Immunopathologia Persa
DOI:10.15171/ipp.2019.17
http www.immunopathol.com

A review on application of nanoparticles for cancer therapy

Mohamad Ali Dayani*
Department of Radiology, Shahrekord University of Medical Sciences, Shahrekord, Iran

***Correspondence to**
Mohamad Ali Dayani, Email: dayani@skums.ac.ir

Received 11 April 2019
Accepted 10 June 2019
Published online 14 July 2019

Keywords: Cancer, Nanoparticles, Liposomes, Dendrimers, Albumin, Endocytosis, Photoluminescence, Carbon nanotubes, Nanomedicine

Abstract

In recent years, scientific societies had warmly embraced nanotechnology as an emerging field in cancer therapy. Nanotechnology has had a profound influence on almost every aspect of the twenty-first century's diurnal life. During the past years, nanomaterials have been successfully applied in different biomedical fields; especially in cancer therapy. While cancer is one of the deadliest disorders worldwide, there is a need to develop novel anticancer approaches. In this review, we explained various kinds of nanoparticles such as liposome-based and polymeric nanoparticles and dendrimers along with their applications in cancer therapy.

Citation: Dayani MA. A review on application of nanoparticles for cancer therapy. Immunopathol Persa. 2019;5(2):e17. DOI:10.15171/ipp.2019.17.

Introduction

With the emergence of more than 10 million new cancer cases every year, the worldwide incidence of cancer has rapidly increased in the past decades. Treatment of cancer is hard delivering malignancies as major causes of morbidity and mortality in populations (1). Although anticancer drugs can be efficient in cancer therapy, their activities and effective dosages are generally manipulated by various factors. Traditional anti-cancer agents such as chemotherapeutic drugs nonspecifically target both cancerous and normal cells in the body. This event limits the dose of drug delivered to tumors resulting in suboptimal therapeutic efficiency.

Targeted therapy has been appeared as an approach to overcome unspecific targeting of cancer cells by traditional chemotherapeutic agents (2). After reaching tumor cells, drugs should release their active forms in a controlled way to selectively target tumor cells without influencing normal tissue. This phenomenon is critical for improving both quality of life and survival of patients by increasing the intracellular concentration of drugs and limiting dose-related toxicities. As efficient drug carrier systems, nanoparticles seem to fulfil both specificity and efficiency requirements of cancer therapeutics (3). During recent years, researchers have tried to develop new diagnostic strategies for cancer. In this regard, nanotechnology has been under focus as one of the most promising fields to diagnosis and treat cancers.

Key point

In this review, we explained various kinds of nanoparticles such as liposome-based and polymeric nanoparticles and dendrimers along with their applications in cancer therapy.

Nanotechnology is the knowledge of engineering substances and practices at molecular measure. In medicine, comprehensive studies on nanomaterials have culminated in their application as drug- release vehicles. These nano-carriers are mostly <100 nm in size and have the capability to carry and supply the therapeutics agents to intended cells (4).

In cancer treatment, the efficiency of nanoparticles depends on their penetrability and ability to be stored and retained in tumor tissues (5). As mentioned, intravenous injection of noxious chemotherapeutic drugs poses a critical risk to healthy tissues limiting their tolerable doses (6). In brief, nanoparticles can increase the intracellular absorption of drugs by cancer cells and prevent toxicity against normal cells by recruiting both passive and active targeting approaches (7, 8). Moreover, after binding to particular receptors, nanoparticles can penetrate into cells as endosomes through receptor-mediated endocytosis. In this way, they can bypass the action of P-glycoprotein as one of the major drug resistance

mechanisms in cancerous cells (9). In this review, we discussed various nanoparticles used in cancer therapy.

Materials and Methods

For this review, we used a variety of sources including PubMed, Web of Science, Embase, EBSCO, Google Scholar and Scopus. The search was conducted, using combinations of the following key words and or their equivalents; cancer, nanoparticles, liposomes, dendrimers, albumin, endocytosis, photoluminescence, carbon nanotubes and nanomedicine.

Liposomes

Liposomes were introduced by Bangham et al in 1965. Liposomes are among very first nanoparticle-based platforms utilized for therapeutic purposes (10). They consist of amphiphilic lipid molecules gathered into bilayer spherical vesicles with an aqueous core and a vesicle shell (4,6).

Depending on their designs, liposomes vary in diameter ranging from tens of nanometers to micrometers. Features such as biocompatibility and biodegradability, in addition to the unique capability to encapsulate both hydrophilic (inside the aqueous core) and hydrophobic (inside the lamellae) drugs deliver liposomes as brilliant drug carriers. Likewise, to enhance their constancy and half-life in circulation, liposomes can also be covered with polymers like polyethylene glycol (11).

Liposomal medicine formulations usually amend the pharmacokinetics and biodistribution of a drug. There are currently more than 11 liposomal formulations permitted for clinical application, and many other formulations are in clinical and preclinical phases (4). The liposomal formulations currently used in cancer therapy include DepoCyt (12, 13), ONCO-TCS (14), Doxil (15,16) and DaunoXome (17,18) which are formulations of doxorubicin, daunorubicin, cytarabine and vincristine respectively (6).

Another liposome-based formulation has been used to co-deliver SiRNAs and chemotherapeutics. SiRNAs are developing classes of cancer therapeutics interfering with gene expression through targeting mRNAs. In 2008, Saad et al developed a liposome system to transport SiRNAs targeting BCL_2 (a protein responsible for resistance of cells to apoptosis) and MRP_1 (a multifunctional defiance -associated protein) in combination with doxorubicin into human H69AR lung cancer cells (19). Table 1 provides a brief description regarding anti-cancer liposome-based combinational treatments.

Polymeric nanoparticles

Biodegradable and biocompatible polymeric nanoparticles have been under investigations to transport and target drugs (6). Many polymeric nanoparticles have been investigated in comprehensive clinical and preclinical studies as biocompatible and biodegradable drug carriers (26).

As polymers propose higher synthetic freedom, they allow various particles to be tailored for particular clinical needs. Due to these unique properties, polymeric nanoparticles have attracted enormous interests among scientific and industrial societies even though they are still in the early phases of investigations (6). The hydrophobic core of polymers is able to carry high amount of drugs whereas the hydrophilic shell supplies a steric defense for the nanoparticle. Polymeric nanoparticles have also been able to encapsulate either micro or macromolecules (such as nucleic acids and proteins) with hydrophilic or hydrophobic properties (27).

In comparison with liposomes, polymeric nanoparticles generally have better stability, sharper size distribution, more advantageous physicochemical attributes, sustained and more manageable drug-release profiles, and better loading capacity for water-insoluble drugs (6).

Dendrimers

Dendrimers are a new class of nanoparticles developed as drug-delivery vehicles in cancer therapy. They are well described branched spherical macromolecules (28). Dendrimers are produced in a stepwise and iterative method. The structure of dendrimers constitutes from a core surrounded by layers of branched repeated units with functional groups on the outmost layer (6).

They are commonly derived from either synthetic or natural elements like nucleotides, sugars, and amino acids. These nanoparticles can be simply conjugated to therapeutics. Through holes in their cores, dendrimers can be loaded with drugs via hydrophobic interactions,

Table 1. Liposome-based combinations used as cancer therapeutics

Formulation	Indication	Reference
CPX-351	Acute myeloid leukemia	(20)
Liposome co-encapsulating 6-mercaptopurine and daunorubicin	Acute lymphocytic leukemia	(21)
Liposome co-encapsulating quercetin and vincristine	Breast cancer	(22)
CPX-1	Colorectal cancer	(23)
Transferrin-conjugated liposome co-encapsulating doxorubicin and verapamil	Leukemia	(24)
Cationic liposome co-encapsulating SiRNA and doxorubicin	Lung cancer	(19)
CPX-571	Small-cell lung cancer	(25)

as well as hydrogen, and chemical bonds. The preclinical studies on dendrimers have largely focused on developing dendrimer-drug conjugates (4).

Collectively, the unique attributes of dendrimers make them suitable platforms for simultaneous delivery of water soluble and insoluble agents. For example, the hydrophobic core of dendrimers includes a hole encapsulating hydrophobic drugs. On the other hand, the multivalent outer layers can be conjugated with hydrophilic medications (6).

Although several attempts have been made to deliver multiple drugs using dendritic platforms (6), dendrimers have not attracted as much notice as liposomes and polymeric nanoparticles. So far, a dendrimer-based compound (i.e. 5 poly-propyleneimine) has been utilized to co-encapsulate methotrexate (a hydrophobic chemotherapeutic) and all-trans retinoic acid (a hydrophilic drug with mild anticancer activity) (29,30).

Nanoparticle albumin-bound (nab) technology

Albumin is a vital plasma protein carrying hydrophobic molecules by forming reversible noncovalent bonds. Albumin is highly concentrated in tumors, and therefore nanoparticle albumin-bound (nab) platforms can be promising carriers to deliver hydrophobic chemotherapeutics to tumors (31).

The traditional formulations for constructing hydrophobic remedial agents use toxic solvents and surfactants such as Cremophor EL and Tween. These agents can deter the dispersal and delivery of the active drug component by micellar sequestration. On the contrary, the "nab" technology allows combination of hydrophobic molecules with albumin through noncovalent hydrophobic interactions to build 50–150 nm colloidal nanoparticles (32). These nab-paclitaxel nanoparticles have a narrow size distribution with an average particle size of round 130 nm as verified by dynamic laser light scattering (32, 33).

Briefly, the "nab" technology is a nanoparticle-based drug delivery platform constructed on the unique functional attributes of albumin which permits efficient diffusion of drug in tumor tissues and obviates the need for using toxic solvents (32).

Recent research based on the maximum-tolerated dosage showed that antitumor activity of nab-paclitaxel was superior or at least equal to that of polysorbate-based docetaxel in prostate, breast, colon, and lung cancer xenograft models (34). In preclinical investigations on pancreatic cancer models, the combinational therapy with nab-paclitaxel and gemcitabine showed strong antitumor activity with higher concentration of gemcitabine within the tumor which may be attributed to either the capability of nab-paclitaxel to disturb tumor stroma (35) or reduce the activity of cytidine deaminase, the primary gemcitabine metabolizing enzyme (36).

Metal nanoparticles

In recent years, metal oxide nanoparticles have grabbed significant attentions in biomedical fields (37), in particular developing nanovaccine scaffolds. Due to their tendency to penetrate into a wide range of cells, these nanoparticles have also been interesting candidates for cancer therapy (38,39).

Metal oxide nanoparticles have unique physical (e.g. fluorescent enhancement and plasmonic resonance) and chemical (e.g. catalytic activity) properties delivering them appropriate agents as drug carriers (40-47). Metal nanoparticles have larger surface area, higher surface area to volume ratio, and characteristics physicochemical properties (such as high toxicity against cancer cells due to structural properties and inducing reactive oxygen species, as well as photothermal, and hyperthermia effects) which make them potential platforms for cancer therapy. Regarding their unique properties such as photoluminescence and superparamagnetic attributes, metal nanoparticles have also been investigated in diagnostic and imaging procedures (41-43). Metallic nanoshells which usually contain metals such as gold (Au) or titanium (Ti) have been employed to control the gradual release of chemotherapeutic agents in tumor tissues (45-47).

Silica nanoparticles

Silica is a critical constituent of human cells. Amorphous silica is a nontoxic, biocompatible and biodegradable agent that is widely distributed throughout the human body and excreted in urine (48).

For the first time, Unger-K et al, conjugated drugs to sol-gel derivative of silica (SiO_2) in 1983 (49). Since then, silica-based substances have been well characterized as drugs and molecules carriers (50,53), gene transfection elements (51) and cell identifiers (52).

A challenging problem in cancer treatment is the unavailability of efficient biocompatible systems to transfer many hydrophobic remedial anticancer drugs (54). Amongst various drug-delivery methods, mesoporous silica substances (55) have been effective in transferring water-insoluble medicines. The large surface area and spongy interiors of silica substances potentiate them for loading large quantities of hydrophobic therapeutics (54). On the other hand, mesoporous silica nanoparticles including fluorescein isothiocyanate (a widely used fluorescence color) are highly biocompatible promising an efficient system to deliver hydrophobic anticancer medicines (56).

In this regard, *in vitro* investigations showed that mesoporous silica nanoparticles were effective in simultaneous delivering of doxorubicin and SiRNA to cancer cells promoting the efficiency of chemotherapy (6).

As a matter of fact, the great capacity of mesoporous silica substances to absorb drugs can be enhanced by controlling their attributes such as the size and the number

of surface holes of the particles. Furthermore, the capacity of mesoporous silica nanoparticles to absorb drugs can also be promoted by optimizing medicine incorporation environment (57, 58).

Carbon nanotubes

In recent years, carbon nanotubes (CNTs) have gained increasing interests by many scientists worldwide. The drug and gene delivery capacities of CNTs along with their surface properties and unique physicochemical attributes beacon novel and efficient nanomaterial-based systems for cancer treatment (59).

Single-wall carbon nanotubes (SWNTs) present notable opportunities to address progressive challenges of drug delivery methods (60, 61). Some approaches have been introduced to link biological molecules such as proteins, DNA, and smaller molecules to SWNTs (62, 63). Based on their biocompatibility, excretion properties, and minor toxicity, chemically functionalized SWNTs have been effective in combinational cancer-targeted therapy in mice (64).

Overall, functionalized and solubilized SWNTs can carry proteins, peptides, DNA, and genes (65, 66) by penetrating through cell membranes with minor cytotoxicity (67, 68). SWNTs present large surface area per unit of weight delivering great drug loading capacity (69). In addition, *in vivo* and *in vitro* studies on cancer cells viability have clarified that oxidized SWNTs bio-conjugated with cisplatin and epidermal growth factor (EGF) receptor ligand can selectively and effectively target squamous carcinoma cells overexpressing EGF receptor (59).

Discussion

Targeted delivery

Numerous novel biotechnological methods have been developed in the past decades to treat cancer. Nanomedicine represents a filed aiming to develop diagnostic and therapeutic instruments and approaches based on nanoparticles (70). Because of providing safe and effective platforms, nanomedicine is rapidly getting recognition especially in anticancer therapy (71).

Although chemotherapeutic agents encapsulated within nanoparticles are highly powerful against cancer cells, they may inflict collateral harms on adjacent healthy tissues as well. Therefore, targeted delivery of these compounds toward tumor cells is highly important in the development of nanoparticle-based therapeutics. Although nanoparticles can passively be accumulated at the tumor site because of their high permeability and stability, active targeting of these compounds can further facilitate the process (6).

Conclusively, nanoparticles encapsulated drugs (such as Genexol- PM 1 and Doxil 1) boost pharmaceutical solubility and pharmacokinetic properties of drugs and lessen the cytotoxicity of chemotherapeutics in used for cancer therapy (71).

Recent studies have confirmed that liposomes, polymeric nanoparticles and dendrimers have surface functional groups which can be conjugated with target ligands such as antibodies (4, 6,72, 73), peptides (Lyp1 and RGD) (74), oligonucleotides (aptamers) (75) and antibody variants (single-chain changeable pieces and diabodies) (76) to specifically target drugs toward tumors.

Although nanoparticles as drug carriers have many benefits, there are still many limitations such as poor oral bioavailability, week traceability in circulation, insufficient tissue supply, and toxicity which need to be resolved.

Conclusion

As mentioned, the unique attributes of nanoparticle-based drug carriers generate suitable agents for therapeutic purposes in oncology. While nanomedicine is a comparatively novel science, it is rapidly transforming into a practical field in medicine. Nanoparticle-encapsulated chemotherapeutics are expected to attain widespread applications as cancer therapeutics in the future. In spite of this, limited number of them have been approved for clinical use, and there are still disadvantages needed to be resolved before their widespread clinical application. More clinical studies are required to completely understand the benefits and harms of nanoparticle remedials.

Author's contribution

Mohamad Ali Dayani is the single author of the paper.

Conflicts of interest

The author declared no competing interests.

Ethical considerations

Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the author.

Funding/Support

None.

References

1. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. Nat Nanotechnol. 2007;2:751-60. doi: 10.1038/nnano.2007.387.
2. Ross JS, Schenkein DP, Pietrusko R, Rolfe M, Linette GP, Stec J, et al. Targeted therapies for cancer 2004. Am J Clin Pathol.2004;122:598-609. doi: 10.1309/5CWP-U41A-FR1V-YM3F.
3. Cho K, Wang X, Nie S, Shin DM. Therapeutic nanoparticles for drug delivery in cancer. Clin Cancer Res. 2008;14:1310-6. doi: 10.1158/1078-0432.CCR-07-1441.
4. Wang AZ, Langer R, Farokhzad OC. Nanoparticle delivery of cancer drugs. Ann Rev med. 2012;63:185-98.
5. Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer Res. 1986;46:6387-92.
6. Hu C-MJ, Aryal S, Zhang L. Nanoparticle-assisted combination therapies for effective cancer treatment. Ther Deliv. 2010;1:323-34.
7. Allen TM. Ligand-targeted therapeutics in anticancer therapy.

Nat Rev Cancer. 2002;2:750-63. doi: 10.1038/nrc903.
8. Maeda H. The enhanced permeability and retention (EPR) effect in tumor vasculature: the key role of tumor-selective macromolecular drug targeting. Adv Enzyme Regul. 2001;41:189-207.
9. Larsen AK, Escargueil AE, Skladanowski A. Resistance mechanisms associated with altered intracellular distribution of anticancer agents. Pharmacol Ther. 2000;85:217-29.
10. Bangham A. Liposomes: the Babraham connection. Chem Phys Lipids. 1993;64:275-85.
11. Torchilin VP. Recent advances with liposomes as pharmaceutical carriers. Nat Rev Drug Discov. 2005;4:145-60. doi: 10.1038/nrd1632.
12. Glantz MJ, Jaeckle KA, Chamberlain MC, Phuphanich S, Recht L, Swinnen LJ, et al. A randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal methotrexate in patients with neoplastic meningitis from solid tumors. Clin Cancer Res. 1999;5:3394-402.
13. Jaeckle KA, Batchelor T, O'Day SJ, Phuphanich S, New P, Lesser G, et al. An open label trial of sustained-release cytarabine (DepoCyt™) for the intrathecal treatment of solid tumor neoplastic meningitis. J Neurooncol. 2002;57:231-9.
14. Anonymous. Vincristine liposomal–INEX: lipid-encapsulated vincristine, onco TCS, transmembrane carrier system–vincristine, vincacine, vincristine sulfate liposomes for injection, VSLI. Drugs R D. 2004;5:4.
15. Hubert A, Lyass O, Pode D, Gabizon A. Doxil (Caelyx): an exploratory study with pharmacokinetics in patients with hormone-refractory prostate cancer. Anticancer Drugs. 2000;11:123-7.
16. Judson I, Radford JA, Harris M, Blay J-Y, Van Hoesel Q, Le Cesne A, et al. Randomised phase II trial of pegylated liposomal doxorubicin (DOXIL/CAELYX) versus doxorubicin in the treatment of advanced or metastatic soft tissue sarcoma: a study by the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer. 2001;37:870-7.
17. Forssen E, Male-Brune R, Adler-Moore J, Lee M, Schmidt P, Krasieva T, et al. Fluorescence imaging studies for the disposition of daunorubicin liposomes (DaunoXome) within tumor tissue. Cancer Res. 1996;56:2066-75.
18. Guaglianone P, Chan K, Dela Flor-Weiss E, Hanisch R, Jeffers S, Sharma D, et al. Phase I and pharmacologie study of liposomal daunorubicin (DaunoXome). Invest New Drugs. 1994;12:103-10.
19. Saad M, Garbuzenko OB, Minko T. Co-delivery of siRNA and an anticancer drug for treatment of multidrug-resistant cancer. Nanomedicine (Lond). 2008;3:761-76. doi: 10.2217/17435889.3.6.761.
20. Tardi P, Johnstone S, Harasym N, Xie S, Harasym T, Zisman N, et al. In vivo maintenance of synergistic cytarabine: daunorubicin ratios greatly enhances therapeutic efficacy. Leuk Res. 2009;33:129-39. doi: 10.1016/j.leukres.2008.06.028.
21. Agrawal V, Paul MK, Mukhopadhyay AK. 6-Mercaptopurine and Daunorubicin Double Drug Liposomes—Preparation, Drug-Drug Interaction and Characterization. J Liposome Res. 2005;15:141-55. doi: 10.1080/08982100500364081.
22. Wong M-Y, Chiu GN. Simultaneous liposomal delivery of quercetin and vincristine for enhanced estrogen-receptor-negative breast cancer treatment. Anticancer Drugs. 2010;21:401-10. doi: 10.1097/CAD.0b013e328336e940.
23. Batist G, Gelmon KA, Chi KN, Miller WH, Chia SK, Mayer LD, et al. Safety, pharmacokinetics, and efficacy of CPX-1 liposome injection in patients with advanced solid tumors. Clin Cancer Res. 2009;15:692-700. doi: 10.1158/1078-0432.CCR-08-0515.
24. Wu J, Lu Y, Lee A, Pan X, Yang X, Zhao X, et al. Reversal of multidrug resistance by transferrin-conjugated liposomes co-encapsulating doxorubicin and verapamil. J Pharm Pharm Sci. 2007;10:350-7.
25. Tardi PG, Dos Santos N, Harasym TO, Johnstone SA, Zisman N, Tsang AW, et al. Drug ratio–dependent antitumor activity of irinotecan and cisplatin combinations in vitro and in vivo. Mol Cancer Ther. 2009;8:2266-75. doi: 10.1158/1535-7163.MCT-09-0243.
26. Leiknes I, Lien U-T, Severinsson E. The Relationship among Caregiver Burden, Demographic Variables, and the Clinical Characteristics of Patients with Parkinson's Disease—A Systematic Review of Studies Using Various Caregiver Burden Instruments. Open J Nursing. 2015;5:855-877.
27. Gu F, Zhang L, Teply BA, Mann N, Wang A, Radovic-Moreno AF, et al. Precise engineering of targeted nanoparticles by using self-assembled biointegrated block copolymers. Proc Natl Acad Sci U S A. 2008;105:2586-91. doi: 10.1073/pnas.0711714105.
28. Baker JR. Dendrimer-based nanoparticles for cancer therapy. Hematology Am Soc Hematol Educ Program. 2009:708-19. doi: 10.1182/asheducation-2009.1.708.
29. Tekade RK, Kumar PV, Jain NK. Dendrimers in oncology: an expanding horizon. Chem Rev. 2008;109:49-87.
30. Tekade RK, Dutta T, Gajbhiye V, Jain NK. Exploring dendrimer towards dual drug delivery: pH responsive simultaneous drug-release kinetics. J Microencapsul. 2009;26:287-96. doi: 10.1080/02652040802312572.
31. Hawkins MJ, Soon-Shiong P, Desai N. Protein nanoparticles as drug carriers in clinical medicine. Adv Drug Deliv Rev. 2008;60:876-85. doi: 10.1016/j.addr.2007.08.044.
32. Desai N. Nanoparticle Albumin-Bound Anticancer Agents. Non-Biological Complex Drugs:. Springer; 2015. p. 335-54.
33. Gradishar WJ. Albumin-bound paclitaxel: a next-generation taxane. Expert Opin Pharmacother. 2006;7:1041-53. doi: 10.1517/14656566.7.8.1041 .
34. Desai NP, Trieu V, Hwang LY, Wu R, Soon-Shiong P, Gradishar WJ. Improved effectiveness of nanoparticle albumin-bound (nab) paclitaxel versus polysorbate-based docetaxel in multiple xenografts as a function of HER2 and SPARC status. Anticancer Drugs. 2008;19:899-909. doi: 10.1097/CAD.0b013e32830f9046.
35. Alvarez R, Musteanu M, Garcia-Garcia E, Lopez-Casas P, Megias D, Guerra C, et al. Stromal disrupting effects of nab-paclitaxel in pancreatic cancer. Br J Cancer. 2013;109:926-33. doi: 10.1038/bjc.2013.415.
36. Frese KK, Neesse A, Cook N, Bapiro TE, Lolkema MP, Jodrell DI, et al. nab-Paclitaxel potentiates gemcitabine activity by reducing cytidine deaminase levels in a mouse model of pancreatic cancer. Cancer Discov. 2012;2:260-9. doi: 10.1158/2159-8290.CD-11-0242.
37. Kostarelos K, Bianco A, Prato M. Promises, facts and challenges for carbon nanotubes in imaging and therapeutics. Nat Nanotechnol. 2009;4:627-33. doi: 10.1038/nnano.2009.241.
38. Kostarelos K, Lacerda L, Pastorin G, Wu W, Wieckowski S, Luangsivilay J, et al. Cellular uptake of functionalized carbon nanotubes is independent of functional group and cell type. Nat Nanotechnol. 2007;2:108-13. doi: 10.1038/nnano.2006.209.
39. Kovacsovics-Bankowski M, Rock K. A phagosome-to-cytosol pathway for exogenous antigens presented on MHC class I molecules. Science. 1995;267:243-6. doi: 10.1126/science.7809629.
40. Cole AJ, Yang VC, David AE. Cancer theranostics: the rise of targeted magnetic nanoparticles. Trends Biotechnol. 2011;29:323-32. doi: 10.1016/j.tibtech.2011.03.001.
41. Ahmed N, Fessi H, Elaissari A. Theranostic applications of nanoparticles in cancer. Drug Discov Today. 2012;17:928-34.

doi: 10.1016/j.drudis.2012.03.010.
42. Khan MS, Vishakante GD, Siddaramaiah H. Gold nanoparticles: a paradigm shift in biomedical applications. Adv Colloid Interface Sci. 2013;199-200:44-58. doi: 10.1016/j.cis.2013.06.003.
43. Li J, Gupta S, Li C. Research perspectives: gold nanoparticles in cancer theranostics. Quant Imaging Med Surg. 2013;3:284-291. doi: 10.3978/j.issn.2223-4292.2013.12.02.
44. Minelli C, Lowe SB, Stevens MM. Engineering nanocomposite materials for cancer therapy. Small. 2010;6:2336-57. doi: 10.1002/smll.201000523.
45. Kleibert A, Rosellen W, Getzlaff M, Bansmann J. Structure, morphology, and magnetic properties of Fe nanoparticles deposited onto single-crystalline surfaces. Beilstein J Nanotechnol. 2011;2:47-56. doi: 10.3762/bjnano.2.6.
46. Rasmussen JW, Martinez E, Louka P, Wingett DG. Zinc oxide nanoparticles for selective destruction of tumor cells and potential for drug delivery applications. Expert Opin Drug Deliv. 2010;7:1063-77. doi: 10.1517/17425247.2010.502560.
47. Sharma H, Mishra PK, Talegaonkar S, Vaidya B. Metal nanoparticles: a theranostic nanotool against cancer. Drug Discov Today. 2015;20:1143-51. doi: 10.1016/j.drudis.2015.05.009.
48. Rosenholm JM, Meinander A, Peuhu E, Niemi R, Eriksson JE, Sahlgren C, et al. Targeting of porous hybrid silica nanoparticles to cancer cells. ACS Nano. 2009;3:197-206. doi: 10.1021/nn800781r.
49. Unger K, Rupprecht H, Valentin B, Kircher W. The use of porous and surface modified silicas as drug delivery and stabilizing agents. Drug Dev Ind Pharm. 1983;9:69-91.
50. Arruebo M, Galán M, Navascués N, Téllez C, Marquina C, Ibarra MR, et al. Development of magnetic nanostructured silica-based materials as potential vectors for drug-delivery applications. Chem Mater. 2006;18:1911-9.
51. Radu DR, Lai C-Y, Jeftinija K, Rowe EW, Jeftinija S, Lin VS-Y. A polyamidoamine dendrimer-capped mesoporous silica nanosphere-based gene transfection reagent. J Am Chem Soc. 2004;126:13216-7.
52. Lin Y-S, Tsai C-P, Huang H-Y, Kuo C-T, Hung Y, Huang D-M, et al. Well-ordered mesoporous silica nanoparticles as cell markers. Chem Mater. 2005;17:4570-3.
53. Lai C-Y, Trewyn BG, Jeftinija DM, Jeftinija K, Xu S, Jeftinija S, et al. A mesoporous silica nanosphere-based carrier system with chemically removable CdS nanoparticle caps for stimuli-responsive controlled release of neurotransmitters and drug molecules. JAm Chem Soc. 2003;125:4451-9.
54. Lu J, Liong M, Zink JI, Tamanoi F. Mesoporous silica nanoparticles as a delivery system for hydrophobic anticancer drugs. Small. 2007;3:1341-6.
55. Kresge C, Leonowicz M, Roth W, Vartuli J, Beck J. Ordered mesoporous molecular sieves synthesized by a liquid-crystal template mechanism. Nature. 1992;359:710-2.
56. Lu J, Liong M, Sherman S, Xia T, Kovochich M, Nel AE, et al. Mesoporous silica nanoparticles for cancer therapy: energy-dependent cellular uptake and delivery of paclitaxel to cancer cells. Nanobiotechnology. 2007;3:89-95. doi: 10.1007/s12030-008-9003-3.
57. Rosenholm J. Modular design of mesoporous silica materials: towards multifunctional drug delivery systems: Åbo Akademi University; 2008.
58. Rosenholm JM, Lindén M. Towards establishing structure–activity relationships for mesoporous silica in drug delivery applications. J Control Release. 2008;128:157-64. doi: 10.1016/j.jconrel.2008.02.013.
59. Bhirde AA, Patel V, Gavard J, Zhang G, Sousa AA, Masedunskas A, et al. Targeted killing of cancer cells in vivo and in vitro with EGF-directed carbon nanotube-based drug delivery. ACS nano. 2009;3:307-16. doi: 10.1021/nn800551s.
60. Bianco A, Kostarelos K, Prato M. Opportunities and challenges of carbon-based nanomaterials for cancer therapy. Expert Opin Drug Deliv. 2008;5:331-42. doi: 10.1517/17425247.5.3.331 .
61. Dai H. Carbon nanotubes: synthesis, integration, and properties. Acc Chem Res. 2002;35:1035-44.
62. Bianco A, Kostarelos K, Partidos CD, Prato M. Biomedical applications of functionalised carbon nanotubes. Chem Commun (Camb). 2005 :571-7. doi: 10.1039/b410943k.
63. Singh R, Pantarotto D, McCarthy D, Chaloin O, Hoebeke J, Partidos CD, et al. Binding and condensation of plasmid DNA onto functionalized carbon nanotubes: toward the construction of nanotube-based gene delivery vectors. J Am Chem Soc. 2005;127:4388-96.
64. Liu Z, Chen K, Davis C, Sherlock S, Cao Q, Chen X, et al. Drug delivery with carbon nanotubes for in vivo cancer treatment. Cancer Res. 2008;68:6652-60. doi: 10.1158/0008-5472.CAN-08-1468.
65. Kam NWS, Dai H. Carbon nanotubes as intracellular protein transporters: generality and biological functionality. J Am Chem Soc. 2005;1276021-6.
66. Liu Z, Winters M, Holodniy M, Dai H. siRNA Delivery into Human T Cells and Primary Cells with carbon-nanotube transporters. Angew Chem Int Ed Engl. 2007;46:2023-7. doi: 10.1002/anie.200604295.
67. Schipper ML, Nakayama-Ratchford N, Davis CR, Kam NWS, Chu P, Liu Z, et al. A pilot toxicology study of single-walled carbon nanotubes in a small sample of mice. Nat Nanotechnol. 2008;3:216-21. doi: 10.1038/nnano.2008.68.
68. Singh R, Pantarotto D, Lacerda L, Pastorin G, Klumpp C, Prato M, et al. Tissue biodistribution and blood clearance rates of intravenously administered carbon nanotube radiotracers. Proc Natl Acad Sci U S A. 2006;103:3357-62. doi: 10.1073/pnas.0509009103.
69. Dhar S, Liu Z, Thomale J, Dai H, Lippard SJ. Targeted single-wall carbon nanotube-mediated Pt (IV) prodrug delivery using folate as a homing device. J Am Chem Soc. 2008;130:11467-76.
70. Sanna V, Pala N, Sechi M. Targeted therapy using nanotechnology: focus on cancer. Int J Nanomedicine. 2014;9:467-483.
71. Xu X, Ho W, Zhang X, Bertrand N, Farokhzad O. Cancer nanomedicine: from targeted delivery to combination therapy. Trends Mol Med. 2015;21:223-32. doi: 10.1016/j.molmed.2015.01.001.
72. Park J, Kirpotin D, Hong K, Shalaby R, Shao Y, Nielsen U, et al. Tumor targeting using anti-her2 immunoliposomes. J Control Release. 2001;74:95-113.
73. Sapra P, Allen TM. Internalizing antibodies are necessary for improved therapeutic efficacy of antibody-targeted liposomal drugs. Cancer Res. 2002;62:7190-4.
74. Arap W, Pasqualini R, Ruoslahti E. Cancer treatment by targeted drug delivery to tumor vasculature in a mouse model. Science. 1998;279:377-80. doi: 10.1126/science.279.5349.377.
75. Farokhzad OC, Cheng J, Teply BA, Sherifi I, Jon S, Kantoff PW, et al. Targeted nanoparticle-aptamer bioconjugates for cancer chemotherapy in vivo. Proc Natl Acad Sci U S A. 2006;103:6315-20.
76. Leyton JV, Olafsen T, Sherman MA, Bauer KB, Aghajanian P, Reiter RE, et al. Engineered humanized diabodies for microPET imaging of prostate stem cell antigen-expressing tumors. Protein Eng Des Sel. 2009;22:209-16. doi: 10.1093/protein/gzn055.