Cancer drug delivery in the nano era: An overview and perspectives (Review)

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Received December 2, 2016; Accepted May 29, 2017

DOI: 10.3892/or.2017.5718

Abstract. Nanomaterials are increasingly used as drug carriers for cancer therapy. Nanomaterials also appeal to researchers in the areas of cancer diagnosis and biomarker discovery. Several antitumor nanodrugs are currently being tested in preclinical and clinical trials and show promise in therapeutic and other settings. We review the development of nanomaterial drug carriers, including liposomes, polymer nanoparticles, dendritic polymers, and nanomicelles, for the diagnosis and treatment of various cancers. The prospects of nanomaterials as drug carriers for future clinical applications are also discussed.

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Key words: nanoparticles, drug carriers, cancer treatment, delivery system, clinical trials

1. Introduction

According to the World Health Organization's World Cancer Report 2014, cancer caused 8.2 million deaths worldwide in 2012, and this number is expected to rise to 22 million by 2035 (1). Along with surgery and radiotherapy, chemotherapy is a mainstay of cancer treatment. Chemotherapy is the most frequently used systemic treatment for suppressing cancer cell proliferation, disease progression and metastasis. However, chemotherapeutic drugs not only kill proliferating cancer cells but also inevitably attack normal cells, causing adverse effects. Therefore, antitumor drug vehicles that maintain or improve the efficacy of chemotherapy while reducing the severity of reactions and side effects are urgently needed.

Nanoparticles, which can be adapted to have various biological properties and can be used in a range of settings, provide a safer and effective means of delivering chemotherapy (2-4). In the past decade, approximately 12,000 reports on the topic of nanomaterials as drug carriers in cancer treatment have been published. However, there remains a gap between technological advances and clinical applications. Many nanodrugs have been developed over the last 50 years (Fig. 1). In 1965, a group led by Bangham discovered liposomes (5). A liposomal formulation of doxorubicin (Doxil), was approved by the US Food and Drug Administration (FDA) in 1995 for treating AIDS-related Kaposi sarcoma (6). In 2005, an albumin-based nanoparticle, protein-bound paclitaxel (Abraxane) (7), has been approved by the FDA for clinical use in the treatment of breast cancer, non-small cell lung cancer, and pancreatic cancer. More recently, in 2013, targeted ado-trastuzumab emtansine (DM1) (Kadcyla) was approved for use in patients with human epidermal growth factor receptor 2-positive breast cancer (8).

Nanomaterials have a number of advantages as drug carriers. Nanocarriers can: i) increase water solubility and protect drugs dissolved in the bloodstream, improving the pharmacokinetic and pharmacological properties of the drugs; ii) target the delivery of drugs in a tissue- or cell-specific manner, thereby limiting drug accumulation in the kidneys, liver, spleen, and other non-targeted organs and enhancing therapeutic efficacy; and iii) deliver a combination of imaging

and therapeutic agents for real-time monitoring of therapeutic efficacy (9,10).

This review summarizes recent developments in the use of nanomaterials in cancer therapy. Specifically, we discuss the use of liposomes, polymer nanoparticles, dendritic polymers, and micelles as drug carriers (Fig. 2). Each category of nanomaterials has unique strengths and limitations; thus, a major goal of this review is to unveil the emerging possibilities of different nanovectors for different therapeutic applications, their relevant molecular targets, and their advantages and disadvantages.

2. Liposomes

Liposomes consist of an aqueous core surrounded by one or several layers of phospholipids and cholesterol that form a lipid bilayer. Because of this unique structure, liposomes can load and hold hydrophilic agents in the aqueous compartment and hydrophobic agents in the lipid space (11). Because their composition is similar to that of the cell membrane, liposomes are more biocompatible than other synthetic materials. In addition, distinct surface modification with functional ligands and differences in size and charge make liposomes coat with polyethylene glycol (PEG) useful for specific drug delivery tasks.

Liposomes have several additional advantages as nanocarriers for drug delivery applications. Liposomes protect the loaded drug from degradation and prevent undesirable exposure of the drug to the environment, which may slow the rate of drug release (12-14). Specific lipid species, such as cholesterol and rigid saturated lipids, stabilize the lipid bilayer to resist attack from plasma proteins and reduce drug leakage (13,14). However, the present challenge facing the development of liposomes as drug carriers is how to control their distribution and removal *in vivo*.

Recently, a number of studies have focused on modifying liposome drug-releasing mechanisms. For example, drug release from liposomes can be triggered by ultrasound (15,16), enzymes (17,18), light (19,20), magnetism (21-23), or hyperthermia (24). Drug-releasing liposomes may also be combined with ligand-mediated targeted delivery of nucleic acids (25-28).

Further, multifunctional and multicomponent formulations (29) have been designed to enhance localization selectivity, allowing specific targeting of distinct tissue types. Chen *et al* (30) used a glycyrrhetinic acid (GA)-modified liposome to load oxaliplatin (OX) for liver-targeted biodistribution studies and demonstrated that the ratio of the area under the curve (AUC) of GA-OX-liposomes to the AUC of OX-liposomes was 3.84. These results suggest that liposomes exhibit excellent tissue- and organ-specific targeting.

Liposomes not only increase the intracellular uptake of drugs but also can be used to modify anticancer agents, antibiotics, and DNA. Using an AAN-TAT-liposome platform, Liu *et al* (31) created a doxorubicin carrier that enhanced the drug tumoricidal effect and reduced systemic adverse effects. The RNA liposome platform is another promising strategy for boosting therapeutic efficacy (32). Recently, protocells have been designed to incorporate various types of modification to achieve a comprehensive nanodrug delivery system (Fig. 3). Chemotherapy agents, short interfering RNA, and nanoparticles, for instance, can be coupled with or encapsulated in a nanoporous silica core for simulating chemotherapy treatment with site-specific drug delivery. The supporting lipid bilayer can also be decorated with surface-targeting molecules, such as fusogenic peptide and polyethylene glycol, according to tumor type or vasculature.

Liposomes can also be used as a nonviral vector for gene delivery, making the liposome/DNA complex one of the most promising tools for cancer gene therapy (33). For example, Felgner and colleagues (34) developed cationic liposome-mediated gene delivery, in which a liposome was incorporated with an antisense oligodeoxynucleotide specific for growth factor receptor-bound protein 2 (Grb2) mRNA (L-Grb2). These liposomes inhibited Grb2 protein expression, reduced proliferation of bcr-abl-positive leukemia cells, and extended survival durations in mice bearing bcr-abl-positive leukemia xenografts (35) (Table I).

3. Polymers

Polymers can be categorized as: i) natural polymers, such as proteins, peptides, glycans, starches, and cellulose; ii) synthetic polymers, which are synthesized from natural monomers, for instance, polylactic acid (PLA) and poly (lactic-co-glycolic acid) (PLGA); and iii) microbial fermentation polymers, such as polyhydroxybutyrate (36). Natural and synthetic polymers constitute a diversified platform for synthesis of a variety of nanoparticles, including liposomes, dendrimers, and micelles (Fig. 2).

Polymer nanoparticles, micelles, nanosponges (37,38), nanogels (39), and nanofibers for wound healing have been widely investigated (40,41). Natural polymers that are extensively used in nanoparticle synthesis include chitosan, dextran, albumin, heparin, gelatin, and collagen (42,43). Chitosan-coated PLGA nanoparticles (44,45) and chitosan nanoparticles (46-49) can carry and deliver proteins in an active form and transport them to specific organs. Synthetic polymers, such as PEGylated PLA nanoparticles and PLA-PEG-PLA nanoparticles (50-54), poly-PLGA nanoparticles (55), monomethoxypolyethylene glycol-block-polycaprolactone nanoparticles (56), and N-(2-hydroxypropyl)-methacrylamide copolymers (57), assist in the transport of proteins within the drug capsules. Furthermore, a PEG coating improves the stability of PLA nanoparticles exposed to gastrointestinal fluids and prolonged circulating time (58). Thermosensitive polymers, for which temperature is the triggering signal, can also be used to control and target drug delivery (59).

Nanosponges, which are made from biocompatible, biodegradable polymer nanoparticles, are prepared by fusing erythrocyte membrane vesicles onto PLGA nanoparticles by means of extrusion. Nanosponges are composed of hyper-cross-linked cyclodextrins connected in a three-dimensional network. Nanosponges form porous nanoparticles with sizes <500 nm, so they easily circulate in the bloodstream. As 'sponges', they can absorb toxins, secretions, and fragments produced by tumor cells themselves (37,38,60). Their spherical shape and negative surface charge give them a good capacity for incorporating small molecules, macromolecules, ions, and gases within their structure. Therefore, nanosponges have been designed to improve chemotherapeutic efficacy by targeting drug-resistant cells (60-62). The erythrocyte membrane can

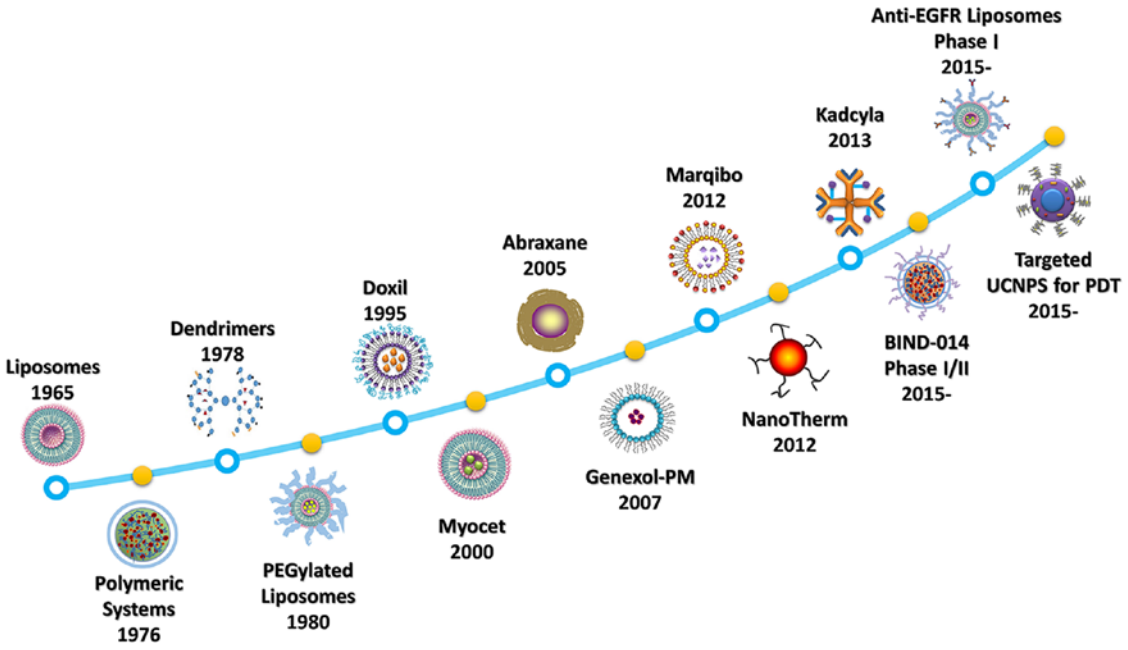

Figure 1. Timeline of the development of nanomedicines. Liposomes (5), polymeric systems (151), dendrimers (152), and PEGylated liposomes (153) were developed as nanodrug carriers in the early phase of discovery (before 1995). Doxil (doxorubicin) was the first FDA-approved liposome for use in cancer (154). As nanomedicine developed, the non-PEGylated liposome Myocet (doxorubicin) (155), the albumin-based nanoparticle (NP) Abraxane (doxorubicin) (63), the PEG-PLA polymeric micelle Genexol-PM (paclitaxel) (98), the vincristine sulfate liposome Marqibo (156), the iron oxide NP NanoTherm (157), and the targeted ado-trastuzumab emtansine (DM1) liposome Kadcyla (158) have been approved for clinical use. PEG-PLGA polymeric NPs (BIND-014) completed phase II clinical trials in advanced cancers (68) and anti-epidermal growth factor receptor (EGFR) immunoliposomes is in phase II clinical trials recruiting of breast cancer (159,160). The physical properties of upconversion nanoparticles (UCNPs) used in photodynamic therapy (PDT) also represent a promising direction in future research (115).

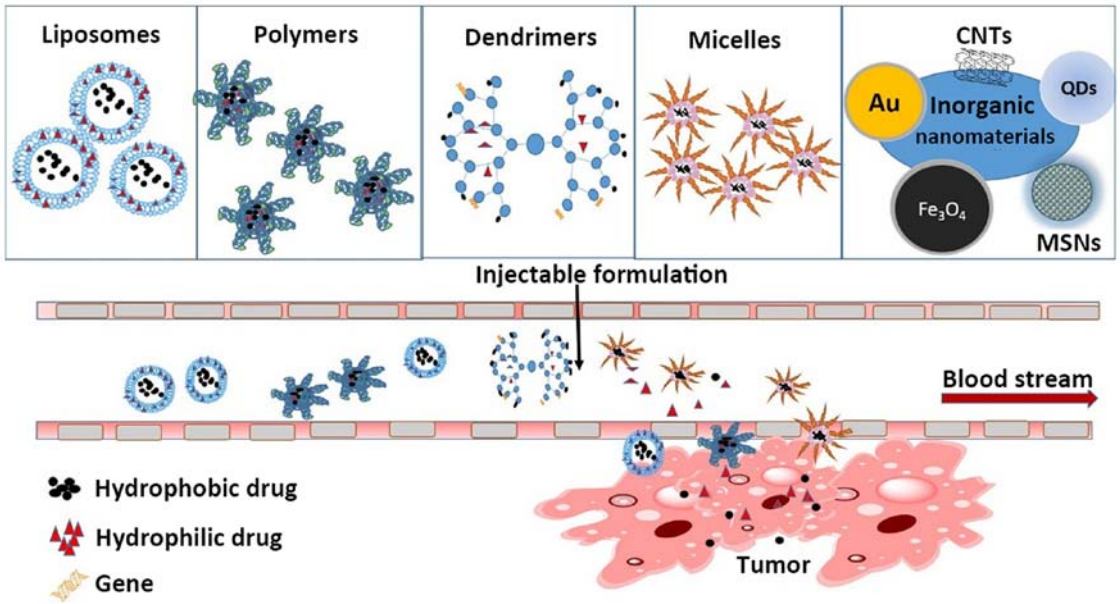

Figure 2. Nanomaterials used as drug carriers for cancer therapy. With their distinct biological characteristics, nanomaterials can improve the enhanced permeability and retention effect, increase bioavailability, reduce the toxicity of chemotherapy drugs, release hydrophobic or hydrophilic chemotherapy drugs into the bloodstream, and achieve cytotoxic effects against cancer cells. CNTs, carbon nanotubes; QDs, quantum dots; MSNs, metal nanoparticles.

be used as a cloak containing >3,000 nanosponges. Once they are fully loaded with toxins, nanosponges are safely disposed of by the liver with low toxicity. Therefore, nanosponges are designed to work with any type of cancer or poisoning that exhibits dysregulation of, or abnormalities in, cellular membranes.

Among the polymer-based delivery systems, only one albumin-based nanoparticle, protein-bound paclitaxel (Abraxane) (63), has been approved by the FDA for clinical use in the treatment of breast cancer, non-small cell lung cancer, and pancreatic cancer (Table II). Albumin nanoparticle that incorporates paclitaxel has improved the water solubility of

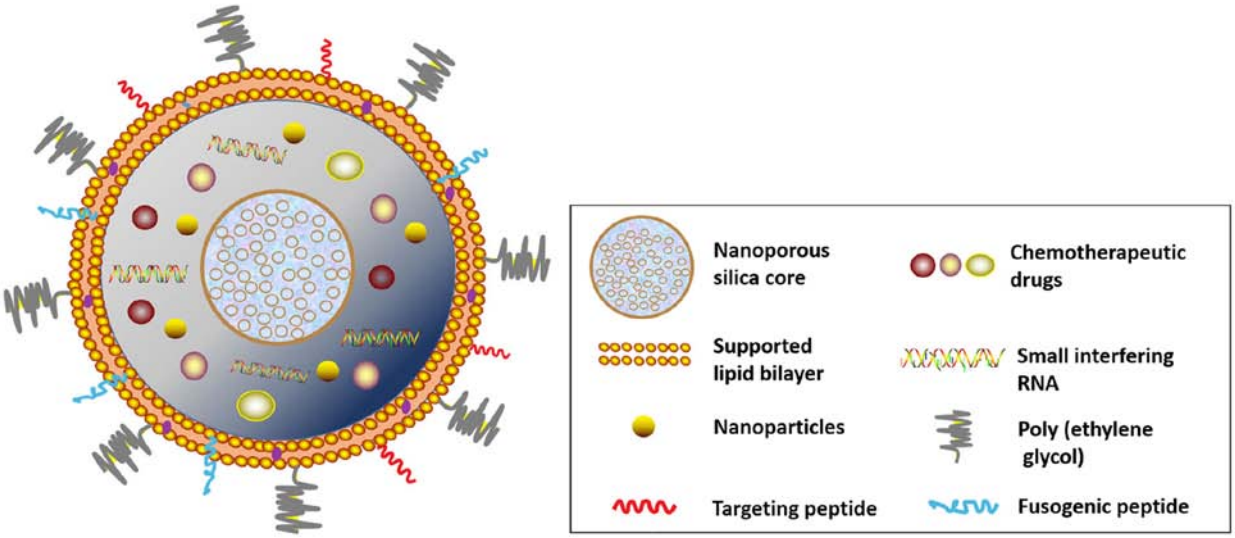

Figure 3. Lipid bilayer-wrapped nanoporous drug delivery system in protocells. It can be decorated with multi-types chemotherapy agents and surface-targeting molecules.

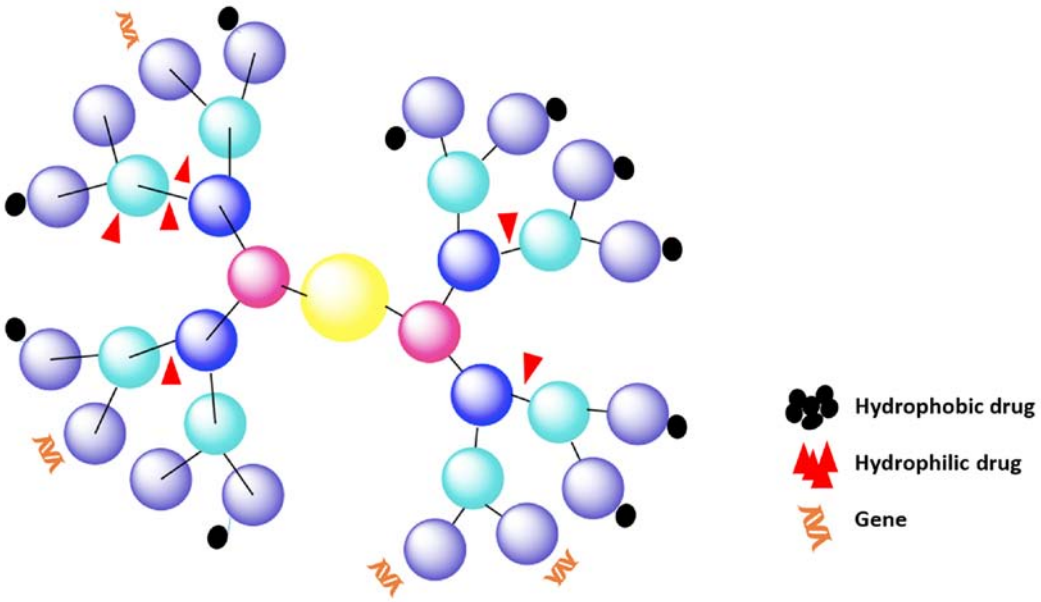

Figure 4. Structure of a dendrimer with four generations of side branches. Each generation is represented with a different color.

the drug and reduced its dose-limiting toxicity by modifying its pharmacokinetic formulation (64). Given these successes, various albumin-based nanoparticles, such as ABI-008 (65), ABI-009 (66), and ABI-011 (67), are currently undergoing clinical trials. BIND-014 (68) is the first PEG-PLGA targeted polymeric nanoparticle to reach phase I/II studies for the treatment of metastatic cancer and KRAS-positive or squamous cell non-small cell lung cancer. Its pharmaceutical activity is 10-fold higher than that of conventional docetaxel in tumor sites, and it prolongs the time the drug is maintained in the circulation. Also, a targeted cyclodextrin-polymer hybrid nanoparticle (CALAA-01), a short interfering RNA inhibitor designed to inhibit tumor growth and/or reduce tumor size (69), was tested in phase I clinical trial. Current research on polymer nanocarriers focuses on elucidating their mechanisms of action, environmental responses, active targeting, and composite materials. Relevant diagnostic and therapeutic platforms still need to be constructed and evaluated.

4. Dendrimers

Dendrimers are a unique class of polymeric macromolecules found in nature. Dendrimers began to be synthesized during the period 1970-1990 by Buhleier *et al* (70) and Tomalia *et al* (71). They are globular, nanosized (1-100 nm) macromolecules with complex spherical structures. Dendrimers are characterized by: i) a central core; ii) branches, called 'generations', emanating from the core; iii) repeat units with at least one branch junction; and iv) many terminal functional groups (Fig. 4) (72,73). Unlike linear polymers, dendrimers

Table I. Liposome formulations in clinical trials or clinical use.

Product	Drug	Status	Applications	Refs.
Doxil	Doxorubicin	Approved	Kaposi sarcoma, ovarian and breast cancers	(6,161)
DaunoXome	Daunorubicin	Approved	Kaposi sarcoma	(162)
LipoDox	Doxorubicin	Approved	Ovarian and breast cancers	(163)
Myocet	Doxorubicin	Approved	Combination therapy for metastatic breast cancer	(155)
Marqibo	Vincristine	Approved	Metastatic malignant uveal melanoma	(156)
Onivyde	Irinotecan	Approved	Advanced pancreatic cancer	(164)
Lipoplatin	Cisplatin	Phase III	Pancreatic, head and neck, breast, gastric, and non-squamous non-small cell lung cancers, mesothelioma	(165)
Stimuvax	BLP25 Tecemotide	Phase III	Vaccine for multiple myeloma-developed encephalitis	(166)
ThermoDox	Doxorubicin	Phase III	Non-resectable hepatocellular carcinoma	(167)
CPX-351	Cytarabine + daunorubicin	Phase III	Acute myeloid leukemia	(168)
Aroplatin	Cisplatin analog	Phase II	Metastatic colorectal carcinoma	(169)
Atragen	Tretinoin	Phase II	Acute promyelocytic leukemia, hormone-refractory prostate cancer	(170)
Atu027	PKN3 siRNA	Phase II	Solid tumors	(171)
EndoTAG-1	Paclitaxel	Phase II	Breast and pancreatic cancers	(172)
LEP-ETU	Paclitaxel	Phase II	Ovarian, breast, and lung cancers	(173)
LE-SN38	SN38	Phase II	Metastatic colorectal cancer	(174)
MBP-426	Oxaliplatin	Phase II	Gastric, gastroesophageal, and esophageal adeno-carcinomas	(175)
OSI-211	Lurtotecan	Phase II	Ovarian and head and neck cancers	(176)
SPI-077	Cisplatin	Phase II	Ovarian and head and neck cancers	(177)
Liposomal annamycin	Annamycin	Phase I/II	Acute lymphocytic leukemia	(178)
S-CKD-602	Camptothecin analog	Phase I/II	Recurrent or progressive carcinoma of the uterine cervix	(179)
OSI-7904L	Thymidylate synthase inhibitor	Phase I/II	Advanced colorectal, head and neck, gastric, and gastroesophageal cancers	(180)
Anti-EGFR immuno-liposomes	Doxorubicin	Phase I	Solid tumors	(159)
INX-0076	Topotecan	Phase I	Advanced solid tumors	(181)
INX-0125	Vinorelbine	Phase I	Advanced solid tumors	(182)
LEM-ETU	Mitoxantrone	Phase I	Leukemia, breast, stomach, liver, and ovarian cancers	(183)
Liposomal Grb-2	Grb2-antisense oligodeoxynucleotide	Phase I	Acute myeloid leukemia, chronic myelogenous leukemia, and acute lymphoblastic leukemia	(184)
Lipoxal	Oxaliplatin	Phase I	Advanced gastrointestinal cancer	(185)
LiPlaCis	Cisplatin	Phase I	Advanced or refractory tumors	(186)

EGFR, epidermal growth factor receptor.

have a precisely controllable architecture with tailor-made surface groups. The branches of dendrimers can be decorated with a wide variety of molecules that can be utilized for passive entrapment and eventual release of drugs or other cargoes. The molecular structure of dendrimers can be fine-tuned, and because they are geometrically symmetrical and have many

Table II. Drug-loaded polymer nanoparticles in clinical trials or clinical use.

Product	Drug	Platform	Status	Applications	Refs.
Abraxane	Paclitaxel	Albumin nanoparticle	Approved	Breast cancer, non-small cell lung cancer, pancreatic cancer	(63)
BA-003	Doxorubicin	Polymeric nanoparticle	Phase III	Hepatocellular carcinoma	(187)
DHAD-PBCA-NPs	Mitoxantrone	Polymeric nanoparticle	Phase II	Hepatocellular carcinoma	(188)
ProLindac	DACHPt	HPMA-polymeric nanoparticle	Phase II/III	Advanced ovarian cancer	(189)
ABI-008	Docetaxel	Albumin nanoparticle	Phase I/II	Metastatic breast cancer, prostate cancer	(65)
ABI-009	Rapamycin	Albumin nanoparticle	Phase I/II	Solid tumors	(66)
ABI-011	Thiocolchicine dimer	Albumin nanoparticle	Phase I/II	Solid tumors, lymphoma	(190)
BIND-014	Docetaxel	PEG-PLGA polymeric nanoparticle	Phase I/II	Non-small cell lung cancer	(68)
Cyclosert	Camptothecin	Cyclodextrin nanoparticle	Phase I/II	Solid tumors, rectal cancer, renal cell carcinoma, non-small cell lung cancer	(191)
CALAA-01	siRNA targeting	Cyclodextrin nanoparticle	Phase I	Solid tumors	(69)
Docetaxel-PNP	Docetaxel	Polymeric nanoparticle	Phase I	Solid tumors	(192)
Nanotax	Paclitaxel	Polymeric nanoparticle	Phase I	Peritoneal neoplasms	(193)

DHAD-PBCA-NPs, mitoxantrone-loaded polybutylcyanoacrylate nanoparticles; DACHPt, dicholoro (1,2-diaminocyclohexane) platinum (II); HPMA, N-(2-hydroxypropyl) methacrylamide.

peripheral functional groups, an internal molecular cavity, controlled molecular weight, and nanometer size, they are excellent nanocarriers with good fluid mechanic performance, versatility, and strong adsorption ability.

Dendrimers are self-assembled and stabilize by forming organic or inorganic hybrid nanoparticles. Dendrimers can be linked to liposomes (74-76), nanoparticles (77,78), and carbon nanotubes (79-81) to modulate their solubility for use as drug carriers (74,82) and target-specific carriers (82-84) of detecting agents (such as dye molecules), affinity ligands, radioligands, imaging agents, or pharmaceutically active anticancer compounds.

Thanks to recent advances in synthetic chemistry and characterization techniques, novel dendritic carriers are rapidly being developed. Dendrimers are being widely investigated as gene delivery vectors. For example, polyamidoamine (PAMAM) dendrimers have the ability to condense DNA for transfection. Liu *et al* (85) used five fluorinated polypropylenimine (PPI) dendrimers to improve DNA transfection efficacy. The heptafluorobutyric acid modified on the PPI dendrimer improved the efficacy of enhanced green fluorescent protein transfection in all five fluorinated PPI dendrimers by 89% over that of regular PPIs. The uptake efficacy achieved with PPI dendrimers (as indicated by both the percentage of positively stained cells and the mean fluorescence intensity) was superior to that of G5-Arg110, bPEI 25K, and four commercial transfection reagents, including Lipofectamine 2000 (with as high as 71% improvement).

Highly branched dendrimer-amplified aptamer probes can be easily rebuilt and have high affinity and specificity for a wide range of targets. They are able to reach various targets with such high sensitivity, reliability, and selectivity because of their novel optical, magnetic, electric, chemical, and biological properties (86). For instance, surface-functionalized PAMAM dendrimers with carboxyl groups, whose particles are spherical colloidal crystal clusters decorated with dendrimer-amplified aptamer probes, are designed to immobilize DNA aptamers; thus, they can serve as high-efficacy probes that target cancer cells. Malik *et al* (87) showed that conjugates of cisplatin with the negatively charged 4th-generation PEGylated PAMAM dendrimer exhibited antitumor activity against B16F10 solid melanoma tumors. Methotrexate conjugated to PEGylated poly-L-lysine (PLL) dendrimers (G5, PEG1100) has been shown to accumulate in HT1080 fibrosarcoma tumors in rats and mice (88). Al-Jamal *et al* (89) reported that the complexation of doxorubicin with the novel 6th-generation cationic PLL dendrimer Gly-Lys63 (NH2)64 (molecular weight 8149 kDa) produced systemic anti-angiogenic activity in tumor-bearing mice. Dendrimer nanotechnology has also been used to produce contrast

Table III. Micellar nanoparticles in clinical trials or clinical use.

Product	Drug	Platform	Status	Applications	Refs.
Genexol-PM	Paclitaxel	mPEG-PLA polymeric micelle	Approved	Breast cancer	(98)
Paclical	Paclitaxel	Polymeric micelle	Phase III	Ovarian cancer	(194)
SP1049C	Doxorubicin	Pluronic L61 and F 127 polymeric micelle	Phase II/III	Lung cancer	(195)
NK105	Paclitaxel	PEG-PAA polymeric micelle	Phase II/III	Breast and gastric cancers	(196)
NC-6004	Cisplatin	PEG-PGA polymeric micelle	Phase II/III	Solid tumors, gastrointestinal and genitourinary cancers	(197)
NK012	SN-38	PEG-PGA polymeric micelle	Phase II	Colorectal, lung, and ovarian cancers	(198)
Lipotecan	Camptothecin analog	Polymeric micelle	Phase I/II	Liver and renal cancer	(199)
NC-4016	Oxaliplatin	Polymeric micelle	Phase I	Solid tumors	(200)
NC-6300	Epirubicin	PEG-*b*-PAH polymeric micelle	Phase I	Solid tumors	(201)
NK911	Doxorubicin	PEG-PAA polymeric micelle	Phase I	Solid tumors	(202)

mPEG, methoxypolyethylene glycol; PLA, polylactic acids; PEG, polyethylene glycol; PAA, polyacrylic acid; PGA, polyglutamic acid; PAH, polycyclic aromatic hydrocarbon.

agents, including agents used in molecular imaging (90). Qiao and Shi (86), and Yang *et al* (91), for instance, successfully synthesized ultrasmall iron oxide nanoparticles by conjugating them with Arg-Gly-Asp-modified dendrimers (G5.NHAc-RGD-Fe_3O_4 NPs) for targeted magnetic resonance imaging of C6 glioma cells.

Dendrimers have the advantages of being biocompatible and easily eliminated from the body. PAMAM dendrimer nanoparticles, with their large number of surface amino groups, are more biocompatible and circulate for longer in the serum than do small-molecule drugs. Dendrimer nanoparticles are eventually eliminated from the human body through the kidneys along the same metabolic pathways taken by folate (84,92), growth factors (93), peptides (94,95), and antibodies (96). However, dendrimers also have the drawbacks of being cytotoxic to normal cells, and that the end groups present on their peripheries (97) such as PAMAM, PPI, and PLL are cationic groups with physiological stability. This stability increases their cytotoxicity that can inevitably attack normal cells.

5. Micellar nanoparticles

Micellar nanoparticles possess a core and a shell structure. PEG is often used as a hydrophilic shell; shells with hydrophobic domains include PLA (52), PLGA (44,45), polystyrene, poly (cyanoacrylate), poly (vinylpyrrolidone), and polycaprolactone (56). These copolymers are widely used owing to their natural biodegradability and biocompatibility as well as their ability to entrap hydrophobic drugs. A primary mPEG-PLA polymeric micelle loaded with paclitaxel (Genexol-PM) was approved by the FDA in 2007 (98,99). It is loaded with a free-Taxol formulation and has been shown to reduce the severity of toxic effects such as hypersensitivity reactions, hyperlipidemia, and peripheral neuropathy.

Micellar nanoparticles are obtained from self-assembly of amphiphilic block copolymers in aqueous media above the critical micelle concentration (100). The core, consisting of the hydrophobic domain, acts as a reservoir and protects the drug from being dissolved, whereas the hydrophilic shell mainly confers aqueous solubility and steric stability to the micellar structure (27). With this technique, undissolvable drugs, such as paclitaxel and docetaxel, can be covered with a water-solute layer to enhance their hydrophilicity and ultimately facilitate their bioavailability. The hydrophilic shell affords protection and lengthens circulation *in vivo*, providing enhanced permeability and retention. In recent years, a number of nanomicellar drugs have advanced to clinical trials or to the market (Table III).

With the rise of precision medicine, micellar nanoparticles have become increasingly important for passive targeted cancer therapy. Peptide modification on the surface

of the micelle can be used effectively for precise targeting. Integrin-binding sequence peptides with covalent bonds to the micelle can actively target tumors (101). Block copolymers are environmental response modifiers that display a physicochemical response to stimuli such as temperature (102-104), pH (105), light (106), or electricity (107). Some block copolymers can produce functional signals and higher levels of signaling (103,108); thus, micelles made from them are called 'intelligent' block copolymer micelles. The self-assembly of such polypeptide-based copolymers can be triggered by temperature and pH changes (105). Poly (N-isopropylacrylamide) (PNIPAM) is a temperature-sensitive polymer segment with a lowest critical solution temperature of 31-32˚C (105). It quickly switches from a hydrated to a dehydrated state, using PNIPAM-OH and the ring-opening polymerization reaction synthesis of PLA (PNIPAM-*b*-PLA) (104) and self-assembles into dual-response micelle carriers. A series of dual-stimuli responsive polymers such as PNIPAM-*b*-PGA and PNIPAM-*b*-PLL have been synthesized as copolymer micelle materials (108). Doxorubicin can be effectively encapsulated in PNIPAM-*block*-poly (L-histidine) (PNIPAM-*b*-PLH) micelle carriers as a controlled delivery system for the treatment of hepatocellular carcinoma (109). Light-sensitive groups, including the azide, cinnamon acyl, screw pyran, coumarin, and 2-nitrobenzyl groups, have also been widely used in cancer therapeutic settings (106,110,111). Photodynamic therapy (PDT) is a non-invasive treatment modality for a variety of diseases including cancer (112). PDT based on upconversion nanoparticles (UCNPs) has received much attention in recent years. Under near-infrared (NIR) light excitation, UCNPs are able to emit high-energy visible light, which can activate surrounding photosensitizer (PS) molecules to produce singlet oxygen and kill cancer cells (113,114) also represent a promising direction in future research (115,116).

The greatest benefit of biodegradable drug delivery systems is the controlled release of the drug payload to a specific site and the degradation into nontoxic materials for elimination from the body via metabolic pathways (117). Organelle-targeted biodegradable copolymers, mitochondria-targeting gold-peptide, and radiation-hyperthermia nanoassembly-copolymers (118,119) are used to evaluate micro-environmental change by taking advantage of the sensitivity of mitochondria to temperature elevation. In the presence of a thermal stimulus, the passive targeted biodegradable micellar nanoparticles of a copolymer-controlled drug release system are activated, resulting in slow degradation of the nanoparticles into smaller fragments and the release of carried products, which eventually enhance the drug's cytotoxic effects on cancer cells. Currently, new biocompatible and/or biodegradable stimuli-responsive copolymers that form stable micellar systems capable of encapsulating a broad range of chemotherapeutic agents are being developed (120,121).

It is generally accepted that nonviral vectors are safer than viral vectors for gene transfer (122). Biodegradable copolymers based on polylysine were the first nanoparticles used for gene transfer. Currently, PEG-grafted PLGA-PLL (123), pluronic polyethylenimine (PEI), polyphosphoric acid (124), and phosphate (125) micelles are being used as gene carriers for biological separation and cancer diagnosis. However, applications of cationic polymer-based gene delivery systems are limited because the polymers interact with the cell membrane and produce increased toxicity (122).

6. Inorganic nanomaterials

Various forms of inorganic nanoparticles, including quantum dots, superparamagnetic iron oxides, gold nanoparticles, carbon nanotubes, and other metallic and non-metallic nanoparticles or nanoclusters, enhance the efficiency of radiotherapy and improve tumor imaging (119,126). Several of these inorganic nanoparticles are sufficiently small (10-100 nm) to penetrate the capillaries and can be taken up in distinct tissues. Others are larger and need to be delivered at disease-specific anatomic sites for passive targeting. Multifunctional nanodevices are also emerging as tools to target cancer (42,43,127). Such devices can contain not only the drug payload but also specific receptor-targeting agents, such as antibodies or ligands, as well as magnetic resonance imaging contrast agents. Quantum dots and gold nanoparticles exhibit unique optical, electrical, and magnetic properties (128) that are beneficial for imaging the intracellular localization and trafficking of multifunctional carriers. Drugs can also be delivered at specific sites after they are attached, encapsulated, absorbed, entrapped, or dissolved in the nanomaterial matrix. However, in early-stage clinical trials, some inorganic nanomaterials, such as gold nanoparticles (129) and silica nanoparticles (130), have encountered obstacles, including toxicity and a lack of stability. Of the iron oxide nanoparticles, NanoTherm (131), used for the treatment of glioblastoma, is the only one that has obtained approval for clinical use. With NanoTherm, tumors can be thermally ablated by magnetic hyperthermia induced by entrapped superparamagnetic iron oxides.

7. Challenges for extending patient survival by using nanocarriers

Many solid tumors develop several biological features distinguished from those of normal tissues (132). Abnormal tumor structures including physically compromised vasculature, abnormal extracellular matrix (ECM), and high interstitial fluid pressure (IFP), can create constraints that compromise effective delivery of nanotherapeutics (133,134). There are also extravascular barriers to overcome, whereby nanoparticles can extravasate but cannot penetrate through the ECM of the tumors (135). It is well recognized that the irregularity of the tumor vasculature with its abnormal blood flow and impaired venous and lymphatic drainage creates high interstitial fluid pressure, making the diffusion of nutrients and chemotherapeutics throughout the tumor very inefficient, thus presenting challenges to effective diffusion of nanocarriers as well (136).

Liposomes and polymers are the most widely used biodegradable nanocarriers because of their biocompatibility, biodegradability, and mechanical properties. However, because of adverse effects and the still-unclear mechanisms of interaction among nanoparticles, the tumor microenvironment, and tumor cells, these nanocarriers may offer only brief extension of patient survival (Table IV). Despite numerous achievements in liposomal drug delivery, current liposomal formulations have primarily reduced systemic toxicity rather

Table IV. Nanomaterials as drug carriers: advantages and disadvantages.

Nanomaterials	Advantages	Disadvantages
Liposomes	Controlled release, reduced toxicity, improved stability	Distribution and removal mechanism, breakage *in vivo*
Polymers	Variety, controllable molecular weight	Inflammatory response, degradation pathway
Dendrimers	Nanosized cavity, controlled release, self-assembly	Immunoreaction, hematological toxicity
Micellar nanoparticles	Simple prescription, passive targeting	Scale-up production, cytotoxicity
Inorganic nanomaterials	Multifunctional, modifiable, ability to combine diagnosis and treatment	Metal toxicity, stability, storage

than increasing efficacy. For instance, hydrophilic drugs such as cisplatin are decorated with liposomal bilayers to reduce drug internal toxicity. However, it needs time to degrade the liposome vehicle for the release of the embedded pharmaceutical. Therefore, long systemic circulation and minimal side effects could result in poor efficacy *in vivo*. Nevertheless, it is still challenging to achieve an optimal balance between high and specific drug bioavailability in tumor tissue and prolonged liposome stability in systemic circulation (137).

Despite many advances in the production of more stable, efficient, and safe biopolymers, there remain controversies regarding the safety of polymeric nanomaterials. Some polymers are themselves cytotoxic (41,138). It has been demonstrated, for example, that PEI destabilizes the plasma membrane and activates effector caspase-3; thus, PEI appears to be a proapoptotic agent (138). Inflammatory and immune responses have also been reported (139-141). However, PLGA can be formulated as an acidic product to provoke inflammatory responses, and it has shown minimal systemic toxicity and excellent biocompatibility *in vitro* and *in vivo* (142). Thus, advancements in formulating, synthesizing, and modifying biodegradable polymers promise to improve treatment efficacy and reduce adverse effects.

Compared to other types of nanocarriers, dendrimers provide more opportunities for design and adaptation owing to their peculiar tailor-made surfaces. Toxicity associated with dendrimers is primarily attributed to the end groups present on their peripheries (97). Cationic dendrimers with high charge density and high molecular weight, such as PAMAM, PPI, and PLL, are more stable in physiological conditions. This stability increases their cytotoxicity, owing to the excess positive charges on the periphery, which destabilize the cell membrane. However, stability may also cause several adverse effects (143-145). Fortunately, neutral or anionic groups such as sulfonated, carboxylated, and phosphonated groups have been shown to be less toxic (73). In light of this progress, the next step will be to modify the surface groups of dendrimers with minimally toxic reagents in order to adapt them to physiological conditions.

Other nanoparticles of particularly urgent concern are micelles and inorganic nanomaterials, which present challenges with instability, potential toxicity, cytotoxicity, immune response, and chronic inflammation (146,147). For specific targeted therapy, micelles and inorganic nanomaterials can be decorated with receptor-stimuli agents such as PH, light and magnetic resonance imaging contrast agents, one major limitation of this treatment methodology in clinical applications is the poor tissue penetration ability (148,149).

Research aimed at overcoming these drawbacks will facilitate the use of nanomaterials as drug delivery vehicles and eventually improve patient survival. Ideally, an anticancer nanotherapeutic should be able to reach tumors without systemic loss, easily penetrate into the core of the tumor mass, enter tumor cells where their target molecules reside, and completely eradicate the tumors.

8. Conclusion and prospects

Nanotechnology receives extraordinary attention, and its applications in cancer treatment are relatively new and ever-evolving. Nonetheless, it is clear that nanomaterials are promising tools for cancer treatment. In spite of the progress being made in developing drug delivery systems for cancer therapy, a number of critical issues still need to be addressed. Molecularly targeted drugs preferentially modulate functional proteins, so they can be used to treat diseases (150), like cancers, that are characterized by abnormal protein expression and activation. However, such targeting mechanisms can be challenged by the stability of nanomaterials, the development of multi-drug resistance, and the dysregulated accumulation of cancer cells. The ability to decorate nanomaterial shells with multiple chemically or physically active components permits the delivery of different drugs. Therefore, nanomaterial drug carriers can be organized and optimized for site-specific chemotherapy, thermotherapy, photodynamic therapy, and radiotherapy. Although the benefits of metal-based nanoparticles are remarkable, toxicity remains a critical issue. Nano-toxicological issues also need to be addressed so that more effective cancer therapeutic strategies can be developed. Notably, combination therapeutic regimens for different cancer types remain a challenge because of the diverse mechanisms of cancer development. Combination therapy with nanoparticle drug carriers, therefore, warrants further study at the preclinical and clinical levels. Other challenges exist for modified and functionalized nanomaterials with well-established formulations, including improving the localization, biodistribution, biocompatibility, and efficacy of nanodrug systems *in vivo*, to meet the requirements of precision cancer diagnosis and therapy.

Acknowledgements

We thank Ms. Yazmin Salina at the Department of Clinical Cancer Prevention, and Dr Amy Ninetto, ELS at the Department of Scientific Publications, The University of Texas MD Anderson Cancer Center for proofreading and editing of this manuscript. This study was supported by the Scholarship Award for Excellent Doctoral Student Granted of Yunnan Province (6011418150 to Z. Li), the Foundation of Leading Talent Program of Health and Family Planning Commission of Yunnan Province (no. L-201205 to K. Wang), and the Foundation of Institute of Gastroenterology, Research institutions attached to Health and Family Planning Commission of Yunnan Province (2014NS122 to K. Wang).

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