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Small-molecule delivery by nanoparticles for anticancer therapy

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Abstract

Using nanoparticles for the delivery of small molecules in anticancer therapy is a rapidly growing area of research. The advantages of using nanoparticles for drug delivery include enhanced water solubility, tumor-specific accumulation and improved antitumor efficacy, while reducing nonspecific toxicity. Current research in this field focuses on understanding precisely how small molecules are released from nanoparticles and delivered to the targeted tumor tissues or cells, and how the unique biodistribution of the drug-carrying nanoparticles limits toxicity in major organs. Here, we discuss existing nanoparticles for the delivery of small-molecule anticancer agents and recent advances in this field.

Advantages of nanoparticles for the delivery of small-molecule anticancer agents

In recent years, the development of therapeutic nanoparticles (TNPs) for the delivery of small-molecule anticancer agents has received great attention from the medical research community [1–6]. Small molecules, although in routine use as chemotherapeutic agents for cancer treatment, have characteristics that limit their use in clinical applications, including a lack of water solubility, nonspecific biodistribution and targeting as well as low therapeutic indices. Moreover, the development of drug resistance shortly after initial treatment further reduces the efficacy of not only conventional chemotherapeutics but also newer targeted therapeutic agents. However, the delivery of therapeutic small molecules by nanoparticles has advantages that overcome these limitations.

Nanoparticles, as defined by the US National Cancer Institute, are colloidal particles in the size range of 1–100 nanometers (nm). Although there is no strict definition of a TNP size range, it is likely that TNPs larger than 10 nm and smaller than 100 nm are most effective. On the basis of sieving coefficients measured for the glomerular capillary wall, the threshold for first-pass elimination by the kidneys is estimated at 10 nm (diameter) [7]. Tumor vasculature, by contrast, is immature, allowing macromolecules leaking from the blood to accumulate in the interstitial space in tumor tissues. This phenomenon is called the “enhanced permeability and retention (EPR) effect” [8]. Accumulating evidence has suggested that the EPR effect is operational in both animal tumor models and human cancers. Chemical entities in the range of 100 nm can leak out of the blood and accumulate within tumor tissues. By contrast, larger macromolecules or nanoparticles show restricted diffusion into the extracellular space [9], which would limit the efficacy of TNPs by preventing them from easily reaching cancer cells. Experiments with animal models suggest that small (<150 nm), neutral or slightly negatively charged particles can move through tumor tissue [10]. Nanoparticles in the 50–100 nm range with a nearly neutral charge can

penetrate throughout large tumors following systemic administration [11]. Furthermore, the addition of a targeting moiety to TNPs can guide the TNPs to tumor tissues and cells. This selective accumulation in tumor tissues and cells gives TNPs the potential to significantly improve the therapeutic outcome of cancer treatments while minimizing the devastating side effects associated with many current therapies. The expected advantages of TNPs carrying small-molecule anticancer agents that could enhance drug efficacy include (i) improved solubility, which facilitates drug delivery; (ii) increased half life ($t_{1/2}$) in circulation, owing to resistance to the reticuloendothelial system or mononuclear phagocytic system (MPS); (iii) enhanced drug accumulation in target cancer tissue and cells; (iv) constant and stable drug release; and (v) reduced efflux pump-mediated drug-resistance (Figure 1).

Owing to these specific characteristics, the development of TNPs has been pursued. Newly developed TNPs have shown greater anticancer efficacy and lower toxicity than their corresponding free agents. Some TNPs are already approved by the FDA for clinical use or are under clinical trials as summarized in a review article [12]. The preclinical evaluations of TNPs have also been reviewed elsewhere [12–18]; however, the mechanisms underlying these encouraging outcomes have not been fully elucidated. Major challenges remaining in the development and clinical application of TNPs are to understand precisely how anticancer agents are released from TNPs and delivered to the targeted tumor tissues and cells, and how the biodistribution of TNPs affects their toxicity in major organs. These important issues correlate with favorable pharmacokinetics (PK) and the impressive efficacy of TNPs. Here, we discuss recent progress in understanding these questions.

TNPs for the delivery of small-molecule anticancer agents

TNPs can be formulated with several materials such as lipids (liposomes), polymers (macromolecules, micelles or dendrimers) and viruses (viral-like nanoparticles) with distinct characteristics (Table 1). Many formulations have been tested in clinical trials. Moreover, metals and inorganic and organometallic compounds, such as gold, iron oxide, silica and nanotube nanoparticles, can be used as small-molecule carriers [19–22], although currently there are no clinical applications using this class of TNPs.

Lipid-based TNPs

Liposome-formulated drug delivery systems were the first class of TNPs and have been in development for decades. Liposomes are self-assembling closed colloidal structures composed of lipid bilayers and have a spherical shape, holding a central aqueous space. Several cancer drugs have been encapsulated in lipid-based systems; among them, the liposomal formulations of the anthracyclines doxorubicin (Doxil, Myocet) and daunorubicin (DaunoXome) are approved for the treatment of metastatic breast cancer and AIDS-related Kaposi's sarcoma [23–26].

Polymer-based TNPs

Polymers used for TNP formulation can be natural or synthetic. Depending on the method of preparation, the drug is either physically entrapped by or covalently bound to the polymer matrix [27]. Natural polymers such as albumin, chitosan and heparin have been used for the delivery of small-molecule drugs. One successful example is the albumin-based formulation of paclitaxel (Abraxane) [28,29]. N-(2-hydroxypropyl)-methacrylamide copolymer (HPMA), polystyrene-maleic anhydride copolymer (SMA), polyethylene glycol (PEG) and poly-L-glutamic acid (PGA) are all synthetic polymers. PGA was the first biodegradable polymer to be used for the conjugation of small molecules [30]. Xyotax (PGA–paclitaxel) [31] and CT-2106 (PGA–camptothecin) are now in clinical trials [32,33]. HPMA and PEG are the most widely used nonbiodegradable synthetic polymers [34]. PK1 is a conjugate of

HPMA with doxorubicin [35]. Another polymeric TNP is IT-101, which is a camptothecin-based TNP formulated with a cyclodextrin-containing polymer [12,36].

Micelles, based on amphiphilic block copolymers, can assemble to form nanosized core/shell structures in aqueous media. The hydrophobic core region serves as a reservoir for hydrophobic drugs, whereas the hydrophilic shell stabilizes the hydrophobic core and renders the polymer water soluble, making the particle an appropriate candidate for the intravenous administration of small-molecule anticancer agents [37]. The first polymeric micelle (PM) TNP was Genexol-PM (PEG-poly(D,L-lactide)-paclitaxel) [38]. Multifunctional PMs containing targeting ligands and imaging and therapeutic agents are being actively developed [39]. One of the most promising micelle structures is formulated by PEGylated polypeptide block copolymers originally developed by Nishiyama and Kataoka [40]. Compared with liposomes, the particle size, stability, drug-loading capacity and releasing kinetics of this type of micelle can be modulated by the structures and physicochemical properties of the constituent block copolymers. A dendrimer is a synthetic polymeric macromolecule of nanometer dimensions composed of multiple highly branched monomers. Properties associated with dendrimers, such as their modifiable surface functionality, water solubility and available internal cavity, make them attractive for delivering drugs, such as cisplatin [41,42].

Viral or viral-like TNPs

A variety of viruses including cowpea mosaic virus (CPMV), cowpea chlorotic mottle virus (CCMV), canine parvovirus (CPV), heat shock protein (HSP) cage and bacteriophages have been developed for biomedical and nanotechnology applications that include tissue targeting and drug delivery. Several targeting molecules and peptides can be displayed in a biologically functional form on their capsid surface using chemical or genetic means. Therefore, several ligands or antibodies including transferrin, folic acid and single-chain antibodies have been conjugated to viruses for specific tumor targeting *in vivo* [43]. In addition to artificial targeting, a subset of viruses has a natural affinity for receptors, such as the transferrin receptor, that are upregulated on tumor cells [44]. An HSP-based dual-function protein cage with specific targeting has been used for the delivery of doxorubicin [45,46].

Controlled release of therapeutic agents from TNPs

Improving the PK of TNP-delivered anticancer agents

Table 2 lists PK information for TNPs from clinical trials. The earliest form of TNPs, liposome-based TNPs, were rapidly cleared by the MPS because of their size (>200 nm). The clearance rate was later significantly reduced by coating their surfaces with PEG [1,14,47–50]. For example, Doxil® has a 105-fold longer $t_{1/2}$ and a 720-fold lower clearance rate than free doxorubicin in the human body [12,51]. Using PEG for TNP surface grafting or conjugation provides steric stabilization and confers “stealth” properties, such as the prevention of protein absorption, and has been applied to surface coating for a variety of TNPs [52]. Usually, proteins absorbed on the surface of a nanoparticle induce aggregation and rapid clearance from the bloodstream [53–55]. In addition to PEG, other polymers have been used for coating anticancer agents. IT-101 coated by cyclodextrin has a 13-fold longer $t_{1/2}$ and 450-fold lower clearance rate than the free drug topotecan (a camptothecin analog). Similarly, the PGA-coated paclitaxel TNP Xyotax has a significantly improved circulation ($t_{1/2}$ 70–120 hours) and clearance rate (0.07–0.12 mL/min·kg) compared with free paclitaxel ($t_{1/2}$ 21.8 hours; 3.9 mL/min kg) in human blood [56].

The surface properties of TNPs can greatly affect their behavior in humans [57]. Because of the size of TNPs, they have high surface-to-volume ratios and controlling their surface

properties is crucial to controlling their behavior in human circulation. TNPs that are neutral or slightly negatively charged tend to have minimal self:self and self:-nonself interactions. Because the inside surfaces of blood vessels and the surfaces of cells contain many negatively charged components, TNPs with negative charges are repelled by these surfaces. The complete removal of these nonspecific interactions is not currently possible, so there is generally some loss of particles owing to these unwanted interactions. By improving our understanding of the size and surface property requirements that control biodistribution, the localization of TNPs to specific sites can be accomplished.

Anticancer drug release from TNPs

Whether an anticancer drug can be stable in circulation and then released from nanocarriers at the targeting site are crucial factors in the development of TNPs. The burst release of drugs by liposome-based TNPs can result in uncontrolled drug delivery. To improve drug delivery, polymer-based TNPs have been designed for controlled drug release and studied *in vitro* and *in vivo*. The kinetics of drug release from polymeric nanoparticles depends on many factors including polymer architecture, hydrophobicity/hydrophilicity and the physicochemical characteristics of the drug molecule and its mode of association with the polymer, such as surface adsorption, dispersion homogeneity in the polymer matrix and covalent linkage with the polymer backbone [58–60]. Karnik and colleagues developed poly (D,L-lactide-co-glycolic acid) (PLGA)–PEG encapsulated docetaxel; the addition of free PLGA doubled drug loading [61]. Chan and colleagues developed new TNPs using PLGA–lecithin–PEG with encapsulated docetaxel; varying the total lipid/polymer weight ratio altered the drug-release profile [62]. To describe this relationship, the authors proposed that the lipid monolayer serves as a molecular fence, keeping docetaxel in the hydrophobic core and preventing PLGA hydrolysis. Therefore, in this TNP the lipid monolayer is a limiting factor in controlled drug release.

The major mechanisms used to control drug release in targeted tumor cells include pH or temperature changes and enzyme-mediated drug release, which have previously been reviewed [63]. As an example, Bae and colleagues formulated a pH-sensitive PM using PEG–poly(aspartate hydrazone adriamycin [PEG–p(Asp-Hyd-ADR)]) [64,65]. In this TNP, the anticancer drug adriamycin (ADR) was conjugated to the core-forming segments through hydrazone linkers that are stable under physiological conditions (pH 7.4) but cleavable in the acidic environments of endosomes and lysosomes (pH 5–6). This pH-triggered drug release is particularly important for TNPs with ligands targeting cell surface receptors, because these TNPs are designed to enter the targeted tumor cells by endocytosis and pass through the acidic endosomal compartments. Bae and colleagues also reported a Pluronic nanocapsule with thermally responsive wall permeability [66]. The nanoparticle can retain the sugar molecule trehalose with negligible release for cellular uptake at 37 °C and yet rapidly release the sugar when the temperature drops to 22 °C, providing a potential temperature-dependent delivery tool for anticancer treatment.

Tumor-specific distribution of therapeutic agents delivered by TNPs

TNPs allow anticancer agents to be delivered and accumulate specifically in tumor tissues and cells. In addition to using the EPR effect, which is a form of “passive targeting”, one of the major advantages of TNPs is that the attachment of a specific targeting ligand can achieve “active targeting”. Table 3 briefly summarizes the biodistribution studies of some TNPs in mouse models.

Targeting tumor cells

The addition of targeting ligands that mediate specific interactions between TNPs and the tumor cell surface can play a role in the ultimate localization of TNPs. By incorporating a targeting molecule that specifically binds to an antigen or receptor that is either uniquely expressed or overexpressed on the tumor cell surface, the ligand-targeted TNP is expected to selectively deliver drugs to tumor cells and enhance intracellular drug accumulation. The mechanisms of TNP internalization into target cells via receptor-mediated endocytosis have been previously reviewed [13,15].

Ligands targeting cell surface receptors can be natural molecules such as folate or growth factors such as epidermal growth factor, which have the advantages of lower molecular weights and lower immunogenicities than antibodies. Modified antibodies can also be used as targeting moieties in an active targeting approach. Monoclonal antibodies (mAbs) or antibody fragments, such as antigen-binding fragments or single chain variable fragments, are the most frequently used ligands for targeted therapies. Compared with mAbs, antibody fragments can reduce immunogenicity and improve the pharmacokinetic profiles of nanoparticles [47]. For example, liposomes coupled with antibody fragments instead of mAbs showed decreased clearance rates and increased $t_{1/2}$, allowing the liposomes sufficient time in circulation to be distributed and bind to the targeted cells [47,67]. Affibodies are engineered nonimmunoglobulin scaffold proteins with high affinity and specificity to given protein targets and have been used for imaging and radiotherapy [68,69]. Affibodies against HER2 have been conjugated to thermosensitive liposomes (Affisomes) [70] and poly-(D,L-lactic acid (PLA)–PEG–maleimide copolymers for the delivery of paclitaxel [71]. Owing to its small size and stability, affibodies have great potential as ligands on TNPs for targeting the delivery of small-molecule anticancer agents.

Once active targeting is achieved, the next important question is whether the targeted TNPs can be internalized by the target cell. If ligand binding cannot trigger internalization, the drug can still enter cells by simple diffusion or through other transport systems after being released from the targeted conjugate at or near the cell surface. However, drugs released outside the cell can disperse or redistribute to the surrounding normal tissues rather than be delivered exclusively to the cancer cells. *In vitro* and *in vivo* comparisons using internalizing or noninternalizing ligands have shown that the intracellular concentration of the drug is much higher when it is released from TNPs into the cytoplasm after internalization [72,73].

Several studies have illustrated the binding and internalization of targeted TNPs. Transmission electron micrographs have shown a polymer-based TNP containing a human transferrin protein-targeting agent bound to the cell surface, internalized into the cytoplasm and localized in the endosome [12,74]. Using fluorescence dye labeling, the localization of folate-targeted TNP in the endosome after ligand-mediated endocytosis has also been observed [75]. In an *in vivo* animal study, targeted TNP-delivered paclitaxel was mainly located in tumor cells, whereas nontargeted TNP-delivered paclitaxel was detected intercellularly. The intracellular concentration of paclitaxel delivered by the targeted TNP was four times greater than that delivered by the nontargeted TNP [75]. One of these, HPMA copolymer–doxorubicin–galactosamine (PK1, FCE28068) has progressed to a phase II clinical trial [76]. In this TNP, galactosaminemoieties bind to the asialoglycoprotein receptor on hepatocytes [77,78]. These promising early clinical results suggest the potential of targeted TNPs as anticancer drug delivery systems.

Targeting the tumor microenvironment

There is an ongoing debate as to whether attaching a targeting ligand to a TNP is necessary because the EPR effect is believed to direct TNP accumulation in a cancer tissue area. When tumor vasculature is developed to a stage when the majority of blood vessels are incomplete, this might be true; however, for small tumors that lack a well-developed vasculature, targeting tumor cells or even the tumor microenvironment could be more effective. The accumulation of Abraxane owing in part to endothelium transcytosis is initiated by the binding of albumin to a cell surface glycoprotein gp60 receptor and secreted protein acid and rich in cysteine (SPARC), which induces the binding of gp60 with an intracellular protein caveolin and forms transcytotic vesicles (i.e. caveolae). These data support the notion that targeting caveolae might provide a universal portal to pump drugs out of the blood and into nearby tissue [29,79–81]. Karmali and colleagues demonstrated that the addition of two tumor-homing peptides LyP-1 and Cys-Arg-Glu-Lys-Ala (CREKA) selected from phage display to Abraxane enhances the accumulation in tumor tissue [82]. LyP-1–Abraxane inhibited tumor growth in a breast cancer xenograft model significantly better than the nontargeted Abraxane. CREKA can bind to clotted plasma proteins present in tumor vessels and the interstitium [83]. It has been used as a tumor-homing ligand and tested in an orthotopic prostate cancer model. As expected, the CREKA-conjugated nanoparticles blocked tumor vasculature, reduced blood flow, induced necrosis and thereby significantly inhibited tumor growth [84]. Other ligands targeting endothelial cells include RGD and urokinase plasminogen activator (uPA). The RGD motif in many proteins has a strong affinity and selectivity for cell surface $\alpha v \beta 3$ integrins, which are overexpressed on the surface of endothelial cells of neocapillaries and also in some types of tumor cells. Therefore, RGD has been used as a ligand for the tumor tissue targeting of TNPs [85,86]. A tumor-homing internalizing RGD (iRGD; CRGDK/RGPD/EC) on TNPs binds to tumor vessels and spreads into the extravascular tumor parenchyma, whereas the conventional RGD ligand only delivered nanoparticles to the blood vessels [87].

uPA is a serine protease that regulates multiple pathways involved in matrix degradation, cell motility, metastasis and angiogenesis. uPA receptor (uPAR) complexes control the motility of both tumor and endothelial cells [88]. By contrast, the majority of normal tissues or organs have very low or undetectable levels of uPAR. Therefore, uPA might serve as an ideal TNP ligand for simultaneously targeting the tumor vasculature and stromal and tumor cells [89].

Targeting metastatic cancers

Cancer metastasis is a major prognostic factor. The survival of cancer patients whose cancer has metastasized is significantly shorter than those whose cancers have not. Based on the “seed and soil” theory, there are common metastatic sites for certain types of cancers [90,91]. For example, breast cancer frequently metastasizes to lung and bone and lung cancers usually spread to the brain. The enhanced understanding of the molecular mechanisms behind this theory has provided a solid basis for targeting metastatic cancer using TNPs, which is a new emphasis for research in the field (Figure 2). Targeting the microenvironment, such as the tumor vasculature, to inhibit the colonization of metastatic cancer cells in a new organ is one the applications of TNPs in the treatment of metastatic disease. Targeting the extracellular signature of metastatic cancer cells is another goal. Garg and colleagues developed PEGylated liposomes modified with a fibronectin–mimetic peptide [92] to target metastatic colon cancer cells, which overexpress integrins $\alpha 5 \beta 1$; fibronectin binds to this integrin pair [93].

Osteopontin, one of the factors contributing to the bone metastasis of breast cancer, is overexpressed in both osteoclasts and breast cancer cells and might be responsible for the

interaction between the bone and cancer cells for osteolysis. This protein serves as a target to prevent bone metastasis [94]. The sustained delivery of polymeric nanoparticles carrying antisense DNA against osteopontin and bone sialoprotein in rats with breast cancer bone metastasis showed a significant reduction of bone metastasis, indicating that this nanoparticle could be a promising therapeutic agent [95]. Currently, the development of TNPs for the treatment of metastatic cancer specifically is limited by organ-specific orthotopic animal models, which are essential for these evaluations. Furthermore, catching and killing circulating metastatic cells or cancer stem cells that metastasize with targeted TNPs is another strategy to prevent metastasis [96]. The validation of TNPs for targeting circulating cells as a strategy to reduce metastasis also requires appropriate animal models. Advances in this area are expected in the near future.

The reduction of nonspecific organ distribution and toxicity by TNPs

The selective accumulation of TNPs in tumor tissues should reduce nonspecific organ distribution and toxicity, and the biodistribution of TNPs has been studied in animal models. Bae and colleagues systematically examined the biodistribution of a PM-based TNP carrying ADR [PEG-p(Asp-Hyd-ADR)] at several time points in experimental mice [64]. The concentration of micelles in circulation, as measured by the area under the curve (AUC), was 15-fold greater than that of free ADR. There was also a greater concentration of micelles than of free ADR in the tumor and a lower concentration in the heart and kidney, explaining the enhanced efficacy of the micelle-delivered ADR and the reduction in side effects, such as cardiotoxicity and nephrotoxicity. Tumor-specific accumulation lasted for up to 50 hours without significant decline. At the same time, a constant level of micelle accumulation in the liver and spleen was also observed. Results from a recent study of the heparin-folic acid-paclitaxel TNP are consistent with these observations and further illustrate the differences between targeted and nontargeted TNPs in their tissue distribution [75]. The authors found that 48 hours after drug injection, both the targeted and nontargeted TNPs mainly accumulated in the tumor tissue, but the targeted TNPs showed greater intracellular localization than the nontargeted TNPs. There was detectable liver and kidney accumulation of both TNPs at a level 2–4 times lower than those in the tumor tissue. In most relevant studies, the accumulation of TNPs in the liver, spleen or kidney is commonly observed depending on the size and surface characteristics of each individual TNP, and this accumulation constitutes the major concern regarding the toxicity of TNPs. No tissue damage was observed in the heparin-folic acid-paclitaxel TNP study [75]. However, the quantification and systematic evaluation of TNP tissue distribution and tissue damage have not been reported. Long-term observations are still needed to estimate any potential harmful effects of TNPs on major organ tissues.

Conclusions and future prospects

Nanoparticles have many advantages as tools for the delivery of small-molecule anticancer agents such as TNPs. Owing to their flexible structures TNPs have tunable sizes and surface characteristics and can be conjugated to different tumor-specific ligands. Combined with the accumulating knowledge of cancer progression at the molecular level, TNPs should play an increasing role in personalized cancer medicine in the future. The current challenges for the development of TNPs include (i) a limited drug-loading capacity; (ii) uncontrolled drug release and cellular/tissue distribution; and (iii) the inability to simultaneously target both tumor cells and the tumor microenvironment (Box 1). To overcome these challenges, precise structural improvements of TNPs, multiple ligand design for targeted drug delivery, pharmacokinetic and pharmacodynamic analysis and quantified tissue distribution should be the current and future focus in the development of TNPs.

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Box 1. Outstanding questions

1. How can we enhance drug loading capacity while retaining appropriate particle sizes?
2. How can drug release at both cellular and tissue levels be quantified *in vitro* and *in vivo*?
3. How can the tumor tissue accumulation of TNPs be enhanced *in vivo*?
4. How are TNPs eliminated from animal and human bodies?
5. How can image-guided treatment using TNPs be optimized?

TRENDS in Molecular Medicine

Figure 1. The advantages of using nanoparticles for delivering small-molecule anticancer agents (a) TNPs improve the solubility of anticancer agents; (b) TNPs enhance the circulation time of anticancer agents in the blood vessels; (c) TNPs facilitate the accumulation of anticancer agents in targeted tumor tissues; (d) the targeting features of TNPs allow drug uptake by tumor cells through endocytosis, resulting in increased intracellular drug concentrations; (e) TNPs achieve controlled and stable drug release; and (f) TNPs are not substrates for ATP-binding cassette proteins, thereby minimizing efflux pump-mediated drug-resistance.

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Figure 2. Targeting metastatic cancer by TNPs

(a) TNPs could specifically block the tumor vasculature in both primary and metastatic sites by targeting tumor-associated endothelial cells; (b) TNPs could recognize cancer cells with metastatic signatures; (c) TNPs could catch and kill metastatic cancer cells in circulation; and (d) TNPs could inhibit metastatic cells by blocking the interaction between cancer cells and new microenvironments.

Table 1

Nanocarriers for delivery of small-molecule anticancer agents

System	Characteristics	Name of TNPs	Status	Ref.
Liposomal Carrier	1. Amphiphilic, biocompatible 2. Ease of modification 3. Targeting potential	Pegylated liposomal DOX (Doxil)	Market	[25]
		NonPEGylated liposomal DOX (Myocet)	Market	[26]
		Liposomal Daunorubicin (DaunoXome)	Market	[23]
Polymeric Carrier	1. Water soluble, nontoxic, biodegradable 2. Surface modification (PEGylation) 3. Specific targeting of cancer cells	Albumin-Taxol	Market	[28]
		(Abraxane)		[29]
		PGA-Taxol (Xyotax)	Clinical trial	[31]
		PGA-Camptothecin (CT-2106)	Clinical trial	[32]
		HPMA-DOX (PK1)	Clinical trial	[35]
		HPMA-DOX-galactosamine (PK2)	Clinical trial	[77]
Micelle Carrier	1. Suitable carrier for water-insoluble drug 2. Biocompatible, self-assembling, biodegradable 3. Ease of functional modification 4. Targeting potential	IT-101	Clinical trial	[36]
		PEG-PAA-DOX (NK911)	Clinical trial	[37]
		PEG-PLA-Taxol (Genexol-PM)	Clinical trial	[38]
Dendrimeric Carrier	1. Biodistribution, PK can be tuned 2. High structural and chemical homogeneity 3. Ease of functionalization, high ligand density 4. Multifunctionality	PAMAM-MTX	Preclinical	[41]
		PAMAM-platinite	Preclinical	[42]
Viral-like Carrier	1. Water soluble, biocompatible 2. Multifunctionality	HSP-DOX	Preclinical	[45]
		CPMV-DOX	Preclinical	[43]

PGA: poly-(L-glutamate); HPMA: N-(2-hydroxypropyl)-methacrylamide copolymer; PEG: polyethylene glycol; PAA: poly-(L-aspartate); PLA: poly-(L-lactide); PAMAM: poly(amidoamine); HSP: heat shock protein; CPMV: cowpea mosaic virus; DOX: doxorubicin; MTX: methotrexate.

Table 2

Pharmacokinetic information for TNPs in humans

Name	Carrier	Drug	Circulation time($t_{1/2}$, h)	Clearance (mL/min·kg)	Fold change compared to free drug (Circulation; Clearance)	Ref.
SP1049C	Pluronic micelle	Doxorubicin	2.4	12.6	3.1; 0.88	[51]
NK911	PEG-Asp micelle	Doxorubicin	2.8	6.7	3.5; 0.47	[51]
Doxil	PEG-liposome	Doxorubicin	84	0.02	105; 0.001	[51]
Genexol-PM	PEG-PLA micelle	Taxol	11	4.8	0.50; 1.3	[51]
Abraxane	Albumin	Taxol	21.6	6.5	0.99; 1.7	[28] [29]
XYOTAX	PG	Taxol	70–120	0.07–0.12	3.2–5.5; 0.18–0.03	[56]
CT-2106	PG	Camptothecin	65–99	0.44	5.6–8.5; 0.076	[32]
IT-101	Cyclodextrin-containing polymer	Camptothecin	38	0.03	3.3; 0.52	[12]

Biodistribution of TNPs in mice

Table 3

Name	mAb2C5-Doxil	CTS/PEG-glycyrrhetic (GA)-DOX	Transferrin-nanoparticle-siRNA	IT-101	Apt-PLGA-PEG-Doc	PG-TXL
Carrier	PEG-liposome	CTS/PEG-GA	Cyclodextrin-containing polycations	Cyclodextrin-containing polymer	PLGA-b-PEG	Poly(L-glutamic acid
Drug	Doxorubicin	Doxorubicin	DOTA-siRNA	Camptothecin	Docetaxel	Paclitaxel
Tumor Distribution	14:1 (tumor:muscle) 48 h	N/A	Near 0% injection dose (ID)/cm ³ 1 hr	11% ID/cm ³ 24 h	1% ID/gm tissue	66 000 digital light units(DLU)/ mm ² 24 hrs
Liver	23–30% dose/gm tissue 25 h	50% activity 3 hrs	20% ID/cm ³ 1 hr	8% ID/cm ³ 24 hrs	5% ID/gm tissue 24 h	136 000 DLU/mm ² 24 h
Spleen	32–40% dose/gm tissue 24 h	4% activity 3 hrs	N/A	N/A	25% ID/gm tissue 24 h	N/A
Lung	3% dose/gm tissue 25 h	6% activity 3 h	Near 0% ID/cm ³ 1 h	N/A	1% ID/gm tissue 24 h	64 000 DLU/mm ² 24 h
Heart	N/A	1% activity 3 h	N/A	N/A	1% ID/gm tissue	N/A
Kidney Distribution	3.5–4.5% dose/gm tissue 25 h	10% activity 3 h	10% ID/cm ³ 1 h	4% ID/cm ³ 24 h	1% ID/gm tissue 24 h	135 000 DLU/mm ² 24 h
References	[97]	[98]	[99]	[100, 101]	[102]	[103]

Abbreviations: siRNA, small interfering RNA