ANNA RADOMSKA^{1, A–F}, JAROSŁAW LESZCZYŹYŃ^{2, A–F}, MAREK W. RADOMSKI^{1, 3, A–F}

The Nanopharmacology and Nanotoxicology of Nanomaterials: New Opportunities and Challenges

¹ School of Pharmacy and Pharmaceutical Sciences and Trinity Biomedical Sciences Institute,
The University of Dublin, Trinity College, Dublin, Ireland

² Eleonora Reicher National Institute of Geriatrics, Rheumatology and Rehabilitation, Warszawa, Poland

³ Kardio-Med Silesia, Zabrze, Poland

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
D – writing the article; E – critical revision of the article; F – final approval of article

Abstract

The very dynamic growth of nanotechnology, nanomaterials (sized 1–100 nm) and their medical applications over the past 10 years has promised to add a new impetus to the diagnostics and therapeutics of a wide range of human pathologies, including cancer, cardiovascular diseases and diseases of the central nervous system. This growth in nanomedicine also fuels advances in bioengineering, regenerative medicine and the development of medical devices. However, as with all new pharmaceuticals and medical devices, new opportunities are inherently accompanied by new challenges due to the ability of nanomaterials to interact with the body on the cellular, subcellular and molecular levels. This article reviews some of the most compelling problems related to the nanopharmacology and nanotoxicology of nanomaterials. The overview focuses on opportunities emerging from the development of multifunctional nanomaterials and nanotheranostics for the diagnostics and therapy of both major and rare diseases. Challenges related to the hemocompatibility of nanomaterials are also discussed (*Adv Clin Exp Med* 2016, 25, 1, 151–162).

Key words: nanotechnology, nanomedicine, pharmacology, toxicology.

The 2011 European Commission recommendation defines “nanomaterial” as: “a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1–100 nm. In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50 % may be replaced by a threshold between 1 and 50%. [...]” [1].

The world market for nanomaterials has been growing extremely fast. It is estimated that 11 million ton of nanomaterials are produced annually, with a market value of 20 billion euros; in 2015 products underpinned by nanotechnology were valued at 2 trillion euros [1]. It is important to note that nanotechnology is viewed by the European Union (EU) as one of the major technological

drivers of innovation and has been identified as a key enabling technology (KET) for the EU [2].

Medicine is expected to be one of the major beneficiaries of the growth of nanotechnology. This is reflected by a great interest on the part of the scientific community in medical applications of nanotechnology. At the time when this article was written (October 2015) a search for “nanomedicine” and “nanoparticles” in Pubmed listed 11,114 and 109,996 publications, respectively. A significant portion of these contributions have been published in newer journals entirely focusing on nanotechnology and nanomedicine, including *Nature Nanotechnology*, *Nanomedicine* (London), *Nanomedicine NBM* or *The International Journal of Nanomedicine*, to name only a few.

In 2007 in a highly accessed and widely cited article published in *The British Journal of Pharmacology* the authors alerted the pharmaceutical community to the new and growing field of

nanotechnology research relevant to pharmacology and toxicology [3]. Over the past eight years the field has grown very rapidly, resulting in the publication of a great number of original and

review articles. Table 1 presents selected published reviews covering a cross section of topics from nanomedicine, nanopharmacology and nanotoxicology.

Table 1. Selected nanomedical reviews

Reference [#]	Topic
Ali-Boucetta and Kostarelos 2013 [53]	Toxicokinetics of carbon nanotubes
Allen and Cullis 2013 [54]	State-of-the-art of liposomal drug delivery systems
Alvarim et al. 2014 [55]	Therapy using SPION-labelled stem cells
Andersen et al. 2012 [56]	Adverse immune effects of carbon nanotubes
Arora et al. 2012 [57]	Using <i>in vitro</i> methods in nanotoxicology
Bao et al. 2013 [58]	Multifunctional NPs for drug delivery and imaging
Bartenck et al. 2014 [59]	Nanomedicine to treat liver diseases
Benetti et al. 2014 [60]	Nanometallomics in nanotoxicology
BeruBe et al. 2007 [61]	Pulmonary toxicity of combustion-derived nanoparticles
Billi et al. 2010 [62]	Nanotoxicology of metallic nanoparticles in total joint arthroplasty
Bussy et al. 2013 [63]	Interactions of carbon nanotubes with blood
Caputo et al. 2014 [64]	Engineered nanomaterials as antioxidants
Carraciolo 2015 [65]	Liposome-protein corona in targeted drug delivery
Chaudhury et al. 2014 [66]	Regenerative nanomedicine: current state and future perspectives
Chen and Liu 2015 [67]	Pharmaceutics of nanofibers and their role in delivery of antimicrobials
Chen et al. 2014 [68]	State-of-the-art and perspectives of therapeutic and diagnostic use of theranostic nanoparticles
Chen et al. 2013 [69]	Use of advanced nuclear analytical techniques in nanotoxicology
Cheng et al. 2015 [70]	Therapeutic potential of polymeric nanoparticles
Cockburn et al. 2012 [27]	Safety of nanomaterials used in food industry: guidelines
Conde and Artzi 2015 [71]	Gold nanobeacons in smart nanotheranostics
Costa et al. 2015 [72]	Layer-by-layer technology for preparation of nanoreservoirs for controlled drug release
Das Neves et al. 2015 [73]	Nanocarriers for vaginal drug delivery
De Vries et al. 2015 [74]	Delivery of antimicrobial peptides using nanocarriers
Del Pino 2014 [43]	Interactions of medically-relevant nanoparticles with electromagnetic fields
Deshayes et al. 2014 [75]	Cage nanoparticles for drug delivery
Doktorovova et al. 2014 [76]	Nanotoxicology of solid lipid nanoparticles
Donaldson et al. 2010 [77]	Genotoxicity of nanoparticles
Donaldson et al. 2013 [78]	Adverse effects of nanoparticles in the cardiovascular system
Estelrich et al. 2015 [79]	Nanoparticles for magnetic resonance imaging
Feng et al. 2015 [80]	Toxicity of dental nanomaterials
Fernandes et al. 2015 [81]	Targeting digestive cancers using nanotreatments
Franci et al. 2015 [82]	Silver nanoparticles as antibacterials

Table 1. Selected nanomedical reviews – cont.

Reference [#]	Topic
Frohlich 2015 [83]	Nanoparticle immunotoxicity <i>in vivo</i>
Fubini et al. 2010 [84]	Nanotoxicity in relation to physico-chemical features of nanoparticles
Gainza et al. 2015 [85]	Nanocarriers in wound healing and skin regeneration
Gendelman et al. 2015 [86]	Nanotreatment for degenerative, inflammatory and infectious diseases of the nervous system
Gharagozloo et al. 2015 [87]	Nanomedical treatment of autoimmune diseases
Gregori et al. 2015 [88]	Nanomedical treatment of Alzheimer's disease
Grieger et al. 2012 [50]	Environmental risk of nanomaterials
Guo and Huang 2014 [89]	Enhancing solubility of anticancer drugs
Gusic et al. 2014 [90]	Nanoscaffolding in bone regeneration
Holden et al. 2014 [91]	Bacteria for assessing environmental hazards and fates of nanomaterials
Hristozov et al. 2014 [92]	Hazard screening of engineered nanomaterials
Hubbs et al. 2014 [93]	Augmented microscopy assessment in nanotoxicology
Ilinskaya and Dobrovolskaia 2013 (part II) [94]	Undesirable action of nanoparticles on blood clotting
Ilinskaya and Dobrovolskaia 2013 (part I) [95]	Desirable action of nanoparticles on blood clotting
Jo et al. 2015 [96]	Nanoparticles in treatment of retinal diseases: nanotherapeutic agent characteristics
Johnston et al. 2013 [52]	Risk of engineered nanomaterials
Kandi and Kandi 2015 [97]	Overcoming anti-bacterial resistance with nanoparticles
Kermanizadeh et al. 2015 [98]	Role of redox mechanisms in nanomaterial toxicity
Kim et al. 2015 [99]	Nanoparticles for siRNA delivery in cancer therapy
Kodiha et al. 2015 [100]	Gold nanoparticles for cancer therapy
Lakkakula et al. 2014 [101]	Cyclodextrin nanoparticles for drug delivery
Landriscina et al. 2015 [102]	Biodegradable chitosan nanoparticles in drug delivery systems
Larson et al. 2014 [103]	Reproductive toxicity of nanomaterials
Laurent et al. 2014 [104]	Superparamagnetic iron oxide nanoparticles in therapy
Li et al. 2015 [105]	Photodynamic therapy using graphene-based nanoplateforms
Li YF et al. 2015 [106]	Use of advanced light beams generated by synchrotron for nanotechnology and nanotoxicology
Lukowiak et al. 2015 [107]	Unimolecular micelles for drug delivery
Lux et al. 2015 [108]	Gadolinium-based nanotheranostics
Madl et al. 2015 [109]	Nanotoxicology of hip implants part I
Madl, Kovoichich et al. 2015 [110]	Nanotoxicology of hip implants part II
Mottaghitlab et al. 2015 [111]	Silk fibroin nanoparticle in drug delivery systems
Mulder et al. 2014 [112]	Diagnosis and treatment of atherosclerosis using nanomedical tools
Muller et al. 2011 [113]	Nanotoxicology of nanocrystals
Murugan et al. 2015 [114]	Mechanisms of cellular trafficking of nanostructures

Table 1. Selected nanomedical reviews – cont.

Reference [#]	Topic
Nel 2013 [115]	Safety assessment of nanomaterials using alternative test strategies
Nel et al. 2013 [116]	Predictive toxicological approach and high-throughput screening in nanotoxicology
Nielsen et al. 2014 [117]	Nanomedicine in the treatment of inflammatory bowel disease
Nunez-Anita et al. 2014 [118]	Toxicity of antimicrobial nanoparticles used in prosthetic devices
Osmond et al. 2010 [119]	Nanotoxicity of modern sunscreens
Palekar et al. 2015 [19]	Molecular imaging of atherosclerosis using nanoparticle-based fluorinated magnetic resonance contrast agents
Panzarini and Dini 2014 [120]	Overcoming multidrug cancer cell resistance using nanomaterials
Paul 2015 [121]	Myocardial therapy using nanocomposite hydrogels
Polak and Shefi 2015 [122]	Neuronal regeneration using nanoparticles
Sadikot 2014 [123]	Nanomaterials in critical care medicine
Schrofel et al. 2014 [124]	Biomedical applications of metallic nanoparticles
Sehedic et al. 2015 [125]	Overcoming radioresistance of glioblastoma using nanomaterials
Shvedova and Kagan 2010 [126]	Pulmonary toxicity of single-wall carbon nanotubes
Sosnik and Carcaboso 2014 [127]	Nanomedicine in paediatrics
Sriraman et al. 2014 [128]	Brain tumour targeting using multifunctional nanoparticles
Tan et al. 2011 [129]	Quantum dots and carbon nanotubes in oncology
Tomaszewski et al. 2015 [38]	Nanopharmacology and nanotoxicology in platelet-vascular wall interactions
Torchilin 2014 [130]	Multifunctional and stimuli-sensitive drug delivery systems
Tseng and Liu 2015 [131]	Delivery of analgesics using nanofibers
Veiseh et al. 2015 [132]	Nanodrug discovery and the treatment of diabetes mellitus
Vellayappan et al. 2015 [133]	Nanocomposites for grafts and stents
Vinogradov et al. 2014 [134]	Targeting macrophages associated with tumour using nanoparticles
Walmsley et al. 2014 [135]	Nanotechnology in bone tissue engineering
Wang et al. 2015 [136]	Boron-functionalized nanocarriers for cancer treatment
Weissig et al. 2014 [6]	Approved and commercially available nanopharmaceuticals
Weissig and Guzman-Villanueva 2014 [137]	Approved and commercially available nanopharmaceuticals
White-Schenk et al. 2015 [138]	Nanopharmaceuticals in spinal cord injury
Winkler et al. 2014 [139]	Structure-activity relationship (SAR) approach in nanotoxicology
Zhao et al. 2014 [140]	Nanotechnology in glycopeptide detection and glycoproteomics
Zhen et al. 2014 [141]	Ferritins as multifunctional nanoplatforms

As with all medical research and development (R&D), diagnostic and therapeutic options in nanomedicine, in addition to the new opportunities, involve certain risks, and the risk/benefit balance is likely to influence the fate of nanomedical R&D.

This overview focuses on opportunities emerging from the development of multifunctional nanomaterials for diagnostics and therapeutics. Challenges related to the biocompatibility of newly developed nanomaterials are also discussed, highlighting blood-nanoparticle interactions.

Opportunities

Most nanodrug research to date has been based on the principle of using nanoparticles as drug delivery platforms. In fact, the first nanodrug approved by the US Food and Drug Administration (FDA) for use in men was Doxil [4], in which liposomal encapsulation of doxorubicin was used to increase the drug/carrier ratio and to decrease the cardiac toxicity and adverse effects associated with the use of this anticancer drug [5].

To the time of writing, more than 40 nanopharmaceuticals have been approved by regulatory authorities, including liposomes, non-liposomal lipid formulations, PEGylated proteins, peptides, aptamers, nanocrystals, polymer-based nanoformulations, protein-drug conjugates, surfactant-based nanoformulations, metal-based nanoformulations and virosomes [6].

The field of anticancer drug delivery has been a major beneficiary of nanomedical R&D, with a number of FDA-approved anticancer formulations, such as nanosized antibody-drug conjugates brentuximab and trastuzumab [7], liposome-containing daunorubicin [8] and vincristine [9], as well as paclitaxel formulated using a nanosized albumin carrier [10]. As with Doxil, the use of nano-platforms is likely to increase the selectivity and efficacy of these anticancer drugs while reducing the adverse effects.

A number of nanotherapeutic products are commercially available in the EU, including nanocrystals (sirolimus, fenofibrate and aprepitant), nanoemulsions (cyclosporine and ritonavir) polymeric drugs (sevelamer) and liposomes (amphotericin B, cytarabine, doxorubicin and daunorubicin) [11].

Recently, yet another dimension of nanoparticle drug delivery systems has been gaining increasing momentum in nanomedical R&D: nanotheranostics, based on the use of multifunctional nanoparticles that integrate diagnostic and therapeutic functions in one system [12]. For cancer treatment, nanotheranostic platforms can provide advanced diagnostics, hyperthermia treatment and targeted delivery of anticancer drugs [13]; superparamagnetic iron oxide nanoparticles (SPIONs) are an example of such platforms [14, 15]. SPIONs have also been developed as a part of the MULTIFUN EU consortium (<http://www.multifun-project.eu/>) [16] and offer distinct advantages over other drug delivery platforms used with anticancer medications: a) the pharmacokinetics of SPIONs are easily determined using non-invasive imaging techniques such as nuclear magnetic resonance (NMR); b) SPIONs can easily be guided to cancer tissues using the electromagnetic field (EM);

Fig. 1. A) The general design and functionalization of multifunctional magnetic nanoparticles: a magnetic core capable of scattering or absorption of an interacting electromagnetic field, allowing diagnostics and treatment; a pharmaceutical load for selective delivery of therapeutics; antibodies that target specific cellular markers, and biocompatibility with polyethylene glycol (PEG), allowing a longer half-life of nanoparticles in the bloodstream [13, 43, 54]

B) A proposed design for multifunctional ferromagnetic nanoparticles for the treatment of Kasabach-Merrit disease: a ferromagnetic core using ferric oxide; a pharmaceutical load with a chemotherapeutic agent [25] a nitric oxide (NO)/barbiturate hybrid, a strong inhibitor of cancer-cell proliferation and secretion [142], and iloprost, an analog of prostacyclin, a potent inhibitor of platelet aggregation that synergizes with NO [143]; targeting hemangioma cells using antibodies against vascular endothelial growth factor receptors [144] and an EM field; and a coating providing biocompatibility with PEG

c) SPIONs can selectively generate energy to destroy cancer cells; and d) when functionalized with antibodies against cancer biomarkers, SPIONs can selectively deliver a “cocktail” of therapeutic pharmaceuticals (Fig. 1a).

Nanotheranostics can be also used for the management of atherosclerosis and its cardiovascular and cerebrovascular manifestations [17–19]. As with cancer, it is expected that multimodal nanoparticles will allow for non-invasive detection, long-term monitoring (for example using

gadolinium-based contrasts and dynamic contrast enhanced magnetic resonance imaging) and treatment of atherosclerotic plaques [20, 21]. The European Union actively supports projects related to the use of nanomedicine to combat atherosclerosis. One of the ongoing projects is the Nano-Athero consortium (<http://www.nanoathero.eu/>), which aims at targeted imaging and treatment of advanced atherothrombotic disease in humans.

In addition to major diseases such as cancer and cardiovascular diseases, nanotheranostics can also be applied to the diagnostics and treatment of rare diseases. The Kasabach-Merritt syndrome [22], also known as the Kasabach-Merritt phenomenon (KMP) or thrombocytopenia with a vascular lesion, is a rare condition [23] that complicates the course of two rare vascular tumors: kaposiform hemangioendothelioma (KHE) and tufted angioma (approximately 1% of all hemangiomas), believed to be on the spectrum of the same disease [24]. Albeit a rare disease, KMP is a life-threatening one leading to profound thrombocytopenia (3,000–60,000/ μ L), hypofibrinogenemia, bleeding and sometimes to disseminated intravascular coagulation. The exact pathogenesis of KMP is uncertain; however, platelets being trapped in a hemangioma with an abnormal proliferating endothelium is the most likely cause [25]. Despite various treatment modalities including surgery, supportive and systemic pharmacological treatment, the prognosis of KMP remains uncertain [26] and there is therefore an urgent need to develop more effective treatments. The use of multifunctional ferromagnetic nanoparticles may represent a theranostic option (Fig. 1 b).

Challenges

Nanomaterials can enter the body *via* a number of portals, such as the skin, respiratory tract or gastrointestinal tract, or through parenteral administration [27, 28]. The translocation of nanoparticles to the bloodstream allows interactions between nanomaterials, plasma and blood elements to take place. Nanoparticles' contact with plasma proteins leads to the formation of a "protein corona" [29], which may modify the biological and pharmacological properties of the nanoparticles [30].

Over the past 10 years the authors have pioneered and studied the effects of nanoparticles on vascular hemostasis and blood platelet function, as platelet-nanoparticle interactions are likely to play a major role in the hemocompatibility of nanomaterials. These studies have shown that soluble and surface-bound carbon nanoparticles have the ability to stimulate platelet aggregation and to increase

thrombosis *in vitro* and *in vivo* [31, 32]. Other inorganic nanomaterials, such as silica nanoparticles [33], gold nanoparticles [34] and quantum dots [35], may also stimulate platelet activation. Interestingly, organic nanoparticles appear to be more platelet-compatible than inorganic nanomaterials [36], and this compatibility can also be increased by nanoparticle surface functionalization [34]. The molecular mechanisms involved in the interactions of platelets with nanomaterials are multifactorial, but they may be triggered by the generation of reactive oxygen and nitrogen species such as peroxynitrite [33, 37], and depend on the modification of receptors, transport systems and intraplatelet transduction mechanisms [38].

The authors have also designed unique test systems for studying the effects of nanoparticles on platelets. The use of a quartz crystal microbalance facilitates highly sensitive measurement of platelet microaggregate formation during interactions among nanoparticles, platelets and other cells under flow conditions [32, 34, 35, 38–42].

An understanding of the subcellular mechanisms involved in nanomaterial hemocompatibility, as well as the availability of sensitive methods for studying such interactions, will be of great assistance when developing diagnostic and therapeutic options using multifunctional nanomaterials. Multifunctional nanoparticles including materials with ferromagnetic cores rely on their ability to interact efficiently with EM fields to produce a response through the scattering or absorption of the interacting field [43]. EM-mediated responses may be used for selective detecting, targeting, monitoring and treating a wide cross section of human diseases. However, the impact of an EM field on interactions between multifunctional nanoparticles, cells and subcellular structures needs to be carefully evaluated to determine the risk/benefit ratio of such pharmaceuticals.

It is also important to point out that there are compelling differences between various medically relevant nanomaterials. Therefore, the R&D as well as the registration of novel nanodiagnostic/nanotherapeutic agents with the FDA and European Medicines Agency is likely to proceed on a case-to-case basis. The pharmaceutical industry may, however, be vitally interested in nanotherapeutic ventures. Indeed, over the past few years large, research-intensive pharmaceutical companies have had to deal with the effects of the so-called "patent cliff". The patent cliff results from the expiry of patents for major pharmaceutical blockbusters, which leads to decreased revenues for the producers of the patented product. Therefore, uniquely formulated nanodrugs based on existing compounds may be one way to go for the

research-intensive pharmaceutical industry to deal with patenting problems [44].

Finally, it is worth commenting on risk and safety assessment associated with the use of nanopharmaceuticals. As indicated in the “Opportunities” section above, both the FDA and the EU have already set up robust schemes for the approval and legislation of new nanopharmaceuticals; these schemes appear to be working well, and provide comprehensive pharmacological/toxicological profiles of novel nanopharmaceuticals. A challenge that requires very careful consideration is the environmental presence and persistence of engineered nanoparticles. It is likely that organic, biodegradable nanoparticles will be of lesser concern, as they will be degraded by metabolic pathways [27]. In contrast, inorganic,

non-biodegradable nanoparticles, including multifunctional magnetic nanoparticles, may persist for considerable periods and result in prolonged exposure of humans, animals and the environment with still-to-be-determined consequences. This could potentially add to the pool of engineered nanomaterials present in the environment, which is continually delivered by nanoproducts produced by the food, agriculture and cosmetics industries [27, 45–47]. The outcome of biological interactions between nanomaterials and xenobiotics present in the environment may also be of concern [48, 49]. Therefore, serious assessment of the environmental risks associated with the growing presence of nanotechnology products in the environment most definitely needs to be carefully considered [50–52].

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Address for correspondence:

Marek W. Radomski
School of Pharmacy and Pharmaceutical Sciences
The University of Dublin
Trinity College
Dublin
Ireland
Tel: +35 31 896 2819
E-mail: marek.radomski@tcd.ie

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