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Anticancer Agents: Polymeric Nanomedicines

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Abstract

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 entry 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. This entry was originally published as “Anticancer Polymeric Nanomedicines” in the journal Polymer Reviews, Vol. 47, No. 3, 345–381.

AN INTRODUCTION TO POLYMERIC NANOMEDICINES IN CANCER DRUG DELIVERY

Nanotechnology is making a significant impact on drug delivery. There is growing interest in integrating nanotechnology with medicine, creating the 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 in both the United States and the European Union, highlighting the importance of this evolving field. In drug delivery, nanomedicine is a newly developed term to describe nanometer-sized (1–1000 nm) multicomponent 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 multifunctionalize 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 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] Use of colloidal nanoparticles in drug delivery can date back 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 have impacted and will continue to impact the development of nanomedicine.

Application of nanotechnology to clinical cancer therapy, also known as cancer nanotechnology, was recently detailed by Ferrari.[11] 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 entry will focus only on various polymer-based nanocarriers that have been developed for cancer therapy. Polymeric-drug nanomedicines to be discussed in detail are polymer–drug conjugates[16–19] and polymeric micelles,[10,20–26] some of which have either been approved for clinical use or currently under clinical investigations.[12,18,27] 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 molecules 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. In his postulated model of polymer–drug conjugates, multiple drug molecules are bound to polymer side chains through covalent, cleavable bonds. The cleavage of the polymer–drug linkage 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. Their efforts led to a handful of HPMA-drug conjugates that later entered several clinical trials. Using the same strategy, Maeda and colleagues developed SMANCS conjugate (styrene maleic acid neocarzinostatin) by covalently linking the anticancer drug neocarzinostatin to two styrene...
maleic anhydride polymer chains. They successfully brought this antitumor protein conjugate to the Japanese market in 1994 as the first polymer–protein conjugate approved for human cancer treatment. Since these early studies, many different polymers have been developed and evaluated as delivery vehicles for both protein and small molecules. However, only a limited number of polymeric carriers have reached clinical trials (Fig. 2). Nanosized polymer–drug conjugates based on these polymers as well as the other promising candidates will be discussed in the “Polymer–Drug Conjugates” section.

The physical encapsulation approach controlling drug release from a polymer matrix was originated from the seminal work by Folkman and Long in 1964. 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. They found that soybean trypsin inhibitor could be encapsulated and released from an ethylene–vinyl acetate copolymer matrix over a 100-day period. This is the first report of sustained release of protein and other macromolecules from the 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, 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) or the self-assembly of the hydrophobic polymer domain of amphiphilic block copolymers (polymeric micelles and vesicles). Compared to polymer–drug conjugates with sizes generally around 10 nm or less, nanoaggregates formed through phase-separation are larger, typically in a range of 20–100 nm for micelles and 100 nm to a few micrometers for polymer vesicles. Nanocarriers based primarily on physical encapsulation will be covered in the “Polymeric Micelles” section.

**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.\cite{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, conjugation of hydrophilic polymers to proteins is frequently employed to overcome these drawbacks. Covalent linking 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).\cite{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.\cite{58} Conjugation of PEG to a protein or peptide can shield antigenic epitopes of the polypeptide, resulting in significant reduction of recognition by the 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 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 functional groups on lysine, other conjugation sites include the side chain of cysteine, histidine, tyrosine, and serine.\cite{59} Uncontrollable, multisite pegylation is one of the major drawbacks of pegylation, which leads to pharmaceutical products with heterogeneous structures and reduced activities.\cite{60} For instance, interferon-α2b (IFN-α2b) conjugated with an activated 12 kDa mPEG forms as many as 15 different PEG-IFN-α2b products.\cite{58} Less than 10% of bioactivity (relative to the original IFN-α2b) remains after the conjugation of PEG on Lys-83 and Lys-121 of IFN-α2b.\cite{59} 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.\cite{61} 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 by the FDA for the treatment of neovascular age-related macular degeneration,\cite{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 has mainly focused on the use of branched or heterodifunctional linear PEG that is capable of controlling site-specific, step-wise conjugation. A unique site-specific pegylation through the formation of a three-carbon bridge was reported by Brocchini, Shaunk, and coworkers.\cite{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 into the disulfide bond showed minimum disturbance to the protein structures. This technique can be potentially applied to site-specific pegylation of numerous proteins containing disulfide bonds.

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.\cite{62,63} Click chemistry usually gives very high yields, and proceeds under very mild conditions. Ligand conjugation induced by click chemistry has been successfully carried out both in situ\cite{64} and in vitro.\cite{65,66} One type of click chemistry, the Azide–Alkyne Huisgen cycloaddition, is particularly important for site-specific protein conjugation through the formation of 1,2,3-triazole between an azide and an alkyne.\cite{66} In this reaction, a 1,3-dipolar cycloaddition between an azide and an alkyne gives a 1,2,3-triazole.\cite{66} Conjugation of cellular glycans with fluorescent tags through click chemistry, for example, resulted in rapid, versatile, and site-specific covalent labelings.\cite{66}

Tirrell and coworkers demonstrated that click chemistry can be used for site-specific conjugation of fluorescent tag with genetically engineered proteins containing non-natural homopropargylglycine or ethynylphenylalanine.\cite{67,68} The introduced alkynyl groups on these non-natural amino acids provide sites for the attachment of fluorescent dyes containing azide groups (Fig. 3). Recent advance in protein engineering makes it possible to incorporate many non-natural amino acids at 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**

Conjugation of hydrophobic small molecule drugs to hydrophilic polymers has been actively pursued for improved pharmacological and pharmacokinetic properties of the
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 multidrug resistance.

Other polymers that have been successfully included HPMA copolymer,

linear PEG only has two terminal hydroxyl groups for conjugation, which limits its drug-carrying capacity. A PEG–CPT conjugate (Prothecan), for example, only has about 2 wt% CPT linked to PEG.

PEG–CPT conjugates showed antitumor efficacy in various preclinical studies, and have also been tested clinically. In a biodistribution study, the plasma half-life of a 20 kDa PEG–DOXO conjugate was found to be less than 10 hours. Protracted antitumor activity was observed with prolonged circulation and improved tumor accumulation due to the enhanced permeability and retention (EPR) effect (Fig. 4).

A phase-I clinical study, PEG–CPT showed a 77-hour plasma clearance half-life, which is much greater than that of a similar system in mice. A 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 when compared to free CPT. Extended circulation and slow release of CPT may also contribute to the observed neutropenia and thrombocytopenia.

HPMA–drug conjugates are another type of conjugates that have been extensively evaluated in clinic.

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. Most HPMA copolymers tested in vivo are 30 kDa or shorter. However, HPMA–drug conjugates with such low MWs showed fast renal clearance, which may adversely affect their antitumor efficacy. Enhanced accumulation through the EPR effect for polymer–drug conjugates with MWs at or around their renal clearance threshold (40–45 kDa) is as effective as their higher MW analogs. Compared to PEG, HPMA has a large number of pendant 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. HPMA–CPT conjugates with PTXL, CPT, DOXO, and platinate 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 or CPT 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 harsh endolysosomal environment. PTXL and CPT conjugated to pGlu showed enhanced preclinical antitumor efficacy in several preclinical tumor models presumably due to the EPR-mediated passive tumor targeting. Interestingly, pGlu–PTXL also showed positive response in taxane-resistant patients in several Phase I and II studies of various cancers. A 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
### Table 1  Polymer–drug conjugates in clinical trials

<table>
<thead>
<tr>
<th>Name</th>
<th>Polymer</th>
<th>Drug</th>
<th>Linker</th>
<th>Company</th>
<th>Target</th>
<th>Status</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothecan&lt;sup&gt;®&lt;/sup&gt;</td>
<td>PEG (40 kDa)</td>
<td>CPT</td>
<td>Ester</td>
<td>Enzon</td>
<td>SCLC</td>
<td>Phase II</td>
<td>[97,99]</td>
</tr>
<tr>
<td>PK1</td>
<td>HPMA (30 kDa)</td>
<td>DOXO</td>
<td>Gly-Phe-Leu-Gly</td>
<td>CRC/Pharmacia</td>
<td>Various cancers</td>
<td>Phase II</td>
<td>[70,106]</td>
</tr>
<tr>
<td>PK2</td>
<td>HPMA (30 kDa)</td>
<td>DOXO</td>
<td>Gly-Phe-Leu-Gly</td>
<td>CRC/Pharmacia</td>
<td>Various cancers</td>
<td>Phase I</td>
<td>[112]</td>
</tr>
<tr>
<td>PNU-166945</td>
<td>HPMA (40 kDa)</td>
<td>PTXL</td>
<td>Ester</td>
<td>Pharmacia</td>
<td>Various cancers</td>
<td>Phase I</td>
<td>[107]</td>
</tr>
<tr>
<td>MAG-CPT</td>
<td>HPMA (30 kDa)</td>
<td>CPT</td>
<td>Gly-6-aminohexanoyl-Gly</td>
<td>Pharmacia</td>
<td>Various cancers</td>
<td>Phase I</td>
<td>[108,111]</td>
</tr>
<tr>
<td>AP5346</td>
<td>HPMA (25 kDa)</td>
<td>Oxaliplatin</td>
<td>Gly-Gly-Gly</td>
<td>Access</td>
<td>Head and neck cancer</td>
<td>IND approved</td>
<td>[221]</td>
</tr>
<tr>
<td>CT-2103 (XYOTAX)</td>
<td>PG (40 kDa)</td>
<td>PTXL</td>
<td>Ester</td>
<td>Cell Therapeutics</td>
<td>Various cancers</td>
<td>Phase III</td>
<td>[114–117,222–224]</td>
</tr>
<tr>
<td>CT-2106</td>
<td>PG (50 kDa)</td>
<td>CPT, 5-Fu</td>
<td>Gly-ester</td>
<td>Cell Therapeutics</td>
<td>Various cancers</td>
<td>Phase I</td>
<td>[79]</td>
</tr>
<tr>
<td>MTX-HSA</td>
<td>Albumin (67 kDa)</td>
<td>MTX</td>
<td>—</td>
<td>AK St. Georg</td>
<td>Advanced cancers</td>
<td>Phase II</td>
<td>[92,225–228]</td>
</tr>
<tr>
<td>DOXO-EMCH</td>
<td>Albumin (67 kDa)</td>
<td>DOXO</td>
<td>Hydrazine</td>
<td>Tumor Biology Center</td>
<td>Various cancers</td>
<td>Phase I</td>
<td>[141]</td>
</tr>
<tr>
<td>IT-101</td>
<td>CD polymer</td>
<td>CPT</td>
<td>Gly-ester</td>
<td>Insert Therapeutics</td>
<td>Various cancers</td>
<td>Phase I</td>
<td>[87–90]</td>
</tr>
<tr>
<td>DAVANAT</td>
<td>Polymannopyranose</td>
<td>5-Fu, AVand LV</td>
<td>—</td>
<td>Propharmaceuticals</td>
<td>Colorectal cancer</td>
<td>Phase II</td>
<td>[91]</td>
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<tr>
<td>AD-70</td>
<td>Dextran (70 kDa)</td>
<td>DOXO</td>
<td>Schiff base</td>
<td>Alpha Therap. GmbH</td>
<td>—</td>
<td>Phase I</td>
<td>[122]</td>
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<tr>
<td>HuC242-DM4</td>
<td>humAb huC242</td>
<td>MTS-DM4</td>
<td>—</td>
<td>ImmunoGen</td>
<td>Various cancers</td>
<td>Phase I</td>
<td>—</td>
</tr>
<tr>
<td>BB-10901</td>
<td>humAb N901</td>
<td>MTS-DM1</td>
<td>—</td>
<td>ImmunoGen</td>
<td>SCLC and CD56-SC</td>
<td>Phase II</td>
<td>[93–95,144]</td>
</tr>
</tbody>
</table>

**Abbreviations:** 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.
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may participate in regulating the in vivo efficacy of pGlu-PTXL. pGlu-PTXL was found to be efficacious only in certain group of patients, such as premenopausal 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.\(^{[79]}\)

CD-containing polymer is a new class of hydrophilic biomaterials that has 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.\(^{[118]}\) CD-containing polymers have also been developed and used for decades.\(^{[119,120]}\) 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, \(\beta\)-cyclodextrin polymer (\(\beta\)-CDP)\(^{[121]}\) bearing cationic pendant groups for gene delivery.\(^{[121–126]}\) 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

Fig. 4 Schematic illustration of the EPR effect.

Fig. 5 Schematic illustration of IT-101, a conjugate between 20(S)-camptothecin and a linear, \(\beta\)-CD-based polymer through a glycine ester linker.
increase the solubility of CPT by three orders of magnitude after conjugation.[88]

A pharmacokinetic study in rats showed that the half-life of bound CPT in IT-101 is 17–19 hours, which is significantly longer than that of 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 (~50–80 nm) in solution presumably through the interchain interaction between CPT and CD. This unusual nanoaggregation is in sharp contrast to most polymer–drug conjugates reported so far whose sizes typically ranged from 5 to 15 nm. The increase in particle size of IT-101 likely reduces its clearance through glomerular filtration, thus enhances its in vivo antitumor efficacy.[90] 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 multidrug resistance. An open-label, dose-escalation Phase I study using IT-101 in patients with inoperable or metastatic solid tumors has been initiated.

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 the 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 was 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 applications (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 uptake of dextran by the RES.[127] DE-310, another dextran-based conjugate with a 340 kDa carboxymethylx-dextran polyalcohol conjugated with CPT analog DX-8951 through an Gly-Gly-Phe-Gly linker, was also tested in clinic.[84,128–130] 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 proteases. Thus drug release can be specifically controlled inside cells.[84] A Phase I study showed dose-limiting toxicities due to thrombocytopenia and neutropenia.[129]

As polymer accumulation in tumor through the EPR effect is usually enhanced with increased polymer MW,[102] 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).[109,131,132] The acetal moiety was chosen because it can undergo faster hydrolysis under mildly acidic conditions but is stable at pH ~7.4.

**Fig. 6** pH-Sensitive polyacetal for DOXO delivery.
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 the range of 1.8–2.6).\textsuperscript{109,131,132} The polyacetals displayed remarkable tunability for pH-induced degradation. Enhanced hydrolysis was observed at pH 5.5 (41% \(M_w\) loss in 25 hours) when compared with that at pH 7.4 (10% \(M_w\) loss in 73 hours). In addition, the polyacetals and their degradation products are non-toxic \textit{in vitro} (IC\(_{50}\) > 5 mg/mL in B16F10 cells) and \textit{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 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.\textsuperscript{109} Both polyacetal-DOXO and HPMA copolymer-DOXO displayed similar biphasic patterns of plasma clearance with a \(t_{1/2}\) of \(-1\) hour presumably due to the presence of low MW fragments. But the plasma levels of polyacetal-DOXO were significantly higher than those of HPMA copolymer-DOXO with a \(t_{1/2}\) of 19 hours and 3.5 hours for polyacetal-DOXO (Fig. 6) and HPMA copolymer-DOXO, respectively. The \(t_{1/2}\) of polyacetal-DOXO is quite similar to that of the CD polymer with a similar MW (85 kDa, \(t_{1/2} = 17–19\) hours).\textsuperscript{106} Because prolonged plasma circulation is the driving force for increased passive tumor targeting,\textsuperscript{113,114} polyacetals with higher MWs and lower polydispersities may give improved circulation half-life and tumor accumulation. It is noted that polyacetal-DOXO, although with MW much higher than HPMA copolymer conjugates, showed reduced accumulation in liver and spleen.\textsuperscript{110} 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. Papiov and coworkers developed acyclic hydrophilic polyalds through the lateral cleavage of polyaldoses and polyketoses.\textsuperscript{130,136} Polyls obtained through this method consist of acyclic carbohydrate substructures that are potentially biocompatible. The intrachain acetal or ketal groups should enable hydrolytic biodegradation upon cell uptake. In an \textit{in vivo} toxicity study, all mice survived intravenous administration 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 been evaluated as drug carriers in clinical trials. A methotrexate–human serum albumin conjugate (MTX-HSA) was synthesized by coupling MTX to HSA.\textsuperscript{115–118} MTX-HSA showed significant accumulation in rat tumors and displayed high \textit{in vivo} antitumor activity. In a Phase I study, patients with renal cell carcinoma and mesothelioma responded to treatment with MTX-HSA therapy.\textsuperscript{119} In a Phase II study of MTX-HSA in combination with cisplatin as first line treatment of advanced bladder cancer,\textsuperscript{120} 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-maleimido-caproyl-hydrazone linker.\textsuperscript{140} The covalently linked DOXO prevents its rapid diffusion of DOXO into healthy tissue after intravenous administration and allows passive accumulation of DOXO-EMCH through the EPR effect in solid tumors. DOXO is then released in the acidic environment of tumor tissue through the cleavage of the hydrazone 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\(^2\).\textsuperscript{141}

Antibody has 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 II/III clinical trials.\textsuperscript{133–135,142} Immunoconjugates for cancer treatment is beyond the coverage of this entry, and has been reviewed elsewhere.\textsuperscript{143} It is worth reporting that an alternative strategy of using aptamers for targeted DOXO delivery was developed.\textsuperscript{144}

### 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). Polymeric micelles have a condensed, compact inner core, which serves as the nanocontainer of hydrophobic compounds. As polymeric micelles are generally more stable than hydrocarbon-based micelles, sustained drug release from polymeric micelles becomes possible.\textsuperscript{120,124} Numerous types of amphiphilic copolymers have been employed to form micelles\textsuperscript{4,10,20,32,45–47} or other similar architectures such as nanogels\textsuperscript{148} and polymer nanoparticles.\textsuperscript{151} Details of copolymers structure and drug molecule encapsulated or conjugated are summarized in Table 2.

Polymeric micelles can accumulate in tumors after systemic administration. Their biodistributions are largely determined by their physical and biochemical properties,
Fig. 7  Polymeric micelle core–shell structure and drug encapsulation.

Table 2  Polymeric nanoparticles: Polymer structures and drug incorporated

<table>
<thead>
<tr>
<th>Block copolymer</th>
<th>Drug (or Dye) [reference]</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG-b-polypeptide</td>
<td>DOXO, methotrexate, indomethacin, amphotericin-B, KRN 5500, cisplatin, and Nile Red</td>
</tr>
<tr>
<td>PEG-b-pAsp</td>
<td>Clonazepam</td>
</tr>
<tr>
<td>PEG-b-pGlu(Bn)</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>PEG-b-pHis/PLA</td>
<td>pH-sensitive micelles; DOXO</td>
</tr>
<tr>
<td>PEG-b-pLys</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>PEG-b-polyester</td>
<td>Indomethacin, dihydrotestosterone, FK506, L-685,818, nimodipine</td>
</tr>
<tr>
<td>PEG-b-PCL</td>
<td>PTXL, DOXO</td>
</tr>
<tr>
<td>PEG-b-PLGA</td>
<td>DOXO, PTXL, DTXL, DOXO/combretastatin</td>
</tr>
<tr>
<td>PEG-b-polyether (nanogel)</td>
<td>Daunorubicin, DOXO, vinblastine, mitomycin, cisplatin, methotrexate, epirubicin, PTXL, etoposide, and digoxin</td>
</tr>
<tr>
<td>Pluronic-P85</td>
<td>Nystatin</td>
</tr>
<tr>
<td>Pluronic-F127</td>
<td>Nystatin</td>
</tr>
<tr>
<td>Pluronic-F68</td>
<td></td>
</tr>
<tr>
<td>Other homopolymers and block polymers</td>
<td></td>
</tr>
<tr>
<td>PEG-b-PMA</td>
<td>Pyrene and Nile Red</td>
</tr>
<tr>
<td>pLys(EG)-b-pLeu</td>
<td>DiOC dye</td>
</tr>
<tr>
<td>pArg-b-pLeu</td>
<td>Fluorescein</td>
</tr>
<tr>
<td>pLys-b-pLeu</td>
<td>DiOC dye</td>
</tr>
<tr>
<td>PUA-b-PNIPAm</td>
<td>N/A</td>
</tr>
<tr>
<td>PNIPAAm/PDMAAm-b-PCL/PLA</td>
<td>DNA vaccine</td>
</tr>
<tr>
<td>PLA-PEG-PLA</td>
<td>DNA and dye</td>
</tr>
<tr>
<td>Poly(orthoester)</td>
<td>N/A</td>
</tr>
<tr>
<td>Poly(β-amino ester)</td>
<td>N/A</td>
</tr>
<tr>
<td>Polyketal</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PNIPAAm, poly(N-isopropylacrylamide); PUA, poly(undecylenic acid); pAsp, poly(aspartate); pGlu(Bn), poly(benzyl-glutamate); pLys, polylysine; pHis, polyhistidine; 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).
such as particle sizes, hydrophobicity and hydrophilicity of the polymers and drugs, and surface biochemical properties.\textsuperscript{[150]} A major issue that limits the systemic application of micellar nanocarriers is the non-specific uptake by the RES. It is critical to have systems that can circulate for long time without significant accumulation in liver or spleen. The sizes and the surface features of micelles have to be controlled for favored biodistribution and intracellular trafficking.\textsuperscript{[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 adsorption of plasma proteins onto nanoparticle surfaces.\textsuperscript{[22]} Micellar nanocontainers are typically in the 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.\textsuperscript{[150]} It was also found that the effect of size on polymeric micelle biodistribution is organ specific and non-linear.\textsuperscript{[153]} 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 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.\textsuperscript{[152]}

PEG-Polypeptide Micelle

PEG-b-poly(aspartic acid) [PEG-b-pAsp] micelles and their DOXO conjugates (NK911) were developed by Kataoka and coworkers.\textsuperscript{[153]} This is one of the most intensively investigated micellar drug delivery systems. DOXO molecules were conjugated to the 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 π–π interaction with the encapsulated DOXO molecules.\textsuperscript{[154]} In a Phase I study, the toxicity of NK911 resembled that of free DOXO, and the dose-limiting toxicity was neutropenia.\textsuperscript{[153]} NK911 is currently being evaluated in a Phase II clinical trial.\textsuperscript{[4]}

The compatibility between the core-forming blocks and the drugs to be loaded controls the drug loading capacity and release rate. For example, 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.\textsuperscript{[156]} 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-butanoate modified PEG-b-pAsp to form polymeric micelles (NK105).\textsuperscript{[157]} 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 the EPR effect.

Because carboxylate groups can chelate with multivalent metal ions, amphiphilic copolymers containing pAsp and pGlu have been used to complex with anticancer platinum compounds, such as cis-dichlorodiammineplatinum(II) (cisplatin).\textsuperscript{[156]} 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 for 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), 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 into the micellar hydrophobic core through physical encapsulation although conjugation of DOXO through a covalent bond to the terminal hydroxyl group of PLGA has also been tested.\textsuperscript{[159]}

Low MW methoxy-PEG-b-PLA was employed to encapsulate PTXL to form copolymer micelles.\textsuperscript{[160]} Evaluation of the in vivo antitumor efficacy of this micelle in SKOV-3 human ovarian cancer implanted xenograft mouse demonstrated significantly enhanced antitumor activity when 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.\textsuperscript{[161]}

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.\textsuperscript{[162]} Recently, aptamers were also developed and used in targeted drug delivery.\textsuperscript{[163]} An A10 2′-fluoropyrimidine RNA aptamer that recognizes the extracellular domain of the prostate-specific membrane antigen was conjugated to a 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 DTXL-aptamer nanoparticle resulted in complete tumor remission in five of seven LNCaP xenograft nude mice when compared to tumor remission in two of the seven mice in the control group.

Stimuli-Responsive Polymeric Micelle

Polymeric 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 ≈ 6.5) as well as in the endosomal intracellular compartments (pH ~4.5–6.5) may trigger drug release from pH-sensitive micelles upon their arrival at the targeted disease sites. Fréchet and coworkers developed a pH-dependent micelle that can release encapsulated cargos significantly faster at pH 5 than at pH 7.4. 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 hydrazone linker to conjugate DOXO to pAsp. A kinetic study demonstrated pH-dependent release of DOXO, in a manner resembling what was observed in Fréchet’s pH-sensitive micelles.

Fréchet and coworkers also reported an alternative release triggering mechanism through the use of infrared light (Fig. 10). The amphiphilic structure has a 2-diazo-1,2-naphthoquinone at the terminal of hydrophobic end and an oligo(ethylene glycol) as the hydrophilic block. When the micelles were exposed to infrared light, 2-diazo-1,2-naphthoquinone undergoes a Wolff rearrangement and forms hydrophilic 3-indenecarboxylate, which destabilizes micelle and causes drug releasing. Because high-wavelength light is safer and has better tissue penetration when compared with 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 also called filomicelles can be formed by controlling the fraction of hydrophilic domains. Discher and coworkers studied the biodistribution of a class of filomicelles that are multiple μm long and 22–60 nm in diameters. 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.

Other delivery vehicles, such as nanospheres and nanogels, can be prepared using similar methods as micelles by forming nanoaggregates of hydrophobic polymer segments. These systems have been extensively reviewed elsewhere and therefore will not be covered in this entry although some specific systems are highlighted in Table 2.

Fig. 8 DTXL-encapsulated, PLGA-b-PEG-COOH micelle and its aptamer conjugate for targeted prostate cancer therapy.
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 \( (f = 0.2–0.42) \). Polymeric vesicles form a liposome-like structure with a hydrophobic polymer membrane and hydrophilic inner cavity, therefore they are also called polymersomes. 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,\(^{[168]}\) and polypeptides for conformation-specific vesicle assembly.\(^{[35,36]}\) Hydrophilic blocks used in polymeric vesicles include non-ionic PEG or oligo(ethylene-oxide)-modified polypeptide,\(^{[36,37,168]}\) and ionic poly(acrylic acid) or polypeptides.\(^{[35,54]}\) Triblock\(^{[181–184]}\) and tetrablock\(^{[185]}\) copolymer vesicles have also been developed and studied. Polypeptides have more diverse conformations (coils, \( \alpha \)-helices, and \( \beta \)-sheets) compared to synthetic polymers, therefore they are very versatile building blocks for polymeric vesicles. 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

**OTHER PROMISING NANOCARRIERS FOR DRUG DELIVERY**

**Polymeric Vesicles**

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Block copolymers self-assemble into vesicles by forming bilayers through the close packing of lipid-like, amorphous polymer hydrophobic segments in a way similar to 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,\(^{[168]}\) and polypeptides for conformation-specific vesicle assembly.\(^{[35,36]}\) Hydrophilic blocks used in polymeric vesicles include non-ionic PEG or oligo(ethylene-oxide)-modified polypeptide,\(^{[36,37,168]}\) and ionic poly(acrylic acid) or polypeptides.\(^{[35,54]}\) Triblock\(^{[181–184]}\) and tetrablock\(^{[185]}\) copolymer vesicles have also been developed and studied.

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![Fig. 9](image1.png) pH-Sensitive polymeric micelles that can be disrupted at pH 5.

![Fig. 10](image2.png) Formation of IR light-sensitive micelles.
vesicles, the conformation was found to be another important parameter controlling the formation of peptide vesicles. Conventional uncharged amphiphilic block copolymer vesicles require high hydrophobic contents (approximately 30–60 mol%) to form stable vesicles. However, the block copolyptides 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 when compared to PBD-PEG or PLA-PEG vesicles that have more flexible polymer segments. Copoly peptides 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. 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. 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 the burst effect. In polymeric vesicles, precise tuning of drug release rate 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. A polyarginine–polyelucine copolymer vesicle demonstrated excellent intracellular trafficking properties. The arginine domains not only promote vesicle formation but also mimic the properties of protein transduction domain 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. Dendrimers contain layered structures (also known as generations) that extend outwards from a multifunctional core on which dendritic subunits are attached. The sizes of dendrimers are in the range of 1–15 nm. Syntheses of multigeneration dendrimers involve alternative repetition of a generation-growth and an activation step. Depending on the direction towards which dendrimer grows, the synthetic strategies can be classified as divergent or convergent. Preparation of dendrimers requires alternate and stepwise control on each chain propagation step, which resembles solid-phase peptide synthesis to some extent, therefore synthesis of dendrimers 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. In the past 10 years, significant efforts have been devoted to explore the potential applications of dendrimers in drug delivery.

Drug molecules can either be conjugated on the surface or encapsulated inside 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.

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

The same type of dendrimer, but with increased size (G-5 PAMAM), was developed and used for the delivery of MTX. The dendrimer surface charge was first reduced by modifying peripheral amines of the G-5 PAMAM dendrimers with acetyl groups. Folate and MTX 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 overexpressed folate receptors. Significant in vivo antitumor activity of the dendrimer-MTX conjugate was also observed.

Szöke and Fréchet developed an asymmetric dendrimer for small molecule delivery. In contrast to the non-degradable PAMAM that forms globular structures, their degradable polyester dendrimers have bow-tie shaped molecular architecture (Fig. 11). 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 hours, which is significantly longer than linear polymer conjugates with similar MW. The branched structure of dendrimers 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 analogs with similar MWs. 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, 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, this approach is still in the 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.
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