NANOPHARMACOLOGY AND NANOTOXICOLOGY OF NANOMATERIALS: NEW OPPORTUNITIES AND CHALLENGES

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Abstract

An unprecedented 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 diagnostics and therapeutics of a wide range of human pathologies including cancer, cardiovascular diseases, and diseases of the central nervous system. The growth of nanomedicine fuels also advances in bioengineering, regenerative medicine and medical devices development. 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 at cellular, subcellular and molecular levels. This article reviews some of the most compelling problems related to nanopharmacology and nanotoxicology of nanomaterials. In our overview, we will focus on opportunities brought about by the development of multifunctional nanomaterials and nanotheranostics for diagnostics and therapeutics of major and rare diseases. We will also discuss challenges related to haemocompatibility of nanomaterials.

Introduction

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 nm-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 size for nanomaterials has been growing extremely fast. It is estimated that 11 million tonnes of nanomaterials are annually produced with the market value of 20 bln € and products underpinned by nanotechnology are valued in 2015 at 2 trn € [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 the key enabling technology (KET) for the EU [2].

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

In 2007 in a highly-accessed and –cited article published in British Journal of Pharmacology [3] we have alerted pharmaceutical community to a new and growing field of nanotechnology research relevant to pharmacology and toxicology. Over the past 8 years the field has grown very rapidly resulting in publication of a great number of original and review articles. Table 1 presents selected published reviews covering a cross section of nanomedicine, nanopharmacology and nanotoxicology topics.

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

In this overview, we will focus on opportunities brought about by the development of multifunctional nanomaterials for diagnostics and therapeutics. We will also discuss challenges related to biocompatibility of newly developed nanomaterials highlighting blood-nanoparticle interactions.

Opportunities

Most of 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 Food and Drug Administration (FDA) for use in men was Doxil [4] where liposomal encapsulation of doxorubicin was used to increase the drug/carrier ratio and decrease cardiac toxicity and adverse effects associated with the use of this anticancer drug [5].

Up to date >40 nanopharmaceuticals have been approved by the 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 daunorubicine [8] and vincristine [9], as well as paclitaxel formulated using nanosized albumin carrier [10]. As with Doxil the use of nanoplatforms is likely to increase the selectivity and efficacy and reduce the adverse effects of these anticancer drugs.

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

Recently, yet another dimension of nanoparticle drug delivery system has been gaining increasing momentum in the nanomedical R&D. This is nanotheranostics based on the use of multifunctional nanoparticles that integrate diagnostic and therapeutic functions in one system [12]. For cancer treatment nanotheranostics platforms comprise advanced diagnostics, hyperthermia treatment and targeted delivery of anticancer drugs [13]. Ferromagnetic iron oxide nanoparticles (SPION) are an example of such platforms [14, 15]. They have been also developed as a part of our MULTIFUN EU consortium (http://www.multifun-project.eu/) [16] and offer distinct advantages over other drug delivery platforms used to deliver anticancer medications: a) the pharmacokinetics of SPION is easily determined using non-invasive imaging techniques such as NMR, b) SPION can be easily guided to cancer tissues using electromagnetic field (EM), c) SPION can selectively generate energy to destroy cancer cells and d) SPION when functionalized with antibodies against cancer biomarkers can selectively deliver a “cocktail” of therapeutic pharmaceuticals (Figure 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 NanoAthero consortium (http://www.nanoathero.eu/) that aims at targeted imaging and treatment of advanced atherothrombotic disease in humans.

In addition to major diseases such as cancer and cardiovascular diseases, nanotheranostics may also be applied to the diagnostics and treatment of rare diseases. Kasabach – Merrit syndrome [22] also known as Kasabach – Merrit Phenomenon (KMP) or thrombocytopenia with a vascular lesion is a rare condition (National Organization for Rare Disorders, NORD, http://rarediseases.org/) that complicates the course of two rare vascular tumours kaposiform haemangioendothelioma (KHE) and tufted angioma (approximately 1% of all haemangioma) believed to be a spectrum of the same disease [23]. Albeit a rare disease, KMP is a life threatening one leading to profound thrombocytopenia (3,000-60,000/μL) hypofibrinogenaemia, bleeding and sometimes to disseminated intravascular coagulation. The exact pathogenesis of KMP is uncertain; however, trapping of platelets in haemangioma with abnormal proliferating endothelium is the most likely cause [24]. Despite various treatment modalities including surgery, supportive and systemic pharmacological treatment the prognosis of KMP remains uncertain [25] and, therefore, there is an urgent need to develop more effective treatments. The use of multifunctional ferromagnetic nanoparticles may represent such a theranostic option (Figure 1 b).

Challenges

Nanomaterials can enter the body via a number of portals such as skin, respiratory tract, and gastrointestinal tract or through parenteral administration [26, 27]. Translocation of nanoparticles to the bloodstream allows for interactions between nanomaterials plasma and blood elements to take place. The contact of nanoparticles with plasma proteins leads to formation of "protein corona" [28], which may modify the biological and pharmacological properties of nanoparticles [29].

Over the past 10 years our group has pioneered and studied the effects of nanoparticles on vascular haemostasis and blood platelet function as platelet-nanoparticle interactions are likely to play a major role in haemocompatibility of nanomaterials. We have shown that soluble and surface-bound carbon nanoparticles have the ability to stimulate platelet aggregation and increase thrombosis *in vitro* and *in vivo* [30, 31]. Other inorganic nanomaterials such as silica nanoparticles [32], gold nanoparticles [33] as well as quantum dots [34] may also stimulate platelet activation. Interestingly, organic nanoparticles appear to be more platelet compatible when compared with inorganic nanomaterials [35] and this compatibility can also be increased by nanoparticle surface functionalization [33]. Molecular mechanisms involved in the interactions of platelets with nanomaterials are multifactorial, yet they may be triggered off by generation of reactive oxygen and nitrogen species such as peroxynitrite [32, 36] and depend on modification of receptors, transport systems as well as intraplatelet transduction mechanisms [37].

We have also designed unique test systems for studying the effects of nanoparticles on platelets. The use of quartz crystal microbalance facilitates the measurement with great sensitivity platelet microaggregate formation during the interactions between nanoparticles, platelets and other cells under flow conditions [31, 33, 34, 37-41].

The understanding of subcellular mechanisms involved in nanomaterial haemocompatibility, 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 core rely on their ability to interact efficiently with EM fields to produce a response via scattering or absorption of the interacting field [42]. The EM-mediated responses may be used for selective detecting, targeting, monitoring and treating a wide cross section of human diseases. However, the impact of EM field on interactions between mutlifunctional nanoparticles, cells and subcellular structures needs to be carefully evaluated to compile the risk/benefit ratio of such pharmaceuticals.

It is also important to point out that despite the commonality of nanosize there are compelling differences between various medically relevant nanomaterials. Therefore, the R&D as well as registration of novel nanodiagnostic/nanotherapeutic agents with FDA and EU is likely to proceed on the 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 so-called "patent-cliff". The patent-cliff results from expiry of patents for major pharmaceutical blockbusters, which leads to decreased pharma sales. Therefore, uniquely formulated nanodrugs based on the existing compounds may be one way to go for the research-intensive pharma industry to deal with patenting problems [43].

Finally, it is worth to comment on the risk and safety assessment associated with the use of nanopharmaceuticals. As indicated in the **Opportunities** section, both FDA and EU have already set up robust schemes for approval and legislation of new nanopharmaceuticals and these schemes appear to be working well and provide the comprehensive pharmacological/toxicological profile of novel nanopharmaceuticals. The challenge that requires a 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 [26]. In contrast, inorganic, non-biodegradable nanoparticles, including multifunctional magnetic nanoparticles, may persist long enough and result in prolonged exposure of humans, animals and the environment with still to be determined consequences of such exposure. This, potentially, could add to the pool of engineered nanomaterials present in environment that is continually enriched with nanoproducts produced by food, agriculture and cosmetics industries [26, 44-46]. The outcome of biological interactions between nanomaterials and xenobiotics present in the environment may also be of concern [47, 48]. Therefore, beyond any reasonable doubt the assessment of environmental risks associated with growing presence of nanotechnology products in the environment needs to be carefully considered [49-51].

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Table 1. Selected nanomedical reviews.

Reference [#]	Topic
Ali-Boucetta and Kostarelos 2013 [52]	Toxicokinetics of carbon nanotubes.
Allen and Cullis 2013 [53]	State-of-the-art of liposomal drug delivery systems.
Alvarim et al 2014 [54]	Therapy using SPION-labelled stem cells.
Andersen et al 2012 [55]	Adverse immune effects of carbon nanotubes.
Arora et al 2012 [56]	Using in vitro methods in nanotoxicology.
Bao et al 2013 [57]	Multifunctional NPs for drug delivery and imaging.
Bartenck et al 2014 [58]	Nanomedicine to treat liver diseases.
Benetti et al 2014 [59]	Nanometallomics in nanotoxicology.
BeruBe et al 2007 [60]	Pulmonary toxicity of combustion-derived nanoparticles.
Billi et al 2010 [61]	Nanotoxicology of metallic nanoparticles in total joint arthroplasty.
Bussy et al 2013 [62]	Interactions of carbon nanotubes with blood.
Caputo et al 2014 [63]	Engineered nanomaterials as antioxidants.
Carraciolo 2015 [64]	Liposome-protein corona in targeted drug delivery.
Chaudhury et al 2014 [65]	Regenerative nanomedicine: current state and future perspectives.
Chen and Liu 2015 [66]	Pharmaceutics of nanofibers and their role in delivery of antimicrobials.
Chen et al 2014 [67]	State-of-the-art and perspectives of therapeutic and diagnostic use of theranostic nanoparticles.
Chen et al 2013 [68]	Use of advanced nuclear analytical techniques in nanotoxicology.
Cheng et al 2015 [69]	Therapeutic potential of polymeric nanoparticles.
Cockburn et al 2012 [26]	Safety of nanomaterials used in food industry: guidelines.
Conde and Artzi 2015 [70]	Gold nanobeacons in smart nanotheranostics.
Costa et al 2015 [71]	Layer-by-layer technology for preparation of nanoreservoirs for controlled drug release.
Das Neves et al 2015 [72]	Nanocarriers for vaginal drug delivery.
De Vries et al 2015 [73]	Delivery of antimicrobial peptides using nanocarriers.
Del Pino 2014 [42]	Interactions of medically-relevant nanoparticles with electromagnetic fields.
Deshayes et al 2014 [74]	Cage nanoparticles for drug delivery.
Doktorovova et al 2014 [75]	Nanotoxicology of solid lipid nanoparticles.
Donaldson et al 2010 [76]	Genotoxicity of nanoparticles.
Donaldson et al 2013 [77]	Adverse effects of nanoparticles in the cardiovascular system.

Estelrich et al 2015 [78]	Nanoparticles for magnetic resonance imaging.
Feng et al 2015 [79]	Toxicity of dental nanomaterials.
Fernandes et al 2015 [80]	Targeting digestive cancers using nanotreatments.
Franci et al 2015 [81]	Silver nanoparticles as antibacterials.
Frohlich 2015 [82]	Nanoparticle immunotoxicity in vivo.
Fubini et al 2010 [83]	Nanotoxicity in relation to physico-chemical features of nanoparticles.
Gainza et al 2015 [84]	Nanocarriers in wound healing and skin regeneration.
Gendelman et al 2015 [85]	Nanotreatment for degenerative, inflammatory and infectious diseases of the nervous system.
Gharagozloo et al 2015 [86]	Nanomedical treatment of autoimmune diseases.
Gregori et al 2015 [87]	Nanomedical treatment of Alzheimer's disease.
Grieger et al 2012 [49]	Environmental risk of nanomaterials.
Guo and Huang 2014 [88]	Enhancing solubility of anticancer drugs.
Gusic et al 2014 [89]	Nanoscaffolding in bone regeneration.
Holden et al 2014 [90]	Bacteria for assessing environmental hazards and fates of nanomaterials.
Hristozov et al 2014 [91]	Hazard screening of engineered nanomaterials.
Hubbs et al 2014 [92]	Augmented microscopy assessment in nanotoxicology.
Ilinskaya and Dobrovolskaia 2013 (part II) [93]	Undesirable action of nanoparticles on blood clotting.
Ilinskaya and Dobrovolskaia 2013 (part I) [94]	Desirable action of nanoparticles on blood clotting.
Jo et al 2015 [95]	Nanoparticles in treatment of retinal diseases: nanotherapeutic agent characteristcs.
Johnston et al 2013 [51]	Risk of engineered nanomaterials.
Kandi and Kandi 2015 [96]	Overcoming anti-bacterial resistance with nanoparticles.
Kermanizadeh et al 2015 [97]	Role of redox mechanisms in nanomaterial toxicity.
Kim et al 2015 [98]	Nanoparticles for siRNA delivery in cancer therapy.
Kodiha et al 2015 [99]	Gold nanoparticles for cancer therapy.
Lakkakula et al 2014 [100]	Cyclodextrin nanoparticles for drug delivery.
Landriscina et al 2015 [101]	Biodegradable chitosan nanoparticles in drug delivery systems.
Larson et al 2014 [102]	Reproductive toxicity of nanomaterials.
Laurent et al 2014 [103]	Superparamagnetic iron oxide nanoparticles in therapy.
Li et al 2015 [104]	Photodynamic therapy using graphene-based nanoplatforms.

Li YF et al 2015 [105]	Use of advanced light beams generated by synchrotron for nanotechnology and nanotoxicology.
Lukowiak et al 2015 [106]	Unimolecular micelles for drug delivery.
Lux et al 2015 [107]	Gadolinium-based nanotheranostics.
Madl et al 2015 [108]	Nanotoxicology of hip implants part I.
Madl, Kovochich et al 2015 [109]	Nanotoxicology of hip implants part II.
Mottaghitalab et al 2015 [110]	Silk fibroin nanoparticle in drug delivery systems.
Mulder et al 2014 [111]	Diagnosis and treatment of atherosclerosis using nanomedical tools.
Muller et al 2011 [112]	Nanotoxicology of nanocrystals.
Murugan et al 2015 [113]	Mechanisms of cellular trafficking of nanostructures
Nel 2013 [114]	Safety assessment of nanomaterials using alternative test strategies.
Nel et al 2013 [115]	Predictive toxicological approach and high-throughput screening in nanotoxicology.
Nielsen et al 2014 [116]	Nanomedicine in the treatment of inflammatory bowel disease.
Nunez-Anita et al 2014 [117]	Toxicity of antimicrobial nanoparticles used in prosthetic devices.
Osmond et al 2010 [118]	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 [119]	Overcoming multidrug cancer cell resistance using nanomaterials.
Paul 2015 [120]	Myocardial therapy using nanocomposite hydrogels.
Polak and Shefi 2015 [121]	Neuronal regeneration using nanoparticles.
Sadikot 2014 [122]	Nanomaterials in critical care medicine.
Schrofel et al 2014 [123]	Biomedical applications of metallic nanoparticles.
Sehedic et al 2015 [124]	Overcoming radioresistance of glioblastoma using nanomaterials.
Shvedova and Kagan 2010 [125]	Pulmonary toxicity of single-wall carbon nanotubes.
Sosnik and Carcaboso 2014 [126]	Nanomedicine in paediatrics.
Sriraman et al 2014 [127]	Brain tumour targeting using multifunctional nanoparticles.
Tan et al 2011 [128]	Quantum dots and carbon nanotubes in oncology.
Tomaszewski et al 2015 [37]	Nanopharmacology and nanotoxicology in platelet-vascular wall interactions.

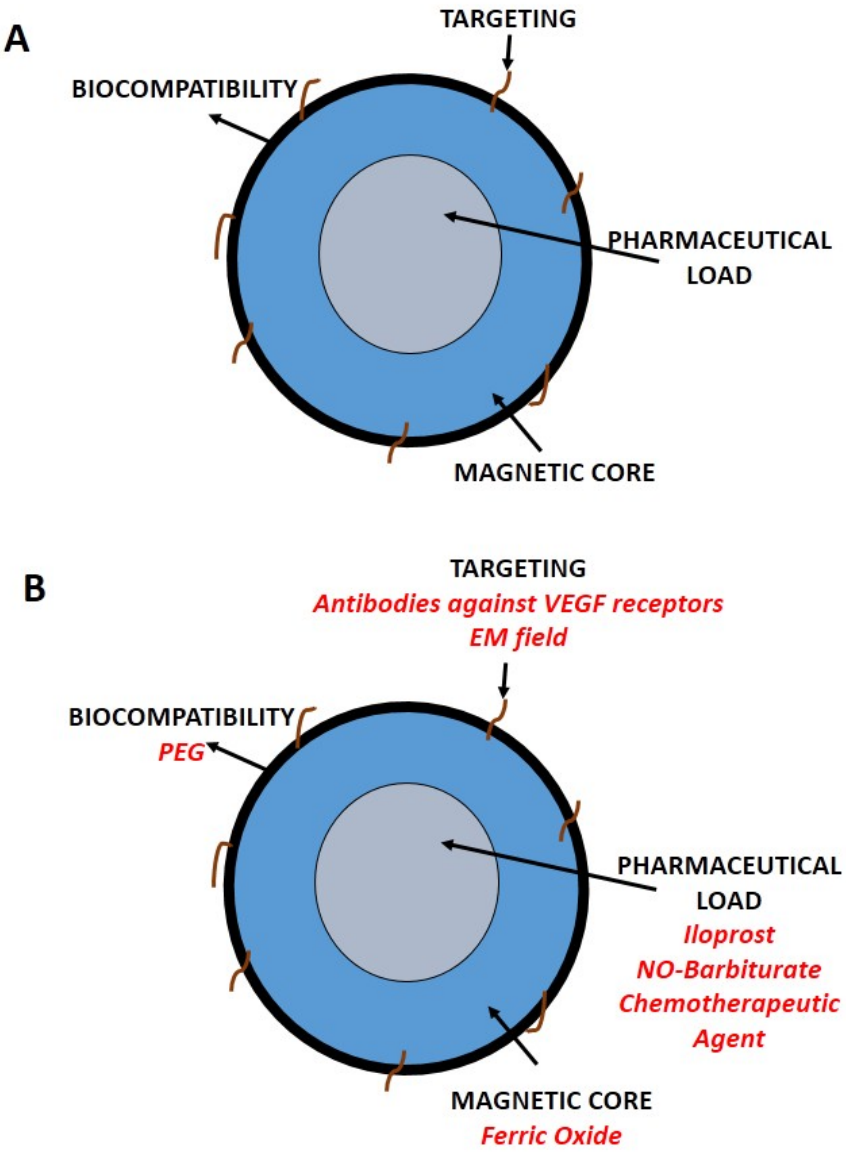
Torchilin 2014 [129]	Multifunctional and stimuli-sensitive drug delivery systems.
Tseng and Liu 2015 [130]	Delivery of analgesics using nanofibers.
Veiseh et al 2015 [131]	Nanodrug discovery and the treatment of diabetes mellitus.
Vellayappan et al 2015 [132]	Nanocomposites for grafts and stents.
Vinogradov et al 2014 [133]	Targeting macrophages associated with tumour using nanoparticles.
Walmsley et al 2014 [134]	Nanotechnology in bone tissue engineering.
Wang et al 2015 [135]	Boron-functionalized nanocarriers for cancer treatment.
Weissig et al 2014 [6]	Approved and commercially available nanopharmaceuticals.
Weissig and Guzman-Villanueva 2014 [136]	Approved and commercially available nanopharmaceuticals.
White-Schenk et al 2015 [137]	Nanopharmaceuticals in spinal cord injury.
Winkler et al 2014 [138]	Structure-activity relationship (SAR) approach in nanotoxicology.
Zhao et al 2014 [139]	Nanotechnology in glycopeptide detection and glycoproteomics.
Zhen et al 2014 [140]	Ferritins as multifunctional nanoplatforms.

Figure 1.

A) A general design and functionalization of multifunctional magnetic nanoparticles: *magnetic core* capable of scattering or absorption of the interacting electromagnetic field allowing for diagnostics and treatment; *pharmaceutical load* for selective delivery of therapeutics; *targeting* using antibodies against specific cellular markers and *biocompatibility* with polyethylene glycol (PEG) allowing for longer half-life of nanoparticles in the bloodstream [13, 42, 53].

B) A proposed design of multifunctional ferromagnetic nanoparticles for the treatment of Kasabach-Merrit disease: *ferromagnetic core* using ferric oxide; *pharmaceutical load* with a chemotherapeutic agent [24], NO-barbiturate a strong inhibitor of cancer cell proliferation and secretion [141] and iloprost, an analogue of prostacyclin, a potent inhibitor of platelet aggregation that synergizes with NO [142]; *targeting* haemangioma cells using antibodies against vascular endothelial growth factor receptors [143] and EM field; and *biocompatibility* coat with PEG.

Figure 1


A
TARGETING
BIOCOMPATIBILITY
PHARMACEUTICAL LOAD
MAGNETIC CORE
B
TARGETING
Antibodies against VEGF receptors
EM field
BIOCOMPATIBILITY
PEG
PHARMACEUTICAL LOAD
Iloprost
NO-Barbiturate
Chemotherapeutic Agent
MAGNETIC CORE
Ferric Oxide