

## Review Article

# Targeted Delivery System of Nanobiomaterials in Anticancer Therapy: From Cells to Clinics

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Targeted delivery systems of nanobiomaterials are necessary to be developed for the diagnosis and treatment of cancer. Nanobiomaterials can be engineered to recognize cancer-specific receptors at the cellular levels and to deliver anticancer drugs into the diseased sites. In particular, nanobiomaterial-based nanocarriers, so-called nanoplatforms, are the design of the targeted delivery systems such as liposomes, polymeric nanoparticles/micelles, nanoconjugates, norganic materials, carbon-based nanobiomaterials, and bioinspired phage system, which are based on the nanosize of 1–100 nm in diameter. In this review, the design and the application of these nanoplatforms are discussed at the cellular levels as well as in the clinics. We believe that this review can offer recent advances in the targeted delivery systems of nanobiomaterials regarding *in vitro* and *in vivo* applications and the translation of nanobiomaterials to nanomedicine in anticancer therapy.

## 1. Introduction

Cancer is a worldwide disease with a leading cause of mortality, accounting for about 580,350 deaths, almost 1,600 people per day in 2013 from the statistical analysis of American Cancer Society in National Cancer Institute of the US [1]. About 1,660,290 of new cancer cases are also expected to be diagnosed in 2013. The 5-year relative survival rate is still somewhat low, at 68% for all cancers diagnosed between 2002 and 2008, although it has been up from 49% in the period from 1975 to 1977. For this reason, it is essential for targeted therapy for cancer to reduce adverse reactions and mortality rate and to save costs in clinical practice. Recently, targeted anticancer therapeutics such as monoclonal antibodies (mAbs) and tyrosine kinase inhibitors (TKIs) have been approved by the Food and Drug Administration (FDA) for the treatment of cancer [2]. The targeted therapy becomes an important element for the treatment of cancer as it helps to develop the anticancer therapeutics based on imaging and therapy (reducing the tumor size).

In this concept of targeted anticancer therapy, nanoplatforms are introduced with nanobiomaterial-based formulations or conjugation techniques in nanotechnology [3, 4]. Nanotechnology is a nanoscale-based technique in the fields of biomedical applications of pharmacology, bioengineering, biology, and medicine [5]. It currently relies on definitions provided by the National Nanotechnology Initiative (NNI) as follows [6]: (1) development of research and technology at the atomic, molecular, or macromolecular levels, within the scale of nanosize of approximately 1 to 100 nanometer in range, (2) devices and systems that have novel properties and functions based on the nanobiomaterials, because of their small and/or intermediate size, and (3) ability to control or manipulate at the atomic level. A variety of nanoparticulate systems span the range from a few nanometers to hundreds of nanometers. When such nanoparticle-based systems are usually applied in solving the clinical problems, we often use the term “nanoplatforms” [7].

Nanoplatforms have been developed to manufacture nanomedicines in preclinical and clinical studies for the

administration of small molecules, genes, and peptides with improvement of given *in vivo* behavior [8–10]. Figure 1 shows the schematic diagrams of targeted delivery systems with nanoplateforms, such as liposome, polymeric micelle, nanoconjugate, gold nanoparticle, carbon nanotube, dendrimer, and phage-based nanoplateform. Several characteristics of an ideal tumor-targeted nanomedicine with nanoplateforms are presented for translational research of ideal anticancer therapeutics as follows: (1) increase of drug localization into the tumor by passive targeting or active targeting, (2) decrease of drug localization in sensitive, nontargeted, and normal tissues, (3) minimal drug leakage during transit to the target, (4) prevention of degradation and premature clearance of the drug, (5) retention of the drug at the target site during the desired period, (6) facilitation of cellular uptake and intracellular trafficking, and (7) biocompatibility and biodegradability of nanoplateforms [10]. Table 1 illustrates the recently developed nanoplateforms for cancer targeting in preclinical studies. We introduce recent studies of targeted anticancer system in the part of “recently developed nanoplateforms for cancer targeting in preclinical studies.”

For successful translational research of nanoplateforms in anticancer therapy, Doxil is an FDA approved drug for the treatment of ovarian cancer, which is a long-acting pegylated liposomal formulation of doxorubicin [11, 12]. This product is based on a study of liposomal drug delivery systems for over four decades overcoming the limitations of anticancer drug and liposomes such as poor stability and reproducibility [13, 14]. It is one of the successful cases for the development of nanomedicines offering significant improvements over doxorubicin alone in clinical use. We deal with the translational research of nanomedicines in Table 2 and introduce the anticancer drugs approved by FDA in Table 3. Based on the ideal characteristics of nanoplateforms, they can be designed for the following: (1) sustained release of the drug, (2) passive accumulation of the tumor tissue, (3) ligand-based targeting of cell surface antigens or receptors with the modulation of endosomal uptake and membrane disruption, (4) drug release into the cytoplasm, and (5) protection from enzymatic degradation [15, 16]. Additionally, in this review, we demonstrate the applications of targeted delivery systems from the cells to the clinics for anticancer therapy, diagnostics, nanoimaging, bimodal imaging, and real-time intraoperative imaging.

## 2. Mechanism of Cancer Targeting by Nanoplateforms

Many nanobiomaterial-based platforms have been designed and evaluated for drug targeting to cancers as shown in Figure 2. Most of these platforms are “passive targeting” concepts to improve the circulation time of the conjugated or encapsulated therapeutic drug such as liposomes, polymers, micelles, and nanoparticles. Solid tumors have blood vessels with enhanced vascular permeability and a lack of functional lymphatics, which allow extravasation of carrier materials with sizes of up to several hundreds of nanometers and

are unable to eliminate extravasated nanomaterials. From the several reports, this EPR effect was shown even for the particles size of 1-2  $\mu\text{m}$  (e.g., *Lactobacillus* sp., *Salmonella* sp., etc.), which could make the particles accumulated in tumor tissues [17, 18]. Therefore, long-circulating nanomedicines are able to be accumulated in tumors over time based on a mechanism known as the enhanced permeability and retention (EPR) effect [19, 20]. The EPR effect is a unique phenomenon of solid tumors related to their anatomical and pathophysiological differences from normal tissues and is the most important strategy to improve the delivery of therapeutic agents to tumors for anticancer drug development. Examples of passively targeted nanoplateforms approved for clinical use are Doxil (Caelyx in Europe; pegylated liposomal doxorubicin), DaunoXome (nonpegylated liposomal daunorubicin), DepoCyt (nonpegylated liposomal cytarabine), Myocet (nonpegylated liposomal doxorubicin), Oncaspar (pegylated L-asparaginase), Abraxane (albumin-based paclitaxel), and Genexol-PM (paclitaxel-containing polymeric micelles, approved in Korea). In particular Doxil is a pegylated liposome-based, doxorubicin-loaded anticancer drug, which is FDA approved for the treatment of ovarian cancer as mentioned above. This drug has a severe cardiotoxicity although it overcomes poor stability and reproducibility of liposomes and improves a biodistribution of doxorubicin in tumor tissues by EPR effect. In addition, Abraxane is a Cremophor EL-free albumin-bound paclitaxel. It reduced Cremophor EL-associated side effects of Taxol such as severe anaphylactoid hypersensitivity reactions, hyperlipidaemia, abnormal lipoprotein patterns, aggregation of erythrocytes, and peripheral neuropathy [21]. Next-generation nanomedicines for anticancer therapy are developing alternative approaches with recently developed nanoplateforms minimizing side effects of surfactants in formulations and targeting tumor tissues. Several additional passively tumor-targeted nanomedicines are currently in clinical trials (Table 2), and many other ones are in early and late-stage preclinical development [9, 22–25].

On the other hand, “active targeting” strategy indicates the use of targeting ligands like antibodies and peptides which are attached to drugs and drug delivery nanoplateforms for binding to receptor expressed at the target site. In this strategy, active targeting systems with ligands and antibodies need to be accumulated first in tumor tissues by EPR effect, and then active targeting could be achieved. Targeting ligands for actively targeting nanomedicines are improving cellular internalization via endocytosis-prone surface receptors, such as folate [26], galactosamine [27], EGF [28], and transferrin [29]. To date, targeting techniques for active targeting are advanced at the preclinical level, however, only antibody-based nanomedicines have been approved for clinical use (Tables 2 and 3). Zevalin (CD20-targeted  $^{90}\text{Y}$ trium-ibritumomab tiuxetan), Bexxar (CD20-targeted iodine-131 tositumomab), Ontak (CD25-targeted diphtheria toxin-IL-2 fusion protein), and Mylotarg (CD33-targeted gemtuzumab oxogamicin) have been successfully used for non-Hodgkin's lymphoma, T-cell lymphoma, and acute myeloid leukemia. In addition, it has necessitated the use of peptides to enable the

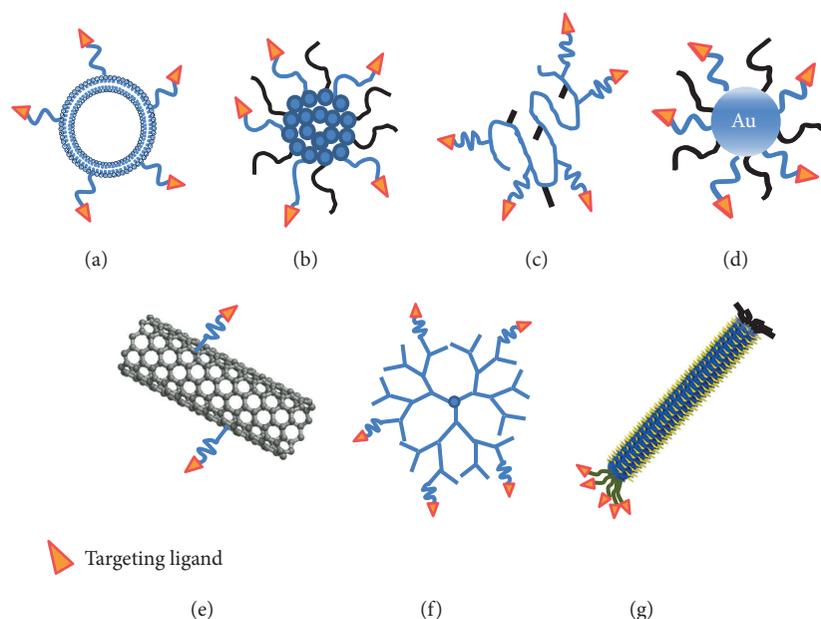


FIGURE 1: Schematic diagrams of the targeted delivery systems: (a) liposome, (b) polymeric micelle, (c) nanoconjugate, (d) gold nanoparticle, (e) carbon nanotube, (f) dendrimer, and (g) filamentous phage (M13, Fd).

cell internalization of cancer drugs such as cell-penetrating peptides, protein-transduction domains, oligoarginine, and TAT [30].

Active targeting to receptors, which are overexpressed by angiogenic endothelial cells, can reduce blood supply to tumors that deprive the tumor cells from oxygen and nutrients in solid tumors. Ligands used for drugs and drug delivery platforms to tumor vasculature include antibody fragment L19 [31], as well as several cyclic and linear derivatives of the oligopeptide RGD and NGR, which bind to angiogenic endothelium through the integrins ( $\alpha_{2b}\beta_3$ ,  $\alpha_v\beta_3$ , and  $\alpha_5\beta_1$ ) and aminopeptidase-N (CD13), respectively [32, 33].

Although active targeting systems are extensively studied to develop anticancer therapeutics, there has been a less example of clinical use compared to passive targeting systems. Discussing these problems to overcome, active targeted nanoplatfoms are physicochemically unstable for blood circulation in the body and hard to be accumulated in tumor tissues due to their size of conjugated targeting ligands of formulations (e.g., monoclonal antibodies) [34]. In addition, active targeting systems can be eliminated by nanoparticulate surface opsonization (nonspecific protein adsorption) and nanoparticulate uptake and retention to reticuloendothelial systems resulting in poor efficiency of active targeting system *in vivo* [35]. Based on these fundamental problems and technical barriers, multifunctionality, targetability, and stability are necessary to overcome the low efficiency of active targeting nanoplatfoms.

### 3. Nanoplatfoms of Anticancer Therapeutics and Application in Clinical Trials

Targeted delivery systems of nanobiomaterials are currently in the process of developing nanoscale-sized platforms or

surface modification of nanoplatfoms with active targeting ligands that support multifunctionality due to poor solubility of anticancer drugs or toxic effect of drugs on noncancerous cells and tissues [36, 37]. Most of the anticancer drugs are poorly soluble or insoluble in water. Thus, organic solvents or toxic surfactants are usually applied for the formulation of anticancer therapeutics even used in clinics. In addition, anticancer drug alone has a toxic effect on normal cells and tissues without target specificity [38, 39]. Therefore, several nanoplatfoms in 100 nm diameter based on nanobiomaterials have been used to administer the anticancer drugs to minimize the adverse toxicity and to maximize the drug effect within the therapeutic index [40].

Nanoplatfoms offer solubility of poorly soluble anticancer drugs in water preparing soluble suspensions with the minimum need for organic solvents and surfactants which cause toxicity [40, 41]. These platforms are accumulated in the tumor tissues by the EPR effect, as mentioned above. The nanoplatfoms are also used in the targeted delivery systems of active targeting using the decoration with receptor-targeted ligands or tumor antigen sensitive antibodies together with anticancer drugs [22, 37, 42–44]. The anticancer drugs encapsulated into the nanoplatfoms, specifically liposomal nanoplatfoms and polymer-based nanoplatfoms, are undergoing clinical trials [43, 45, 46]. Table 2 shows the nanomedicines of anticancer drugs in clinical trials.

**3.1. Doxorubicin.** Doxorubicin, a very effective anticancer drug, is widely used in the treatment of breast, ovarian, bladder, and lung cancers [47]. Mechanism of action of doxorubicin is the blocker of topoisomerase II, which is an important enzyme in the DNA replication process that unwinds the DNA helix. The mechanisms of doxorubicin

TABLE 1: Recently developed nanoplatforms for cancer targeting in preclinical studies.

Nanoplatforms	Drug	Average size (nm)	Ligand/target	Descriptions	Possible applications	References
Liposomes	Doxorubicin	108	Cyclic Asn-Gly-Arg (cNGR) peptides/CD13 and aminopeptidase N	cNGR decorated, lysolipid-containing temperature sensitive liposomes	Human fibrosarcoma (HT-1080), <i>in vitro</i> binding study	[95]
Liposomes inorganic nanoparticles (gold nanorods, ironoxide nanoworms)	Doxorubicin	55	A truncated, tumor-targeted human protein tissue factor (tTF RGD) to induce coagulation on binding to angiogenic $\alpha_v\beta_3$ receptors to heat specifically directed coagulation-cascade activation in tumours	“Signalling” modules (PEG-decorated gold nanorods, tumor-targeted truncated tissue factor proteins) that target tumors and then locally activate the coagulation cascade to broadcast tumor location to clot-targeted “receiving” nanoparticles in circulation that carry a diagnostic or therapeutic cargo (ironoxide nanoworms, doxorubicin-loaded liposomes)	<i>In vivo</i> MDA-MB-435 xenograft tumors, i.v. injection	[97]
Liposomes carbon nanotubes	Paclitaxel	164	anti-ErbB2 (Her2) mAb	Each nanohorn encapsulated within one immunoliposome formulated with PEG and thermally stable and pH sensitive phospholipids for pH sensitive and prolonged release of paclitaxel	SK-BR-3 and BT-20 breast cancer cells, <i>in vitro</i> cytotoxicity	[98]
Polymeric nanoparticles	siRNA	80 × 320	—	Cationic lipid-coated PLGA nanoparticles, a unique soft lithography particle molding process (particle replication in nonwetting templates, PRINT)	<i>In vitro</i> prostate cancer cell lines	[108]
Polymeric micelles	1,2-Diaminocyclohexane-platinum(II) (DACHPt) (the parent complex of oxaliplatin)	30	—	Long-circulating, drug-loaded polymeric micelles enhancing tumour permeability with a TGF $\beta$ inhibitor	Poorly permeable pancreatic tumors in the mice model (C26 or BxPC3 tumors), i.v. injection	[209]
Nanoconjugates	Splice-switching oligonucleotides (SSOs) (phosphorodiamidate morpholino oligomer (PMO))	13	RGD/integrin $\alpha_v\beta_3$ , a cell surface glycoprotein that is preferentially expressed in angiogenic endothelia	Albumin-based nanoconjugates with fluorescence labeling which are small, highly specific, and nontoxic	Tumor spheroids of A375/GFP cell, tumor spheroid study using A375/GFP cells to confirm the uptake and penetration of nanoconjugates in three-dimensional (3D) culture	[128]

TABLE 1: Continued.

Nanoplatfoms	Drug	Average size (nm)	Ligand/target	Descriptions	Possible applications	References
	Paclitaxel	2-3	ultrasmall hyaluronic acid (HA)/CD44	Paclitaxel-ultrasmall HA (3–5 kDa) nanoconjugates internalized via CD44 receptor-mediated endocytosis, which allowed paclitaxel to bypass the P-glycoprotein-mediated efflux on the surface of cancer cells	Brain metastasis of breast cancer using MDA-MB-231Br breast cancer cells, i.v. injection	[129]
Gold nanoparticles	Chemiresistors based on functionalized gold nanoparticles in combination with pattern recognition methods	5	—	A sensor array for breath testing of exhaled breath in lung cancer patients	A noninvasive diagnostic tool for lung cancer, <i>in vitro</i> array	[137]
Gold nanoparticles magnetic microparticles	An assay for PSA detection with gold nanoparticles based on the PSA-specific Abs and short DNA sequences (barcodes)	30	Prostate-specific antigen (PSA)	Magnetic microparticles conjugated with PSA-specific antibodies to extract trace amounts of the target analyte (PSA) in serum samples from patients and gold nanoparticles with PSA-specific antibodies and short DNA sequences (the barcodes) attached to detect this analyte	An ultrasensitive assay for prostate cancer, <i>in vitro</i> barcode array	[138]
Carbon nanotube	Single-walled carbon nanotube (SWCNT) with fluorescence labelling	200–300	—	Biodistribution and examination of glomerular filtration in kidney	NIR fluorescence imaging, dynamic PET imaging, <i>in vitro</i> (HK-2 cells at the transwell), <i>in vivo</i> (mice, NCr/nu/nu), i.v. injection U87MG human glioblastoma and HT-29 human colorectal cancer cell lines, U87MG and HT-29 tumour xenograft models for biodistribution (PET), i.v. injection 4T1 bearing Balb/c mice, KB and U87MG xenograft models, PTT, i.v. injection	[147]
	Water soluble carbon nanotubes functionalized with PEG, radio labels, and RGD peptide	1–5 (diameter), 100–300 (length)	RGD/integrins $\alpha_v\beta_3$	RGD-pegylated SWCNTs, radio-labelled SWCNTs		[148]
Graphene	Nanographene sheet (NGS) for photothermal therapy (PTT)	10–50	—	Six-armed PEG-NGS with fluorescent labeling		[155]

TABLE 1: Continued.

Nanoplatforms	Drug	Average size (nm)	Ligand/target	Descriptions	Possible applications	References
	Reduced graphene oxide (RGO) for PTT	20–80	Human/murine chimeric IgG1 mAb (TRC105)/both human and murine CD105	RGO conjugated to the anti-CD105 antibody TRC105	Tumor vasculature targeting and imaging in living mice as a theranostic agent, <i>in vitro</i> (4T1 murine breast cancer, MCF-7 human breast cancer, and human umbilical vein endothelial cells (HUVECs)), <i>in vivo</i> (4T1 breast cancer model), i.v. injection	[156]
	Imaging and therapy HSVtk + ganciclovir + [ <sup>18</sup> F]FDG and [ <sup>18</sup> F]FEAU	7 × 1,000	RGD4C/integrins	Hybrid vector with adeno-associated virus (AAV) and fd-tet derived bacteriophage [AAV/phage (AAVP)] RGD-4C AAVP-HSVtk (herpes simplex virus thymidine kinase)	KSI767 cells RGD-4C AAVP-HSVtk PET images with [ <sup>18</sup> F]FDG and [ <sup>18</sup> F]FEAU obtained before and after ganciclovir treatment	[194]
Phage	Magnetic iron oxide [(maghemite (γ-Fe <sub>2</sub> O <sub>3</sub> ) or magnetite (Fe <sub>3</sub> O <sub>4</sub> )] for MRI	6.6 × 880	Acidic and rich in cysteine (SPARC)	SPARC-binding peptide (SPTGIN) and triglutamate displayed on p3 and p8 coat proteins of M13 phage, respectively	Tumor targeting against prostate cancer	[202]

mAb: monoclonal antibody; PEG: polyethylene glycol; PLGA: poly(lactic-co-glycolic) acid; RGD, arginine, glycine, and aspartic acid (Arg-Gly-Asp).

TABLE 2: Nanomedicines in clinical trials.

Nanoplatforms	Drug	Current status	Mode of delivery*	Ligand/target	Average size (nm)	Descriptions	Types of cancer
	Doxorubicin (Myocet)	Phase III	NT	—	100–230	No IRRs, high response, and reduced cardiotoxicity	Kaposi's sarcoma and metastatic breast cancer (phase I/II)
	Vincristine sulfate (Marqibo)	FDA approved (Ph-adult ALL), Phase II (NHL), Phase I (pediatric ALL)	NT	—	115	Extended PK	Acute lymphocytic leukemia (ALL) and non-Hodgkin's lymphoma (NHL)
	Cytarabine	Phase III	NT	—	100	Extended PK, high response	Acute myeloid leukemia (AML)
	Daunorubicin (CPX-351)	Phase III	NT	—	160–180	Cationic liposomal formulation	Various solid tumors
	Paclitaxel (Endo TAG-1)	Phase II completed	NT	—	150	Reduced myelosuppression and high response	Ovarian cancer
	Lurtotecan (OSI-211/NX211)	Phase II completed	NT	—	150	No IRRs and high response	Metastatic breast cancer
	Paclitaxel (LEP-ETU)	Phase I/II	NT	—	100	Pegylated liposomal camptothecin and extended PK	Advanced solid tumors
	Oxaliplatin (MBP-426)	Phase I/II	T	transferrin/transferrin receptor	180	Extended PK	Advanced/metastatic solid tumors
	Doxorubicin (MCC-465)	Phase I (discontinued)	T	F(ab') <sub>2</sub> fragment of human mAb GAH or tumor-specific antigen	140	No hand-foot syndrome or cardiotoxicity	Metastatic stomach cancer
	p53 gene (SGT53-01)	Phase Ib	T	scFv/transferrin receptor	90	Improved response	Solid tumors
	RB94 plasmid DNA (SGT-94)	Phase I	T	scFv/transferrin receptor	108	Improved response	Solid tumors
	Doxorubicin (MM-302)	Phase I	T	scFv/Erbb2 (HER2)	75–110	Stable and safe	Advanced breast cancer
	Melanoma antigens and IFN $\gamma$ (Lipovaxin-MM)	Phase I	T	Single domain antibody (dAb) fragment (VH)/DC-SIGN			Melanoma vaccine
	Paclitaxel (Genexol-PM)	Approved (Korea); phase II/III (USA)	NT	—	<50	Polymic micelles, increased paclitaxel MTD, high response	Metastatic breast cancer and urothelial carcinoma
	Paclitaxel (NK105)	Phase III	NT	—	85	Core-shell-type polymeric micelles, extended PK, high response, and reduced hypersensitivity	Metastatic/recurrent breast cancer

TABLE 2: Continued.

Nanoplatfoms	Drug	Current status	Mode of delivery*	Ligand/target	Average size (nm)	Descriptions	Types of cancer
	Doxorubicin (SPI049C)	Phase I completed	NT	—	30	Polymeric micelles, high response, and no hand-foot syndrome	Advanced adenocarcinoma of esophagus and gastroesophageal system
	Doxorubicin (NK911)	Phase II (Asia)	NT	—	40	Polymeric micelles, extended PK	Metastatic/recurrent solid tumors
	Paclitaxel-poliglumex (Opaxio)	Phase III	NT	—	10–150	Polymeric micelles, extended PK	Ovarian cancer
	Camptothecin (CRLX101)	Phase Ib/IIa	NT	—	20–50	A pH-sensitive polymer nanocarrier releasing camptothecin in the acidic environment of cancer cells, extended PK, and high response	Advanced solid tumors
Polymers	Irinotecan (SN-38, NK012)	Phase I/II	NT	—	20	Polymeric micelle-based active metabolites of camptothecin derivative and extended PK	Solid tumors
	Cisplatin (NC-6004, Nanoplatin)	Phase I/II (Asia)	NT	—	30	Polymeric micelles and extended PK (with the aim of reducing kidney toxicity compared with cisplatin alone)	Advanced/metastatic pancreatic cancer (evaluating nanoplatin in combination with gemcitabine in patients with advanced or metastatic pancreatic cancer)
	Docetaxel (BIND-014)	Phase I completed	T	Peptide/PSMA (solid or metastatic prostate cancer cells by binding to prostate-specific membrane antigen)	100	Enhanced therapeutic efficacy and partial response	Solid tumors
	RRM2 siRNA (CALAA-01)	Phase I	T	Transferrin/transferrin receptor	70	Cyclodextrin-based nanoparticle containing anti-RRM2 siRNA and no DLTs	Solid tumors

PK: pharmacokinetics; DRR: drug release rate; IRs: infusion-related reactions; Ph-: Philadelphia Chromosome Negative; MTD: maximum tolerable dose; DLTs: dose-limiting toxicities; DC: dendritic cell.

\*Mode of delivery: NT: nontargeted (passive targeting), T: targeted (active targeting).

TABLE 3: FDA approved anticancer drugs.

Nanoplatfoms	Drug	Company	Properties	Indications	Routes of administration
	Abelcet	Enzon	Liposomal amphotericin B	Fungal infections	i.v.
	AmBisome	Gilead Sciences	Liposomal amphotericin B	Fungal and protozoal infections	i.v.
	Amphotec	Three Rivers Pharmaceuticals	Cholesteryl sulfate-based amphotericin B	Fungal infections	i.v.
	DepoCyt	SkyePharma	Liposomal cytarabine	Malignant lymphomatous meningitis	i.t.
	DaunoXome	Gilead Sciences	Liposomal daunorubicin	HIV-related Kaposi's sarcoma	i.v.
Liposomes	Doxil/Caelyx	Ortho Biotech, Schering-Plough	Liposome-PEG doxorubicin	HIV-related Kaposi's sarcoma, metastatic breast cancer, and metastatic ovarian cancer	i.m.
	Myocet	Zeneus	Liposomal doxorubicin	Combination therapy with cyclophosphamide in metastatic breast cancer	i.v.
	Visudyne	QLT, Novartis	Liposomal verteporfin	Photodynamic therapy (PDT) for age-related macular degeneration, pathologic myopia, and ocular histoplasmosis	i.v.
	Adagen	Enzon	PEG-adenosine deaminase	Severe combined immunodeficiency disease associated with ADA deficiency	i.m.
Polymers	Copaxone	TEVA Pharmaceuticals	L-Glutamic acid, L-alanine, L-lysine, and L-tyrosine copolymer	Multiple sclerosis	s.c.
	Genexol-PM	Samyang	Methoxy-PEG-poly(D, L-lactide) paclitaxel	Metastatic breast cancer	i.v.
	Macugen	OSI Pharmaceuticals	PEG-anti-VEGF aptamer	Age-related macular degeneration	i.r.

TABLE 3: Continued.

Nanoplatforms	Drug	Company	Properties	Indications	Routes of administration
	Neulasta	Amgen	PEG-GCSF	Neutropenia associated with cancer	s.c.
	Oncaspar	Enzon	Pegaspargase (PEG-L-asparaginase)	Chemotherapy Acute lymphoblastic leukemia	i.v., i.m.
	Renegel	Genzyme	Poly(allylamine hydrochloride)	End-stage renal disease	Oral
	Somavert	Nektar, Pfizer	PEG-HGF	Acromegaly	s.c.
	Abraxane	Abraxis BioScience, AstraZeneca	Albumin-bound paclitaxel	Metastatic breast cancer	i.v.
	Estrasorb	Novavax	Estradiol emulsion	Vasomotor symptoms associated with menopause	Topical and transdermal
	Emend	Elan, Merck Strativa	Nanocrystalline aprepitant	Antiemetic	Oral
Others	Megace ES	Pharmaceuticals, subsidiary of Par Pharmaceutical, Inc. Elan, Wyeth	Nanocrystalline megestrol acetate	Anorexia, cachexia, or an unexplained significant weight loss in AIDS patients	Oral
	Rapamune	Pharmaceuticals Elan, Abbott	Nanocrystalline sirolimus	Immunosuppressant	Oral
	TriCor	Pharmaceuticals Elan, Abbott	Nanocrystalline fenofibrate	Antihyperlipidemic	Oral
	Feridex	Bayer Healthcare Pharmaceuticals	Femmoxides solution (superparamagnetic iron oxide)	MRI contrast agent	i.v.

ADA: adenosine deaminase; GCSF: granulocyte colony-stimulating factor; HGF: hepatocyte growth factor; HIV: human immunodeficiency virus; i.m.: intramuscular; i.r.: intravitreal; i.t.: intrathecal; i.v.: intravenous; PEG: polyethyleneglycol; s.c.: subcutaneous; VEGF: vascular endothelial growth factor.

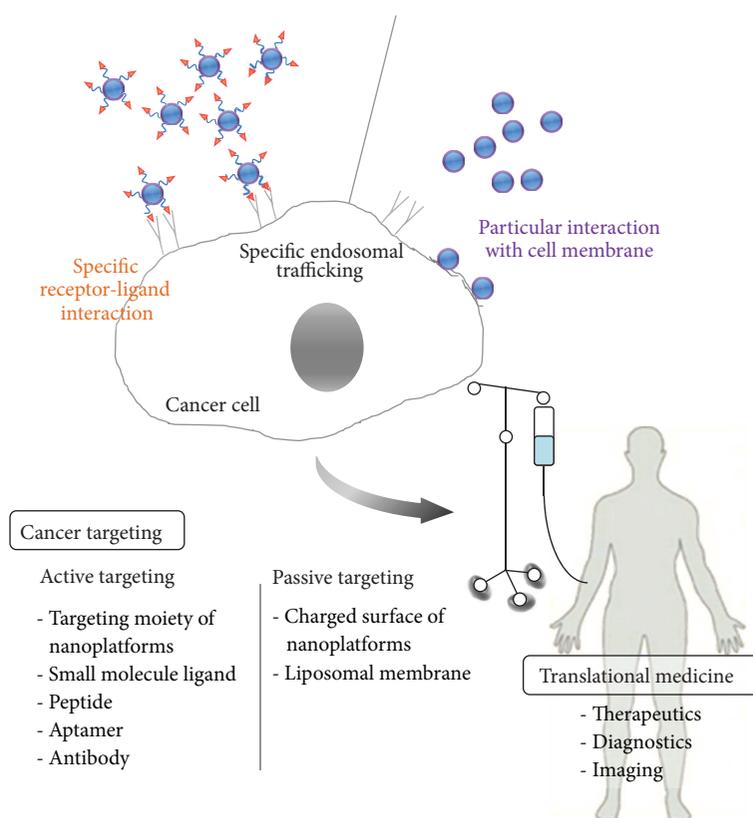


FIGURE 2: Overview of cancer targeting strategies from the cells to the clinics. This overview illustrates the most clinically relevant targeting strategies for anticancer therapy: passive targeting and active targeting. Passive targeting strategy is defined as the accumulation of nanoplatforms at the cancer cells by EPR effect, which uses nanoplatforms without targeting moieties. In this way, particular interaction will be proceeded to be internalized onto the cancer cells. On the other hand, active targeting strategy means the ligand-targeted or the receptor-mediated approach based on the cancer-specific targeting moieties of nanoplatforms, which interact with the specific receptor-ligand interaction on the cancer cells. Based on the cancer targeting strategies, translational medicine will be developed for the diagnostics, therapeutics, and imaging.

also include DNA cross-link and ROS generation besides inhibiting topoisomerase II. Based on these mechanisms of action, doxorubicin has a potent antitumor activity in tumor cells inducing cell death. However, doxorubicin is associated with the severe side effects on the heart including irreversible myocardiotoxicity and fatal congestive heart failure [48]. To decrease the toxicity of doxorubicin, nanoplatforms were introduced to enhance pharmacokinetic parameters with an accumulation of drugs in the tumor tissues, thereby minimizing the cardiotoxicity. Liposomes and polymeric nanoplatforms were studied and developed as nanomedicines via an intravenous route. Myocet, MCC-465, MM-302, SPI049C, and NK911 are the liposomal or polymeric nanoplatforms of doxorubicin in the clinical trials [49]. Myocet, MCC-465, and MM-302 are based on the liposomal nanoplatforms at the range of 100–140 nm in diameter [50]. In the cases of MCC-465 and MM-302, the target-specific ligands of F(ab')<sub>2</sub> fragment in human mAb GAH or tumor-specific antigen and scFv/ErbB2 (HER2) are incorporated into the liposomal nanoplatforms, respectively. In other words, SPI049C and NK911 are used in the polymeric micelles. SPI049C is a Pluronic-based micellar formulation of doxorubicin [51] and

NK911 is a core-shell-type polymeric micellar nanoplatform of doxorubicin which consists of a block copolymer of PEG (m.w., 5000) and poly(aspartic acid) (30 units) conjugated with doxorubicin [52]. Doxorubicin is entrapped into the highly hydrophobic inner core of the polymeric micellar nanoplatforms.

**3.2. Paclitaxel.** Paclitaxel is a chemotherapeutic agent for the ovarian, breast, and lung cancers as well as Kaposi's sarcoma [53]. It is a mitotic inhibitor with a stabilizing activity of the microtubule assembly interfering the normal breakdown of microtubules during cell division. Paclitaxel was originally extracted from the Pacific yew tree, *Taxus brevifolia*. Bristol-Myers Squibb commercially developed paclitaxel, a famous trademark, Taxol. However, paclitaxel itself has severe adverse responses such as peripheral sensory neuropathy [54, 55], anaphylaxis, and hypersensitivity reactions due to its solubilizing materials (Cremophor EL and ethanol) [55]. Therefore, the development of nanoplatforms is essential to overcome these problems of formulation for the improvement of pharmacokinetic parameters and the toxic adverse

reactions in the normal tissues [56]. EndoTAG-1 [57], LEP-ETU [58], Genexol-PM [59], NK105 [60], and Opaxio [61] are developed as paclitaxel-loaded nanoplatforms undergoing clinical trials. EndoTAG-1 and LEP-ETU are based on the liposomal nanoplatforms. In particular, EndoTAG-1 is based on the cationic liposomal formulation, which can interact with the newly developed and negatively charged endothelial cells in the disease states for the growth of tumor blood vessels targeting the blood supply to the tumor cells [57]. Polymeric nanoplatform-based paclitaxel formulations are also developed such as Genexol-PM, NK105, and Opaxio. Paclitaxel is conjugated to poly(L-glutamic acid) (PGA) in Opaxio [61], monomethoxy poly(ethylene glycol)-block-poly(D,L-lactide) (mPEG-PDLL) in Genexol-PM [59], and NK105 polymers of PEG as the hydrophilic segment and modified polyaspartate as the hydrophobic segment in NK105 [62], respectively.

**3.3. Platinum-Based Anticancer Drugs.** Cisplatin (cisplatinum or *cis*-diamminedichloroplatinum (II)) is also used in chemotherapy, which is a platinum-based anticancer drug for the treatment of various cancers including sarcomas, some carcinomas (e.g., small cell lung cancer and ovarian cancer), lymphomas, and germ cell tumors [63, 64]. Mechanism of action in platinum-based anticancer drug is DNA cross-linking to interfere with the cell division by mitosis triggering apoptosis or cell death. Oxaliplatin and carboplatin are also included in platinum-based anticancer therapeutics. In clinical trials, oxaliplatin (MBP-426) [65] and cisplatin (NC-6004, Nanoplatin) [66] are studied for their applicability to advanced/metastatic solid tumors. In particular, Nanoplatin in combination with gemcitabine is evaluated for the treatment of advanced/metastatic pancreatic cancers. MBP-426 is reported as an oxaliplatin-based liposomal nanoformulation with the surface modification of transferrin targeting transferrin receptors in disease states. In the case of polymeric nanoplatforms, Nanoplatin, a polymeric micelle-based cisplatin of 30 nm in diameter, is studied for its kidney toxicity reduction capabilities compared to cisplatin alone.

**3.4. Camptothecins.** Camptothecin and irinotecan, a water-soluble derivative of camptothecin, are cytotoxic alkaloids isolated from *Camptotheca acuminata* [67]. The target of these camptothecins and their derivatives is topoisomerase I to inhibit the replication in the cells. They bind to the topoisomerase I and DNA complex generating a stabilized ternary complex to prevent DNA religation and to cause DNA damage resulting in apoptosis. Camptothecin and its derivative are limitedly used due to lipophilicity and instability of the lactone ring structure by hydrolysis despite their superior anticancer activity [68]. Therefore, the nanoplatform-based camptothecin (S-CKD-602 [69] and CRLX101 [70]) and irinotecan (SN-38, NK012 [71]) are developed undergoing clinical trials. S-CKD-602 and CRLX101 are used in the nanoplatforms of a pegylated liposome and a polymeric micelle, respectively. In the case of irinotecan (SN-38, NK012), it is a polymeric micelle-based active metabolite of camptothecin to exploit the EPR effect in the diameter

size of 20 nm. This system is constructed in an amphiphilic block copolymer, PEG-PGlu (SN-38), by the self-assembly in the aqueous media. NK012 had an antitumor activity with tolerance that included partial responses and several occurrences of prolonged stable disease across a variety of advanced refractory cancers in the clinical studies.

**3.5. Gene Therapy.** Plasmid DNA and siRNA for cancer gene therapy are also used for the treatment of cancers in the clinical trials. The aim of gene therapy is to kill the cancer cells blocking the transduction of the tumor cells or inhibiting the disease-induced proteins without any damage to the normal cells, using cancer-specific genetic materials [72]. For the current clinical trials, p53 gene (SGT53-01) [73], RB94 plasmid DNA (SGT-94) [74], and RRM2 siRNA (CALAA-01) [75] are studied for the treatment of solid tumors. These materials are based on tumor-specific nanoplatforms, which are the liposomal (SGT53-01 and SGT-94) or cyclodextrin-based nanoparticulate (CALAA-01) systems decorated with a target ligand of transferrin receptors in the tumor cells. These nanoplatforms are necessary in delivering the genetic materials into the tumor cells due to the instability in the biological fluids (e.g., enzymatic digestion) and the hydrophilicity of genetic materials (e.g., poor uptake to cells).

## 4. Recently Developed Nanoplatforms for Cancer Targeting in Preclinical Studies

**4.1. Liposomes.** Liposomes have been developed as bioinspired nanoplatforms, which define the phospholipid bilayer showing the properties of the cell membrane [76, 77]. The liposomal nanoplatform can carry the hydrophilic drug at the aqueous core inside the bilayer and the hydrophobic drug at the lipid membrane. This nanoplatform has a lot of advantages for the delivery system with a great attention given their biocompatibility and targetability from the *in vitro* characterization to translational research [50, 78, 79]. For cancer targeting, liposomes are extensively used as passive targeting agents and ligand-mediated or stimuli-sensitive targeting agents (active targeting agents) [80]. Based on their biocompatibility, liposomes have been early developed as nanoplatforms to transfer small molecules in the tumor tissues [14]. Various anticancer drugs such as doxorubicin, doxorubicin derivatives, paclitaxel, and platinum-based anticancer drugs are usually loaded into the liposomal platforms (Table 1). These are 100–200 nm in average size, which makes liposomes take a trip into the tumor tissues.

Liposomes can also be used in the targeted delivery system with several modification of the liposomal surface design [81–84]. Cancer targeting systems are rapidly used in broad applications for the tumor-specific ligands [85, 86] or tumor-associated antigens [87] although liposomes are possible to be used in anticancer therapy as the delivery carriers for passive cancer targeting. The cancer-targeted therapy with targeting ligands includes leukocyte differentiation antigen (CD33) for acute myeloid leukemia [88], GD2 for neuroblastoma [89], and the folate receptor for wide human tumors [90, 91]. In addition, integrins [92], vascular endothelial growth

factor receptors (VEGFR) [93], and CD13/aminopeptidase N [94] are also used as the targeting ligands. Liposomes with cyclic Asn-Gly-Arg (cNGR) peptide targeted to CD13 were currently formulated with lysogenic lipids-loaded doxorubicin for the potential treatment of human fibrosarcoma [95]. These systems are not only ligand-targeted systems for cancer metastasis, but also the hyperthermia-targeted systems for tumor hyperthermia, which regulates the release of doxorubicin specifically in the hyperthermal tissues for cancer targeting.

Liposomes can also be used as one of the components in the nanohybrid systems [96]. A study by Von Maltzahn et al. reported a complexed nanohybrid system for the treatment of human breast cancer in the xenograft tumor model of MDA-MB-435 cells [97]. This system is the complex of “signaling modules” to activate and broadcast the tumor location and “receiving modules” to carry the nanopatform-based diagnostic agents and therapeutic drugs. They used the doxorubicin-loaded liposomes as therapeutic cargos with iron oxide nanoworms as the diagnostic agents in circulation. In addition, for the activation of doxorubicin-loaded liposomal cargos, PEG-decorated gold nanorods and tumor-targeted truncated tissue factor proteins (tTF-RGD) were previously introduced as the signaling modules to induce the heat specifically directed coagulation on binding to the angiogenic receptors in tumors before adding the doxorubicin-loaded liposomes. This system can be applied for the targeted theranostic agents to detect and treat the tumors together. Liposomes can also be used together with carbon nanotubes [98, 99]. Huang et al. reported carbon nanotubes encapsulated into the liposomes, which carried paclitaxel and anti-ErBb2 (Her2) mAb for this system SK-BR-3 and BT-20 breast cancer cells and checked the *in vitro* cytotoxicity [98]. This system can also be applied to theranostics for the potentiality of diagnostics and therapeutics.

**4.2. Polymeric Nanoparticles/Micelles.** Polymers are innovative nanobiomaterials to be engineered for the delivery system of drugs, genes, and peptides [41, 100]. Polymeric nanoparticles or micelles are easily prepared to be nanosized with various designs, which are relatively smaller in size compared to lipid-based formulations that generally range in size of 1–50 nm. Polymers can be used to carry multiple ligands for cancer targeting and imaging molecules for cancer diagnostics with a simple conjugation-based structural modification [101]. Among the polymers, PEG and poly(lactic-co-glycolic) acid (PLGA) are extensively used as biocompatible polymers for translational medicine [102, 103].

PLGA is one of the most widely used polymers due to its biocompatibility, which is degraded to the monomers of lactic acid and glycolic acid in the body [104]. PLGA was approved by US FDA and European Medicine Agency (EMA). PLGA-based nanoparticles are successfully applied for drug delivery of the biomedical approaches for the development of translational medicine [105]. For example, paclitaxel-encapsulated PLGA nanoparticles were formulated with a strong enhancement of the cytotoxic effect of paclitaxel on the tumor cells *in vitro* and *in vivo* compared to commercial formulation,

Taxol [106, 107]. Hasan et al. published the cationic lipid-coated PLGA nanoparticles with a unique soft lithography particle molding process, which was applied for the delivery of siRNA in the prostate cancer cells [108]. In this study, they coated the PLGA nanoparticles with cationic lipid for a successful internalization to the cells based on a charge-charge interaction of the cell membrane and nanoparticles because PLGA has a negative charge. Based on the addition of targeting ligands like cLABL (ICAM-1 targeting) [109], folate (folate receptor) [110, 111], prostate-specific receptor antigen (prostate-specific receptor targeting) [112, 113], RGD (integrins  $\alpha_v\beta_3$ ) [114, 115], and AS1411 (nucleolin targeting) [116, 117], PLGA nanoparticles have the potential to improve drug efficacy via target specificity of nanopatforms *in vitro* and *in vivo*.

Although these nanoparticles have an effective function in cancer therapy in preclinical trials, these nanoparticles can be removed in circulation based on the biological barrier and reticuloendothelial system (RES), which performs an opsonization to macrophages that are internalized by phagocytosis [118]. PEG is the most commonly used polymeric moiety for the surface modification of nanopatforms [119]. Nanoparticles can be usually decorated with targeting ligands conjugated with PEG. PEG originally has a function to make nanoparticles sterically stable for the prolonged circulation in the blood after administration. This method is called “pegylation” [120]. It demonstrates the hydrophilic moiety of PEG on the particular surface in the nanopatforms, which provides the steric hindrance of a particular system to be shielded against the RES system for a prolonged delivery of the drug. Aravind et al. studied the long-circulating, drug-loaded polymeric micelles enhancing tumor permeability with a TGF $\beta$  inhibitor in the poorly permeable pancreatic tumors in a murine model of the C26 or BxPC3 tumors [116]. They loaded 1,2-diaminocyclohexane-platinum(II)(DACHPt), which is the parent complex of oxaliplatin, in the polymeric micelles of PEG-b-poly(glutamic acid) (PEG-b-P(Glu)) copolymer and P(Glu) homopolymer. After the size-based screening of permeability into the tumors, 30 nm sized micelles had a relatively enhanced tumor permeability, when transforming growth factor  $\beta$  was administrated together with the micelles.

**4.3. Nanoconjugates.** Nanoconjugates have extensively been studied as the smart nanopatforms with active functional groups to prepare the covalent binding for the anticancer therapeutics [121]. Polymeric nanoconjugates are generally synthesized with a simple conjugation of the functional groups in the polymer such as –OH, –COOH, and –NH<sub>2</sub>. These steps are stepwise reactions, which need to avoid uncontrollable side chemical synthesis. Nanoconjugates include the nanopatforms of polymeric nanoparticles/micelles and other nanoparticles based on the characteristics of conjugation technique to prepare the nanoconjugate platforms using the functional groups of nanobiomaterials. Polymer-drug conjugates [122, 123] or mAb conjugates [42] were reported for targeted anticancer therapy. Xiong et al. introduced the cisplatin-based poly( $\gamma$ , l-glutamic acid)-citric acid-based nanoconjugates [123], and Segal

and Satchi-Fainaro illustrated the polymeric nanoconjugate-based therapeutics with favorable polymers such as N-(2-hydroxypropyl)methacrylamide (HPMA), polyglutamic acid (PGA), and  $\beta$ -poly(L-malic acid) (Polycefyn) [122]. In addition, Julien et al. showed mAb-targeted nanobiomaterials for anticancer therapy [42]. They described the mAb-drug conjugates with an introduction of mAb-based therapeutics such as CD20 (Rituxan for B-cell lymphoma), HER2 (Herceptin for breast cancer), VEGF (Avastin for colon, lung, breast, and renal cancer), and EGFR (Erbix for colon and lung cancer).

These platforms have more advantages than other nanopatforms, like micelles and liposomes, in the way that they are small in size and chemically stable in biological fluid. For this reason, these platforms are easily applied to the functionalization of multiple-target ligands or theranostic agents with polymers, peptides, proteins, or other nanoparticles. For example, folate is a widely used ligand for cancer targeting, which can have an interaction with the overexpressed folate receptors in cancer states [124]. Folate receptors are highly overexpressed in epithelial, ovarian, cervical, breast, lung, kidney, colorectal, and brain tumors while they are restrictedly expressed in the normal tissues, such as the lung, kidney, placenta, and choroid plexus, which are limited to the apical surface of the polarized epithelia [124, 125]. Folate has a lot of advantages to be used for a targeting ligand through the conjugation to nanobiomaterials based on its small molecular weight (441 Da) and the easy preparation method of folate-linked nanobiomaterials due to the stability of folate over a broad range of temperatures and pH values [126]. Zwicke et al. focused on the folate-based nanoconjugates for anticancer therapy with doxorubicin or paclitaxel and cancer imaging with other contrast agents like gold nanoparticles, iron oxide nanoparticles, or carbon nanotubes [127].

The nanoconjugate systems can be the effective targeting nanopatforms of macromolecules to the tumor tissues based on their ultrasmall size although they carried the ligand-based targeting systems of cell surface antigens, peptides, or polymers. The albumin-based nanoconjugates were introduced by Ming et al. [128], which carried phosphorodiamidate morpholino oligomer (PMO) type splice-switching oligonucleotides (SSOs) with a RGD peptide for integrin  $\alpha_v\beta_3$ , a cell surface glycoprotein, as an active targeting ligand and a fluorescence label. This system was very small based on 13 nm of size. It had a high specificity without cytotoxicity. In particular, it was applied to the tumor spheroids of A375 cells to check the uptake and penetration of the albumin-based nanoconjugates into the three-dimensional (3D) cultures. In addition, these nanoconjugates can overcome the drawbacks of conventional chemotherapy such as drug toxicity to normal cells and cancer drug resistance by specific targeting and activating the cancer cells via the multiple decorations of target ligands on the nanoconjugates. Mittapalli et al. also reported the paclitaxel-ultrasmall hyaluronic acid (HA) nanoconjugates [129], which is a CD44 receptor targeting system for the treatment of brain metastasis of breast cancer in a model of MDA-MB-231 breast cancer cells. They used an ultrasmall HA (3–5 kDa) as a target ligand to interact with CD44 receptors on the surface of the cancer cells. In addition,

this ultrasmall HA-mediated cellular uptake of paclitaxel avoided the P-glycoprotein-mediated efflux showing the drug resistance in cancer cells. In particular, this system exhibited a small size of 2–3 nm, like a single molecule of the nanoconjugates, and can self-assemble into larger particles.

**4.4. Inorganic Nanoparticles—Iron Oxide Nanoparticles, Superparamagnetic Iron Oxide Nanoparticles, and Gold Nanoparticles.** Inorganic nanoparticles have been currently investigated as contrast agents in clinical practice [130]. Iron oxide nanoparticles and superparamagnetic iron oxide nanoparticles have been studied extensively as contrast agents because they enhance the negative contrasts and give us darker images of the interest regions in magnetic resonance imaging (MRI). Iron oxide nanoparticles have a magnetic moment to be changed by an ambient thermal energy. This system has been widely used for MRI contrast enhancements, as well as tissue-specific release of therapeutic agents [131]. Superparamagnetic iron oxide (SPIO) nanoparticles are either form which includes the inside of the core of magnetic nanoparticles with a polymeric coating or a homogeneous integration into the polymeric nanoparticles [4]. This nanoparticulate system has a small size with the range of 3–6 nm of the core size and 20–150 nm after dextran coating such as Feridex and Combidex, which is a superior biocompatible magnetic material-based biomedical technique with respect to other magnetic materials, both based on oxides or pure metals [132]. In addition, this system can deliver anticancer drugs such as doxorubicin and methotrexate, which is used as theranostic cargo system due to its small size [133, 134]. In addition, the gold nanoparticles were used together with the iron oxide nanoparticles to study the MRI contrast agents, as well as the optical probes exploiting the reflectance signal of the gold nanoparticles [135].

The gold nanoparticles can also be used in an ultrasensitive assay technique to detect cancers [136]. Peng et al. introduced the functionalized gold nanoparticles in combination with the pattern recognition methods to diagnose the lung cancer from breath testing [137]. This method is an *in vitro* sensor array technique of the detection of biomarkers in exhaled breath of lung cancer patients as a noninvasive diagnostic tool. In addition, Thaxton et al. reported the combination system based on the magnetic microparticles and the gold nanoparticles conjugated with the prostate-specific antigen- (PSA-) specific antibodies to diagnose prostate cancers [138]. In this system, the magnetic microparticles conjugated with PSA-specific antibodies were used to extract the traceable amounts of PSA in the serum samples from patients, and the gold nanoparticles with PSA-specific antibodies and short DNA sequences (the barcodes) were attached to detect this analyte for *in vitro* barcode assay.

**4.5. Carbon-Based Nanopatforms—Carbon Nanotubes and Graphene.** Graphite is one of the carbon-based natural materials that are widely used in large-scale industrial applications such as steelmaking and battery electrodes [139]. From graphite, carbon-based nanobiomaterials have been engineered with the deeper nanofabrication techniques,

which include carbon nanotubes and graphene [140]. These nanobiomaterials are currently and widely regarded as highly attractive biomedical application systems that have a multifunctional nature. In addition, they are incorporated into the conventional existing nanobiomaterials, so-called the hybrid system with further function [141, 142].

Carbon nanotubes are cylindrical nanostructure-based carbon materials, which are synthesized by an arc discharge or chemical vapor deposition of graphite [143]. They are shaped like rolling sheets of carbon into the hollow tubes. Their sizes are ultrasmall, 0.4 to 2 nm in diameter of single-walled carbon nanotubes (SWCNTs) [144, 145]. This system can also be modified to be suitable for biological applications with an addition of functional groups, targeting molecules, and polymers, and so forth to enhance the solubility and biocompatibility [146]. Ruggiero et al. studied the biodistribution and glomerular filtration in the kidney of SWCNT with fluorescence label. This system was applied to the near infrared (NIR) fluorescence imaging and dynamic positron emission tomography (PET) imaging [147]. For the enhancement of solubility of the carbon nanotubes, Liu et al. reported the water soluble carbon nanotubes functionalized with PEG [148]. In addition, this water soluble carbon nanotube system with radio labels and RGD peptide targeted integrins  $\alpha_v\beta_3$  for the treatment of human glioblastoma and human colorectal cancer in the U87MG and HT-29 tumor xenograft models. They checked the biodistribution of this system using PET scan in the murine tumor model after intravenous injection.

Graphene is a single planar sheet structured carbon-based material, which is a single atomic plane of graphite, in a honey comb crystal lattice [149]. It is isolated by a simple method for extracting graphene from graphite via exfoliation [150]. Graphene is similar to carbon nanotubes in that it has similar electrical, optical, and thermal properties, although the structure of graphene is two-dimensional atomic sheet different from carbon nanotubes [151]. Graphene can be an attractive material since it has the possibility of being engineered to be structurally thin and flexible. For the biomedical applications, graphene oxide and reduced graphene oxide are more commonly used due to its solubility in aqueous environments and capability of chemical functionalization [152]. Graphene oxide was produced by the oxidation of graphite under acidic conditions (e.g., the modified Hummer's method), and reduced graphene oxide was provided from a reduction of graphene oxide with several reducing reagents (e.g., hydrazine) [153]. They are applied to the biomedical nanomedicine including injectable drug delivery systems for anticancer therapy as carbon nanotubes [154]. For example, the nanographene sheet (NGS) for photothermal therapy (PTT) was reported by Shi et al. [155], which was a six-armed PEG-NGS of 10–50 nm in size with fluorescence labeling for PTT of cancers in the models of 4T1 bearing Balb/c mice, as well as KB and U87MG xenograft models after intravenous injection. In addition, reduced graphene oxide was applied to PTT in tumor models by Yang et al. [156] who used the reduced graphene oxide conjugated with the chimeric

form of anti-CD105 mAb, TRC 105, to target and detect the tumor vasculature in the living mice as a theranostic agent.

**4.6. Dendrimers.** Dendrimers are three-dimensional spherical-shaped nanobiomaterials with repeated branches of dendron which contains a single chemical group, called a focal point [157, 158]. The structure of dendrimers consists of a core of initiator, repeated branching units, terminal functional groups, and void spaces, which are rooms for molecular cargo [159]. In the globular and nanosized structures of dendrimers, the terminal functional groups of the outer surface are essential in determining the properties of dendritic macromolecules, which can be interacted and conjugated with other molecules to target the cancer cells and tissues. The commonly used dendrimers in nanomedicines are polyamidoamines (PAMAM) [160], poly(L-lysine) scaffold dendrimers (PLL) [161], polyesters (PGLSA-OH) [162], polypropylamines (PPI) [163], and poly(2,2-bis(hydroxymethyl) propionic acid scaffold dendrimers (bis-MPA) [164]. Some of them are commercially available such as PAMAM dendrimers (Starburst) and PPI dendrimers (Astramol) [165, 166]. Dendrimers can be applied to cancer targeting conjugated with the targeting ligands such as folate, transferrin, antibodies, peptides, and aptamers [167]. In addition, multifunctionality of dendrimers can be a major advantage based on an incorporation of anticancer therapeutics as well as imaging agents [158, 165, 168].

**4.7. Virus-Based Nanoplatfoms (Phage System).** Virus-based nanomaterials have been dramatically investigated in recent years [169]. Viruses are biochemical complexes composed of genomic and proteomic materials. The desired functions of materials for bionanomedicine can be engineered by designing the shape and size of nanoparticles as well as the specific sequence of DNA and proteins. The self-assembled viral architecture can occur in a wide range of shapes and sizes [170] and can offer remarkable structural features of virus that make them excellent candidates for bionanomedicine [171, 172]. Advancements in nanoscale biological engineering of viral particles provide a development of novel pathways to develop nanomedicine for cancer therapeutics. Various types of viruses, such as adenovirus, adeno-associated virus, and bacteriophages, have been utilized for targeted cancer therapy and imaging through genetic and chemical modifications of the virus [173–175].

A bacteriophage (phage) is a prokaryotic virus that can infect the bacterial host cells exploiting the host's biosynthetic machinery to produce many identical copies of the phage itself [176]. There are many types of phages with different genomic materials, replication processes, and shapes such as linear (M13, Fd, and F1) [177] or spherical (MS2) [178]. Some shapes are quite sophisticated; for example, T4 and T7 phages possess an icosahedral head and a long tail connected through a cylindrical body [170]. Over the last two decades, the biochemical landscape of the phage structure has been greatly expanded through genetic engineering [179–182] and site-specific organic synthesis approaches [183–186]. Through

genetic engineering, many foreign or synthetic DNAs have been integrated into the phage genome and expressed at various sites of the phage body [182, 187]. Several groups are investigating the engineered filamentous bacteriophage for *in vivo* screening via phage display within organs [188] or cancerous tissue [189, 190], for the purpose of targeted drug delivery [191, 192] or as an imaging agent [193]. For gene delivery applications, therapeutic genetic material can be incorporated into the phage DNA and carried into the cells following a receptor uptake [194]. The phage can be locally targeted to the cell receptors by incorporation of specific targeting and/or internalization peptides (i.e., via RGD or other ligands). To make the phage even more effective than the DNA delivery vehicles, phage can be further decorated with peptides that facilitate endosomal escape or nuclear localization motifs that target the nuclear envelope [195]. The most widely used bacteriophages for gene delivery are M13 filamentous phages [173, 196, 197] and lambda phages [198]. To enhance gene delivery efficiency, the phage with the multifunctional peptides can be produced using a phagemid system, which facilitates manipulation of expressed proteins on viral vectors [197]. Phage display technology has allowed for identification of novel homing peptides that target the unknown cell surface proteins. The targeting peptides can be incorporated into the phage coat proteins through genetic engineering techniques or chemical modifications to improve targeting efficiency [194]. These include peptides (RGD, glioma-binding peptide) [197, 199], HER2 receptor targeting antibody [173], growth factors (EGF and FGF2) [200, 201], and the penton base of adenovirus [198]. Hajitou et al. constructed a hybrid phage with two genes from the phage and nucleus integrating gene from an adeno-associated virus (AAV), called inverted terminal repeats [194]. Although eukaryotic viruses such as AAV have fantastic transgene delivery capabilities, they require an elimination of the native tropism for mammalian cells. In contrast, M13 phages have no tropism for mammalian cells; however, their gene delivery efficiency is poor. Thus, there has been an effort to combine the advantageous aspects of AAV and M13 phages into a single system [194]. This phage displayed integrin-binding peptides (cyclic RGD) on the minor coat proteins and carried the herpes simplex virus thymidine kinase gene (HSVtk). The resulting AAV/phage system provided a superior tumor transduction over the phage alone and was used as the PET imaging agent with [<sup>18</sup>F]FDG and [<sup>18</sup>F]FEAU as well as cancer therapeutics with ganciclovir treatment (Table 1). Ghosh et al. investigated the selective tumor targeting phage-based material for *in vivo* imaging for prostate cancer, acidic and rich in cysteine (SPARC), which is upregulated in various cancers and correlated with poor prognosis [202]. The capsid organization of M13 spatially separates the targeting and imaging moieties. Using p3 to display the targeting ligands (SPARC-binding peptide, SPPTGIN) while assembling multiple magnetic iron oxide nanoparticles (MNPs) along the p8 capsid achieves effective targeting and delivers a larger payload of MNPs per SPARC compared with directly functionalized nanoparticles (Table 1). Compared with nanoparticles that are directly

functionalized with targeting peptides, this approach improves the contrast because each SPARC-targeting molecule delivers a larger number of nanoparticles into the cells. Moreover, the targeting ligand and nanoparticles could be easily exchanged for others, making this platform attractive for *in vivo* screening and molecular detection (Table 1).

## 5. Applications of Targeted Delivery Systems from Cells to Clinics

Nanoplatforms generally have the potential to be applied as cancer diagnosis, imaging, and treatment *in vitro* and *in vivo*. Targeted delivery strategies of nanoplatforms are special formulations and carriers with anticancer drugs such as pegylated liposomes, polymeric nanoparticles/micelles, and albumin-based drug carriers. These nanoplatforms that we mentioned above can be applicable to the biomedical approaches such as cancer diagnostics [145], anticancer therapy [203], nanoimaging [204], bimodal imaging [205, 206], and real-time intraoperative imaging [26]. The FDA has approved clinical use of a significant number of anti-cancer drug products in the nanometer size range including the applications in Table 3. In particular, nanoimaging has become based on the diagnostic potential of an earlier detection in the cancer and other human diseases [207]. In the case of bimodal contrast imaging, bimodal contrast agents allow the assessment of regions of interest using two independent imaging modalities such as MRI reagents and fluorescent agents. In the case of MRI and fluorescence imaging, MRI has an excellent spatial resolution, and fluorescence imaging compensates for the sensitivity of MRI overcoming the limitations of a single-modality imaging [208]. For intraoperative fluorescence imaging, the first human trial in advanced-stage ovarian cancer proceeded with tumor-specific folate receptor- $\alpha$  targeted fluorescent agent [26]. This study offers the potential application of intraoperative staging with tumor-specific fluorescence imaging in patients with ovarian cancer by folate receptor- $\alpha$  overexpression.

## 6. Conclusion

Human genomic map has accelerated the current biomedical application for the improvement of human healthcare and future therapies encompassing a full understanding of the gene function. Increasing information regarding the gene regulation process will provide the fundamental knowledge for the development of novel therapy in the disease state of cancer. For this streamline of biomedical research, nanoplatforms can take the center stage of participating in the development of targeted nanomedicine for anticancer therapy in the foreseeable future. Using these nanoplatform techniques, targeted anticancer therapy of nanomedicine without toxicity will be able to detect, confirm, and treat various types of cancers as a part of personalized medicine. This therapeutic potential will require more approaches to develop ideal targeted nanoplatforms overcoming toxicity and enhancing biocompatibility, as well as multifunctionality

of nanoplatforms. We believe that these cancer targeting studies of nanoplatforms can contribute to the scientific achievement of nanotechnology and nanoplatforms for the development of targeted anticancer therapeutics.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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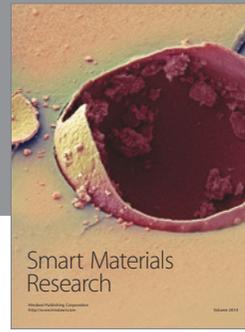
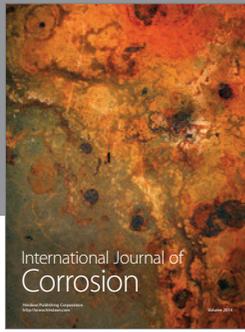
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