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Nanoparticles in Medicine: Therapeutic Applications and Developments

L Zhang[1], FX Gu[1], JM Chan[2], AZ Wang[3,4], RS Langer[1] and OC Farokhzad[4]

Nanotechnology is the understanding and control of matter generally in the 1–100 nm dimension range. The application of nanotechnology to medicine, known as nanomedicine, concerns the use of precisely engineered materials at this length scale to develop novel therapeutic and diagnostic modalities.[1,2] Nanomaterials have unique physicochemical properties, such as ultra small size, large surface area to mass ratio, and high reactivity, which are different from bulk materials of the same composition. These properties can be used to overcome some of the limitations found in traditional therapeutic and diagnostic agents.

The use of materials in nanoscale provides unparallel freedom to modify fundamental properties such as solubility, diffusivity, blood circulation half-life, drug release characteristics, and immunogenicity. In the last two decades, a number of nanoparticle-based therapeutic and diagnostic agents have been developed for the treatment of cancer, diabetes, pain, asthma, allergy, infections, and so on.[3,4] These nanoscale agents may provide more effective and/or more convenient routes of administration, lower therapeutic toxicity, extend the product life cycle, and ultimately reduce health-care costs. As therapeutic delivery systems, nanoparticles allow targeted delivery and controlled release. For diagnostic applications, nanoparticles allow detection on the molecular scale: they help identify abnormalities such as fragments of viruses, precancerous cells, and disease markers that cannot be detected with traditional diagnostics. Nanoparticle-based imaging contrast agents have also been shown to improve the sensitivity and specificity of magnetic resonance imaging. Given the vast scope of nanomedicine, we will focus on the therapeutic applications, in particular, drug delivery applications, of nanoparticles.

Many advantages of nanoparticle-based drug delivery have been recognized.[5,6] It improves the solubility of poorly water-soluble drugs, prolongs the half-life of drug systemic circulation by reducing immunogenicity, releases drugs at a sustained rate or in an environmentally responsive manner and thus lowers the frequency of administration, delivers drugs in a target manner to minimize systemic side effects, and delivers two or more drugs simultaneously for combination therapy to generate a synergistic effect and suppress drug resistance. As a result, a few pioneering nanoparticle-based therapeutic products have been introduced into the pharmaceutical market, and numerous ensuing products are currently under clinical testing or are entering the pipeline.

NANOPARTICLE-BASED THERAPEUTICS APPROVED FOR CLINICAL USE

In the past two decades, there has been a progressive increase in the number of commercially available nanoparticle-based therapeutic products. A global survey conducted by the European Science and Technology Observatory in 2006 showed that more than 150 companies are developing nanoscale therapeutics.[7] So far, 24 nanotechnology-based therapeutic products have been approved for clinical use, with total sales exceeding $5.4 billion.[7] Among these products, liposomal drugs and polymer–drug conjugates are two dominant classes, accounting for more than 80% of the total amount (**Table 1**).

Liposomes are spherical lipid vesicles with a bilayered membrane structure composed of natural or synthetic amphiphilic lipid molecules.[8,9] Liposomes have been widely used as pharmaceutical carriers in the past decade because of their unique abilities to (a) encapsulate both hydrophilic and hydrophobic therapeutic agents with high efficiency, (b) protect the encapsulated drugs from undesired effects of external conditions, (c) be functionalized with specific ligands that can target specific cells, tissues, and organs of interest, (d) be coated with inert and biocompatible polymers

[1]Department of Chemical Engineering and Division of Health Science and Technology, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA; [2]Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA; [3]Department of Radiation Oncology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [4]Laboratory of Nanomedicine and Biomaterials, Department of Anesthesiology, Brigham Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA. Correspondence: OC Farokhzad (ofarokhzad@partners.org)

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Table 1 Clinically approved nanoparticle-based therapeutics

Composition	Trade name	Company	Indication	Administration
Liposomal platforms				
Liposomal amphotericin B	Abelcet	Enzon	Fungal infections	i.v.
Liposomal amphotericin B	AmBisome	Gilead Sciences	Fungal and protozoal infections	i.v.
Liposomal cytarabine	DepoCyt	SkyePharma	Malignant lymphomatous meningitis	i.t.
Liposomal daunorubicin	DaunoXome	Gilead Sciences	HIV-related Kaposi's sarcoma	i.v.
Liposomal doxorubicin	Myocet	Zeneus	Combination therapy with cyclophosphamide in metastatic breast cancer	i.v.
Liposomal IRIV vaccine	Epaxal	Berna Biotech	Hepatitis A	i.m.
Liposomal IRIV vaccine	Inflexal V	Berna Biotech	Influenza	i.m.
Liposomal morphine	DepoDur	SkyePharma, Endo	Postsurgical analgesia	Epidural
Liposomal verteporfin	Visudyne	QLT, Novartis	Age-related macular degeneration, pathologic myopia, ocular histoplasmosis	i.v.
Liposome-PEG doxorubicin	Doxil/Caelyx	Ortho Biotech, Schering-Plough	HIV-related Kaposi's sarcoma, metastatic breast cancer, metastatic ovarian cancer	i.m.
Micellular estradiol	Estrasorb	Novavax	Menopausal therapy	Topical
Polymeric platforms				
L-Glutamic acid, L-alanine, L-lysine, and L-tyrosine copolymer	Copaxone	TEVA Pharmaceuticals	Multiple sclerosis	s.c.
Methoxy-PEG-poly(D,L-lactide) taxol	Genexol-PM	Samyang	Metastatic breast cancer	i.v.
PEG–adenosine deaminase	Adagen	Enzon	Severe combined immunodeficiency disease associated with ADA deficiency	i.m.
PEG-anti-VEGF aptamer	Macugen	OSI Pharmaceuticals	Age-related macular degeneration	i.r.
PEG–α-interferon 2a	Pegasys	Nektar, Hoffmann-La Roche	Hepatitis B, hepatitis C	s.c.
PEG-GCSF	Neulasta	Amgen	Neutropenia associated with cancer chemotherapy	s.c.
PEG-HGF	Somavert	Nektar, Pfizer	Acromegaly	s.c.
PEG-L-asparaginase	Oncaspar	Enzon	Acute lymphoblastic leukemia	i.v., i.m.
Poly(allylamine hydrochloride)	Renagel	Genzyme	End-stage renal disease	Oral
Other platforms				
Albumin-bound paclitaxel	Abraxane	Abraxis BioScience, AstraZeneca	Metastatic breast cancer	i.v.
Nanocrystalline aprepitant	Emend	Elan, Merck	Antiemetic	Oral
Nanocrystalline fenofibrate	Tricor	Elan, Abbott	Anti-hyperlipidemic	Oral
Nanocrystalline sirolimus	Rapamune	Elan, Wyeth Pharmaceuticals	Immunosuppressant	Oral

ADA, adenosine deaminase; GCSF, granulocyte colony-stimulating factor; HGF, hepatocyte growth factor; HIV, human immunodeficiency virus; i.m., intramuscular; i.r., intravitreous; IRIV, immunopotentiating reconstituted influenza virosome; i.t., intrathecal; i.v., intravenous; PEG, polyethyleneglycol; s.c., subcutaneous; VEGF, vascular endothelial growth factor.

such as polyethylene glycol (PEG), in turn prolonging the liposome circulation half-life *in vivo*, and (e) form desired formulations with needed composition, size, surface charge, and other properties.[9,10] Table 1 lists some liposomal products that have been approved in the past 15 years. Doxil was the first liposomal drug formulation approved by the Food and Drug Administration, USA (FDA) for the treatment of AIDS associated with Kaposi's sarcoma in 1995.[11] By encapsulating doxorubicin (a widely used anti-cancer chemotherapeutic drug) into stealth liposome carriers comprised of hydrogenated soy phosphatidylcholine, cholesterol, and PEGylated phosphoethanolamine, Doxil has dramatically prolonged doxorubicin circulation half-life and enhanced drug deposition in the tumor tissue. Other

liposomal drugs used in clinical practice today include AmBisome (amphotericin B liposomes), DaunoXome (daunorubicin liposomes), DepoCyt (cytarabine liposomes), and Visudyne (verteporfin liposomes).

Another extensively studied nanoparticle drug delivery platform currently in clinical practice is polymer–drug conjugates.[12] Small-molecule therapeutic agents, especially anticancer chemotherapeutic agents, usually have two unfavorable properties: short circulation half-life, which leads to frequent administrations, and non-site-specific targeting, resulting in undesired systemic side effects. The conjugation of small-molecule drugs to polymeric nanocarriers can improve the undesirable adverse effects. Polymer–drug conjugates not only prolong the *in vivo* circulation time from several minutes to several hours, but also reduce cellular uptake to the endocytic route. This enhances the passive delivery of drugs to tissues with leaky blood vessels, such as tumors and atherosclerotic plaques.[13,14] Many polymers have been proposed as drug delivery carriers, but only a few of them with linear architecture have been accepted into clinical practice. Challenges abound, but major challenges come from polymer toxicity, immunogenicity, nonspecific biodistribution, *in vivo* circulation instability, low drug-carrying capacity, rapid drug release, and manufacturing. PEG was first introduced into clinical use in the early 1990s.[15] It can enhance the plasma stability and solubility of the drug while reducing its immunogenicity. Today, there are six examples of PEGylated drugs in clinical practice. For example, Adagen (PEG–adenosine deaminase) is used to treat immunodeficiency disease; Macugen (PEG–anti-vascular endothelial growth factor aptamer) is used to treat age-related macular degeneration; Pegasys (PEG–α-interferon 2a) is used to treat hepatitis B and hepatitis C; and Oncaspar (PEG–L-asparaginase) is used to treat acute lymphoblastic leukemia. Besides PEG, other linear polymers such as polyglutamic acid, polysaccharide, and poly(allylamine hydrochloride) have also been harnessed as polymeric drug delivery carriers.

Other macromolecule–drug conjugates or adducts that have a hydrodynamic size of 5–200 nm have also been developed as drug carriers. One example is Abraxane, a 130-nm albumin-bound paclitaxel drug, that was approved by the FDA in 2005 as a second-line treatment for patients with breast cancer.[16] Abraxane concentrates in the tumor partly through the passive enhanced permeability and retention effect and partly through the transendothelial transport mechanisms via the albumin-binding protein gp60. Clinical studies have shown that Abraxane almost doubles the therapeutic response rate and also increases time to disease progression and overall survival in patients with breast cancer.

NANOPARTICLE-BASED THERAPEUTICS IN CLINICAL TRIALS

The medical application of nanoparticles is gaining popularity with an increasing number of nanoparticle-based therapeutics currently in clinical development (Table 2).

Drug-encapsulated liposomes and polymer–drug conjugates such as PEGylated drugs dominate clinical trials. One drawback of the use of liposomes is the fast clearance of liposomes from the blood by phagocytic cells of the reticuloendothelial system, resulting in unfavorable therapeutic index.[9] Several strategies have been developed to reduce this problem. The most widely used strategy is to formulate long-circulating liposomes by coating the liposome surface with inert and biocompatible polymers such as PEG. The polymer layer provides a protective shell over the liposome surface and suppresses liposome recognition by opsonins, and therefore subsequent clearance by the reticuloendothelial system.[17] Another strategy is to increase the accumulation of liposomes in the desired cells, tissues, and organs. By attaching targeting ligands such as antibodies, peptides, and small molecules (*e.g.*, folate and transferrin) to the liposome surface, targeted liposomes have been developed for differential drug delivery.[18] An example is Onco TCS, a liposomal formulation of vincristine developed by INEX Pharmaceuticals (Burnaby, British Columbia, Canada) for the treatment of aggressive non-Hodgkin's lymphoma. Using INEX's liposome-based transmembrane carrier systems (TCSs), Onco TCS has the ability to target intracellular delivery of vincristine. Its clinical trial data (phase I and II) have demonstrated that Onco TCS has longer blood circulation half-life, higher accumulation in tumors, and more sustained drug release profiles than free vincristine. Therefore, liposomal vincristine can potentially increase the efficacy of vincristine and decrease adverse side effects of the drug. In addition, releasing the drug in a controlled manner can also increase the therapeutic efficacy of liposomal drugs. By incorporating a fraction of pH-sensitive phosphatidylethanolamine, dimethyldioctadecylammonium bromide, or oleyl alcohol into the liposome membrane, smart liposomes have been developed for preferential intracellular drug delivery.[19] These liposomes are generally stable in blood while undergoing phase transition under endosomal pH.

PEG has been widely used to enhance the pharmacokinetics of various nanoparticle formulations. PEG is a highly hydrated flexible polymer chain that reduces plasma protein adsorption and biofouling of nanoparticles while reducing renal clearance of relatively smaller drug molecules, and thus prolongs drug circulation half-life.[15] PEG is also non-toxic and non-immunogenic, making it suitable for clinical applications. These favorable characteristics have led to many new PEGylated products under various phases of clinical evaluation; for example, NKTR-118 (PEG–naloxol) in phase I for treating opioid-induced constipation, Hepacid (PEG–arginine deaminase) in phase II for hepatocellular carcinoma, and Puricase (PEG–uricase) in phase III for hyperuricemia.

Another attractive polymer that has been employed to formulate polymer–drug conjugates is *N*-(2-hydroxypropyl) methacrylamide (HPMA). HPMA is a linear hydrophilic polymer with functionalizable side chains that can be activated to enable drug attachment or conjugation with targeting ligands. By conjugating small hydrophobic drugs

Table 2 Nanoparticle-based therapeutics in clinical trials

Composition	Trade name	Company	Indication	Administration	Status
Liposomal platforms					
Liposomal annamycin	L-Annamycin	Callisto	Acute lymphocytic leukemia, acute myeloid leukemia	i.v.	Phase I
Liposomal cisplatin	SLIT Cisplatin	Transave	Progressive osteogenic sarcoma metastatic to the lung	Aerosol	Phase II
Liposomal doxorubicin	Sarcodoxome	GP-Pharm	Soft tissue sarcoma	i.v.	Phase I/II
Liposomal fentanyl	AeroLEF	Delex Therapeutics	Postoperative analgesic	Aerosol	Phase II
Liposomal lurtotecan	OSI-211	OSI Pharmaceuticals	Ovarian cancer	i.v.	Phase II
Liposomal vincristine	Onco TCS	Inex, Enzon	Non-Hodgkin's lymphoma	i.v.	Phase II/III
Polymeric platforms					
HPMA copolymer–DACH platinate	ProLindac	Access Pharmaceuticals	Ovarian cancers	i.v.	Phase II
L-Leucine, L-glutamate copolymer, and insulin	Basulin	Flamel Technologies	Type I diabetes	s.c.	Phase II
PEG-anti TNF-α antibody fragment	Cimzia	Nektar	Rheumatoid arthritis and Crohn's disease	s.c.	Phase III
PEG–arginine deaminase	Hepacid	Phoenix	Hepatocellular carcinoma	i.v.	Phase I/II
PEG–camptothecin	Prothecan	Enzon	Various cancers	i.v.	Phase I/II
PEG–naloxol	NKTR-118	Nektar	Opioid-induced constipation	Oral	Phase I
PEG–uricase	Puricase	Phoenix	Hyperuricemia from gout	i.v.	Phase III
Pluronic block-copolymer doxorubicin	SP1049C	Supratek Pharma	Esophageal carcinoma	i.v.	Phase II
Polycyclodextrin camptothecin	IT-101	Insert Therapeutics	Metastatic solid tumors	i.v.	Phase I
Polyglutamate camptothecin	CT-2106	Cell Therapeutics	Colorectal and ovarian cancers	i.v.	Phase I/II
Polyglutamate paclitaxel	Xyotax	Cell Therapeutics	Non-small-cell lung cancer, ovarian cancer	i.v.	Phase III
Poly(iso-hexyl-cyanoacrylate) doxorubicin	Transdrug	BioAlliance Pharma	Hepatocellular carcinoma	i.a.	Phase I/II
Other platforms					
Calcium phosphate nanoparticle vaccine adjuvant	BioVant	BioSante	Vaccine adjuvant	s.c.	Phase I
Nanocrystalline paliperidone palmitate	Paliperidone palmitate	Elan, Johnson & Johnson	Schizophrenia	i.m.	Phase III
Nanocrystalline 2-methoxyestradiol	Panzem NCD	Elan, EntreMed	Various cancers	Oral	Phase II
Nanoemulsion-based therapy	NB-001	NanoBio	Herpes labialis	Topical	Phase II
Nanoemulsion-based therapy	NB-002	NanoBio	Onychomycosis	Topical	Phase I/II
Paclitaxel nanoparticles in porous, hydrophilic matrix	AI-850	Acusphere	Solid tumors	i.v.	Phase I
Poly-L-lysine dendrimer	VivaGel	Starpharma	Antimicrobial protection from genital herpes and HIV infection	Topical	Phase I
Propofol IDD-D	Propofol IDD-D	SkyePharma	Anesthetic	i.v.	Phase III

DACH, diaminocyclohexane; HIV, human immunodeficiency virus; i.a., intra-arterial; i.m., intramuscular; i.v., intravenous; PEG, polyethylene glycol; s.c., subcutaneous; TNF-α, tumor necrosis factor-α.

such as paclitaxel to an HPMA polymer, drug water-solubility is highly improved. This makes drug formulation and patient administration easier. In addition, HPMA is biodegradable and non-immunogenic. Owing to these desirable attributes, a number of HPMA products have been developed and are currently in clinical trials.[20,21] Examples include ProLindac (HPMA copolymer–diaminocyclohexane palatinate) in clinical phase II for treating recurrent ovarian cancer, FCE28069 (HMPA copolymer–doxorubicin-galactosamine) in phase II for hepatocellular carcinoma, and PNU166945 (HPMA copolymer–paclitaxel) in phase I to document its toxicity and pharmacokinetics for treating refractory solid tumors.

Besides drug-encapsulated liposomes and polymer–drug conjugates, other nanoparticle platforms such as nanoemulsions,[22] dendrimers,[23] and inorganic nanoparticles[24] have also shown therapeutic potential. These platforms have greatly enriched the pool of therapeutic nanoparticles and have demonstrated novel strategies for medical applications. One interesting example is NB-001, a nanoemulsion-based therapeutic product, that just entered its phase II trial in 2007 as topical treatment for genital herpes infection. Another example is VivaGel, a poly-L-lysine dendrimer-based pharmaceutical that is currently in its phase I trial as a safe, convenient, and affordable drug for women to protect themselves from genital herpes and HIV infection.

NANOPARTICLE-BASED THERAPEUTICS IN PRECLINICAL DEVELOPMENT

The recent successes of nanoparticle therapeutics have raised the interest of academic and industry investigators in the field of nanomedicine. There is an increasing momentum in the pace of discovery, which has resulted in the development of more complex nanoparticle systems over the past decade. These include increasing numbers of nanoscale vehicles with distinct chemical, physical, and biological properties for a myriad of clinical indications.[1,25] Besides liposomes and polymeric conjugates, the most common nanoparticle platforms today include polymeric nanoparticles, micelles, nanoshells, dendrimers, engineered viral nanoparticles, albumin-based nanoparticles, polysaccharide-based nanoparticles, metallic nanoparticles, and ceramic nanoparticles (**Figure 1** and **Table 3**). These nanoparticles have shown therapeutic potential for almost every branch of medicine such as oncology, cardiology, immunology, neurology, endocrinology, ophthalmology, pulmonary, orthopedics, and dentistry.[1]

Recently, biodegradable polymeric micelles with a size of 10–200 nm have attracted a lot of attention as drug delivery nanocarriers and have shown remarkable therapeutic potential.[26–32] Polymeric micelles are formed by self-assembly of block copolymers consisting of two or more polymer chains with different hydrophobicity. These copolymers spontaneously assemble into a core–shell micellar structure in an aqueous environment to minimize the system's free energy. Specifically, the hydrophobic blocks form the core to minimize their exposure to aqueous surroundings, whereas the hydrophilic blocks form the corona-like shell to stabilize the core through direct contact with water.[33] This micellar structure provides an ideal drug delivery nanocarrier. Its hydrophobic core is capable of carrying pharmaceuticals, especially poorly soluble drugs, with high loading capacity (5–25% weight). Its hydrophilic shell provides not only a steric protection for the micelle, thereby increasing its stability in blood, but also functional groups suitable for further micelle modification. In contrast with polymer–drug conjugates, each polymeric micelle can carry more drugs due to its considerably larger size and can release these drugs in a more regulated manner. The encapsulated drugs can be

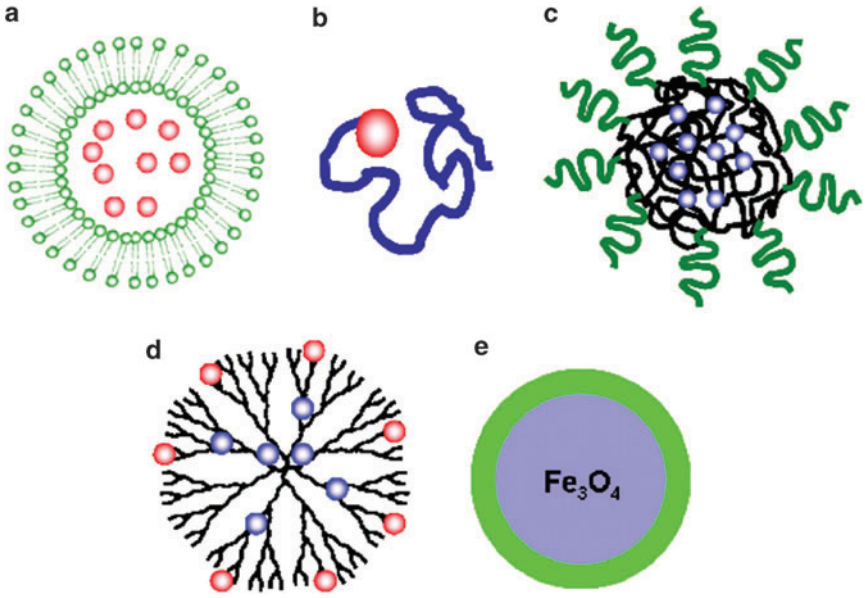

Figure 1 Schematic illustration of therapeutic nanoparticle platforms in preclinical development: (**a**) liposome, (**b**) polymer–drug conjugate, (**c**) polymeric nanoparticle, (**d**) dendrimer, and (**e**) iron oxide nanoparticle. The red dots represent hydrophilic drugs and the blue dots represent hydrophobic drugs.

Table 3 Nanoparticle-based therapeutics in preclinical development

Composition	Therapeutic	Indication	Reference
Polymeric micelles			
Antibody–enzyme-conjugated nanoparticles (immunoenzymosomes)	Antibody-directed enzyme prodrug therapy	Ovarian cancer	26
Biotinylated antibody-conjugated polymeric micelles	Daunomycin	Brain targeting	27
Pluronic block copolymers	Doxorubicin	Various cancers	28
Polymer–lipid hybrid nanoparticles	Doxorubicin	Solid tumors	29
Polymersomes	Hemoglobin	Oxygen carrier	30
Poly(lactic-co-glycolic acid)-block-poly(ethylene glycol)	Docetaxel	Prostate cancers	31
Poly(vinyl alcohol) polymeric micelles	PVA polymer antitumor activity	Neuroblastoma, melanoma	32
Dendrimers			
Folic acid-PAMAM dendrimers	Methotrexate	Epithelial cancer	35
Ligand-conjugated PEG-poly-L-lysine dendrimers	Chloroquine phosphate	Malaria	36
Polypropyleneimine dendrimers	Efavirenz	HIV infection	37
Poly(glycerol-succinic acid) dendrimers	Camptothecin	Various cancers	38
Albumin-based nanoparticles			
Albumin-bound nanoparticles	Doxorubicin, methotrexate	Various cancers	39
Cationic albumin-PEG nanoparticles	NC-1900 vasopressin fragment analog	Scopolamine-induced memory deficits	40
Polysaccharide-based nanoparticles			
Aerosol OT (AOT)-alginate nanoparticles	Doxorubicin	Breast cancer	41
Glycol chitosan nanoparticles	Doxorubicin	Solid tumors	42
Virus-based nanoparticles			
Cowpea mosaic virus PEG nanoparticles	Gene therapy	Various purposes	43
Gold-conjugated cytomegalovirus nanoparticles	Phototherapy, gene therapy	Solid tumors	44
Metallic nanoparticles			
Anti-HER2 antibody-targeted gold/silicon nanoparticles	Nanoshell-assisted infrared photothermal therapy	Metastatic breast cancer	47
Aminosilane-coated iron oxide nanoparticles	Thermotherapy	Brain tumors	45
Starch-coated iron oxide nanoparticles	Magnetically guided mitoxantrone	Tumor angiogenesis	46
Ceramic nanoparticles			
Silica-based nanoparticles	Photodynamic therapy	Various cancers	48
Silica crosslinked block copolymer micelles	Imaging agents, chemotherapies	Imaging, chemotherapy	49

HER2, human epidermal growth factor receptor 2; HIV, human immunodeficiency virus; PAMAM, polyamidoamine; PEG, polyethylene glycol; PVA, polyvinyl alcohol. Polymer conjugates and liposomal nanoparticles are not included in the table.

released through surface or bulk erosion of the biodegradable polymers, diffusion of the drug through the polymer matrix, or polymer swelling followed by drug diffusion. Moreover, external conditions such as change of pH and temperature can also trigger drug release from polymeric micelles.[1,25] On the other hand, polymeric micelles are usually more stable in blood than liposomes and other surfactant micelles because some amphiphilic copolymers have a considerably lower

critical micelle concentration value. These polymeric micelle systems can also be used to co-deliver two or more drugs with similar or different water solubility for combination therapy, or to simultaneously deliver two or more therapeutic modalities such as radiation agents and drugs.[34] The surface modification of these micelles with ligands such as antibodies, peptides, nucleic acid aptamers, carbohydrates, and small molecules can differentially target their delivery and uptake by a subset of cells, which will further increase their specificity and efficacy, and reduce their systemic toxicity.[26,27,31] Poly(D,L-lactic acid), poly(D,L-glycolic acid), poly(ε-caprolactone), and their copolymers at various molar ratios diblocked or multiblocked with poly(ethylene glycol) are the most commonly used biodegradable polymers to form micelles for drug delivery and controlled release, and have been extensively studied in the past.[28,31,33]

Dendrimers have emerged as another novel class of drug delivery nanoparticle platform because of their well-defined architecture and unique characteristics.[35–38] Dendrimers are globular, highly branched, and synthetic polymers consisting of an initiator core and multiple layers with active terminal groups. These layers are comprised of repeating units and each layer is called a generation. The core of a dendrimer is denoted as generation zero. The specific molecular structure of dendrimers enables them to carry various drugs using their multivalent surfaces through covalent conjugation or electrostatic adsorption. Alternatively, dendrimers can be loaded with drugs using the cavities in their cores through hydrophobic interaction, hydrogen bond, or chemical linkage. Recently, researchers in Michigan developed a polyamidoamine-based G5 dendrimer, which has a diameter of about 5 nm and more than 100 functional primary amines on the surface. By attaching folate as the targeting molecule and methotrexate as the therapeutic agent, the G5 dendrimer was about 10 times more effective than methotrexate alone in prohibiting tumor growth. Moreover, the targeted, methotrexate-loaded dendrimer had less systemic toxicity than free methotrexate.[35] The promising properties of polyamidoamine dendrimers as a drug delivery system have led to further studies based on tunable architectures and molecular weights to optimize accumulation in tumors and therapeutic efficacy.

Albumin-, polysaccharide-, and virus-based nanoparticles represent another class of nanoparticle platforms comprised of biopolymers and their self-assemblies. These nanoparticles have peculiar therapeutic potential because of their specific biological characteristics. If small-molecule drugs are conjugated with human serum albumin[39,40] or a polysaccharide such as chitosan,[41,42] their stability and biodistribution can be significantly improved. Viruses can be regarded as living nanoparticles with a core–shell structure. The core contains infectious agents that can control the transcription and translation machinery of the host cells. The shell is comprised of various proteins or proteins embedded in lipid membranes. Virus-based nanoparticles have been extensively used as gene delivery vehicles due to their high gene transfection efficiency.[43,44]

As an interesting contrast with aforementioned nanoparticles that generally belong to ''soft'' matter, some ''hard'' nanoparticles such as metallic nanoparticles and ceramic nanoparticles have also attracted some attention and shown some special therapeutic potential. A typical metallic nanoparticle is iron oxide,[45,46] which can be used as a passive or targeting agent after being coated with dextran, surfactants, phospholipids, or other compounds to improve their stability. Recently, aminosilane-coated iron oxide nanoparticles have been utilized in thermotherapy to treat brain tumors. Using magnetic field-induced excitation of iron oxide superparamagnetic nanoparticles, thermotherapy in the rat model can prolong the survival time 4.5-fold over controls.[45] Gold nanoparticles represent another class of metallic nanoparticles, which have good optical and chemical properties, and thus high infrared phototherapy potential.[47] Ceramic nanoparticles such as silica, titania, and alumina are generally bioinert and have porous structures.[48,49] These nanoparticles have been recently proposed as drug delivery vehicles to carry drugs for various cancer therapies.

CONCLUSION

The application of nanotechnology to drug delivery has already had a significant impact on many areas of medicine. Currently, more than 20 nanoparticle therapeutics are in clinical use, validating the ability of nanoparticles to improve the therapeutic index of drugs. In addition to the already approved nanoparticles, numerous other nanoparticle platforms are currently under various stages of preclinical and clinical development, including various liposomes, polymeric micelles, dendrimers, quantum dots, gold nanoparticles, and ceramic nanoparticles. With continued research and development efforts, nanotechnology is expected to have a tremendous impact on medicine for decades to come.

OUTLOOK

The currently approved nanoparticle systems have in some cases improved the therapeutic index of drugs by reducing drug toxicity or enhancing drug efficacy. The next generation of nanoparticle systems may have targeting ligands such as antibodies, peptides, or aptamers, which may further improve their efficacy or reduce their toxicities. More complex systems such as multifunctional nanoparticles that are concurrently capable of targeting, imaging, and therapy are subject of future research. As the functionality of nanoparticles becomes more complex, such as the addition of targeting ligands, there is a need to precisely engineer optimally designed nanoparticles with the physicochemical and biological properties to achieve each of the desired functions. Indeed, this has been the bottleneck for the translation of targeted particles into clinical practice, underscored by the fact that the first targeted liposome was described more than 20 years ago, yet only a handful of systems have ever made it to clinical trials and none have ever been approved for use. We expect that with the introduction of safer nanomaterials together with novel engineering

approaches that result in optimally designed nanoparticles, we will be seeing an increasing number of multifunctional nanoparticles enter the clinic in the future.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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