

Current Nanomaterials in Nanomedicine

Subjects: **Nanoscience & Nanotechnology**

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Anticancer nanomedicines have been studied over 30 years, but fewer than 10 formulations have been approved for clinical therapy today. Despite abundant options of anticancer drugs, it remains challenging to have agents specifically target cancer cells while reducing collateral toxicity to healthy tissue. Nanocompartments that can be selective toward points deeply within malignant tissues are a promising concept, but the heterogeneity of tumor tissue, inefficiency of cargo loading and releasing, and low uniformity of manufacture required from preclinical to commercialization are major obstacles. Technological advances have been made in this field, creating engineered nanomaterials with improved uniformity, flexibility of cargo loading, diversity of surface modification, and less inducible immune responses.

nanoparticles

nanomedicines

nanomaterials

nanotechnology

1. Introduction

The National Institutes of Health (NIH) defines nanoparticles as structures ranging from 1 to 100 nm in at least one dimension, while current nanoparticles in therapeutic application are acceptable up to hundreds of nm. Considering the tissue junction between capillaries (150–200 μm), nanoscale structures exhibit unique properties to enhance reactive areas as well as across cell or tissue barriers ^[1]. For pharmacokinetic properties, the optimal size of nanoparticles is around 100 nm in a hydrodynamic diameter.

Currently, nanoparticles are applied to conventional drugs to improve their efficacy and reduce morbidity for advanced cancer therapies. Antitumor cargos are either capsuled or covalently linked to the nanocarrier. The advantage of covalent links is a precise number of therapeutical molecules for each nanoparticle, while the encapsulation of materials provides more flexibility. Many antitumor drugs are hydrophobic, posing challenges for physiological uptake (**Table 1**).

Table 1. Hydrophobic and hydrophilic anticancer drugs in clinical use.

Drug	Solubility (in Water; 25 °C)	Clinical Use
<i>Hydrophobic</i>		
Docetaxel	insoluble (<0.3 μg/mL)	Breast, prostate, non-small cell lung cancer, carcinoma, and adenocarcinoma

Drug	Solubility (in Water; 25 °C)	Clinical Use
Paclitaxel	insoluble (<0.3 µg/mL)	AIDS-related Kaposi sarcoma, breast, ovarian, and non-small cell lung cancer
Alitretinoin	0.6 µg/mL	Acute promyelocytic leukemia, and AIDS-related Kaposi sarcoma
Etoposide	0.03 mg/mL	Small cell lung and testicular cancer
Cisplatin	2.5 mg/ml	Testicular, ovarian, breast, glioblastoma, non-small cell lung cancer, malignant mesothelioma, and lymphoma
Methotrexate	2.6 mg/mL	ALL, breast, and lung, head and neck cancer, non-Hodgkin lymphoma, and osteosarcoma
Fludarabine	3.53 mg/mL	CLL
Doxorubicin	10 mg/mL	ALL, AML, neuroblastoma, soft tissue and bone sarcomas, breast, ovary, urinary bladder, thyroid, gastric, thyroid, gastric cancer, Hodgkin's disease
Irinotecan HCL	25 mg/mL	Colon, and rectal cancer
Cyclophosphamide	15.1 mg/mL	ALL, AML, CLL, CML, breast cancer, Hodgkin lymphoma, multiple myeloma, and neuroblastoma
Gemcitabine	51.3 mg/mL	Pancreatic, breast, ovarian, and non-small cell lung cancer
	<i>Hydrophilic</i>	

Besides stabilizing anticancer agents, designed nanoparticles can also enhance the delivery efficacy by targeting cancer lesions. This concept led to variable nanoparticle designs fitting physicochemical properties via surface modification for a multitude of biomedical applications. The targeting ability of nanoparticles, either passive or active, is aimed for enhancement of drug concentration within the specific tissue of interest, such as tumors, while limiting toxicity to healthy organs. Passive targeting depends on pathophysiological characteristics of tumor vessels, enabling nanomaterials to accumulate in the microenvironment. In tumor tissue, fast angiogenesis with highly disorganized and loosened vessel structure leads to enlarged gap junctions between endothelial cells, resulting in enhanced permeability and retention (EPR) effect [2]. The EPR effect allows diffusion of molecules less than 400 nm in diameter, which is suitable for nanoscale complex. The other phenomenon generally observed in tumor tissue is the Warburg effect, a local high metabolic and glycolysis rate result in an acidic environment [3]. Designed pH-sensitive biocarrier could be stable at physiological pH = 7.4, but rapidly disassembled and released payload once it reaches an acidic microenvironment. Common design of pH-sensitive nanoparticle is based on polymers with pKa in the range of 6.5–7.2, such as poly(L-histidine) (PHis) and poly(β-amino esters).

Unlike passive targeting, active delivery incorporates other high-affinity molecules to recognize cells directly. Active targeting based on surface receptors on target cells has been widely explored since malignant cells upregulate

certain tumor-preferred receptors. For example, transferrin receptor (TfR) and folate receptors (FRs) are physiologically expressed on various normal cells but overexpressed in many cancer types in response to their higher metabolic rate [4][5].

Conjugation is the process to join the recognition molecules with the therapeutical complex, including direct conjugation or indirect method via linker. One of the main challenges in conjugation design is homogeneity of the molecules. By using a hydrazone ligation, Dawson et al. synthesized viral nanoparticles and conjugated with VEGFR-1 ligand (F56f peptide) on benzaldehyde cowpea mosaic virus nanoparticle for tumor targeting and imaging [6]. Moreover, considering orientations of ligands or antibodies; thus, conjugation via linker chemistry is better than direct conjugation for targeting molecules to nanoparticle.

Overall, development of nanomedicine from past decades is a proof of concept to selectively increase the concentration of anticancer agents in tumor malignancy but minimize the side effect from healthy tissues (Figure 1).

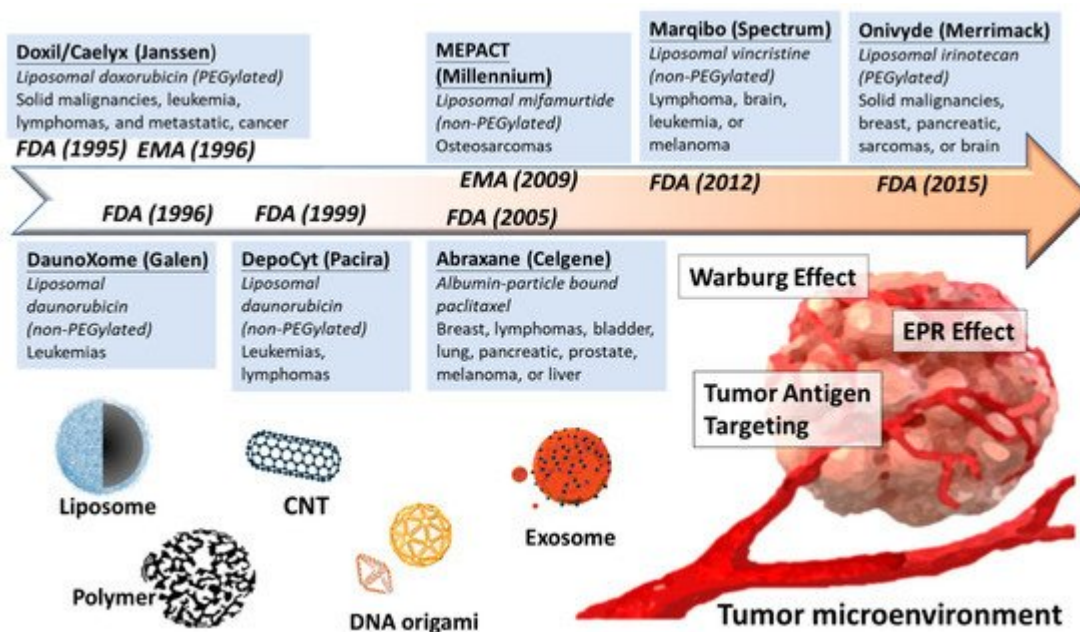


Figure 1. Development for nanomedicine reaching for tumor microenvironment. In past decades, plenty of nanocarriers are moving from preclinical bench work into clinical trial and finally approved for cancer therapy. The driving force of nanomedicine toward tumor microenvironment could be passive or active. Passive delivery relies on loose tumor vessels (EPR effect) and low pH (Warburg effect), while the active delivery can directly recognize tumor antigens by conjugating high-affinity molecules. Various novel and advanced materials of nanocarriers are designed for drug delivery, including liposome, polymer, CNT, DNA origami, and exosome.

2. Current Materials in Nanomedicine

2.1. Lipocomplex

Liposomal nanocomplex is the first delivery tool since the first discovery in the 1960s by A.D Bangham's group. Liposome formulation ranges from 50 to 200 nm with spherical vesicles composed of phospholipids, and steroids form bilayers in aqueous media can benefit as biocarriers [7][8]. The properties of liposome were simply applied to increase the solubility of hydrophobic molecules and accelerate physiological metabolism in the beginning. For example, plenty of liposome formulations tried to fit numerous biochemical agents and provide less toxic than the free form. Liposomes were used to deliver lysophosphatidic acids and its analog which regulate normal or malignant blood cell differentiation and proliferation [9][10]. However, the liposomal formulations in this period faced a severe problem of short pharmacokinetic half-life, until the “stealth liposomes” was designed the 1990s. The second generation of liposome introduced the surface polyethylene glycol (PEG) coating, which highly improved stability and longer circulation time by alleviating the uptake of macrophages [11][12]. The PEGylation, constructed with a hydrophilic film on surface, can protect the liposome from clearance of reticuloendothelial system, making liposomal delivery clinical practical.

Several lipid complexes have been approved for clinical treatment after fifty years studying of lipocomplex (Table 2).

Table 2. Nanotherapeutics approved for oncological therapy.

Name	Particle Base	Anticancer Drug	Cancer Type	Approval
Liposome-based				
Doxil/Caelyx (Janssen)	PEGylated liposome	Doxorubicin	Ovarian, breast cancer, leukemia	FDA, 1995
DaunoXome (Galen)	Non-PEGylated liposome	Daunorubicin	HIV-related Kaposi sarcoma	FDA, 1996
DepoCyt (Pacira)	Non-PEGylated liposome	Cytarabine	AML, non-Hodgkin lymphoma	FDA,1999
Myocet (Teva UK)	Non-PEGylated liposome	Doxorubicin	Metastatic breast cancer	EMA, 2000
Marqibo (Spectrum)	Non-PEGylated liposome	Vincristine	Ph-ALL, Non-Hodgkin's lymphoma	FDA, 2012
Onivyde (Merrimack)	PEGylated liposome	irinotecan	Breast, pancreatic, sarcomas, or brain	FDA, 2015
Polymer-based				
Oncaspar (Sigma Tau)	PEGylation	L-asparaginase	ALL	FDA,1994
Abraxane	Albumin-bound	Paclitaxel	Metastatic pancreatic cancer	FDA, 2005

P.E. Hydrazone ligation strategy to assemble multifunctional viral nanoparticles for cell imaging

Name	Particle Base	Anticancer Drug	Cancer Type	Approval
(Celgene)	polymer			biological

cell membranes. *Nature* 1962, 196, 952–955.

2.2. Polymeric and Dendrimer Nanoparticles

6. Bangham, A.D.; Horne, R.W. Negative Staining of Phospholipids and Their Structural Modification by Surface-Active Agents as Observed in the Electron Microscope. *J. Mol. Biol.* 1964, 8, 660–668. Polymeric nanoparticles (PNPs) are structures with a diameter ranging from 10 to 100 nm, which was made from

9. Benton, A.M.; Gerrard, J.M.; Michiel, T.; Kindom, S.E. Are lysophosphatidic acids or phosphatidic acids better polymers (e.g., polycaprolactone, and polyacrylate) or natural phospholipids (e.g., cardiolipin, cardiolipin, and gelatin)? *J. Biol. Chem.* 1993, 268, 642–649.

10. Chiang, C.L.; Chen, S.S.A.; Lee, S.J.; Tsao, K.C.; Chu, P.L.; Wen, C.H.; Hwang, S.M.; Yao, C.L.; Lee, H. Lysophosphatidic Acid Induces Erythropoiesis through Activating Lysophosphatidic Acid Receptor 3. *Stem Cells* 2011, 29, 1763–1773. the immobilization of drug within PNPs can increase the drug stability as well. For example, docetaxel-loaded polymeric micelle (diameters < 30 nm) can reach poorly permeable pancreatic tumors in vivo [15]. The enhanced stability of the immobilized drug is attributed to the interaction with the polymer carriers to avoid the degradation.

11. Korgel, B.A.; van Zanten, J.H.; Monbouquette, H.G. Vesicle size distributions measured by flow field flow fractionation coupled with multiangle light scattering. *Biophys. J.* 1998, 74, 3264–3272. Once the complex reaches the target tissues, release mechanism would be triggered by tumor microenvironment. Several unique properties of tumor microenvironment have been used for cargo releasing, such as acidic, hyperthermia, and special enzymes secretion in the local environment. The pH-sensitive polymers are relative

12. Harris, J.M.; Martin, N.E.; Moll, M. Pegylation: A novel process for modifying pharmacokinetics. *Clin. Pharmacokinet.* 2001, 40, 539–551. stable at a physiologic pH of 7.4 but can be rapidly destructured and can release active drugs in acidic tumor tissues. For example, poly(lactide-co-glycolide) (PLGA) polymer performed as 2–4-fold doxorubicin release in

13. Garay-Jimenez, J.C.; Turos, E. A convenient method to prepare emulsified polyacrylate nanoparticles from powders [corrected] for drug delivery applications. *Bioorganic Med. Chem. Lett.* 2011, 21, 4589–4591. tumor-bearing tissue than circulation at pH 7.4 [16]. Moreover, thermosensitive polymeric, such as poly (N-isopropylacrylamide-co-acrylamide-co-allylamine) (PNIPAM-AA-AA), could be a potential anticancer drug nanocarrier. Under the hyperthermia of tumor region, the hairy structure of PNIPAM-AA-AA polymer would shrink, while the enclosed doxorubicin releases rapidly [17][18].

14. Wong, B.S.; Teoh, S.H.; Kang, L. Polycaprolactone scaffold as targeted drug delivery system and cell attachment scaffold for postsurgical care of limb salvage. *Drug Deliv. Transl. Res.* 2012, 2, 272–283. Dendrimer is a unique structure of polymer, which was first synthesized by Vögtle group in 1978 with branched structure that provided a high degree of functional surface [19]. This multifunctional property provides the

15. Li, Y.; Li, P.; Jin, M.; Jiang, C.; Gao, Z. Docetaxel-encapsulating small-sized polymeric micelles with higher permeability and its efficacy on the orthotopic transplantation model of pancreatic ductal adenocarcinoma. *Int. J. Mol. Sci.* 2014, 15, 23571–23588. dendrimers more loading space for cargos and interaction with target cells. The cytotoxicity of dendrimer carrier depends on its surface area and the arms of dendrimer, while exchanging the amine groups into hydroxyl group may result in lower levels of cytotoxicity in vivo. The drug could be loaded into the internal structure of dendrimers or covalently linked to dendrimers molecule. Compared to the linear polymers with stochastic structures,

16. Hu, F.Q.; Zhang, Y.; Yu, Z.; Yu, Z.; Yu, Z.; Yu, Z. pH-triggered docetaxel delivery of PEGylated dendrimer-conjugated micelles for tumor targeting therapy. *Mol. Pharm.* 2012, 9, 2469–2478. The hydrophilic conjugate micelles form for tumor targeting therapy. The number of

17. Shen, Z.; Wei, W.; Zhao, Y.J.; Ma, G.H.; Dobashi, T.; Maki, Y.; Su, Z.G.; Wan, J.P. Thermosensitive polymer-conjugated albumin nanospheres as thermal targeting anti-cancer drug carrier. *J. Pharm. Sci.* 2008, 35, 271–282. covalent bonds within a single molecule, the quantity of drug loading could be adjusted. Noncovalent encapsulation is an alternative method only when payload is labile or poorly soluble. Poly(amido amide) (PAMAM), a very common dendrimer widely used in biomedical applications, is easily to have molecular conjugation through its branches of amine terminals [20]. Thioaptamer (TA)-modified PAMAM is developed to target CD44⁺ (TA receptor

18. Soleymani, M.; Edrissi, M.; Alizadeh, A.M. Thermosensitive poly(2-vinylpyridine)-coated La_{0.73}Si_{0.27}MnO₃ nanoparticles: Potential applications in cancer hyperthermia therapy and magnetically activated drug delivery systems. *Polym. J.* 2015, 47, 797–801. positive) breast cancer in vitro and in vivo by using ligand-receptor affinity [21]. Moreover, introducing a folic acid conjugation has been reported to improve the delivery of PAMAM dendrimers loaded with 2-methoxyestradiol to target KB carcinoma cells overexpressing high-affinity folic acid receptors [22].

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2.3. Carbon Nanomaterials

Molecular Cavity Topologies. *Synthesis* 1978, 2, 155–158.

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21. Fan, W.; Wang, X.; Ding, B.; Cai, H.; Wang, X.; Fan, Y.; Li, Y.; Liu, S.; Nie, S.; Lu, Q. Thioaptamer-conjugated CD44-targeted delivery system for the treatment of breast cancer in vitro and in vivo. *J. Drug Target.* 2015, 1–13.
22. Wang, Y.; Guo, R.; Cao, X.; Shen, M.; Shi, X. Encapsulation of 2-methoxyestradiol within multifunctional poly (amidoamine) dendrimers for targeted cancer therapy. *Biomaterials* 2011, 32, 3322–3329.
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2.4. Nucleotide-Based Origami

26. Al Faraj, A.; Shaik, A.P.; Shaik, A.S. Magnetic single-walled carbon nanotubes as efficient drug delivery nanocarriers in breast cancer murine model: Noninvasive monitoring using diffusion weighted magnetic resonance imaging as sensitive imaging biomarker. *Int. J. Nanomed.* 2015, 10, 157–168.
27. Pistone, A.; Iannazzo, D.; Panseri, S.; Montes, M.; Tampieri, A.; Galvagno, S. Hydroxyapatite-magnetite-MWCNT nanocomposite as a biocompatible multifunctional drug delivery system for bone tissue engineering. *Nanotechnology* 2014, 25, 425701.
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29. Rothemund, P.W. Folding DNA to create nanoscale shapes and patterns. *Nature* 2006, 440, 297–302.

2.5. Exosome-Derived Vehicle

30. Shih, W.M.; Quispe, J.D.; Joyce, G.F. A 1.7-kilobase single-stranded DNA that folds into a nanoscale cage. *Nature* 2004, 427, 618–621.
31. Jiang, Q.; Song, C.; Nangreave, J.; Liu, X.; Lin, L.; Qiu, D.; Wang, Z.G.; Zou, G.; Liang, X.; Yan, H.; et al. DNA origami as a carrier for circumvention of drug resistance. *J. Am. Chem. Soc.* 2012, 134, 13396–13403.
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3. Conclusions

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36. Silva, C.O.; Pinho, J.O.; Lopes, J.M.; Almeida, A.J.; Gaspar, M.M.; Reis, C. Current trends in cancer nanotheranostics: Metallic, polymeric, and lipid-based systems. *Pharmaceutics* 2019, 11, 22.

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Increasing the need for a new strategy of disease treatment achieves the coordination of diagnosis and therapy by using advanced nanomaterials. The new direction of nanotechnology attempts to integrate therapeutics and diagnostics into a single nanomaterial, referred to as theranostics. The concept of theranostics provide the major applications in clinics which can improve targeted delivery, achieve gene delivery, and have the disease monitoring with the imaging platform by well-engineered nanoparticles. Currently, the pharmaceutical company Cristal Therapeutics is participating in a phase I clinical trial of CriPec[®] docetaxel combined with the imaging agent Zirconium-89 for PET imaging [35]. The platform evaluates the biodistribution and accumulation of the nanomedicine in solid tumors, leading to a better targeted therapy and follow-up prognosis. In the other clinical trial, Nanobiotix performs phase I/II trials for NBTXR3 comprising hafnium oxide nanoparticles as a radio-enhancer to kill tumor burden by locally additional radiation [36]. This also provides a new perspective to coordinate the imaging and radiology by advanced nanotechnology. Despite considerable development in this direction, nanomedicine of theranostics still faces challenges. The major challenge to successfully translate theranostic nanomedicine into routine clinics is the nano–bio interaction. The therapeutic nanoparticles generally have a larger window of treatment in patients which requires low tolerance of nano–bio interaction, while the diagnostic nanomaterials could be one-dose and real-time imaging every couple months. The cooperation of these different fields of nanomedicine requires further effort on developing innovative nanomaterials to achieve the goal.

Overall, most approved nanomedicines are those developed early and classic antineoplastic, meaning plenty of room for improvement. The next generation of nanomedicines will incorporate more diversity of new small-molecular compounds (pathway inhibitors, such as Rapamycin, a selective mTOR inhibitor) or gene therapeutic agents (siRNA, mRNA and gene editing). This flourishing field of nanoparticle delivery is expected to expand the versatility and potency of nanocarrier for cancer therapeutics. Given recent technical and material advancements in the past decades, smart and precise nanoparticles as drug carriers will revolutionize cancer therapy, not only significantly extending the patient's lifespan but improving their quality of life.