.8–2.6).[111,133,134] The polyacetals displayed remarkable tunability for pH-induced degradation. Enhanced hydrolysis was observed at pH 5.5 (41% M_w loss in 25 h) as compared with that at pH 7.4 (10% M_w loss in 73 h). In addition, the polyacetals and their degradation products are non-toxic in vitro ($IC_{50} > 5$ mg/mL in B16F10 cells) and in vivo. Amine pendant functional groups were incorporated through terpolymerization (Fig. 6), which was used for drug conjugation. A biodistribution study showed no preferential accumulation of the polymer in the major organs. In C57 xenograft mice bearing a subcutaneous B16F10 tumor, the pharmacokinetics of intravenously administered polyacetal-DOXO ($M_w = 86$ kDa, $M_w/M_n = 2.6$) and HPMA copolymer-GPLG-DOXO ($M_w = 30$ kDa, $M_w/M_n = 1.3–1.5$) were compared.[111] Both polyacetal-DOXO and HPMA copolymer-DOXO displayed similar biphasic pattern of plasma clearance with a $t_{1/2}\alpha$ of $\sim$1 h presumably due to the presence of low MW fragments. But the plasma levels of polyacetal-DOXO were significantly higher than those for HPMA copolymer-DOXO with a $t_{1/2}\beta$ of 19 h and 3.5 h for polyacetal-DOXO and HPMA copolymer-DOXO, respectively. The $t_{1/2}\beta$ of polyacetal-DOXO is quite similar to that of the cyclodextrin polymer with a similar MW (85 kDa, $t_{1/2}\beta = 17–19$ h).[90] Because prolonged plasma circulation is the driving force for increased passive tumor targeting,[135,136] polyacetals with higher MWs and lower polydispersities may give improved circulation half-life and tumor accumulation. It is noted that polyacetal-DOXO, although with the MW

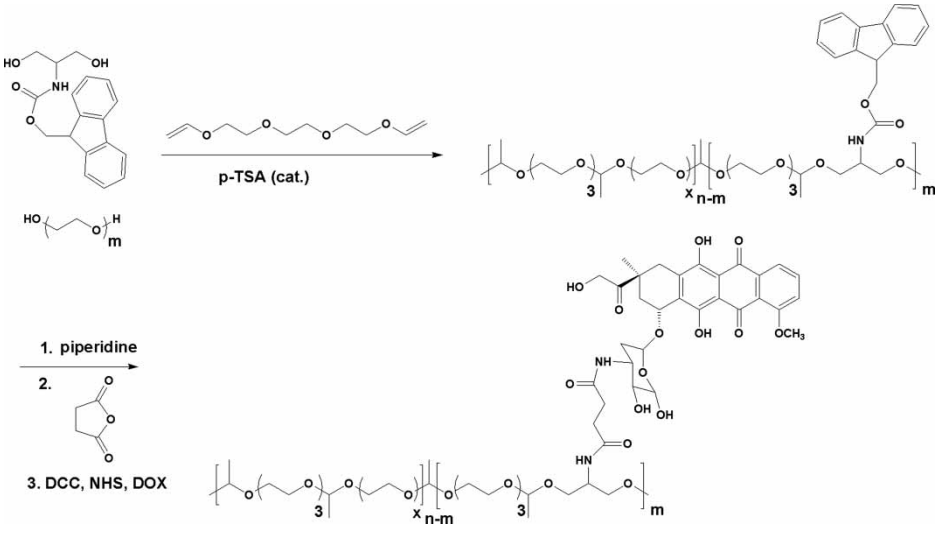

Figure 6. pH-Sensitive polyacetal for DOXO delivery.

much higher than the HPMA copolymer conjugates, showed a reduced accumulation in the liver and the spleen.[133] The high PEG content in polyacetal may contribute to the lower uptake by the RES system.

Polyacetals can also be prepared through selective degradation of polysaccharides. Papisov and coworkers developed acyclic hydrophilic polyals through the lateral cleavage of polyaldoses and polyketoses.[137,138] Polyals obtained through this method consist of acyclic carbohydrate substructures that are potentially biocompatible. The intra-chain acetal or ketal groups should enable hydrolytic biodegradation upon cell uptake. In an in vivo toxicity study, all mice survived intravenous administered of a 160-kDa polyacetal at a dose as high as 4 g/kg. The polymer gave very low RES response and showed low tissue accumulation even at MW as high as 500 kDa. This class of polymers contains a large number of pendant functional hydroxyl groups, which make it easy for structural modification and drug conjugation. However, it is difficult to control the sites of periodate oxidation, which leads to polymers with poorly controlled compositions.

Albumins have also being evaluated as drug carriers in clinical trials. A methotrexate-human serum albumin conjugate (MTX-HSA) was synthesized by coupling MTX to HSA.[139–141] MTX–HSA showed significant accumulation in rat tumors and displayed high in vivo antitumor activity. In a phase I study, patients with renal cell carcinoma and mesothelioma responded to treatment with MTX–HSA therapy.[141] In a phase II study of MTX-HSA in combination with cisplatin as first line treatment of advanced bladder cancer,[92] a positive response was observed. The combination strategy showed promise for the treatment of urothelial carcinomas with acceptable toxicity. An albumin-DOXO conjugate (DOXO-EMCH) was also developed through an acid-sensitive 6-maleimidocaproyl-hydrazone linker.[142] The covalently linked DOXO prevents its rapid diffusion of DOXO into healthy tissue after intravenous administration and allows passive accumulation of DOXO-EMCH through EPR effect in solid tumors. DOXO is then released in the acidic environment of tumor tissue through the cleavage of the hydrozone linker. A Phase I study of DOXO-EMCH in 10 patients (6 female, 4 male) showed that DOXO-EMCH could be tolerated up to 40 mg/m^2.[143]

Antibodies have also been extensively used for drug conjugation, creating immunoconjugates as an important group of therapeutics for cancer treatment. For example, BB-10901 (Table 1), a humanized mAb conjugated with cytotoxic maytansinoid DM1 for small-cell lung cancer treatment is currently in Phase I/II clinical trial.[93–95,144] Immunoconjugates for cancer treatment is beyond the coverage of this review, and has been reviewed elsewhere.[145] It is worth reporting that an alternative strategy of using aptamer for targeted DOXO delivery was developed recently.[146]

Polymeric Micelles

Amphiphilic block copolymers can self-assemble in aqueous solution to form core-shell micellar nanostructures when the concentrations of the amphiphilic block copolymer are above the critical micellar concentration (Fig. 7). Polymer micelles have a condensed, compact inner core, which serves as the nanocontainer of hydrophobic compounds. As polymer micelles are generally more stable than hydrocarbon based micelles, sustained drug release from polymeric micelles becomes possible.[20,24] Numerous types of amphiphilic copolymers have been employed to form micelles[4,10,52,147–150] or other similar architectures such as nanogels[151] and polymer nanoparticles.[51] Detailed copolymers structure and drug molecule encapsulated or conjugated are summarized in Table 2.

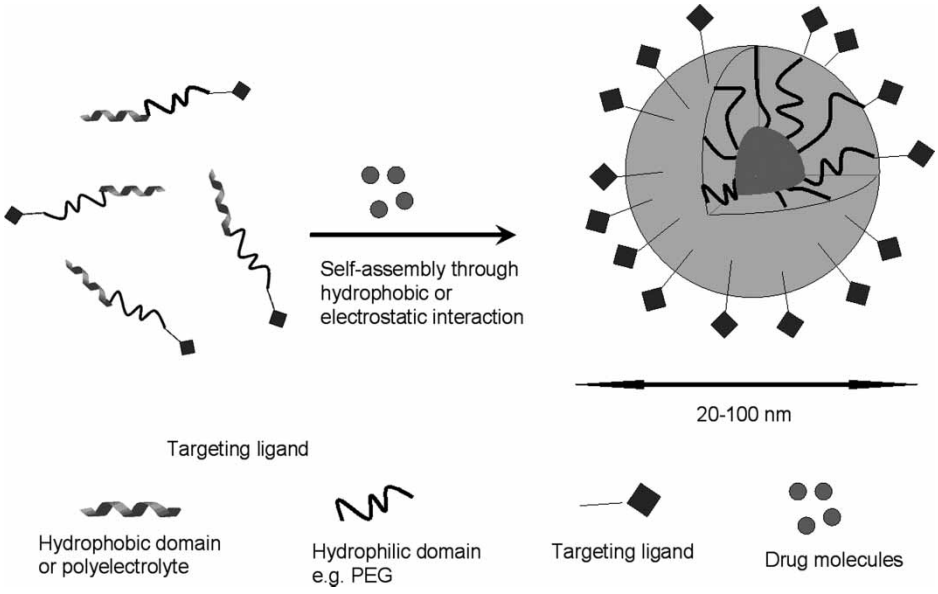

Figure 7. Polymeric micelle core-shell structure and drug encapsulation.

Polymeric micelles can accumulate in tumors after systemic administration. Their biodistributions are largely determined by their physical and biochemical properties, such as particle sizes, hydrophobicity, and hydrophilicity of the polymers and drugs, and surface biochemical properties.[152] A major issue that limits the systemic application of micellar nanocarriers is the nonspecific uptake by the RES. It is critical to have systems that can circulate for a long time without significant accumulation in the liver or the spleen. The sizes and the surface features of micelles have to be controlled for favored biodistribution and intracellular trafficking.[9] The hydrophilic shells of micelles usually consist of PEGs which prevent the interaction between the hydrophobic micelle cores and biological membranes, reduce their uptake by the RES, and prevent the adsorption of plasma proteins onto nanoparticle surfaces.[22] Micellar nanocontainers are typically in a range of 20–100 nm. The sizes of polymeric micelles resemble that of natural transporting systems (e.g. virus and lipoprotein), which allow efficient cellular uptake via endocytosis.[153] It was also found that the effect of size on polymer micelle biodistribution is organ specific and non-linear.[154] Therefore, controlling the sizes of micelles in a predefined range can be critical for desired applications. Parameters controlling the size of micelles include relative length of polymer blocks, polymer composition, and the solvent and drug used for encapsulation. A recent study indicated that the mean volumetric size of PEG-*b*-PLGA micelles correlates linearly with polymer concentration during self-assembly with linear correlation coefficient ≈ 0.99. Such linear correlation may provide means for preparing polymeric micelles with desirable sizes.[155]

PEG-Polypeptide Micelle

PEG-*b*-poly(aspartic acid) [PEG-*b*-pAsp] micelles and their DOXO conjugates (NK911) were developed by Kataoka and coworkers.[156] This is one of the most intensively investigated micellar drug delivery vehicles. DOXO molecules were conjugated to the

Table 2
Polymeric nanoparticles: polymer structures and drug incorporated

Block copolymer	Drug (or Dye)[references]
PEG-*b*-pAsp	Doxorubicin,[233,237] Methotrexate,[238] Indomethacin,[239] Amphotericin-B,[240,243] KRN 5500,[159] Cisplatin,[244,245] Nile Red[168]
PEG-*b*-pGlu(Bn)	Clonazepam[246]
PEG-*b*-pGlu	Cisplatin[161]
PEG-*b*-pHis/PLA	pH-sensitive micelles; Doxorubicin[247,248]
PEG-*b*-pLys	Cisplatin[249]
PEG-*b*-polyester	
PEG-*b*-PCL	Indomethacin,[250,251] Dihydrotestosterone,[252] FK506,[253] [253]L-685,818[253] Nimodipine[254]
PEG-*b*-PLA	Paclitaxel,[255,257] Doxorubicin[258]
PEG-*b*-PLGA	Doxorubicin,[259] Paclitaxel,[260] Docetaxel,[167] [155] Doxorubicin/combretastatin[162]
PEG-*b*-polyether (nanogel)	
Pluronic-P85	Daunorubicin,[261] Doxorubicin,[261,262] Vinblastine,[261] Mitomycin,[261] Cisplatin,[261] Methotrexate,[261] Epirubicin,[261] Paclitaxel,[263] Etoposide,[263] Digoxin[264]
Pluronic-F127	Nystatin[265]
Pluronic-F68	Nystatin[265]

(*continued*)

Table 2
Continued

Block copolymer	Drug (or Dye)[references]
Other homopolymer and block polymers	
PEG-*b*-PMA	Pyrene,[266] Nile Red[170]
pLys(EG)-*b*-pLeu	$DiOC_{18}$ dye[36]
pArg-*b*-pLeu	Fluoreseince[35,54]
pLys-*b*-pLeu	$DiOC_{18}$ dye[47]
PUA-*b*-PNIPAAm	N/A[267]
PNIPAAm/PDMAAm-*b*-PCL/PLA	Pyrene[268]
PLA-PEG-PLA	Doxorubicin[269]
Poly(orthoester)	DNA vaccine[270]
Poly(β-amino ester)	DNA and dye[271,272]
Polyketal	N/A[273]

Abbreviations: PNIPAAm = poly(*N*-isopropylacrylamide); PUA = poly(undecylenic acid) (PUA); pAsp = poly(aspartate); pGlu(Bn) = poly(benzyl-glutamate); pLys = poly(lysine); pHis = poly(histidine); PCL = poly(caprolactone); PLA = poly(D,L-lactide); PLGA = poly(D,L-lactic acid-co-glycolic acid); PMA = polymethacrylate; EG = oligo(ethylene glycol); PDMAAm = poly(N,N-dimethylacrylamide).

copolymers to form micelles with diameters in the range of 15–60 nm. However, DOXO molecules covalently conjugated to the pAsp side chain did not have therapeutic activity. Interestingly, the conjugated DOXO molecules can promote the formation of stable $\pi-\pi$ interaction with the encapsulated DOXO molecules.[157] In a Phase I study, the toxicity of NK911 resembled that of free DOXO, and the dose-limiting toxicity was neutropenia.[158] NK911 is currently being evaluated in a phase II clinical trial.[4]

The compatibility between the core-forming blocks and the drugs to be loaded controls the drug loading capacity and release rate. For example, the encapsulation of hydrophobic therapeutic compound KRN5500, a spicamycin derivative with a long-chain fatty acid, requires a hydrophobic core-forming block of pAsp with similar fatty acids side chain.[159] As the micelle core has no interaction with tissue during circulation, drug loading has a minimal effect on the micelle biodistribution.

PEG-*b*-polypeptide micelles have also been used for the delivery of PTXL. For example, PTXL has been incorporated into the 4-phenyl-1-butanolate modified PEG-*b*-pAsp to form polymeric micelles (NK105).[160] An in vivo antitumor study revealed that NK105 was more potent than free PTXL, possibly because of the enhanced drug accumulation in tumor tissues through EPR effect.

Because carboxylate groups can chelate with multivalent metal ions, amphiphilic copolymer containing pAsp and pGlu have been used to complex with anticancer platinum compounds, such as cis-dichlorodiammineplatinum (II) (cisplatin).[161] Micelles are formed through the ligand substitution of Cl^- on cisplatin with the carboxylate of pAsp or pGlu. In vivo studies displayed similar extended plasma half life and tumor accumulation as reported with other micellar drug delivery vehicles.

PEG-Polyester Micelle

Besides polypeptides, biodegradable polyesters can also be used as a micellar core-forming block. Well-known hydrophobic polyesters include polycaprolactone (PCL), poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and poly(lactide-co-glycolide) (PLGA), all of which have been approved by the FDA in various clinical applications. These polymers have different degradation profiles, which can be used to tune drug release rates. However, because these polyesters have no pendant functional groups for drug conjugation, drugs are predominantly incorporated to the micellar hydrophobic core through physical encapsulation although the conjugation of DOXO through a covalent bond to the terminal hydroxyl group of PLGA has also been tested.[162]

Low MW methoxy-PEG-*b*-PLA was recently employed to encapsulate PTXL to form copolymer micelles.[163] Evaluation of the in vivo antitumor efficacy of this micelle in SKOV-3 human ovarian cancer implanted xenograft mice demonstrated significantly enhanced antitumor activity as compared with free PTXL. At Day 18 after administration, the tumor was undetectable in all mice treated with the micelles at its maximum tolerable dose (60 mg/kg). At the end of the experiment (1 month), all mice remained tumor-free. Currently, this PTXL-containing methoxy-PEG-*b*-PLA micellar vehicles are under Phase II clinical evaluation.[164]

The core-shell structures of amphiphilic micelles allow the attachment of targeting ligands to their external surface for active accumulation in tumor tissues. Many small molecules and antibodies have been utilized as such targeting ligands.[165] Recently, aptamers were also developed and used in targeted drug delivery.[166] An A10 2′-fluoropyrimidine RNA aptamer that recognizes the extracellular domain of the prostate-specific membrane antigen (PSMA) was conjugated to docetaxel (DTXL)-encapsulated COOH-

PEG-*b*-PLGA micelle (Fig. 8). The copolymer micelles have terminal carboxyl groups extruded to the water phase, facilitating the conjugation of aptamer targeting ligands. The aptamer containing micelle displayed enhanced antitumor activity compared to the control group. A single intratumoral injection of docetaxel (DTXL)-aptamer nanoparticle resulted in complete tumor remission in five of seven LNCaP xenograft nude mice as compared to tumor remission in two of the seven mice in the control group.[167]

Stimuli-Responsive Polymeric Micelle

Polymer micelles that are responsive to light, pH, or temperature are potentially exciting nanomedicine modalities for site-specific drug delivery. The mildly acidic pH in tumor and inflammatory tissues (pH $\approx$ 6.5) as well as in the endosomal intracellular compartments (pH $\sim$ 4.5–6.5) may trigger drug release from pH sensitive micelles upon their arrival at the targeted disease sites. Fréchet and coworkers recently developed a pH-dependent micelle that can release encapsulated cargos significantly faster at pH 5 than at pH 7.4.[168] An amphiphilic copolymer with acid-labile hydrophobic block (Fig. 9) can form micelles at the physiological pH. When exposed to mildly acidic pH, an accelerated hydrolysis of the micelle acetal bonds (Fig. 9) results in the formation of hydroxyl groups in the hydrophobic core, disruption of the micellar assembly, and release of the encapsulated cargos. Another interesting pH-sensitive micellar delivery system was reported by Kataoka and coworkers using an acid-labile hydrozone linker to conjugate DOXO to pAsp.[169] A kinetic study demonstrated pH-dependant release of DOXO, in a manner resembling what was observed in Fréchet's pH-sensitive micelles.

Recently, Fréchet and coworkers also reported an alternative release triggering mechanism through the use of infrared light (Fig. 10).[170] The amphiphilic structure has a 2-diazo-1,2-naphthoquinones at the terminal of the hydrophobic end and an oligo(ethylene glycol) as the hydrophilic block. When the micelles were exposed to infrared light,

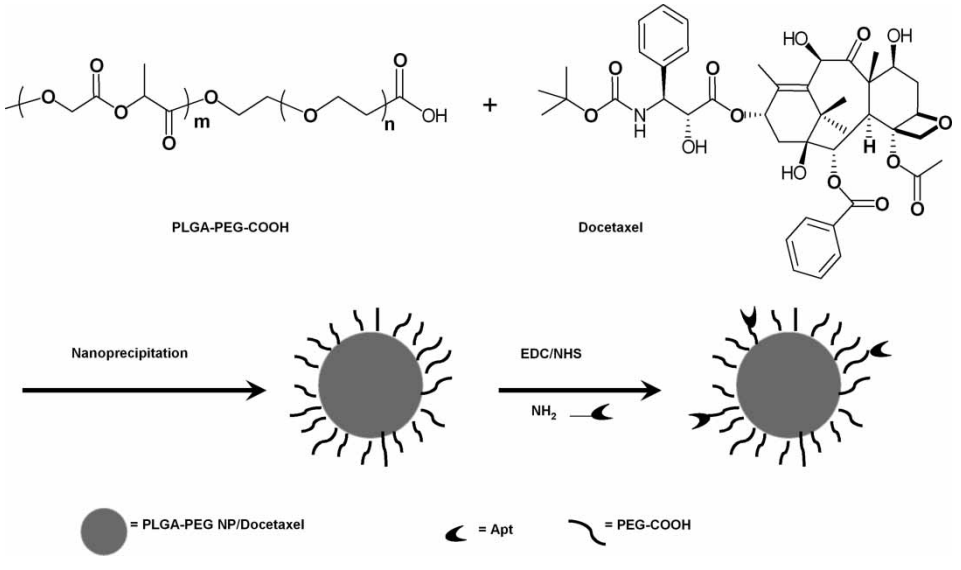

Figure 8. Docetaxel-encapsulated, PLGA-*b*-PEG-COOH micelle and its aptamer conjugate for targeted prostate cancer therapy.

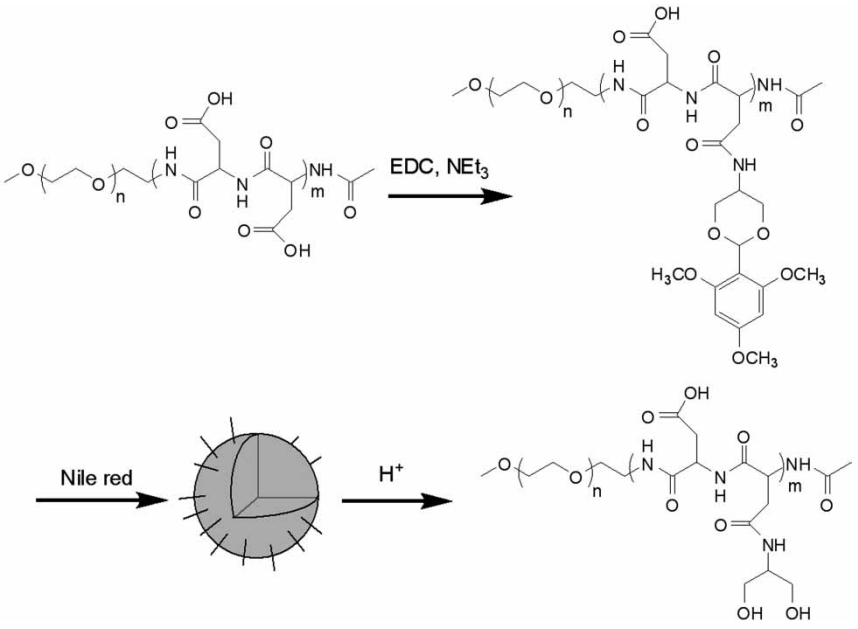

Figure 9. pH-Sensitive polymeric micelles that can be disrupted at pH 5.

2-diazo-1,2-naphthoquinones undergoes a Wolff rearrangement and forms hydrophilic 3-indenecarboxylate, which destabilizes the micelles and causes drug releasing. Because a high-wavelength light is safer and has better tissue penetration as compared with a low-wavelength light, this design may potentially be used to control drug release in deep tissues harmlessly.

Micelles may not always adopt spherical shapes. Under certain conditions, cylindrical-shaped micelles called filomicelles can be formed by controlling the fraction of hydrophilic domains.[171] Recently, Discher and coworkers studied the biodistribution of a class of filomicelles that are multiple μm long and 22–60 nm in diameters.[172] Surprisingly, these long filomicelles can circulate in rodents for up to one week, which is about 10 times longer than any known synthetic nanoparticles. Various in vitro studies suggested that long filomicelles could respond to various biological forces to fragmentize into spheres and short filomicelles that can be taken up by cells more readily than longer filaments.

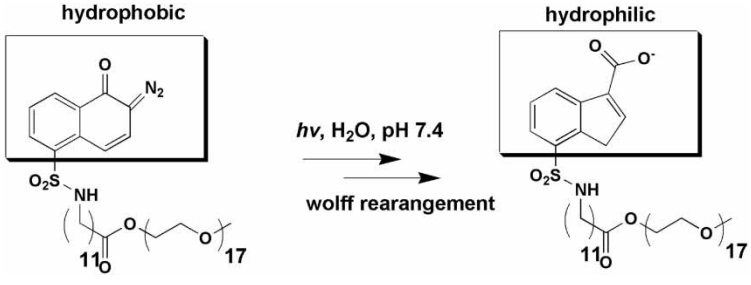

Figure 10. Formation of IR light-sensitive micelles.

Other delivery vehicles, such as nanopsheres[51,173–175] and nanogels[176–178] can be prepared using similar methods as micelles by forming nano-aggregates of hydrophobic polymer segments. These systems have been extensively reviewed elsewhere,[179–183] and therefore will not be covered in this review although some specific systems are highlighted in Table 2.

Other Promising Nanocarriers for Drug Delivery

Polymeric Vesicles

Besides forming micelles, amphiphilic block copolymers can also form vesicles when the fraction (f) of the hydrophobic domain relative to the hydrophilic domain is controlled within a certain range ($f = 0.2–0.42$).[33,34] Polymeric vesicles form liposome-like structures with a hydrophobic polymer membrane and hydrophilic inner cavity, therefore they are also called polymersomes.[33,53]

Block copolymers self-assemble into vesicles by forming bilayers through the close packing of lipid-like, amorphous polymer hydrophobic segments in a way similar as phospholipids (Fig. 1). Compared to liposomes, polymeric vesicles are more stable because their membrane-making polymers form much stronger hydrophobic interactions than the short hydrocarbon segments of liposomes. Polybutadiene (PBD) is a popular bilayer-forming polymer,[33] which can be cross-linked subsequently for enhanced vesicle stability. Other bilayer-forming polymers include biodegradable PLA and PCL for controlled drug release,[171] and polypeptides for conformation-specific vesicle assembly.[35,36] Hydrophilic blocks used in polymeric vesicles include nonionic PEG or oligo(ethylene-oxide) modified polypeptide,[36,37,171] and ionic poly(acrylic acid) or polypeptides.[33,54] Triblock[184–187] and tetrablock[188] copolymers vesicles have also been developed and studied.

Polypeptides have more diverse conformations (coils, α-helices and β-sheets) compared to synthetic polymers, therefore they are very versatile building blocks for polymeric vesicles. Recently, Deming and coworkers developed a series of polypeptide-based vesicles.[35,36,54] In addition to the control on the relative length of hydrophilic and hydrophobic segments that are critical to the formation of vesicles, the conformation was found to be another important parameter controlling the formation of peptide vesicles. Conventional uncharged amphiphilic block copolymer vesicles requires high hydrophobic contents (approximately 30–60 mol%) to form stable vesicles.[189] However, the block copolypeptides deviate from this trend and can form vesicles with 10–40 mol% hydrophobic domains. This difference is presumably because of the rigid chain conformations of polypeptides and strong intermolecular interactions[190] as compared to PBD-PEG or PLA-PEG vesicles that have more flexible polymer segments. Copolypeptides used in vesicle formation can be designed to adopt rod-like conformations in both hydrophobic and hydrophilic domains due to the strong α-helix-forming tendencies.[191] These rod-like conformations provide a flat interface on hydrophobic association in aqueous solution, thus driving the self-assembly into vesicle structures.

Although polymeric vesicles have only been studied for a few years, they have shown great promise in controlling drug loading, systemic biodistribution, and drug release.[171,172] One of the major challenges in particle-based delivery vehicles is to control drug release kinetics. Polymeric nanoparticles, for example, can release more than 50% of the encapsulated drugs within the first several or tens of hours due to burst effect.[192] In polymeric vesicles, precise tuning of the drug release rates can be achieved

through blending vesicle-forming copolymers with a hydrolyzable copolymer (e.g., PLA-PEG). The hydrophilic, hollow interior space of vesicles should also find application in encapsulation and delivery of hydrophilic therapeutics, such as DNA and proteins. Recently, a polyarginine-polyleucine copolymer vesicle demonstrated excellent intracellular trafficking properties.[35] The arginine domains not only promote vesicle formation, but also mimic the properties of protein transduction domain[193] to enhance cell membrane penetration.

Dendrimer and Dendritic Polymer Nanocarriers

Dendrimers are a class of monodisperse macromolecules with highly branched, symmetric, three-dimensional architectures (Fig. 1). They were first reported in the late 1970s and early 1980s.[194–196] Dendrimers contain layered structures (also known as generations) that extend outwards from a multifunctional core on which dendritic subunits are attached.[197] The sizes of dendrimers are in a range of 1–15 nm.

Syntheses of multi-generation dendrimers involve alternative repetition of a generation-growth and an activation step. Depending on the direction to which dendrimer grows, the synthetic strategies can be classified as divergent[195,196,198] or convergent.[199,200] Preparation of dendrimers requires alternate and stepwise control on each chain propagation step which resembles solid-phase peptide synthesis to some extent, therefore the synthesis of the dendrimer can be time-consuming and label-intensive, especially for the preparation of monodisperse dendrimers with high generations. The initial efforts in dendrimer research focused primarily on the development of various synthetic methods and the investigation of the physical and chemical properties of dendrimers.[201–207] In the past 10 years, significant efforts have been devoted to explore the potential applications of dendrimer in drug delivery.[28,29,32,45,198,208,217]

Drug molecules can either be conjugated on the surface or encapsulated inside of a dendrimer. The periphery of a dendrimer usually contains multiple functional groups for the conjugation of drug molecules or targeting ligands. Surface conjugation is straightforward and easy to control, therefore the majority of dendrimer-based drug delivery is through this covalent conjugation approach. Despite numerous designs of dendrimer-based carriers, only a few of them have been evaluated for their in vivo antitumor activities.[31,104,218]

One early example of dendrimer used as anticancer carrier in vivo is a sodium carboxyl-terminated G-3.5 polyamidoamine (PAMAM) dendrimer for the conjugation of cistplatin (20–25 wt%).[31] When administered intravenously to treat a subcutaneous B16F10 melanoma, the dendrimer-Pt conjugate displayed significantly enhanced antitumor activity as compared to free cisplatin.[31]

The same type of dendrimer, but with increased size (G-5 PAMAM), was developed and used for the delivery of MTX.[218] The dendrimer surface charge was first reduced by modifying peripheral amines of the G-5 PAMAM dendrimers with acetyl groups. Folate and MTX (≈9 wt%) were subsequently conjugated to PAMAM. Biodistribution study in mice with subcutaneous tumors using radioactively labeled dendrimers displayed internalization and intracellular accumulation in human KB tumors with over-expressed folate receptors.[104] Significant in vivo antitumor activity of the dendrimer-MTX conjugate was also observed.[104]

Recently Szoka and Fréchet developed an asymmetric dendrimer for small molecule delivery.[32] In contrast to the non-degradable PAMAM that forms globular structures, their degradable polyester dendrimers have bow-tie shaped molecular architecture (Fig. 11).

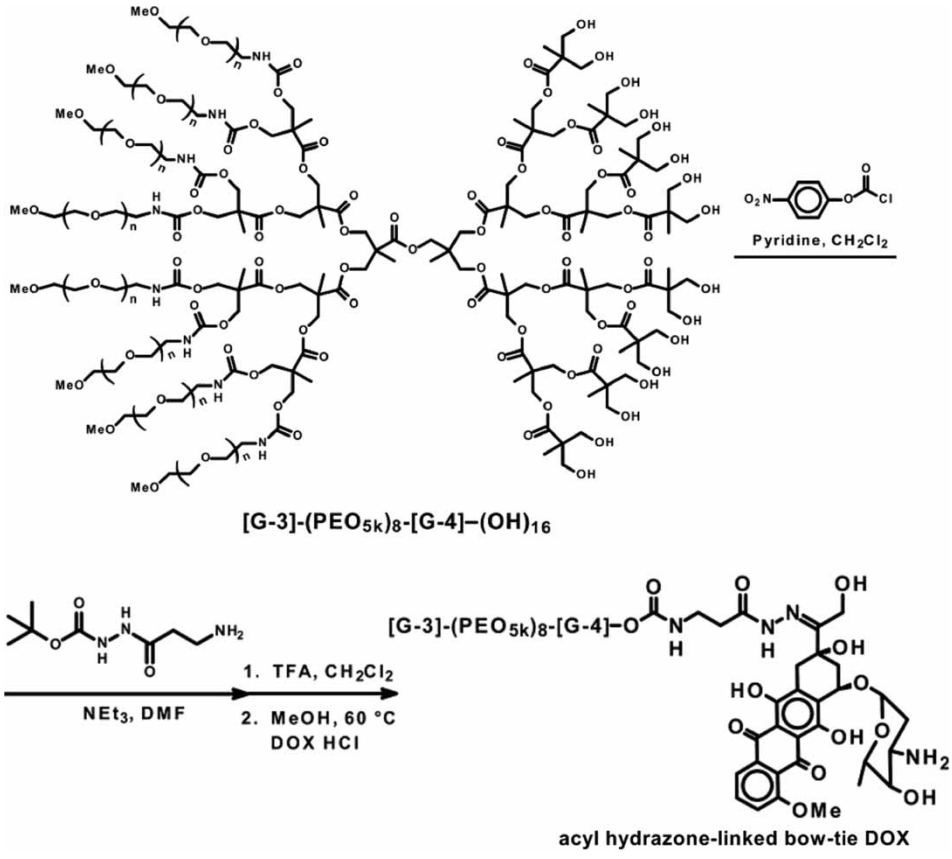

Figure 11. Functionalization of the [G-3]-$(PEO_{5k})_8$-[G-4]-$(OH)_{16}$ bow-tie dendrimers for DOXO conjugation through a pH-sensitive acyl hydrazone linker.

The number and size of the PEG chains, and the number of drug conjugation sites can be changed as desired, allowing the formation of a potentially large number of conjugates with variable PEG sizes, branches and drug-loadings. Bow-tie dendrimers with MW over 40 kDa exhibit plasma clearance half-lives greater than 24 h, which is significantly longer than linear polymer conjugates with similar MW.[104] The branched structure of the dendrimer may attribute to the reduced renal clearance and enhanced plasma half-lives as the dendrimers more likely hinder the glomerular filtration in kidney than their linear analogues with similar MWs.[29] Upon intravenous administration to BALB/c mice with subcutaneously implanted C-26 tumors, dendrimer-DOXO was found to be much more efficacious than free DOXO with less toxicity, which was presumably related to enhanced tumor-uptake. In fact, dendrimer-DOXO displayed comparable in vivo antitumor efficacy as Doxil, an FDA approved, liposome-based DOXO delivery vehicle.

Compared to liposomes and micelles, dendrimer-drug conjugates may be more stable due to their unimolecular structures, and thus are easier to handle (formulation and sterilization). However, in addition to the challenge for the synthesis of monodisperse, high-generation dendrimers, the conjugation of a large number of insoluble drugs to the surface of dendrimers may result in significantly increased peripheral hydrophobicity,

which may subsequently lead to dendrimer aggregation and increased polydispersity. Although surface hydrophobicity induced dendrimer aggregation may be reduced by encapsulating drug molecules inside dendrimers and there are some efforts in developing dendritic nanocarriers for encapsulating drugs,[219] this approach is still in an early stage of development with insufficient studies to give a full assessment.

Conclusion

Nanotechnology is making a significant impact on cancer drug delivery. In conjunction with the development of lipids based drug delivery, the advancement of modern polymer chemistry makes it possible for the preparation of a large variety of synthetic polymeric materials with structures tailored to accommodate the specific needs for systemic drug delivery. We reviewed the progress and current state of polymer-drug conjugates and polymeric micelles, the two most extensively investigated polymeric vehicles for drug delivery. We also discussed the exciting progress in some areas that are potentially of importance for controlled drug delivery and cancer therapy. It is anticipated that synergistic integration of the efforts of chemists, materials scientists, chemical and biomedical engineers and physicians will facilitate the development of polymeric nanomedicine drug delivery at an unprecedented pace, and may eventually allow cancer therapy in a time-, tissue-, or even patient-specific manner.

Acknowledgement

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