# Nanomaterials Potentiating Standard Chemotherapy Drugs' Effect

S. O. Kazantsev[1,2,a)] and M. S. Korovin[2,3,b)]

[1] National Research Tomsk Polytechnic University, Tomsk, 634050 Russia
[2] Institute of Strength Physics and Materials Science SB RAS, Tomsk, 634055 Russia
[3] Siberian State Medical University, Tomsk, 634050 Russia

[a)] Corresponding author: kzso@ispms.tsc.ru
[b)] msk@ispms.tsc.ru

**Abstract.** Application of antitumor chemotherapeutic drugs is hindered by a number of barriers, multidrug resistance that makes effective drug deposition inside cancer cells difficult is among them. Recent research shows that potential efficiency of anticancer drugs can be increased with nanoparticles. This review is devoted to the application of nanoparticles for cancer treatment. Various types of nanoparticles currently used in medicine are reviewed. The nanoparticles that have been used for cancer therapy and targeted drug delivery to damaged sites of organism are described. Also, the possibility of nanoparticles application for cancer diagnosis that could help early detection of tumors is discussed. Our investigations of antitumor activity of low-dimensional nanostructures based on aluminum oxides and hydroxides are briefly reviewed.

## INTRODUCTION

Nanotechnology is a new and promising platform that aims to extend the range of present technologies for biological and biomedical applications [1, 2]. One of the reasons of interest to nanotechnologies is the controlled synthesis of materials and the possibility to obtain predefined physico-chemical characteristics. Also, changing to ultradispersive state gives new characteristics to traditionally used materials that aquire new properties unusual to micrometer-sized materials. Because of their size (less than 100 nm) these materials are similar to cells (10–100 um), natural proteins (5–10 nm), DNA (2 nm wide and 10–100 nm long) in size [3, 4] that allows nanoparticles to be close to biological objects, to interact and to bind with them.

It is known that efficiency of cancer therapy depends not only on the drug itself, but also on drug delivery to target [5]. All cancer cells have various sensitivity to chemotherapeutic drugs. One of the major problems of effective application of standard chemotherapy drugs is the multidrug resistance of cancer cells that makes the deposition of the drug inside tumor cells difficult. As a result of their systemic administration only about 1% of drug reaches tumor cells [6]. In this regard, it is often necessary to increase the concentration of chemotherapy drugs that results in intensive damage of healthy tissues and organs. However, it is known that nanoparticles can deliver drugs to cancer cells and extend drug deposition inside the cells [7–9]. It is also known that nanoparticles with different size have various abilities to penetrate target cells. Some data show that small nanoparticles can penetrate cancer cells more easily than those bigger in size [9, 10]. Therefore, the efficiency of drug delivery by nanoparticles significantly depends on nanoparticles' size and surface functionality.

In the present work, we briefly review the possible application of different nanoparticles in cancer therapy.

### Main Classes of Nanoparticles Used in Medicine

*Biological and biogenic nanoparticles.* DNA and RNA, viruses, ribosomes, etc. are named as biological nanoparticles. The main feature of such objects is their ability to self-organization and aggregation that can be actively used for various artificial constructions imitating natural biological structures. These nanoparticles include

*Physics of Cancer: Interdisciplinary Problems and Clinical Applications*
AIP Conf. Proc. 1882, 020031-1–020031-5; doi: 10.1063/1.5001610
Published by AIP Publishing. 978-0-7354-1562-1/$30.00

liposomes, chitosan, nanoparticles based on nucleic acids, etc. Some of them are being used as targeted drug carriers or in diagnostic applications [11, 12].

*Polymer nanoparticles.* To produce polymer nano-size particles polyethylene glycol, polycaprolactone, polyglycolic acid, etc. are mainly used. As well as biogenic nanoparticles they could be used for drug delivery and for increasing various molecular drug carriers' stability [13].

*Dendrimers.* These are the highly structured polymers. Poliyamides and aminoacid lysine are often used for their synthesis. It is possible to set the definite structure, size, and shape of nanoparticle during their synthesis. The controlled sizes, stability, surface properties and also their effect on membrane pores make the dendrimers very perspective as carriers also for transdermal drug delivery [14].

*Carbon nanoparticles.* Carbon can form hollow spheres, ellipsoids, tubes known as fullerenes, and carbon also so called nanotubes. Carbon nanotubes have two forms: single-walled and multi walled. The unique properties of fullerenes and carbon nanotubes make these particles widely spread. Carbon nanotubes have increased affinity to lipide structures, tumor cells, and may form stable complexes with peptides and DNA-oligonucleotides, which is important for their usage in medicine and in particular in vaccines and genetic material delivery [15–17].

*Inorganic nanoparticles.* Usually nanoparticles based on metal oxides fall into these groups [18–22], and also various metals (silver, gold, iron, aluminum, etc.) [23–27]. These nanoparticles can be used to treat cancer diseases, drugs delivery, and they also can directly effect tumor cells potentiating drugs' effect.

*Micelles.* This type of nanoparticles represents the amphiphilic colloidal structures spontaneously formed in water solutions from monomers and predefined molecules of medical substance after reaching certain monomers concentration (critical micelle concentration) and certain solution temperature (critical micelle temperature). As monomer blocks for micelles' formation it is possible to use polymers (polymeric micelles). Hydrophobic components of amphiphilic molecules form central part of the micelle while hydrophilic form its surface. Micelles have the size of 5–100 nm. Nowadays micelles are used as drug carriers, in particular, for compounds weakly soluble in normal conditions, siRNA, and also for contrast agents' delivery for diagnostics and visualization [28–30].

## Application of Nanoparticles for Cancer Diagnosis

Early diagnosis of cancer diseases is the key to further successful treatment. Modern early diagnostic techniques are based on X-ray computed and magnetic resonance tomography methods. However, these methods allow defining a tumor only when it becomes rather big and contains a large number of cells [31]. In this regard sensitivity and resolution increase are needed. Metal and semiconductor particles can be used in magnetic resonance tomography as contrast agents, and also in fluorescent microscopy and fluorescent tomography. Paramagnetic ions shortening the relaxation time such as Gd3+ are the most used contrast agents for magnetic resonance tomography [32]. It is obvious that using nanoparticles as contrast agents could intensify nuclear magnetic resonance signal. As gadolinium ions cannot be obtained in the form of nanoparticles, gadolinium oxide Gd2O3 nanoparticles are being used [32]. There are also multilayered nanoparticles containing gadolinium ions. Such particles are based on gold nanoparticles with a size of 2 having about 150 gadolinium atoms adsorbed on a surface. These particles increase nuclear magnetic resonance up to 200 times as compared to normal gadolinium ions [32, 33]. Other types of contrast agents used in magnetic resonance therapy are iron oxide nanoparticles with a size of 50 nm. They can significantly improve tomography tumors' image and their early diagnosis [32, 34].

Nanotechnologies and semiconductor nanoparticles gave rise to active luminescent diagnostics. The application of fluorescent nanolabels gives advantage for the tumor image as compared to standard dyes. It is easy to distinguish nanoparticles' fluorescence from the different tissue components or dyes background. Moreover, nanoparticles' fluorescence lifetime is 20-50 ns, which is 10 times more than that of the dyes. Tumor image having 10-100 pathological cells can be obtained using fluorescence nanoparticles [35–38].

## Using Nanoparticles in Drug Delivery

Nowadays, there are many anticancer drugs that effectively fight with tumor cells. Mostly anticancer drugs are hydrophobic, which in its turn complicates their delivery [32]. In this regard finding targeted delivery ways for medical preparations with their minimal damage during delivery, and also minimization or complete elimination of their interaction with normal cells of organism and other biological structures become the key challenge.

The list of nanoparticles that have been applied already or will be applied for drug delivery systems development in the near future is rather big. These are fullerenes, dendrimers, lipoparticles, gold, silver, magnetic nanoparticles, nanoparamagnetics, nanopowders, and nanocrystalls, nanoparticles based on silicon, etc. Generally carbon nanotubes, porous silicon, polymer nanoparticles, micelles and biodegradable liposomes having the best characteristics for encapsulating a large number of drugs [32] are used for drugs delivery.

The most promising items for drugs delivery in oncology are magnetic nanoparticles. This method is based on drug delivery to tumor using magnetic nanoparticles and the external magnetic field focused on them [32, 39–41]. Magnetic liposomes are of great interest. They represent liposomes loaded with magnetic nanoparticles and drugs. Using magnetic liposomes has several advantages such as covering the surface with specific ligands for biological targeting; protection of the drug. Magnetic liposomes allow conducting treatment and diagnostics simultaneously for malignant tumors [6, 39, 42].

## Using Nanoparticles in Cancer Therapy

Cancer therapy has been developed in the traditional and new directions.

Using nanoparticles as photosensitizers in photodynamic therapy is a traditional approach [32]. Photodynamic therapy is based on selective accumulation of photosensitizer in tumor cells and its ability to generate singlet oxygen as a result of light radiation with a certain wavelength, i.e. oxygen passes into an excited state, which results in cancer cell death. As the majority of the standard photosensitizers belong to toxic substances, their application leads to multiple side effects [32]. There has been targeted searching for nontoxic substances that are able to move oxygen to excited state and minimize toxicity of photodynamic therapy. Porous silicon [43] and carbon nanostructures—fullerens [32, 44]—are of great interest among these structures. They can effectively generate singlet oxygen at the same time being less toxic.

Metal particles heating with IR-laser serve as a non-traditional approach in cancer therapy with nanoparticles. Gold or silver nanoparticles are used mainly for such therapy [45, 46]. The main characteristic of metal nanoparticles is the presence of electromagnetic energy resonance absorption while the size of the nanoparticle is much less than a wavelength. It is explained by a surface plasmon resonance—electronic gas collective oscillations on a surface of nanoparticle [32]. Plasmon resonance wavelength depends on nanoparticles' shape and size, on the presence of the cluster or aggregate in composition, and on the properties of their local dielectric environment [32].

Some types of nanoparticles themselves possess antitumor effect. Some data have demonstrated antiproliferative effect of zinc nanoparticles [47], carbon nanotubes [48], copper nanoparticles [49]. It is shown in [18, 19, 50–53] that aluminum hydroxide phases obtained with water oxidation [50–53] of electroexplosive aluminum powders [54, 55] have antitumor activity. It was shown that folded boehmite nanosheet agglomerates have the most antitumor effect [18, 19]. Possible mechanism of antitumor effect is caused by change of the ionic balance of the extracellular environment, also because of pH increase [56, 57]. However, anticancer effect needs further investigating.

## CONCLUSION

Unique properties acquired by nanodimensional substances allow using them widely to improve old and to develop new medical technologies. That is why nanoparticles are widely spread in treatment of cancer diseases. Nanoparticles can be used for targeted drugs' delivery to tumor cells, potentiating effect of standard chemotherapeutic drugs. At the same time, dose of the drug is decreasing resulting in less effect to normal cells. In this review, we tried to characterize the main types of nanoparticles and their applications in oncology. However, more attention should be paid to studying the consequences of the administration of nanoparticles of different sizes and characteristics in a blood stream as they can accumulate in tissues and organs, and also to nanoparticles elimination from organism. Moreover, when using nanoparticles, one should keep in mind their possible toxic and other side effects.

## ACKNOWLEDGMENTS

The presented research was conducted in the frames of the Fundamental Research Program of the State Academies of Sciences for 2016–2020.

## REFERENCES


1. N. V. Svarovskaya, A. V. Berenda, O. V. Bakina, E. A. Glazkova, A. S. Lozhkomoev, E. G. Khorobraya, V. V. Domashenko, M. I. Lerner, and A. N. Fomenko, Prog. Nat. Sci. Mater. Int. **25**(1), 1–5 (2015).
2. A. S. Lozhkomoev, E. A. Glazkova, E. G. Khorobraya, M. I. Lerner, A. N. Maltsev, and V. G. Podkovyrov, Russ. Phys. J. **56**(4), 384–388 (2013).
3. S. E. McNeil, J. Leukocyte Biolog. **78**, 585–594 (2005).
4. O. V. Salata, J. Nanobiotechnology **2:3** (2004).
5. C. Alexiou, W. Arnold, R. J. Klein, F. G. Parak, P. Hulin, C. Bergemann, W. Erhardt, S. Wagenpfeil, and A. S. Lübbe, Cancer Res. **60**, 6641–6648 (2000).
6. G. A. Mikhaylov and O. S. Vasiljeva, Report SB RAS **3**(131), 18–22 (2008).
7. T. K. Jain, M. A. Morales, S. K Sahoo, D. L. Leslie-Pelecky, and V. Labhasetwar, Molecular Pharmaceutics **2**(3), 194–205 (2005).
8. W. Wu, S. Wieckowski, G. Pastorin, M. Benincasa, C. Klumpp, J. P. Briand, R. Gennaro, M. Prato, and A. Bianco, Anqew. Chem. Int. Ed. **44**, 6358–6362 (2005).
9. R. Zhang, X. Wang, C. Wu, M. Song, J. Li, G. Lv, J. Zhou, C. Chen, Y. Dai, F. Gao, D. Fu, X. Li, Z. Guan, and B. Chen, Nanotechnology **17**, 3622–3626 (2006).
10. S. M. Moghimi, A. C. Hunter, and J. C. Murray, Pharmacol. Rev. **53**(2), 283–318 (2001).
11. B. Chu, D. Liang, M. Hadjiargyrou, and B. Hsiao, J. Phys. Condens. Matter **18**, 2513–2525 (2006).
12. C. Riviere, S. Roux, O. Tillement, C. Billotey, and P. Perriat, Ann. Chim. Sci. Mater. **31**, 351–367 (2006).
13. V. M. Lakhtin, S. S. Afanasyev, M. V. Lakhtin, V. A. Aleshkin, Y. V. Nesvizhsky, and V. V. Pospelova, Annals Russ. Acad. Med. Sci. **4**, 50–55 (2008).
14. U. Gupta, H. B. Agashe, A. Asthana, and N. K. Jain, Nanomed. Nanotechnol. Biol. Med. **2**, 66–73 (2006).
15. H. S. Choi, W. Liu, P. Misra, E. Tanaka, J. P. Zimmer, B. I. Ipe, M. G. Bawendi, and J. V. Frangioni, Nat. Biotechnology **25**(10), 1165–1170 (2007).
16. G. Hughes, Nanomed. Nanotechnol. Biol. Med. **1**, 22–30 (2005).
17. B. Trzaskowski, A. Jalbout, and L. Adamowicz, Chem. Phys. Lett. **430**, 97–100 (2006).
18. A. N. Fomenko, M. S. Korovin, O. V. Bakina, S. O. Kazantsev, E. A. Glazkova, N. V. Svarovskaya, and A. S. Lozhkomoev, AIP Conf. Proc. **1683**, 020054 (2015).
19. S. O. Kazantsev, A. N. Fomenko, and M. S. Korovin, AIP Conf. Proc. **1683**, 020080 (2015).
20. R. Zhang, X. Wang, C. Wu, M. Song, J. Li, G. Lv, J. Zhou, C. Chen, Y. Dai, F. Gao, D. Fu, X. Li, Z. Guan, and B. Chen, Nanotechnology **17**, 3622–3626 (2006).
21. J. W. Rasmussen, E. Martinez, P. Louka, and D. G. Wingett, Expert Opin. Drug Deliv **7**(9), 1063–1077 (2010).
22. A. Simon-Deckers, B. Gouget, M. Mayne-L'Hermite, N. Herlin-Boime, C. Reynaud, and M. Carriere, Toxicology **253**, 137–146 (2008).
23. R. K. Thapa, J. H. Kim, J. H. Jeong, B. S. Shin, H. G. Choi, C. S. Yong, and J. O. Kim, Colloids Surfaces B Biointerfaces **153**, 95–103 (2017).
24. C. Fajardo, M. L. Sacca, G. Costa, M. Nande, and M. Martin, Sci. Total Environment **473–474**, 254–261 (2014).
25. S. T. Yang, T. Wang, E. Dong, X. X. Chen, K. Xiang, J. H. Liu, Y. Liu, and H. Wang, Toxicol. Res. **1**, 69–74 (2012).
26. Y. Pan, Q. Wu, R. Liu, M. Shao, J. Pi, X. Zhao, and L. Qin, Bioorgan. Med. Chem. Lett. **24**, 679–684 (2014).
27. M. Prasek, E. Sawosz, S. Jaworski, M. Grodzik, T. Ostaszewska, M. Kamaszewski, M. Wierzbicki, and A. Chwalibog, Nanoscale Res. Lett. **8:251** (2013).
28. R. Mallipeddi and L. C. Rohan, Int. J. Nanomedicine **5**, 533–547 (2010).
29. V. P. Torchillin, Pharm. Res. **24**(1) (2007).
30. K. A. Whitehead, R. Langer, and D. G. Anderson, Nat. Rev. Drug Discov. **8**, 129–138 (2009).
31. B. X. Li, Nano-oncology. Harvard Science Review. Small Science. **19(2)**, 42-45 (2006).
32. Y. P. Meshalkina and N. P. Bgatova, J. Sib. Fed. Univer. Biol. **3**, 248–268 (2008).
33. P.-J. Debouttiere, S. Roux, F. Vocanson, C. Billotey, O. Beuf, A. Favre-Reguillon, Y. Lin, S. Pellet-Rostaing, R. Lamartine, P. Perriat, and O. Tillement, Adv. Funct. Mater. **16**, 2330–2339 (2006).
34. J. H. Lee, Y. M. Huh, Y. W. Jun, J. W. Seo, J. T. Jang, H. T. Song, S. Kim, E. J. Cho, H. G. Yoon, J. S. Suh, and J. Cheon, Nat. Med. **13**(1), 95–99 (2007).
35. P. Alivisatos, Nat. Biotechnol. **22**(1), 47–52 (2004).

36. Q. M. Chermont, C. Chaneac, J. Seguin, F. Pelle, S. Maitrejean, J. P. Jolivet, D. Gourier, M. Bessodes, and D. Scherman, Proc. Natl. Acad. Sci. USA **104**(22), 9266–9271 (2007).
37. S. Nie, Y. Xing, G. J. Kim, and J. W. Simons, Annu. Rev. Biomed. Eng. **9**, 257–288 (2007).
38. L. D. True and X. Gao, J. Molecular Diagnostics **9**(1), 7–11 (2007).
39. A. Ito, M. Shinkai, H. Honda, and T. J. Kobayashi, J. Biosci. Bioeng **100**(1), 1–11 (2005).
40. R. Jurgons, C. Seliger, A. Hilpert, L. Trahms, S. Odenbach, and C. Alexiou, J. Phys. Condens. Mat. **18**, 2893–2902 (2006).
41. H. Nobuto, T. Sugita, T. Kubo, S. Simose, Y. Yasunaga, T. Murakami, and M. Ochi, Int. J. Cancer **109**(4), 627–635 (2004).
42. J. P. Fortin-Ripoche, M. S. Martina, F. Gazeau, C. Menager, C. Wilhelm, J. C. Bacri, S. Lesieur, and O. Clement, Radiology **239**(2), 415–424 (2006).
43. D. Kovalev, E. Gross, N. Künzer, and F. Koch, Phys. Rev. Lett. **89**(13), 137401 (2002).
44. P. Mroz, A. Pawlak, M. Satti, H. Lee, T. Wharton, H. Gali, T. Sarna, and M. R. Hamblin, Free Radical Biol. Med. **43**, 711–719 (2007).
45. I. H. El-Sayed, X. Huang, and M. A. El-Sayed, Cancer Lett. **239**, 129–135 (2006).
46. J. F. Hainfeld, D. N. Slatkin, T. M. Focella, and H. M. Smilowitz, Br. J. Radiol. **79**, 248–253 (2006).
47. O. I. Kit, E. Yu. Zlatnik, and L. V. Peredelova, Bull. Exp. Biol. Med. **156**(9), 367–370 (2013).
48. O. I. Kit, E. Yu. Zlatnik, and L. V. Peredelova, Bull. Exp. Biol. Med. **156**(9), 348–351 (2013).
49. E. V. Shalashnaya, I. A. Goroshinskaya, and P. S. Kachesova, , Bull. Exp. Biol. Med. **11**, 552–556 (2011).
50. A. S. Lozhkomoev, E. A. Glazkova, N. V. Svarovskaya, O. V. Bakina, S. O. Kazantsev, and M. I. Lerner, AIP Conf. Proc. **1683**, 020127 (2015).
51. A. S. Lozhkomoev, E. A. Glazkova, O. V. Bakina, M. I. Lerner, I. Gotman, E. Y. Gutmanas, S. O. Kazantsev, and S. G. Psakhie, Nanotechnology **27**(20), 205603 (2016).
52. O. V. Bakina, E. A. Glazkova, N. V. Svarovskaya, A. S. Lozhkomoev, E. G. Khorobraya, and S. G. Psakhie, AIP Conf. Proc. **1623**, 35 (2014).
53. O. V. Bakina, N. V. Svarovskaya, E. A. Glazkova, A. S. Lozhkomoev, E. G. Khorobraya, and M. I. Lerner, Adv. Powder Tech. **26**(6), 1512–1519 (2015).
54. M. I. Lerner, A. V. Pervikov, E. A. Glazkova, N. V. Svarovskaya, A. S. Lozhkomoev, and S. G. Psakhie, Powder Technol. **288**, 371–378 (2016).
55. M. I. Lerner, E. A. Glazkova, A. S. Lozhkomoev, N. V. Svarovskaya, O. V. Bakina, A. V. Pervikov, and S. G. Psakhie, Powder Technol. **295**, 307–314 (2016).
56. A. S. Lozhkomoev, M. I. Lerner, A. A. Tsukanov, S. O. Kazantsev, O. V. Bakina, and S. G. Psakhie, Phys. Mesomech. **19**(2), 24–31 (2016).
57. A. S. Lozhkomoev, AIP Conf. Proc. **1760**, 020045 (2016).