

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

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**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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## 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

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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 glycyrrhetic 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

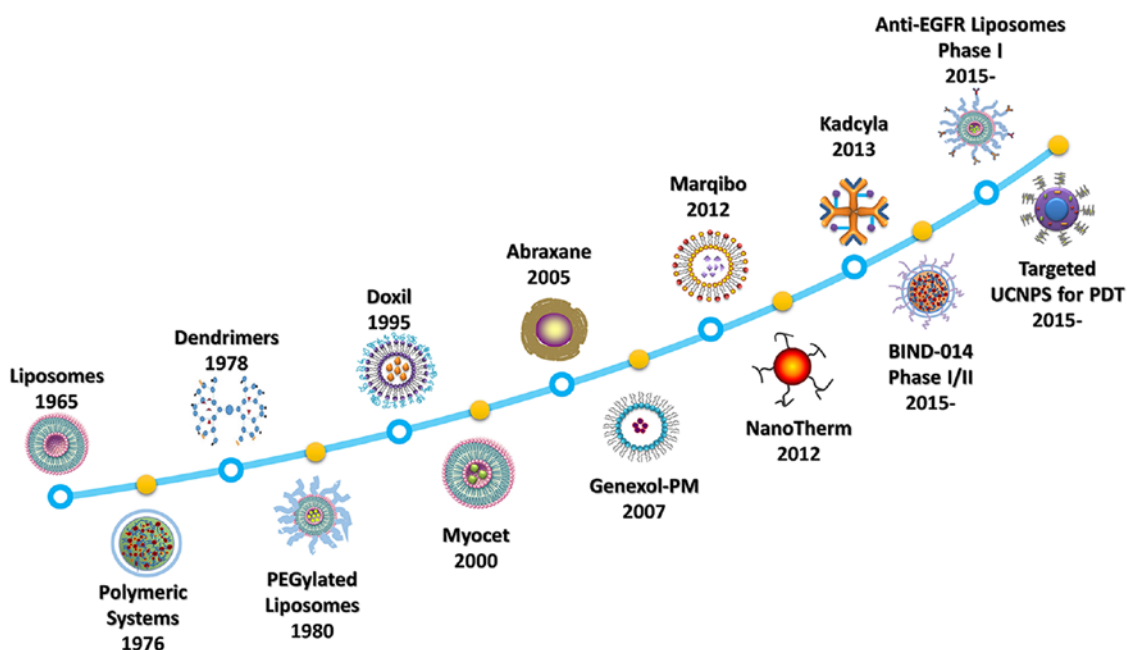


Figure 1. Timeline of the development of nanomedicines. Liposomes (5), polymeric systems (151), dendrimers (152), and PEGylated liposomes (153) were developed as nanodrug carriers in the early phase of discovery (before 1995). Doxil (doxorubicin) was the first FDA-approved liposome for use in cancer (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 Kadcylla (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).

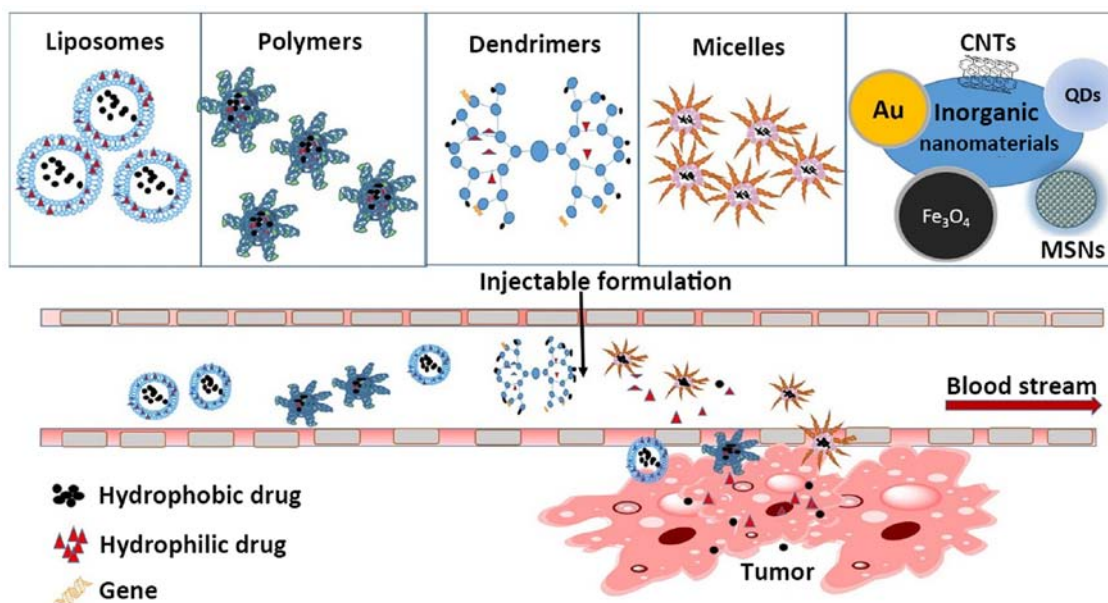


Figure 2. Nanomaterials used as drug carriers for cancer therapy. With their distinct biological characteristics, nanomaterials can improve the enhanced permeability and retention effect, increase bioavailability, reduce the toxicity of chemotherapy drugs, release hydrophobic or hydrophilic chemotherapy 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

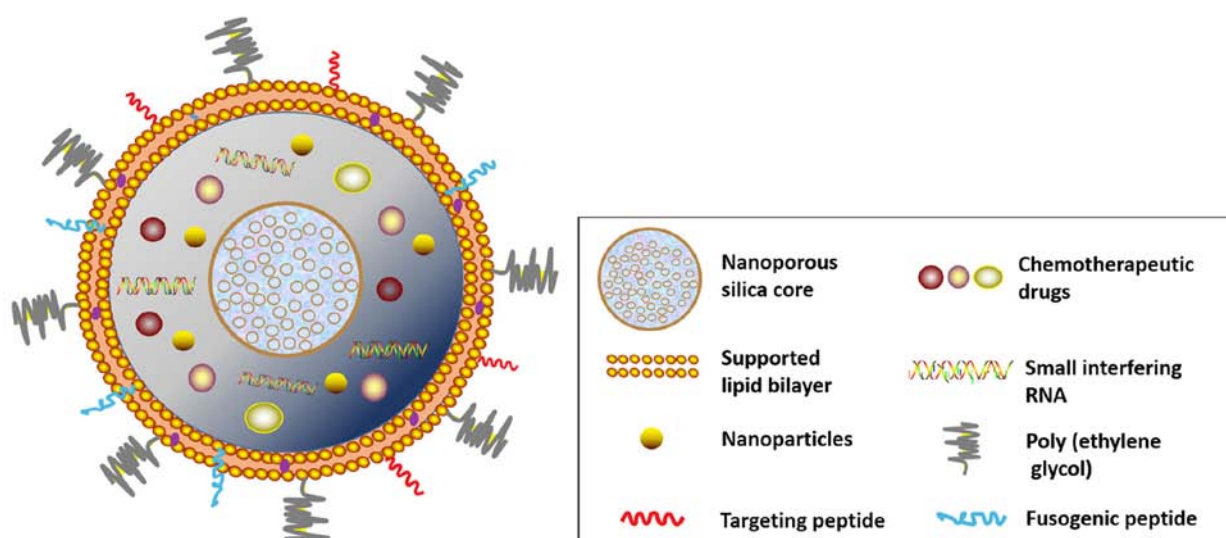


Figure 3. Lipid bilayer-wrapped nanoporous drug delivery system in protocells. It can be decorated with multi-types chemotherapy agents and surface-targeting molecules.

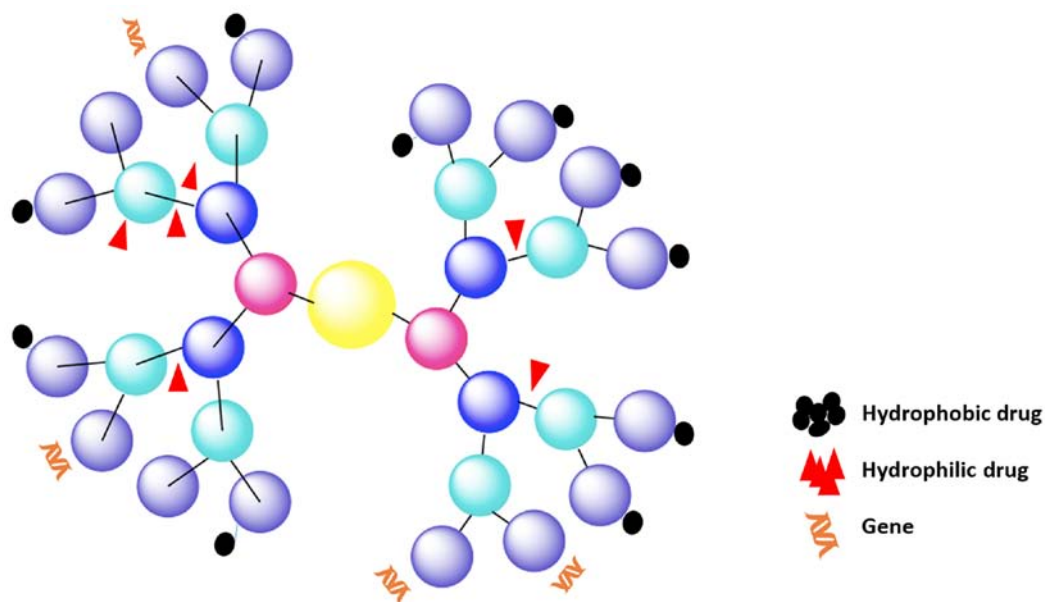


Figure 4. Structure of a dendrimer with four generations of side branches. Each generation is represented with a different color.

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 mecha-

nisms 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 adenocarcinomas  | (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)  |
| Cycloset      | 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, dichloro (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 anti-cancer 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 polypropyleneimine (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 (NH<sub>2</sub>)<sub>64</sub> (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- <i>b</i> -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<sub>3</sub>O<sub>4</sub> 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, cinnamoyl, 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 <i>in vivo</i> |
| 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.

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## References

- Shanthi M: Global Status Report on Noncommunicable Diseases 2014. WHO Press, World Health Organization, Geneva, 2014.
- LaVan DA, McGuire T and Langer R: Small-scale systems for in vivo drug delivery. *Nat Biotechnol* 21: 1184-1191, 2003.
- Shi J, Xiao Z, Kamaly N and Farokhzad OC: Self-assembled targeted nanoparticles: Evolution of technologies and bench to bedside translation. *Acc Chem Res* 44: 1123-1134, 2011.
- Langer R: New methods of drug delivery. *Science* 249: 1527-1533, 1990.
- Bangham AD, Standish MM and Watkins JC: Diffusion of univalent ions across the lamellae of swollen phospholipids. *J Mol Biol* 13: 238-252, 1965.
- James ND, Coker RJ, Tomlinson D, Harris JR, Gompels M, Pinching AJ and Stewart JS: Liposomal doxorubicin (Doxil): An effective new treatment for Kaposi's sarcoma in AIDS. *Clin Oncol (R Coll Radiol)* 6: 294-296, 1994.
- Green MR, Manikhas GM, Orlov S, Afanasyev B, Makhson AM, Bhar P and Hawkins MJ: Abraxane, a novel Cremophor-free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer. *Ann Oncol* 17: 1263-1268, 2006.
- Kamaly N, Xiao Z, Valencia PM, Radovic-Moreno AF and Farokhzad OC: Targeted polymeric therapeutic nanoparticles: Design, development and clinical translation. *Chem Soc Rev* 41: 2971-3010, 2012.
- Burgess P, Hutt PB, Farokhzad OC, Langer R, Minick S and Zale S: On firm ground: IP protection of therapeutic nanoparticles. *Nat Biotechnol* 28: 1267-1270, 2010.
- Farokhzad OC and Langer R: Impact of nanotechnology on drug delivery. *ACS Nano* 3: 16-20, 2009.
- Gulati M, Grover M, Singh S and Singh M: Lipophilic drug derivatives in liposomes. *Int J Pharm* 165: 129-168, 1998.
- Scherphof G, Roerdink F, Waite M and Parks J: Disintegration of phosphatidylcholine liposomes in plasma as a result of interaction with high-density lipoproteins. *Biochim Biophys Acta* 542: 296-307, 1978.
- Allen TM and Cleland LG: Serum-induced leakage of liposome contents. *Biochim Biophys Acta* 597: 418-426, 1980.
- Senior J and Gregoriadis G: Is half-life of circulating liposomes determined by changes in their permeability? *FEBS Lett* 145: 109-114, 1982.
- Huang S-L and MacDonald RC: Acoustically active liposomes for drug encapsulation and ultrasound-triggered release. *Biochim Biophys Acta* 1665: 134-141, 2004.
- Ueno Y, Sonoda S, Suzuki R, Yokouchi M, Kawasoe Y, Tachibana K, Maruyama K, Sakamoto T and Komiya S: Combination of ultrasound and bubble liposome enhance the effect of doxorubicin and inhibit murine osteosarcoma growth. *Cancer Biol Ther* 12: 270-277, 2011.
- Pak CC, Erukulla RK, Ahl PL, Janoff AS and Meers P: Elastase activated liposomal delivery to nucleated cells. *Biochim Biophys Acta* 1419: 111-126, 1999.
- Meers P: Enzyme-activated targeting of liposomes. *Adv Drug Deliv Rev* 53: 265-272, 2001.
- Gerasimov OV, Boomer JA, Qualls MM and Thompson DH: Cytosolic drug delivery using pH- and light-sensitive liposomes. *Adv Drug Deliv Rev* 38: 317-338, 1999.
- Bondurant B, Mueller A and O'Brien DF: Photoinitiated destabilization of sterically stabilized liposomes. *Biochim Biophys Acta* 1511: 113-122, 2001.
- Du B, Han S, Li H, Zhao F, Su X, Cao X and Zhang Z: Multifunctional liposomes showing radiofrequency-triggered release and magnetic resonance imaging for tumor multi-mechanism therapy. *Nanoscale* 7: 5411-5426, 2015.
- Arie AA and Lee JK: Effect of boron doped fullerene C 60 film coating on the electrochemical characteristics of silicon thin film anodes for lithium secondary batteries. *Synth Met* 161: 158-165, 2011.
- Dao TT, Matsushima T and Murata H: Organic nonvolatile memory transistors based on fullerene and an electron-trapping polymer. *Org Electron* 13: 2709-2715, 2012.
- Papahadjopoulos D, Jacobson K, Nir S and Isac T: Phase transitions in phospholipid vesicles. Fluorescence polarization and permeability measurements concerning the effect of temperature and cholesterol. *Biochim Biophys Acta* 311: 330-348, 1973.
- Landen CN Jr, Chavez-Reyes A, Bucana C, Schmandt R, Deavers MT, Lopez-Berestein G and Sood AK: Therapeutic EphA2 gene targeting in vivo using neutral liposomal small interfering RNA delivery. *Cancer Res* 65: 6910-6918, 2005.
- Miller CR, Bondurant B, McLean SD, McGovern KA and O'Brien DF: Liposome-cell interactions in vitro: Effect of liposome surface charge on the binding and endocytosis of conventional and sterically stabilized liposomes. *Biochemistry* 37: 12875-12883, 1998.
- Wolftrum C, Shi S, Jayaprakash KN, Jayaraman M, Wang G, Pandey RK, Rajeev KG, Nakayama T, Charrise K, Ndungo EM, *et al.*: Mechanisms and optimization of in vivo delivery of lipophilic siRNAs. *Nat Biotechnol* 25: 1149-1157, 2007.
- Wang Z, Yu Y, Dai W, Lu J, Cui J, Wu H, Yuan L, Zhang H, Wang X, Wang J, *et al.*: The use of a tumor metastasis targeting peptide to deliver doxorubicin-containing liposomes to highly metastatic cancer. *Biomaterials* 33: 8451-8460, 2012.
- Irvine DJ: Drug delivery: One nanoparticle, one kill. *Nat Mater* 10: 342-343, 2011.
- Chen J, Jiang H, Wu Y, Li Y and Gao Y: A novel glycyrrhetic acid-modified oxaliplatin liposome for liver-targeting and in vitro/vivo evaluation. *Drug Des Devel Ther* 9: 2265-2275, 2015.
- Liu Z, Xiong M, Gong J, Zhang Y, Bai N, Luo Y, Li L, Wei Y, Liu Y, Tan X, *et al.*: Legumain protease-activated TAT-liposome cargo for targeting tumours and their microenvironment. *Nat Commun* 5: 4280-4291, 2014.
- Davis ME, Zuckerman JE, Choi CHJ, Seligson D, Tolcher A, Alabi CA, Yen Y, Heidel JD and Ribas A: Evidence of RNAi in humans from systemically administered siRNA via targeted nanoparticles. *Nature* 464: 1067-1070, 2010.
- Lee JH and Lee MJ: Liposome mediated cancer gene therapy: Clinical trials and their lessons to stem cell therapy. *Bull Korean Chem Soc* 33: 433-442, 2012.
- Felgner PL, Gadek TR, Holm M, Roman R, Chan HW, Wenz M, Northrop JP, Ringold GM and Danielsen M: Lipofection: A highly efficient, lipid-mediated DNA-transfection procedure. *Proc Natl Acad Sci USA* 84: 7413-7417, 1987.
- Tari AM, Gutiérrez-Puente Y, Monaco G, Stephens C, Sun T, Rosenblum M, Belmont J, Arlinghaus R and Lopez-Berestein G: Liposome-incorporated Grb2 antisense oligodeoxynucleotide increases the survival of mice bearing bcr-abl-positive leukemia xenografts. *Int J Oncol* 31: 1243-1250, 2007.
- Yu L, Dean K and Li L: Polymer blends and composites from renewable resources. *Prog Polym Sci* 31: 576-602, 2006.
- Hu C-MJ, Fang RH, Copp J, Luk BT and Zhang L: A biomimetic nanosponge that absorbs pore-forming toxins. *Nat Nanotechnol* 8: 336-340, 2013.
- Hu C-MJ, Zhang L, Aryal S, Cheung C, Fang RH and Zhang L: Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform. *Proc Natl Acad Sci USA* 108: 10980-10985, 2011.
- Sinha M, Banik RM, Haldar C and Maiti P: Development of ciprofloxacin hydrochloride loaded poly (ethylene glycol)/chitosan scaffold as wound dressing. *Nat Mater* 20: 799-807, 2013.
- Nguyen TTT, Ghosh C, Hwang S-G, Dai Tran L and Park JS: Characteristics of curcumin-loaded poly (lactic acid) nanofibers for wound healing. *J Mater Sci Mater Med* 48: 7125-7133, 2013.

41. Tan S, Gan C, Li R, Ye Y, Zhang S, Wu X, Yang YY, Fan W and Wu M: A novel chemosynthetic peptide with  $\beta$ -sheet motif efficiently kills *Klebsiella pneumoniae* in a mouse model. *Int J Nanomedicine* 10: 1045-1059, 2015.
42. Janib SM, Moses AS and MacKay JA: Imaging and drug delivery using theranostic nanoparticles. *Adv Drug Deliv Rev* 62: 1052-1063, 2010.
43. Grossman JH and McNeil SE: Nanotechnology in cancer medicine. *Phys Today* 65: 38-42, 2012.
44. Mishra S, De A and Mozumdar S: Synthesis of thermoresponsive polymers for drug delivery. In: *Drug Delivery System*. Springer, Clifton, pp77-101, 2014.
45. Gundogdu N and Cetin M: Chitosan-poly (lactide-co-glycolide) (CS-PLGA) nanoparticles containing metformin HCl: Preparation and in vitro evaluation. *Pak J Pharm Sci* 27: 1923-1929, 2014.
46. Tajmir-Riahi HA, Nafisi Sh, Sanyakamdhorn S, Agudelo D and Chanphai P: Applications of chitosan nanoparticles in drug delivery. *Methods Mol Biol* 1141: 165-184, 2014.
47. Malhotra M, Tomaro-Duchesneau C, Saha S and Prakash S: Intranasal delivery of chitosan-siRNA nanoparticle formulation to the brain. *Methods Mol Biol* 1141: 233-247, 2014.
48. Raja MAG, Katas H and Jing Wen T: Stability, intracellular delivery, and release of siRNA from chitosan nanoparticles using different cross-linkers. *PLoS One* 10: e0128963, 2015.
49. Malhotra M, Tomaro-Duchesneau C, Saha S and Prakash S: Intranasal delivery of chitosan-siRNA nanoparticle formulation to the brain. In: *Drug Delivery System*. Jain KK (ed). Springer New York, NY, pp233-247, 2014.
50. Yang X, Wu S, Wang Y, Li Y, Chang D, Luo Y, Ye S and Hou Z: Evaluation of self-assembled HCPT-loaded PEG-*b*-PLA nanoparticles by comparing with HCPT-loaded PLA nanoparticles. *Nanoscale Res Lett* 9: 2408, 2014.
51. Sun C, Wang X, Zheng Z, Chen D, Wang X, Shi F, Yu D and Wu H: A single dose of dexamethasone encapsulated in polyethylene glycol-coated polylactic acid nanoparticles attenuates cisplatin-induced hearing loss following round window membrane administration. *Int J Nanomedicine* 10: 3567-3579, 2015.
52. Rabanel J-M, Faivre J, Tehrani SF, Lalloz A, Hildgen P and Banquy X: Effect of the polymer architecture on the structural and biophysical properties of PEG-PLA nanoparticles. *ACS Appl Mater Interfaces* 7: 10374-10385, 2015.
53. Diou O, Greco S, Beltran T, Lairez D, Authelin J-R and Bazile D: A method to quantify the affinity of cabazitaxel for PLA-PEG nanoparticles and investigate the influence of the nano-assembly structure on the drug/particle association. *Pharm Res* 32: 3188-3200, 2015.
54. Asadi H, Rostamizadeh K, Salari D and Hamidi M: Preparation of biodegradable nanoparticles of tri-block PLA-PEG-PLA copolymer and determination of factors controlling the particle size using artificial neural network. *J Microencapsul* 28: 406-416, 2011.
55. Xie Y, Yi Y, Hu X, Shangguan M, Wang L, Lu Y, Qi J and Wu W: Synchronous microencapsulation of multiple components in silymarin into PLGA nanoparticles by an emulsification/solvent evaporation method. *Pharm Dev Technol* 21: 672-679, 2016.
56. Xiong W, Peng L, Chen H and Li Q: Surface modification of MPEG-*b*-PCL-based nanoparticles via oxidative self-polymerization of dopamine for malignant melanoma therapy. *Int J Nanomed* 10: 2985-2996, 2015.
57. Zhang R, Luo K, Yang J, Sima M, Sun Y, Janát-Amsbury MM and Kopeček J: Synthesis and evaluation of a backbone biodegradable multiblock HPMA copolymer nanocarrier for the systemic delivery of paclitaxel. *J Control Release* 166: 66-74, 2013.
58. Wang Q, Tang H and Wu P: Aqueous solutions of poly (ethylene oxide)-poly (N-isopropylacrylamide): Thermosensitive behavior and distinct multiple assembly processes. *Langmuir* 31: 6497-6506, 2015.
59. Priya James H, John R, Alex A and Anoop KR: Smart polymers for the controlled delivery of drugs - a concise overview. *Acta Pharm Sin B* 4: 120-127, 2014.
60. Trotta F, Dianzani C, Caldera F, Moggetti B and Cavalli R: The application of nanosponges to cancer drug delivery. *Expert Opin Drug Deliv* 11: 931-941, 2014.
61. Hu C-MJ, Fang RH, Wang K-C, Luk BT, Thamphiwatana S, Dehaini D, Nguyen P, Angsantikul P, Wen CH, Kroll AV, *et al*: Nanoparticle biointerfacing by platelet membrane cloaking. *Nature* 526: 118-121, 2015.
62. Hu CM, Fang RH, Luk BT and Zhang L: Nanoparticle-detained toxins for safe and effective vaccination. *Nat Nanotechnol* 8: 933-938, 2013.
63. Miele E, Spinelli GP, Miele E, Tomao F and Tomao S: Albumin-bound formulation of paclitaxel (Abraxane ABI-007) in the treatment of breast cancer. *Int J Nanomed* 4: 99-105, 2009.
64. Hawkins MJ, Soon-Shiong P and Desai N: Protein nanoparticles as drug carriers in clinical medicine. *Adv Drug Deliv Rev* 60: 876-885, 2008.
65. Zheng Y-R, Suntharalingam K, Johnstone TC, Yoo H, Lin W, Brooks JG and Lippard SJ: Pt (IV) prodrugs designed to bind non-covalently to human serum albumin for drug delivery. *J Am Chem Soc* 136: 8790-8798, 2014.
66. Cirstea D, Hideshima T, Rodig S, Santo L, Pozzi S, Vallet S, Ikeda H, Perrone G, Gorgun G, Patel K, *et al*: Dual inhibition of akt/mammalian target of rapamycin pathway by nanoparticle albumin-bound-rapamycin and perifosine induces antitumor activity in multiple myeloma. *Mol Cancer Ther* 9: 963-975, 2010.
67. Fu Q, Sun J, Zhang W, Sui X, Yan Z and He Z: Nanoparticle albumin-bound (NAB) technology is a promising method for anti-cancer drug delivery. *Recent Patents Anticancer Drug Discov* 4: 262-272, 2009.
68. Von Hoff DD, Mita MM, Ramanathan RK, Weiss GJ, Mita AC, LoRusso PM, Burris HA III, Hart LL, Low SC, Parsons DM, *et al*: Phase I study of PSMA-targeted docetaxel-containing nanoparticle BIND-014 in patients with advanced solid tumors. *Clin Cancer Res* 22: 3157-3163, 2016.
69. Zuckerman JE, Gritli I, Tolcher A, Heidel JD, Lim D, Morgan R, Chmielowski B, Ribas A, Davis ME and Yen Y: Correlating animal and human phase Ia/Ib clinical data with CALAA-01, a targeted, polymer-based nanoparticle containing siRNA. *Proc Natl Acad Sci USA* 111: 11449-11454, 2014.
70. Buhleier E, Wehner W and Vögtle F: 'Cascade'- and 'nonskid-chain-like' syntheses of molecular cavity topologies. *Synthesis (Mass)* 155-158: 1978, 1978.
71. Tomalia DA, Baker H, Dewald J, Hall M, Kallos G, Martin S, Roeck J, Ryder J and Smith P: A new class of polymers: Starburst-dendritic macromolecules. *Polym J* 17: 117-132, 1985.
72. Gillies ER and Fréchet JM: Dendrimers and dendritic polymers in drug delivery. *Drug Discov Today* 10: 35-43, 2005.
73. Kesharwani P, Jain K and Jain NK: Dendrimer as nanocarrier for drug delivery. *Prog Polym Sci* 39: 268-307, 2014.
74. Khopade AJ, Caruso F, Tripathi P, Nagaich S and Jain NK: Effect of dendrimer on entrapment and release of bioactive from liposomes. *Int J Pharm* 232: 157-162, 2002.
75. Papagiannaros A, Dimas K, Papaioannou GT and Demetzos C: Doxorubicin-PAMAM dendrimer complex attached to liposomes: Cytotoxic studies against human cancer cell lines. *Int J Pharm* 302: 29-38, 2005.
76. Purohit G, Sakthivel T and Florence AT: Interaction of cationic partial dendrimers with charged and neutral liposomes. *Int J Pharm* 214: 71-76, 2001.
77. Karadag M, Geyik C, Demirkol DO, Ertas FN and Timur S: Modified gold surfaces by 6-ferrocenyl)hexanethiol/dendrimer/gold nanoparticles as a platform for the mediated biosensing applications. *Mater Sci Eng C* 33: 634-640, 2013.
78. Tao X, Yang Y-J, Liu S, Zheng Y-Z, Fu J and Chen J-F: Poly (amidoamine) dendrimer-grafted porous hollow silica nanoparticles for enhanced intracellular photodynamic therapy. *Acta Biomater* 9: 6431-6438, 2013.
79. Yoshioka H, Suzuki M, Mugsawa M, Naitoh N and Sawada H: Synthesis and applications of novel fluorinated dendrimer-type copolymers by the use of fluoroalkanoxy peroxide as a key intermediate. *J Colloid Interface Sci* 308: 4-10, 2007.
80. Zeng Y-L, Huang Y-F, Jiang J-H, Zhang X-B, Tang C-R, Shen G-L and Yu R-Q: Functionalization of multi-walled carbon nanotubes with poly (amidoamine) dendrimer for mediator-free glucose biosensor. *Electrochem Commun* 9: 185-190, 2007.
81. Tang L, Zhu Y, Yang X and Li C: An enhanced biosensor for glutamate based on self-assembled carbon nanotubes and dendrimer-encapsulated platinum nanobiocomposites-doped polypyrrole film. *Anal Chim Acta* 597: 145-150, 2007.
82. Prajapati RN, Tekade RK, Gupta U, Gajbhiye V and Jain NK: Dendrimer-mediated solubilization, formulation development and in vitro-in vivo assessment of piroxicam. *Mol Pharm* 6: 940-950, 2009.
83. Chauhan AS, Sridevi S, Chalasani KB, Jain AK, Jain SK, Jain NK and Diwan PV: Dendrimer-mediated transdermal delivery: Enhanced bioavailability of indomethacin. *J Control Release* 90: 335-343, 2003.

84. Quintana A, Raczka E, Piehler L, Lee I, Myc A, Majoros I, Patri AK, Thomas T, Mulé J and Baker JR Jr: Design and function of a dendrimer-based therapeutic nanodevice targeted to tumor cells through the folate receptor. *Pharm Res* 19: 1310-1316, 2002.
85. Liu H, Wang Y, Wang M, Xiao J and Cheng Y: Fluorinated poly (propyleneimine) dendrimers as gene vectors. *Biomaterials* 35: 5407-5413, 2014.
86. Qiao Z and Shi X: Dendrimer-based molecular imaging contrast agents. *Prog Polym Sci* 44: 1-27, 2015.
87. Malik N, Evagorou EG and Duncan R: Dendrimer-platinate: A novel approach to cancer chemotherapy. *Anticancer Drugs* 10: 767-776, 1999.
88. Kaminskas LM, Kelly BD, McLeod VM, Boyd BJ, Krippner GY, Williams ED and Porter CJ: Pharmacokinetics and tumor disposition of PEGylated, methotrexate conjugated poly-L-lysine dendrimers. *Mol Pharm* 6: 1190-1204, 2009.
89. Al-Jamal KT, Al-Jamal WT, Wang JT-W, Rubio N, Buddle J, Gathercole D, Zloh M and Kostarelos K: Cationic poly-L-lysine dendrimer complexes doxorubicin and delays tumor growth in vitro and in vivo. *ACS Nano* 7: 1905-1917, 2013.
90. Huang Z, Sengar RS, Nigam A, Abadjian MC, Potter DM, Grotjahn DB and Wiener EC: A fluorinated dendrimer-based nanotechnology platform: New contrast agents for high field imaging. *Invest Radiol* 45: 641-654, 2010.
91. Yang J, Luo Y, Xu Y, Li J, Zhang Z, Wang H, Shen M, Shi X and Zhang G: Conjugation of iron oxide nanoparticles with RGD-modified dendrimers for targeted tumor MR imaging. *ACS Appl Mater Interfaces* 7: 5420-5428, 2015.
92. Shi X, Wang SH, Van Antwerp ME, Chen X and Baker JR Jr: Targeting and detecting cancer cells using spontaneously formed multifunctional dendrimer-stabilized gold nanoparticles. *Analyst (Lond)* 134: 1373-1379, 2009.
93. Thomas TP, Shukla R, Kotlyar A, Liang B, Ye JY, Norris TB and Baker JR Jr: Dendrimer-epidermal growth factor conjugate displays superagonist activity. *Biomacromolecules* 9: 603-609, 2008.
94. Hill E, Shukla R, Park SS and Baker JR Jr: Synthetic PAMAM-RGD conjugates target and bind to odontoblast-like MDPC 23 cells and the predentin in tooth organ cultures. *Bioconjug Chem* 18: 1756-1762, 2007.
95. Lesniak WG, Kariapper MS, Nair BM, Tan W, Hutson A, Balogh LP and Khan MK: Synthesis and characterization of PAMAM dendrimer-based multifunctional nanodevices for targeting alphavbeta3 integrins. *Bioconjug Chem* 18: 1148-1154, 2007.
96. Thomas TP, Patri AK, Myc A, Myaing MT, Ye JY, Norris TB and Baker JR Jr: In vitro targeting of synthesized antibody-conjugated dendrimer nanoparticles. *Biomacromolecules* 5: 2269-2274, 2004.
97. Chen H-T, Neerman MF, Parrish AR and Simanek EE: Cytotoxicity, hemolysis, and acute in vivo toxicity of dendrimers based on melamine, candidate vehicles for drug delivery. *J Am Chem Soc* 126: 10044-10048, 2004.
98. Ahn HK, Jung M, Sym SJ, Shin DB, Kang SM, Kyung SY, Park JW, Jeong SH and Cho EK: A phase II trial of Cremophor EL-free paclitaxel (Genexol-PM) and gemcitabine in patients with advanced non-small cell lung cancer. *Cancer Chemother Pharmacol* 74: 277-282, 2014.
99. Park S and Healy KE: Nanoparticulate DNA packaging using terpolymers of poly (lysine-*g*-(lactide-*b*-ethylene glycol)). *Bioconjug Chem* 14: 311-319, 2003.
100. Sun T-M, Du J-Z, Yan L-F, Mao H-Q and Wang J: Self-assembled biodegradable micellar nanoparticles of amphiphilic and cationic block copolymer for siRNA delivery. *Biomaterials* 29: 4348-4355, 2008.
101. Gao Y, Zhou Y, Zhao L, Zhang C, Li Y, Li J, Li X and Liu Y: Enhanced antitumor efficacy by cyclic RGDyK-conjugated and paclitaxel-loaded pH-responsive polymeric micelles. *Acta Biomater* 23: 127-135, 2015.
102. Kohori F, Sakai K, Aoyagi T, Yokoyama M, Sakurai Y and Okano T: Preparation and characterization of thermally responsive block copolymer micelles comprising poly (*N*-isopropylacrylamide-*b*-DL-lactide). *J Control Release* 55: 87-98, 1998.
103. He C, Zhao C, Chen X, Guo Z, Zhuang X and Jing X: Novel pH- and temperature-responsive block copolymers with tunable pH-responsive range. *Macromol Rapid Commun* 29: 490-497, 2008.
104. Xu F, Yan T-T and Luo Y-L: Studies on micellization behavior of thermosensitive PNIPAAm-*b*-PLA amphiphilic block copolymers. *J Nanosci Nanotechnol* 12: 2287-2291, 2012.
105. Zhao C, Zhuang X, He C, Chen X and Jing X: Synthesis of novel thermo- and pH-responsive poly (L-lysine)-based copolymer and its micellization in water. *Macromol Rapid Commun* 29: 1810-1816, 2008.
106. Saravanakumar G, Lee J, Kim J and Kim WJ: Visible light-induced singlet oxygen-mediated intracellular disassembly of polymeric micelles co-loaded with a photosensitizer and an anticancer drug for enhanced photodynamic therapy. *Chem Commun (Camb)* 51: 9995-9998, 2015.
107. Bae J, Maurya A, Shariat-Madar Z, Murthy SN and Jo S: Novel redox-responsive amphiphilic copolymer micelles for drug delivery: Synthesis and characterization. *AAPS J* 17: 1357-1368, 2015.
108. Liu Y, Li C, Wang HY, Zhang XZ and Zhuo RX: Synthesis of thermo- and pH-sensitive polyion complex micelles for fluorescent imaging. *Chemistry* 18: 2297-2304, 2012.
109. Johnson RP, Jeong YI, John JV, Chung CW, Kang DH, Selvaraj M, Suh H and Kim I: Dual stimuli-responsive poly (*N*-isopropylacrylamide)-*b*-poly (L-histidine) chimeric materials for the controlled delivery of doxorubicin into liver carcinoma. *Biomacromolecules* 14: 1434-1443, 2013.
110. Zhou F, Zheng B, Zhang Y, Wu Y, Wang H and Chang J: Construction of near-infrared light-triggered reactive oxygen species-sensitive (UCN/SiO<sub>2</sub>-RB + DOX)@PPADT nanoparticles for simultaneous chemotherapy and photodynamic therapy. *Nanotechnology* 27: 235601, 2016.
111. Wu HQ and Wang CC: Biodegradable smart nanogels: A new platform for targeting drug delivery and biomedical diagnostics. *Langmuir* 32: 6211-6225, 2016.
112. Moan J and Peng Q: An outline of the hundred-year history of PDT. *Anticancer Res* 23A: 3591-3600, 2003.
113. Castano AP, Mroz P and Hamblin MR: Photodynamic therapy and anti-tumour immunity. *Nat Rev Cancer* 6: 535-545, 2006.
114. Krammer B: Vascular effects of photodynamic therapy. *Anticancer Res* 21B: 4271-4277, 2001.
115. Monge-Fuentes V, Muehlmann LA and de Azevedo RB: Perspectives on the application of nanotechnology in photodynamic therapy for the treatment of melanoma. *Nano Rev* 5: 24381-24395, 2014.
116. Wang C, Cheng L and Liu Z: Upconversion nanoparticles for photodynamic therapy and other cancer therapeutics. *Theranostics* 3: 317-330, 2013.
117. Marin E, Briceño MI and Caballero-George C: Critical evaluation of biodegradable polymers used in nanodrugs. *Int J Nanomed* 8: 3071-3090, 2013.
118. Ma X, Wang X, Zhou M and Fei H: A mitochondria-targeting gold-peptide nanoassembly for enhanced cancer-cell killing. *Adv Healthc Mater* 2: 1638-1643, 2013.
119. Jung HS, Han J, Lee J-H, Lee JH, Choi JM, Kweon HS, Han JH, Kim JH, Byun KM, Jung JH, *et al.*: Enhanced NIR radiation-triggered hyperthermia by mitochondrial targeting. *J Am Chem Soc* 137: 3017-3023, 2015.
120. Biswas S, Kumari P, Lakhani PM and Ghosh B: Recent advances in polymeric micelles for anti-cancer drug delivery. *Eur J Pharm Sci* 83: 184-202, 2016.
121. Dewit MA and Gillies ER: A cascade biodegradable polymer based on alternating cyclization and elimination reactions. *J Am Chem Soc* 131: 18327-18334, 2009.
122. Deming TJ: Synthetic polypeptides for biomedical applications. *Prog Polym Sci* 32: 858-875, 2007.
123. Sun J, Chen X, Lu T, Liu S, Tian H, Guo Z and Jing X: Formation of reversible shell cross-linked micelles from the biodegradable amphiphilic diblock copolymer poly (L-cysteine)-block-poly (L-lactide). *Langmuir* 24: 10099-10106, 2008.
124. Dourado ER, Pizzorno BS, Motta LM, Simao RA and Leite LF: Analysis of asphaltic binders modified with PPA by surface techniques. *J Microsc* 254: 122-128, 2014.
125. Kim IB, Han MH, Phillips RL, Samanta B, Rotello VM, Zhang ZJ and Bunz UH: Nano-conjugate fluorescence probe for the discrimination of phosphate and pyrophosphate. *Chemistry* 15: 449-456, 2009.
126. Chen PC, Mwakwari SC and Oyelere AK: Gold nanoparticles: From nanomedicine to nanosensing. *Nanotechnol Sci Appl* 1: 45-65, 2008.
127. Huang H-C, Barua S, Sharma G, Dey SK and Rege K: Inorganic nanoparticles for cancer imaging and therapy. *J Control Release* 155: 344-357, 2011.
128. Namiki Y, Fuchigami T, Tada N, Kawamura R, Matsunuma S, Kitamoto Y and Nakagawa M: Nanomedicine for cancer: Lipid-based nanostructures for drug delivery and monitoring. *Acc Chem Res* 44: 1080-1093, 2011.

129. Libutti SK, Paciotti GF, Byrnes AA, Alexander HR Jr, Gannon WE, Walker M, Seidel GD, Yuldasheva N and Tamarkin L: Phase I and pharmacokinetic studies of CYT-6091, a novel PEGylated colloidal gold-rhTNF nanomedicine. *Clin Cancer Res* 16: 6139-6149, 2010.
130. Benezra M, Penate-Medina O, Zanzonico PB, Schaer D, Ow H, Burns A, DeStanchina E, Longo V, Herz E, Iyer S, *et al*: Multimodal silica nanoparticles are effective cancer-targeted probes in a model of human melanoma. *J Clin Invest* 121: 2768-2780, 2011.
131. Sanchez C, Belleville P, Popall M and Nicole L: Applications of advanced hybrid organic-inorganic nanomaterials: From laboratory to market. *Chem Soc Rev* 40: 696-753, 2011.
132. Jain RK and Stylianopoulos T: Delivering nanomedicine to solid tumors. *Nat Rev Clin Oncol* 7: 653-664, 2010.
133. Kamaly N, Yameen B, Wu J and Farokhzad OC: Degradable controlled-release polymers and polymeric nanoparticles: Mechanisms of controlling drug release. *Chem Rev* 116: 2602-2663, 2016.
134. Holback H and Yeo Y: Intratumoral drug delivery with nanoparticulate carriers. *Pharm Res* 28: 1819-1830, 2011.
135. Jain RK, Martin JD and Stylianopoulos T: The role of mechanical forces in tumor growth and therapy. *Annu Rev Biomed Eng* 16: 321-346, 2014.
136. Kim KY: Nanotechnology platforms and physiological challenges for cancer therapeutics. *Nanomedicine (Lond)* 3: 103-110, 2007.
137. Liu D, He C, Wang AZ and Lin W: Application of liposomal technologies for delivery of platinum analogs in oncology. *Int J Nanomed* 8: 3309-3319, 2013.
138. Moghimi SM, Symonds P, Murray JC, Hunter AC, Debska G and Szewczyk A: A two-stage poly (ethylenimine)-mediated cytotoxicity: Implications for gene transfer/therapy. *Mol Ther* 11: 990-995, 2005.
139. Lü J-M, Wang X, Marin-Muller C, Wang H, Lin PH, Yao Q and Chen C: Current advances in research and clinical applications of PLGA-based nanotechnology. *Expert Rev Mol Diagn* 9: 325-341, 2009.
140. Kim J, Dadsetan M, Ameenuddin S, Windebank AJ, Yaszemski MJ and Lu L: In vivo biodegradation and biocompatibility of PEG/sebacic acid-based hydrogels using a cage implant system. *J Biomed Mater Res A* 95: 191-197, 2010.
141. Nicolette R, dos Santos DF and Faccioli LH: The uptake of PLGA micro or nanoparticles by macrophages provokes distinct in vitro inflammatory response. *Int Immunopharmacol* 11: 1557-1563, 2011.
142. Ceonzo K, Gaynor A, Shaffer L, Kojima K, Vacanti CA and Stahl GL: Polyglycolic acid-induced inflammation: Role of hydrolysis and resulting complement activation. *Tissue Eng* 12: 301-308, 2006.
143. Madaan K, Kumar S, Poonia N, Lather V and Pandita D: Dendrimers in drug delivery and targeting: Drug-dendrimer interactions and toxicity issues. *J Pharm Bioallied Sci* 6: 139-150, 2014.
144. Jain K, Kesharwani P, Gupta U and Jain NK: Dendrimer toxicity: Let's meet the challenge. *Int J Pharm* 394: 122-142, 2010.
145. Ma Y, Mou Q, Wang D, Zhu X and Yan D: Dendritic polymers for theranostics. *Theranostics* 6: 930-947, 2016.
146. Dreaden EC, Austin LA, Mackey MA and El-Sayed MA: Size matters: Gold nanoparticles in targeted cancer drug delivery. *Ther Deliv* 3: 457-478, 2012.
147. Gu Y, Zhong Y, Meng F, Cheng R, Deng C and Zhong Z: Acetal-linked paclitaxel prodrug micellar nanoparticles as a versatile and potent platform for cancer therapy. *Biomacromolecules* 14: 2772-2780, 2013.
148. Idris NM, Gnanasammandhan MK, Zhang J, Ho PC, Mahendran R and Zhang Y: In vivo photodynamic therapy using upconversion nanoparticles as remote-controlled nanotransducers. *Nat Med* 18: 1580-1585, 2012.
149. Yang Y, Shao Q, Deng R, Wang C, Teng X, Cheng K, Cheng Z, Huang L, Liu Z, Liu X, *et al*: In vitro and in vivo uncaging and bioluminescence imaging by using photocaged upconversion nanoparticles. *Angew Chem Int Ed Engl* 51: 3125-3129, 2012.
150. Chen H, Yang Z, Ding C, Chu L, Zhang Y, Terry K, Liu H, Shen Q and Zhou J: Fragment-based drug design and identification of HJC0123, a novel orally bioavailable STAT3 inhibitor for cancer therapy. *Eur J Med Chem* 62: 498-507, 2013.
151. Langer R and Folkman J: Polymers for the sustained release of proteins and other macromolecules. *Nature* 263: 797-800, 1976.
152. Lee CC, MacKay JA, Fréchet JMJ and Szoka FC: Designing dendrimers for biological applications. *Nat Biotechnol* 23: 1517-1526, 2005.
153. Torchilin VP: Immunoliposomes and PEGylated immunoliposomes: Possible use for targeted delivery of imaging agents. *Immunomethods* 4: 244-258, 1994.
154. Immordino ML, Dosio F and Cattel L: Stealth liposomes: Review of the basic science, rationale, and clinical applications, existing and potential. *Int J Nanomed* 1: 297-315, 2006.
155. Batist G, Ramakrishnan G, Rao CS, Chandrasekharan A, Gutheil J, Guthrie T, Shah P, Khojasteh A, Nair MK, Hoelzer K, *et al*: Reduced cardiotoxicity and preserved antitumor efficacy of liposome-encapsulated doxorubicin and cyclophosphamide compared with conventional doxorubicin and cyclophosphamide in a randomized, multicenter trial of metastatic breast cancer. *J Clin Oncol* 19: 1444-1454, 2001.
156. Silverman JA and Deitcher SR: Marqibo® (vincristine sulfate liposome injection) improves the pharmacokinetics and pharmacodynamics of vincristine. *Cancer Chemother Pharmacol* 71: 555-564, 2013.
157. Verma J, Lal S and Van Noorden CJ: Inorganic nanoparticles for the theranostics of cancer. *Eur J Nanomed* 7: 271-287, 2015.
158. Kim MT, Chen Y, Marhoul J and Jacobson F: Statistical modeling of the drug load distribution on trastuzumab emtansine (Kadcyla), a lysine-linked antibody drug conjugate. *Bioconjug Chem* 25: 1223-1232, 2014.
159. Mamot C, Ritschard R, Wicki A, Stehle G, Dieterle T, Bubendorf L, Hilker C, Deuster S, Herrmann R and Rochlitz C: Tolerability, safety, pharmacokinetics, and efficacy of doxorubicin-loaded anti-EGFR immunoliposomes in advanced solid tumours: A phase I dose-escalation study. *Lancet Oncol* 13: 1234-1241, 2012.
160. Swiss Group for Clinical Cancer Research: Anti-EGFR-immunoliposomes loaded with doxorubicin in patients with advanced triple negative EGFR positive breast cancer. NCT02833766. <https://clinicaltrials.gov/ct2/show/NCT02833766>. Accessed October 20, 2016.
161. Markman M: Pegylated liposomal doxorubicin in the treatment of cancers of the breast and ovary. *Expert Opin Pharmacother* 7: 1469-1474, 2006.
162. Listed N: Kaposi's sarcoma: DaunoXome approved. *AIDS Treat News* 79: 3-4, 1996.
163. Rau K-M, Lin Y-C, Chen Y-Y, Chen JS, Lee KD, Wang CH and Chang HK: Pegylated liposomal doxorubicin (Lipo-Dox®) combined with cyclophosphamide and 5-fluorouracil is effective and safe as salvage chemotherapy in taxane-treated metastatic breast cancer: An open-label, multi-center, non-comparative phase II study. *BMC Cancer* 15: 423, 2015.
164. DiGiulio S: DiGiulio, S. FDA approves onivyde combo regimen for advanced pancreatic cancer. *Oncol Times* 37: 8, 2015.
165. Stathopoulos G and Boulikas T: Lipoplatin formulation review article. *J Drug Deliv* 2012: 581363, 2012.
166. Ohyanagi F, Horai T, Sekine I, Yamamoto N, Nakagawa K, Nishio M, Senger S, Morsli N and Tamura T: Safety of BLP25 liposome vaccine (L-BLP25) in Japanese patients with unresectable stage III NSCLC after primary chemoradiotherapy: Preliminary results from a Phase I/II study. *Jpn J Clin Oncol* 41: 718-722, 2011.
167. Dou Y, Hynynen K and Allen C: To heat or not to heat: Challenges with clinical translation of thermosensitive liposomes. *J Control Release* 249: 63-73, 2017.
168. Lancet JE, Uy GL, Cortes JE, Newell LF, Lin TL, Ritchie EK, Stuart RK, Strickland SA, Hogge D, Solomon SR, *et al*: Final results of a phase III randomized trial of CPX-351 versus 7+3 in older patients with newly diagnosed high risk (secondary) AM. *J Clin Oncol* 34: 7000, 2016.
169. Dragovich T, Mendelson D, Kurtin S, Richardson K, Von Hoff D and Hoos A: A Phase 2 trial of the liposomal DACH platinum L-NDDP in patients with therapy-refractory advanced colorectal cancer. *Cancer Chemother Pharmacol* 58: 759-764, 2006.
170. Chinsriwongkul A, Chareanputtakhun P, Ngawhirunpat T, Rojanarata T, Sila-on W, Ruktanonchai U and Opanasopit P: Nanostructured lipid carriers (NLC) for parenteral delivery of an anticancer drug. *AAPS PharmSciTech* 13: 150-158, 2012.
171. Strumberg D, Schultheis B, Traugott U, Vank C, Santel A, Keil O, Giese K, Kaufmann J and Drevs J: Phase I clinical development of Atu027, a siRNA formulation targeting PKN3 in patients with advanced solid tumors. *Int J Clin Pharmacol Ther* 50: 76-78, 2012.

172. Awada A, Bondarenko IN, Bonnetterre J, Nowara E, Ferrero JM, Bakshi AV, Wilke C and Piccart M: CT4002 study group: A randomized controlled phase II trial of a novel composition of paclitaxel embedded into neutral and cationic lipids targeting tumor endothelial cells in advanced triple-negative breast cancer (TNBC). *Ann Oncol* 25: 824-831, 2014.
173. Slingerland M, Guchelaar H-J, Rosing H, Scheulen ME, van Warmerdam LJ, Beijnen JH and Gelderblom H: Bioequivalence of Liposome-Entrapped Paclitaxel Easy-To-Use (LEP-ETU) formulation and paclitaxel in polyethoxylated castor oil: A randomized, two-period crossover study in patients with advanced cancer. *Clin Ther* 35: 1946-1954, 2013.
174. Bala V, Rao S, Boyd BJ and Prestidge CA: Prodrug and nanomedicine approaches for the delivery of the camptothecin analogue SN38. *J Control Release* 172: 48-61, 2013.
175. Senzer NN, Matsuno K, Yamagata N, Fujisawa T, Wasserman E, Sutherland W, Sharma S and Phan A: Abstract C36: MBP-426, a novel liposome-encapsulated oxaliplatin, in combination with 5-FU/leucovorin (LV): Phase I results of a Phase I/II study in gastro-esophageal adenocarcinoma, with pharmacokinetics. *Mol Cancer Ther* 8 (Suppl. 1): C36-C36, 2009. doi: 10.1158/1535-7163.TARG-09-C36.
176. Seiden MV, Muggia F, Astrow A, Matulonis U, Campos S, Roche M, Sivret J, Rusk J and Barrett E: A phase II study of liposomal lurtotecan (OSI-211) in patients with topotecan resistant ovarian cancer. *Gynecol Oncol* 93: 229-232, 2004.
177. Noble GT, Stefanick JF, Ashley JD, Kiziltepe T and Bilgicer B: Ligand-targeted liposome design: Challenges and fundamental considerations. *Trends Biotechnol* 32: 32-45, 2014.
178. Wetzler M, Thomas DA, Wang ES, Shepard R, Ford LA, Heffner TL, Parekh S, Andreoff M, O'Brien S and Kantarjian HM: Phase I/II trial of nanomolecular liposomal annamycin in adult patients with relapsed/refractory acute lymphoblastic leukemia. *Clin Lymphoma Myeloma Leuk* 13: 430-434, 2013.
179. Hwang JH, Lim MC, Seo S-S, Park S-Y and Kang S: Phase II study of belotecan (CKD 602) as a single agent in patients with recurrent or progressive carcinoma of uterine cervix. *Jpn J Clin Oncol* 41: 624-629, 2011.
180. Hough B, Posner M, Chung C, *et al.*: A phase II study of single agent OSI-7904L in patients with metastatic or recurrent squamous cell carcinoma of the head and neck (SCCHN). *Journal* 27: e17005, 2009.
181. Pattni BS, Chupin VV and Torchilin VP: New developments in liposomal drug delivery. *Chem Rev* 115: 10938-10966, 2015.
182. Semple SC, Leone R, Wang J, Leng EC, Klimuk SK, Eisenhardt ML, Yuan ZN, Edwards K, Maurer N, Hope MJ, *et al.*: Optimization and characterization of a sphingomyelin/cholesterol liposome formulation of vinorelbine with promising antitumor activity. *J Pharm Sci* 94: 1024-1038, 2005.
183. Ugwu S, Zhang A, Parmar M, Miller B, Sardone T, Peikov V and Ahmad I: Preparation, characterization, and stability of liposome-based formulations of mitoxantrone. *Drug Dev Ind Pharm* 31: 223-229, 2005.
184. McMurtry V, Nieves-Alicea R, Donato N and Tari A: Liposome-incorporated Grb2 antisense oligonucleotides as a novel therapy against drug resistant chronic myelogenous leukemia. *Cancer Res* 68: 1503-1503, 2008.
185. Stathopoulos GP, Boulikas T, Kourvetaris A and Stathopoulos J: Liposomal oxaliplatin in the treatment of advanced cancer: A phase I study. *Anticancer Res* 262B: 1489-1493, 2006.
186. Oncology Venture: Oncology Venture presents LiPlaCis on AACR in New Orleans. <https://www.aktietorget.se/NewsItem.aspx?ID=77244>.
187. Barraud L, Merle P, Soma E, Lefrançois L, Guerret S, Chevallier M, Dubernet C, Couvreur P, Trépo C and Vitvitski L: Increase of doxorubicin sensitivity by doxorubicin-loading into nanoparticles for hepatocellular carcinoma cells in vitro and in vivo. *J Hepatol* 42: 736-743, 2005.
188. Zhou Q, Sun X, Zeng L, Liu J and Zhang Z: A randomized multicenter phase II clinical trial of mitoxantrone-loaded nanoparticles in the treatment of 108 patients with unresected hepatocellular carcinoma. *Nanomedicine (Lond)* 5: 419-423, 2009.
189. Pang X, Du H-L, Zhang H-Q, Zhai Y-J and Zhai G-X: Polymer-drug conjugates: Present state of play and future perspectives. *Drug Discov Today* 18: 1316-1322, 2013.
190. QUILT-3.014: A Trial of ABI-011 administered weekly in patients with advanced solid tumors or lymphomas. NCT02582827. <https://clinicaltrials.gov/ct2/show/NCT02582827>. Accessed March 6, 2017.
191. Giglio V, Sgarlata C and Vecchio G: Novel amino-cyclodextrin cross-linked oligomer as efficient carrier for anionic drugs: A spectroscopic and nanocalorimetric investigation. *RSC Advances* 5: 16664-16671, 2015.
192. Svenson S: Clinical translation of nanomedicines. *Curr Opin Solid State Mater Sci* 16: 287-294, 2012.
193. Williamson SK, Johnson GA, Maulhardt HA, Moore KM, McMeekin DS, Schulz TK, Reed GA, Roby KF, Mackay CB, Smith HJ, *et al.*: A phase I study of intraperitoneal nanoparticulate paclitaxel (Nanotax<sup>®</sup>) in patients with recurrent malignancies. *Cancer Chemother Pharmacol* 75: 1075-1087, 2015.
194. Vergote I, Brize A, Lisyanskaya AS and Lichinitser M: Randomized phase III study comparing paclitaxel-carboplatin with paclitaxel-carboplatin in patients with recurrent platinum-sensitive epithelial ovarian cancer. *J Clin Oncol* 33: 5517, 2015.
195. Pitto-Barry A and Barry NP: Pluronic<sup>®</sup> block-copolymers in medicine: From chemical and biological versatility to rationalisation and clinical advances. *Polym Chem* 5: 3291-3297, 2014.
196. Kato K, Chin K, Yoshikawa T, Yamaguchi K, Tsuji Y, Esaki T, Sakai K, Kimura M, Hamaguchi T, Shimada Y, *et al.*: Phase II study of NK105, a paclitaxel-incorporating micellar nanoparticle, for previously treated advanced or recurrent gastric cancer. *Invest New Drugs* 30: 1621-1627, 2012.
197. Endo K, Ueno T, Kondo S, Wakisaka N, Muroso S, Ito M, Kataoka K, Kato Y and Yoshizaki T: Tumor-targeted chemotherapy with the nanopolymer-based drug NC-6004 for oral squamous cell carcinoma. *Cancer Sci* 104: 369-374, 2013.
198. Tsuji A, Hamaguchi T, Yamaguchi K, *et al.*: A phase II study of NK012, a polymeric micelle formulation of SN-38, in colorectal cancer patients who had received prior oxaliplatin-based regimen. *Journal* 33: 3527, 2015.
199. Ghamande S, Lin C-C, Cho DC, Coleman T, Chaudhary I, Shapiro GI, Silverman M, Kuo M-W, Mach WB, Tseng Y, *et al.*: Abstract A89: A phase I study of the novel DNA topoisomerase-I inhibitor, TLC388 (Lipotecan<sup>®</sup>), administered intravenously to patients with advanced solid tumors. *Mol Cancer Ther* 10 (Supplement 1): 89, 2011.
200. Ueno T, Endo K, Hori K, Ozaki N, Tsuji A, Kondo S, Wakisaka N, Muroso S, Kataoka K, Kato Y, *et al.*: Assessment of antitumor activity and acute peripheral neuropathy of 1,2-diaminocyclohexane platinum (II)-incorporating micelles (NC-4016). *Int J Nanomed* 9: 3005-3012, 2014.
201. Takahashi A, Yamamoto Y, Yasunaga M, Koga Y, Kuroda J, Takigahira M, Harada M, Saito H, Hayashi T, Kato Y, *et al.*: NC-6300, an epirubicin-incorporating micelle, extends the antitumor effect and reduces the cardiotoxicity of epirubicin. *Cancer Sci* 104: 920-925, 2013.
202. Owen SC, Chan DP and Shoichet MS: Polymeric micelle stability. *Nano Today* 7: 53-65, 2012.