Rev.Adv.Mater.Sci. 26(2010) 67-73

MAGNETIC NANOPARTICLES IN CANCER DIAGNOSIS AND TREATMENT: NOVEL APPROACHES

Igor Pantic

University of Belgrade, School of Medicine, Institute of Medical Physiology, Visegradska 26/2, 11000, Belgrade, Serbia

Received: August 13, 2010

Abstract. Despite intensive research efforts, cancer remains one of the leading causes of death in the world. Many new methods and techniques have been developed in order to improve diagnosis and treatment, often promising in the beginning, but with limited results during the course of their application. This concise review focuses on novel approaches in development and production of magnetic nanoparticles, as well as their application in today's cancer diagnosis and treatment.

1. INTRODUCTION

Early in the 21st century, control of cancer is considered to be a major public health issue [1]. Despite intensive research efforts over past few decades, cancer remains one of the leading causes of death in the world. Many new methods and techniques have been developed in order to improve diagnosis and treatment, often promising in the beginning, but with limited results during the course of their application.

Nanotechnology is a relatively new branch of science that studies tools and devices of size 1 to 100 nm with various functions at the cellular, atomic and molecular levels [2]. Some authors define it as "the creation and utilization of materials, devices, and systems through the control of matter on the nanometer-length scale, i.e. at the level of atoms, molecules, and supramolecular structures" [3].

Cancer nanotechnology is currently going through an intense development for applications in cancer imaging, molecular and cellular diagnosis, targeted therapy[4], as well as tissue engineering [5]. The versatility and broad applicability of nanotechnology reflect the spectra of composite materials (e.g. metals, semiconductors or polymers), geometries (e.g. sphere, prism or rod), and structures (e.g. solid, core or shell or dendrimers) that have been generated in order to be used in various cancer diagnostic procedures and treatment [6].

Magnetic nanoparticles (MNPs) are spherical nanocrystals of 10–20 nm of size with a Fe2+ and Fe3+ core, sometimes surrounded by various molecules, such as dextran or polymer polyethylene glycol [7,8]. Their magnetic properties enable them to mark various biomolecules in modern diagnostic procedures (e.g. in Magnetic resonance imaging), and they may also be functionalized for active targeting *in vivo* or for *in vitro* diagnostics [7,8].

There is a great need and interest in developing new nanodelivery systems for drugs that are already on the market, especially for cancer therapeutics [9]. By using nanotechnology, scientists are trying to develop nanomaterials able to deliver the drug to the targeted tissue, release it at a controlled rate, be a biodegradable drug delivery system, and sometimes to be able to escape from degradation processes of the body [9]. Magnetic nanoparticles have some of those characteristics, and that makes them a very important factor in future developmet of can-

Corresponding author: Pantic, e-mail: igorpantic@gmail.com

cer therapy. In this concise review, we focus on the synthesis, functionalization, and application of magnetic nanoparticles, and novel approaches in their application in cancer diagnosis, treatment and prognosis. We also discuss recent findings related to this issue, and present our own suggestions and opinion about the future goals and potential problems that await this part of nanoscience.

2. SYNTHESIS AND FUNCTIONALIZATION OF MAGNETIC NANOPARTICLES

During the last few years, many new magnetic biomaterials have been synthetised, and their physical and chemical properties examined [10-14]. Most synthesis procedures for medically applicable nanomaterials are inexpensive and based on simple chemical reactions. Some commonly used methods are: wet precipitation and co-precipitation, reverse micelle mechanism, chemical vapor condensation, thermal decomposition and reduction, and liquid phase reduction [15].

Since nanoparticles at the target site, despite their small size, do not enter into biological systems easily, many researchers suggest that it is essential to design strategies that enable nanoparticles to recognize the surface molecules/receptors of the target cells and, therefore enabling nanoparticles to enter the cells and their organelles [7]. It is also very important to develop protection strategies to chemically stabilize the naked magnetic nanoparticles against degradation during or after the synthesis – perhaps by grafting/coating with organic materials (surfactants or polymers), or by coating with specific inorganic layers (e.g. silica or carbon) [8]. This may also, in some cases, enable further fictionalization of nanomatirials to make them more efficient in cancer treatment.

Most magnetic nanoparticles today are iron-based and significant advances in their synthesis and development have been achieved, although there have been many experiments and designs with other metals as well. Recently, cobalt ferrite NPs about 30 nm in size were synthesized by a new homogeneous precipitation routes using hexamethylenetetramine as precipitant at low pH environment [16]. The authors state that this method for the synthesis of Cobalt ferrite NPs is simple, low in reaction temperature, high yielding, and inexpensive. However, although most materials with high magnetic moment, such as cobalt, could be effective nanodelivery mediators, most of them are considered toxic, susceptible to oxidation and therefore limited in biomedical applications [17]. Magnetic iron oxide particles (ferromagnetic magnetite-Fe_3O_4, and maghemite-g-Fe_2O_3), on the other hand, are highly biocompatible, because the iron uptake, excretion and storage are well controlled, and the iron excess is efficiently cleared from the body without serious consequences to human health [17]. These facts could make iron-based nanoparticles a possible solution for many problems that today emerge in cancer diagnosis and treatment.

We should also mention that, in recent years, magnetic and other physical properties of many new non-iron based nanoparticles have been examined and described [18-23]. The potential for their application in biomedical sciences yet remains to be determined.

2.1. Magnetic nanoparticles in cancer diagnosis

Recently there have been many efforts to develop nanosized contrast agents for cancer magnetic resonance imaging (MRI), and computed tomography (CT), that are more efficient and affordable than those present on today's market. Some scientists consider superparamagnetic iron oxide particles (50 to 100 nm in size) as promising contrast agents, because they have much greater magnetic susceptibility than traditional MR contrasts, such as gadolinium [24]. Many of those substances might have rapid hepatic uptake after intravenous administration, which could make them very useful for hepatic tumors characterization [24,25].

Today, there are several commercially available contrast agents for MRI. Resovists® (Schering) is made of superparamagnetic iron oxide (SPIO) nanoparticles coated with carboxydextrane [26]. Recently, using "sonochemical method", scientists synthesized SPIO nanoparticles with the ability to be dispersed in chitosan, thus creating ferrofluid used as an enhancement of MRI contrast agents. In the mentioned study, such MRI image contrast readings were similar to those of Resovists [26]. In a recent study, magnetic fluids comprising of polyelectrolyte stabilized magnetite nanoparticles have been produced and demonstrated good biocompatibility and potential for *in vivo* MRI diagnostics [27]. Also, last year, magnetic fluids as image contrasts were synthesized via a high-Tc superconducting quantum interference device (SQUID) in microtesla magnetic fields [28].

In 2009, it was proposed that ultrasmall superparamagnetic particles of iron oxide (USPIO)-enhanced MRI in combination with diffusion-

weighted magnetic resonance imaging (DW-MRI) could be a novel, accurate, and fast method for detecting pelvic lymph node metastases even in normal-sized nodes of patients with bladder or prostate cancer [29]. There has also been some advances in colorectal cancer diagnostics; iron-oxide or iron-cored nanoshells today can be used as contrast agents suitable for MRI imaging, which, in addition to their non-invasive nature, could result in powerful and useful diagnostic tools [6,30].

Ferrite nanoparticles are nontoxic, biocompatible and affordable, however, their specific magnetic moment is low, and, although iron has some properties that makes it more applicable than iron oxides, pure metallic iron nanoparticles are unfortunately, in some circumstances, highly sensitive to oxidation and degradation [30]. Some authors, therefore, suggest that iron nanoparticles might be passivated with a thin ion oxide- or Au-shell and retain the high magnetic moments of pure iron cores, dramatically enhancing the contrast for MRI, reducing the needed particle concentrations, thus making drug delivery possible with much lower magnetic field gradients [30].

The use of magnetic NPs is having a great impact in bioassays for separation and preconcentration [31]. Recently, magnetic micro/nanoparticles have been widely used as signal reporters to detect various biomolecules, and to facilitate location of cancerous cells [32,33]. In bioassays, the most important roles of nanoparticles are: to act as a probe owing to its specific magnetic properties, and to carry on its surface markers for various covalent and non-covalent reactions with antibodies, nucleic acids and other recognition molecules [34].

Synthetic antiferromagnetic (SAF) nanoparticles possess unique tunable magnetic properties, which could in the near future make them essential for developing highly selective and sensitive bioassays for tumor detection and surveillance [35]. Recently, uniform arrays of nanopillars on a silicon wafer have been created, resulting in a low-cost and production-worthy stamps for SAF nanoparticles production [35]. According to the scientists, this magnetic nanosensor technology is capable of rapid, multiplex protein detection with resolution at attomolar concentrations. Also, in 2009, Y. Lalatonne *et al*. have designed a new, hybrid, magnetic nanoplatform for immunoassays using a highly iron complexing agent (HMBP) that contained a carboxylic function as bio-conjugating precursor, demonstrating that magnetic properties differ drastically according to the nanoparticle dipolar interaction and the nanocrystal size [34]. Authors state that these materials are currently being evaluated for bioconjugation and their use in bioassays [34].

The laboratory of J. Gao *et al*. has recently reported a new type of multifunctional nanomaterials, $FePt@Fe_2O_3$ yolk-shell nanoparticles [36]. It was explained that, given the possibilities of surface functionalization of these multifunctional nanoparticles by various molecules (e.g. antibodies), one can develop a particle capable of detecting and monitoring the transformation of the tumor by noninvasive MR imaging, during and after chemotherapeutic treatment [36]. These nanomaterials might have great potential in future cancer bioassay development although their stability in living organisms remains to be examined.

Recently, it was shown that simple non-expensive nanomashines/nanosensors with a potential use in cancer immunodiagnostics, can relatively easily be designed/constructed. Y. Zhang *et al.* have developed a simple, sensitive, and reusable piezoelectric immunosensor, based on biomolecules directly adsorbed on paramagnetic HAP/ γ-Fe_2O_3/Au nanocomposites [37]. According to the authors, the main advantages of this porous HAP/ γ - Fe_2O_3/Au nanocomposites is that they might provide a large loading capacity of biomolecules with well-preserved bioactivity, and that the recognition biomolecules immobilized on the nanocomposites with exposed structure, possess a good degree of flexibility and accessibility to the analyte [37].

2.2. Magnetic nanoparticles in cancer therapy

In recent years, magnetic nanoparticles have become a very significant tool in cancer therapy. According to some authors, the greatest therapeutic potential is probably associated with applications involving 'intelligent' particles with 3 potential parts: 1) a magnetic core (to direct the particles to the proximity of the cancer mass, and also for hyperthermic effects of the particle), 2) a recognition layer (whith adequate receptors / recognition molecules), and 3) a therapeutic load [38]. Some nanoparticles are designed to have all 3 parts, whereas others may lack a therapeutic load, their effect solely based on the action of their surface molecules, or their magnetic core. The "load" is usually an antineoplastic medication. For example, recently, Fe_3O_4-magnetic nanoparticles were loaded with chemotherapeutic agent ADM, chemosensitizer Tet and / or other agents such as 5-bromotetrandrin [39,40]. It was assumed that such drugs polymerized with Fe_3O_4-

magnetic nanoparticles might have curative effects on multidrug resistance [39,40]. Later in the text we will additionally discuss recent advances concerning this type of nanoparticles. On the other hand, the therapeutic effects of magnetic nanoparticles can be based exclusively on their specific inorganic properties. The best example for this are the materials used for so-called "Magnetic targeted hyperthermia".

Magnetic targeted hyperthermia, achieved by using metallic nanoparticles that convert electromagnetic energy into heat, might have a significant role in noninvasive treatment of cancer and other temperature sensitive diseases [41], although the delivery of a hyperthermic material to a specific target site, and heating of surrounding healthy tissues (side effects), is a potential problem [42]. Since surface characteristics (markers, ligands, *etc*.) of the nanoparticles are important factors that determine the biocompatibility and cell adhesion of the hyperthermic thermoseed, some new surface materials, like chitosan-coating, have been developed with encouraging results [42]. Although not yet the therapy of choice, thermotherapy is today used in treatment of some tumors. Interstitial heating using magnetic nanoparticles (prospective phase I trial) was feasible in patients with previously irradiated and locally recurrent prostate cancer [43]. The method of magnetic liquid hyperthermia is also used for glioblastoma therapy [44]. The magnetite nanoparticles were delivered to the tumor with the help of a supersensitive electronic navigation system, allowing treatment of the brain fragments responsible for speech and locomotor functions [44-46]. Still, many challenges remain. The main practical problems with magnetic targeted hyperthermia are: a limited particle supply of the tumour tissue, resulting in insufficient temperature enhancement in parts of the tumour; and a risk of proliferation of cancer cells that survived thermotherapy [47].

Many mediators (growth factors, antibodies, hormones) can be associated with magnetic nanoparticles, making them suitable for specific tumor receptor targeting. These receptors, when targeted, may induce cell apoptosis, changes in cell metabolism, or simply act as a bridge that connects the particle and the cancer cell, allowing transfer of medicaments.

Epidermal growth factor (EGF)-based nanotherapy has shown great potential for possible treatment of colorectal and breast cancers. Recently, EGF was conjugated with carboxymethyldextran (CMDx) coated iron oxide magnetic nanoparticles using carbodiimide chemistry to obtain magnetic nanoparticles that target the epidermal growth factor receptor (EGFR) allowing potential future targeting of EGFR overexpressing colon cancer cells [48]. Today, it is possible to conjugate antibodies to these particle suspensions using a variety of techniques, while still maintaining particle integrity and colloidal stability [49]. Various types of nanoparticles conjugated with the anti- Human Epidermal growth factor Receptor 2 (HER2) monoclonal antibody (also called "trastuzumab"), have been created and analyzed due to promising results in biological and preclinical applications in the treatment of breast cancer [50]. Aqueous based formulation of glycerol monooleate coated magnetic nanoparticle linked HER2 antibody, showed enhanced uptake in human breast carcinoma cell line (MCF-7), giving us hope for future successful chemotherapy of certain types of breast tumors [51].

Another possible approach concerning breast cancers is treatment with hormone-conjugated nanomaterials. For example, some authors state that LHRH- superparamagnetic iron oxide nanoparticles (SPIONs) can be used to target cancer cells in both the primary breast tumors and the lung metastases using transmission electron microscopy to measure sub-cellular distributions of SPIONs in tumors and tissues [52]. Furthermore, yet another study concerning breast cancer revealed that accumulation of individual LHRH- magnetic nanoparticles in the nucleus of liver cells suggests that LHRH-MNPs are also potential carriers for delivering drugs or DNA to liver cells with diseases [53].

Hormone-conjugated nanomaterials are also a potential solution for ovarian cancer treatment, although most recent investigations are focused on specific membrane tyrosine kinase receptor targeting. Magnetic nanoparticles with ligands with a high affinity for EphA2 tyrosine kinase receptors expressed on ovarian cancer cells, could be used to isolate free-floating cancer cells (cells responsible for the majority of ovarian cancer metastases [54]) from peritoneal fluids, decreasing levels of chemical or radiation therapies (or both) and reducing or eliminating the detrimental side effects typically associated with ovarian cancer therapy [55].

We should here mention that, although there are evident benefits of application of these nanomaterials, the toxicity of hormone-conjugated, growth factor-conjugated and other magnetic nanoparticles, however, remains controversial. There are, for example, concerns that magnetic nanoparticles in general may pose a considerable health risk because of their ability to accumulate

within the bloodstream, and probability of embolization [56]. Although many methods for toxicity measuremens / quantification exist, sometimes the results are inconclusive and confusing. This is especially true knowing that many *in vitro* tests show poor correlation with similar tests done *in vivo* [57]. Thus, some laboratories have made a great effort in order to develop new techniques that would examine the *in vitro* toxicity of nanoparticles in a more rigorous manner [58]. The effectivnes and applicability of these methods yet remains to be determined.

Conjugation of antineoplastic medications and/or radioemitters with nanoparticles has become the focus of many recent preclinical and clinical experiments. Knowing the limitations of iron oxide based nanoparticles, various alternative high-quality magnetic nanomaterials are now available, such as ferrites, metals and alloys, with better performance as drug-carrier agents [59], and, perhaps, lower toxicity. A new radioimmunoconjugate—131I–anti-vascular endothelial growth factor (VEGF) monoclonal antibody (Sc-7269)–Dextran Magnetic Nanoparticles (DMN) has been produced by Chen *et al*., and its biodistribution, therapeutic effects and safety was then observed in nude mice bearing human liver cancer [60]. The authors concluded that this technology might be safe and potentially highly efficient in treatment of liver as well as other types of cancer. A few years ago, some laboratories have successfully synthesized a new type of nanoparticles - the magnetic polyethyl-2-cyanoacrylate (PECA) nanoparticles, containing anti-cancer drugs (Cisplatin and Gemcitabine) using the method of so-called inter-facial polymerization [61]. The drug release pattern of Cisplatin (hydrophobic) showed sustained release behavior, suggesting that the magnetic PECA magnetic nanoparticles may have a potential as a highly versatile carrier for targeted delivery approach [61]. In other studies, small size and high hydrophilicity polymers were selected that enabled the integration of iron oxide colloids, chemotherapeutics, and targeting ligands to form sub-50-nm novel Magnetic Nanoparticle Hydro-Gel (MagNaGelTM) nanoparticles, merging drug and device concepts, and increasing the chances of deep tumor penetration [62]. Also, Häfeli *et al*. successfully conjugated magnetic targeted carriers with the therapeutic radioemitter rhenium-188, and the complex was targeted to solid tumors with high efficiency. This may allow the physicians to effectively deliver high doses of radiation to tumors and minimize radiation to surrounding cells and tissues [63].

As for advances in cancer pulmology, some scientists have presented an *in vitro* model designed to investigate the potential of magnetically targeted aerosol deposition, for potential applications in lung cancer treatment [64]. The results of this investigation were encouraging knowing that magnetically targeted site-specific deposition was achieved, and that the deposited particles were not cleansed by the clearance mechanisms. However, it is not clear whether this model could be widely used in patients.

All in all, still many obstacles remain to be overcome for successful *in vivo* application of tumor-targeted iron based nanoparticles: functional group modification of the drugs during conjugation with a nanoparticle, low drug loading efficiency, failure of nanomaterials to enter the tumor tissue from the blood, drugs being transported to endosomes/lysosomes instead to the cytoplasm of cancer cells, decrease of the targeting ability as a result of weak connections with a ligand, lack of magnetization of the core material, toxicity and biodegradation, as well as financial issues concerning production [65-67]. Also, heterogeneity of nanomaterials remains a major problem, and sometimes, it may be difficult to precisely influence the number of functional molecules on the surface of nanoparticles [68].

Many practitioners believe that cancer treatment should be based not only on prognostic factors and chemotherapy, but also on quality of life during and after treatment, and, knowing that, tolerability, compliance and quality of life will, therefore, could become the most important factors in future therapy of cancer [69]. In our opinion, magnetic nanoparticles represent a great hope for successful cancer therapy in the future. Therefore, it is essential that laboratories that deal with design and production of nanoparticles receive adequate funding and support from local health authorities. Chemotherapy and radiotherapy will definitely remain unavoidable tool in fight against cancer, but further development nanotechnology will give us new possibilities in the application of those standard procedures.

REFERENCES

[1] H.J. Eyre // *Prim. Care.* **36** (2009) 859.
[2] S. Sandhiya, S.A. Dkhar and A. Surendiran // *Clin. Pharmacol*. **23** (2009) 263.
[3] P. Pathak and V.K. Katiyar // *J. Nanotechnol.* (2007) DOI: 10.2240/azojono0114 1.
[4] M.D. Wang, D.M. Shin, J.W. Simons and S. Nie // *Expert. Rev. Anticancer. Ther.* **7** (2007) 833.
[5] T. Sasaki, N. Iwasaki, K. Kohno, M. Kishimoto, T. Majima, S. Nishimura and A. Minami // *Mater. Res. A*. **86** (2008) 969.

[6] P. Fortina, L.J. Kricka, D.J. Graves, J. Park, T. Hyslop, F. Tam, N. Halas, S. Surrey and S.A. Waldman // *Trends. Biotechnol*. **25** (2007) 145.
[7] N. Sanvicens and M.N. Marco // *Trends. Biotechnol.* **26** (2008) 425.
[8] A.H. Lu, E.L. Salabas and F. Schüth // *Angew. Chem. Int. Ed. Engl*. **46** (2007) 1222.
[9] D.J. Bharali, M. Khalil, M. Gurbuz, T.M. Simone and S.A. Mousa // *Int. J. Nanomedicine* **4** (2009) 1.
[10] A. Zeleňáková, V. Zeleňák, J. Degmová, J. Kováč, K. Sedláčková, M. Kusý and J. Sitek // *Rev. Adv. Mater. Sci.* **18** (2008) 501.
[11] A. Winter, H. Pascher, M. Hofmayer, H. Krenn, T. Wojtowicz, X. Liu and J.K. Furdyna // *Rev. Adv. Mater. Sci.* **20** (2009) 92.
[12] T. Breczko, D. Bykov, R. Grechishkin, A. Zalyotov, S. Ilyashenko and M. Bramowicz // *Rev. Adv. Mater. Sci*. **20** (2009) 101.
[13] A. Grabias, D. Oleszak and M. Pekala // *Rev. Adv. Mater. Sci*. **18** (2008) 379.
[14] W. Kaszuwara, A. Witkowski, M. Leonowicz, P. Pawlik and J. Paszula // *Rev. Adv. Mater. Sci.* **18** (2008) 497.
[15] S.C. McBain, H.H.Yiu and J. Dobson // *Int J Nanomedicine*. **3** (2008) 169.
[16] L. Zhigang, L. Xiaodong, L. Yonghua, L. Jingbao, L. Shaohong, X. Zhimeng, H. Di, L. Ji-Guang and S. Xudong // *Journal of Nanomaterials* (2008) Article ID 921654, 2008. doi:10.1155/2008/921654
[17] J.L Corchero and A. Villaverde // *Trends. Biotechnol*. **27** (2009) 468.
[18] T. Bodziony, S.M. Kaczmarek and R. Kruk // *Rev. Adv. Mater. Sci.* **23** (2010) 1.
[19] N. Guskos, G. Zolnierkiewicz, J. Typek and A. Blonska-Tabero // *Rev. Adv. Mater. Sci.***23** (2010) 218.
[20] A. Fernández-Osorio, A. Vázquez-Olmos, R. Sato-Berru and R. Escudero // *Rev. Adv. Mater. Sci.* **22** (2009) 60.
[21] G. Yan, L. Wang and L. Zhang // *Rev. Adv. Mater. Sci*. **24** (2010) 10.
[22] R.Z. Wu, Z.K. Qu and M.L. Zhang // *Rev. Adv. Mater. Sci*. **24** (2010) 35.
[23] V. dos Santos, M. Zeni, J.M. Hohemberger and C.P. Bergmann // *Rev. Adv. Mater. Sci.* **24** (2010) 44.
[24] A.G. Cuenca, H. Jiang, S.N. Hochwald, M. Delano, W.G. Cance and S.R. Grobmyer // *Cancer.* **107** (2006) 459.
[25] D.D. Stark, R. Weissleder, G. Elizondo, P.F. Hahn, S. Saini, L.E. Todd, J. Wittenberg and J.T. Ferrucci // *Radiology* **168** (1988) 297.
[26] K. Eun Hee, L. Hyo Sook, K. Byung Kook and K. Byung-Kee // *J. Magn. Magn. Mater.* **289** (2005) 328.
[27] S.A. Corr, S.J. Byrne, R. Tekoriute, C.J. Meledandri, D.F. Brougham, M. Lynch, C. Kerskens, L. O'Dwyer and Y.K. Gun'ko // *J. Am. Chem. Soc*. **130** (2008) 4214.
[28] L. Shu-Hsien, Y. Hong-Chang, H. Herng-Er and S.Y. Yang // *Supercond. Sci. Technol.* **22** (2009): 025003, doi: 10.1088/0953-2048/22/2/025003.
[29] H.C. Thoeny, M. Triantafyllou, F.D. Birkhaeuser, J.M. Froehlich, D.W. Tshering, T.Binser, A. Fleischmann, P. Vermathen and U.E. Studer // *Eur. Urol*. **55** (2009) 761.
[30] Y. Qiang, J. Antony, A. Sharma, J. Nutting, D. Sikes and D. Meyer // *J. Nanoparticle Res.* **8** (2006) 489.
[31] A.G. Hens, J.M.F. Romero and M.P.A. Caballos // *Trends in Anal. Chem.* **27** (2008) 394.
[32] A. Munir, J. Wang, Z. Li and H.S. Zhou // *Microfluid. Nanofluid.* **8** (2009) 641.
[33] Y.T. Lim, M.Y. Cho, B.S. Choi, J.M. Lee and B.H. Chung // *Chem. Commun*. **40** (2008) 4930.
[34] Y. Lalatonne, F. Benyettou , D. Bonnin N. Ličvre, P. Monod, M. Lecouvey, P. Weinmann and L. Motte // *J. Magn. Magn. Mater.* **321** (2009) 1653.
[35] S. Trisha, In: *The 2008 NNIN REU Research Accomplishments* (2008 NNIN REU CONVOCATION, Cornell University, Ithaca, NY, USA), p. 28
[36] J. Gao, G. Liang, J.S. Cheung, Y. Pan, Y. Kuang, F. Zhao, B. Zhang, X. Zhang, E.X. Wu and B. Xu // *J. Am. Chem. Soc.* **130** (2008) 11828.
[37] Y. Zhang, H. Wang, B. Yan, Y. Zhang, J. Li, G. Shen and R. Yu // *J. Immunol. Methods*. **332** (2008) 103.
[38] M. Arruebo, R. Fernández-Pacheco, M.R. Ibarra and J. Santamaría // *Nanotoday* **2** (2007) 22.
[39] Chen B, Sun Q and Wang X // *Int J Nanomedicine* **3** (2008) 277.
[40] B. Chen, J. Cheng, M. Shen, F. Gao, W. Xu, H. Shen, J. Ding, C. Gao, Q. Sun, X. Sun,

H. Cheng, G. Li, W. Chen, N. Chen, L. Liu, X. Li and X. Wang // *Int J Nanomedicine* **4** (2009) 65.
[41] P. Cherukuri, E.S. Glazer and S.A. Curley // *Adv. Drug. Deliv. Rev*. **62** (2010) 339.
[42] D.H. Kim, K.N. Kim, K.M. Kim and Y.K. Lee // *J. Biomed. Mater. Res. A*. **88** (2009) 1.
[43] M. Johannsen, U. Gneveckow, K. Taymoorian, B. Thiesen, N. Waldöfner, R. Scholz, C. Cho, A. Jordan, P. Wust and S. Loening // *Eur. Urol. Suppl.* **6** (2007) 201.
[44] V.N. Nikiforov // *Russian Physics Journal* **50** (2007) 913.
[45] A. Jordan, R. Scholz, K. Maier-Hauff, M. Johannsen, P. Wust, J. Nadobny, H. Schirra, H. Schmidt, S. Deger, S. Loening, W. Lanksch and R. Felix // *J. Magn. Magn. Mater.* **225** (2001) 118.
[46] M. Mitsumori, M. Hiraoka, T. Shibata, Y. Okuno, S. Masunaga, M. Koishi, K. Okajima, Y. Nagata, Y. Nishimura, M. Abe, K. Ohura, M. Hasegawa, H. Nagae and Y. Ebisawa // *Int. J. Hyperthermia* **10** (1994) 785.
[47] R. Hergt and S. Dutz // *J. Magn. Magn. Mater.* **311** (2007) 187.
[48] M. Creixell, A.P. Herrera, V. Ayala, M. Latorre-Esteves, M. Pérez-Torres, M. Torres-Lugo and C. Rinaldi // *J. Magn. Magn. Mater.* (2010), doi:10.1016/ j.jmmm.2010.02.019.
[49] C. Grüttner, K. Müller, J. Teller, F. Westphal, A. Foreman and R. Ivkov // *J. Magn. Magn. Mater.* **311** (2007) 181.
[50] M. Colombo, F. Corsi, D. Foschi, E. Mazzantini, S. Mazzucchelli, C. Morasso, E. Occhipinti, L. Polito, D. Prosperi, S. Ronchi and P. Verderio // *Pharmacol. Res.* **62** (2010) 150.
[51] F. Dilnawaz, A. Singh, C. Mohanty and S.K. Sahoo // *Biomaterials* **31** (2010) 3694.
[52] J. Zhou, C. Leuschner, C. Kumar, J.F. Hormes and W.O. Soboyejo // *Biomaterials* **27** (2006) 2001.
[53] J. Zhou, C. Leuschner, C. Kumar, J. Hormes and W.O. Soboyejo // *Materials Science and Engineering: C* **26** (2006) 1451.
[54] D. Tan, R. Agarwal and S.B. Kaye // *Lancet. Oncol.* **7** (2006) 925.
[55] K.E. Scarberry, E.B. Dickerson, Z.J. Zhang, B.B. Benigno and J.F. McDonald // *Nanomedicine* **6** (2010) 399.
[56] J. Dobson // *Drug. Devel. Res.* **67** (2006) 55.
[57] C.M. Sayes, K.L. Reed and D.B. Warheit // *Toxicol. Sci.* **97** (2007) 163.
[58] M. Mahmoudi, A. Simchi, M. Imani, M.A. Shokrgozar, A.S. Milani, U.O. Häfeli and P. Stroeve // *Colloids. Surf. B. Biointerfaces* **75** (2010) 300.
[59] A. Figuerola, R. Di Corato, L. Manna and T. Pellegrino // *Pharmacol Res.* **62** (2010) 126.
[60] J. Chen, H. Wu, D. Han and C. Xie // *Cancer Lett*. **231** (2006) 169.
[61] J. Yang, H. Lee, W. Hyung, S.B. Park and S. Haam // *J. Microencapsul.* **23** (2006) 203.
[62] C.J. Sunderland, M. Steiert, J.E. Talmadge, A.M. Derfus and S.E. Barry // *Drug. Devel. Res.* **67** (2006) 70.
[63] U. Häfeli, G. Pauer, S. Failing and G. Tapolsky // *J. Magn. Magn. Mater.* **225** (2001) 73.
[64] J. Ally, B. Martin, M.B. Khamesee, W. Roa and A. Amirfazli // *J. Magn. Magn. Mater.* **293** (2005) 442.
[65] K.K. Jain // *Technol. Cancer Res. Treat.* **4** (2005) 645.
[66] T.K. Jain, M.A. Morales, S.K. Sahoo, D.L. Leslie-Pelecky and V. Labhasetwar // *Mol. Pharm.* **2** (2005) 194.
[67] X.H. Peng, X. Qian, H. Mao, A.Y. Wang, Z.G. Chen, S. Nie and D.M. Shin // *Int. J. Nanomedicine* **3** (2008) 311.
[68] J. Gao, H. Gu and B. Xu // *Acc. Chem. Res.* **42** (2009) 1097.
[69] E. Miele, G.P. Spinelli, E. Miele, F. Tomao and S. Tomao // *Int. J. Nanomedicine.* **4** (2009) 99.