Nanotechnology in Medicine

27

M. Nikolova, R. Slavchov, and G. Nikolova

Contents

Abstract

Nanotechnology deals with materials and interactions at molecular and atomic level, sized between 0.1 and 100 nm. The small size of the nanoparticles and the changes of their physical and chemical properties compared to that of their macromolecular analogues offer many advantages for contemporary medicine, including improved drug delivery, opportunities for a better and noninvasive diagnostics, and targeted treatment with reduced adverse and systemic effects. Nonetheless, the same differences in the physical and chemical properties of nanoparticles could lead to serious and unpredictable side effects for the human body and for the global ecosystem, including accumulation, recirculation, and inflammatory, mutagenic, and oncogenic potential. The current review is focused on the current uses, benefits, disadvantages, and risks of nanotechnology in medicine.

. . .our environment, and I mean our man-made world of machines, artificial constructs, computers,

M. Nikolova (✉)
University Hospital Alexandrovska, Clinic of Nephrology, Medical University, Sofia, Bulgaria
e-mail: milena_i_dani@abv.bg

R. Slavchov
Cambridge University, Cambridge, UK

G. Nikolova
University Hospital Acad I. Penchev, Medical University, Sofia, Bulgaria

F. J. Hock, M. R. Gralinski (eds.), *Drug Discovery and Evaluation: Methods in Clinical Pharmacology*,
https://doi.org/10.1007/978-3-319-68864-0_45

> electronic systems, interlinking homeostatic components - all this is in fact beginning more and more to possess what the earnest psychologists fear the primitive sees in his environment: animation. In a very real sense our environment is becoming alive, or at least quasi-alive, and in ways specifically and fundamentally analogous to ourselves. . .
>
> Philip K. Dick. The Android and the Human. SF Commentary #31, December 1972 (delivered as a speech at the University of British Columbia, Vancouver, Canada, February, 1972). https://genius.com/Philip-k-dick-the-android-and-the-human-annotated

Introduction

Nanotechnology is a relatively novel interdisciplinary field of modern science, on the borders between physics, chemistry, biology, and engineering sciences, which deals with materials and interactions at molecular or even atomic level – sized 0.1–100 nm (1 nm = 1×10^{-9} m). Due to their tiny size, these materials are known to have different physical and chemical properties than the larger-scale ones (magnetism, conductance, optical properties, chemical interactions, etc.) (Nikalje 2015). At these tiny-scale sizes, the surface of the material changes significantly, along with its optical, chemical, and magnetic properties, molecular recognition differs much from that on macro-level, the quantum effects may dominate over that of the classical physics, and new and unpredictable effects might appear (Idrees 2015). Their applications in the field of medicine (for diagnostic, therapeutic, and prophylactic purposes) have brought revolutionary successes in many fields, such as cancer and diabetes treatment, anti-infectious agents, vaccine delivery; cell cultures, biosensors, diagnostic tests, tissue regeneration, and nano-robots for repairing and/or replacing cell structures and genetic engineering; etc. (Emerich and Thanos 2003; Gupta and Dinda 2018; Surendiran et al. 2009).

Many natural nanoparticles occur around us, even in our food, such as oil bodies, casein micelles, cellular organelles, and even viruses (McClements and Xiao 2017). They are formed by molecular conjugates. When entering the human body, these natural nanoparticles undergo degradation, or (like viruses) they can affect the living cell and the cell will respond. On the other hand, the man-made nanoparticles represent a new invader for our body, and the cells still have no specific adaptive response against them. The interactions between the cell structures and the synthetic nanoparticles are not well understood, and many unanswered questions remain. Therefore, many ethical and safety issues in the use of nanotechnology in medicine are to be solved.

It has been considered that the nano-era began back in 1959 with the first ideas of R. Feynman on the possibilities to change the properties of the known matter by manipulating the individual atoms, i.e., the "top-to-bottom, or top-down, approach" (Vijayakumar et al. 2013). Nonetheless, these ideas emerged in science fiction long before the plenary lecture of R. Feynman, "There's plenty of room at the bottom: an invitation to enter a new field of physics," delivered at the annual meeting of the American Physical Society in 1959 (Feynman 1959). In the first half of the twentieth century, several science fiction novels pictured the use of subatomic devices for investigations, and in 1954 the great visionnaire Philip K. Dick in his novel "Autofac" described tiny self-assembling and self-reproducing robots (Milbum 2010).

The word "nanotechnology" was introduced by the Japanese scientist Norio Taniguchi in 1974 on a Conference on Production Engineering to describe semiconductor processes – "processing of, separation, consolidation, and deformation of materials by one atom or one molecule" (N Taniguchi Norio (1974). "On the basic concept of 'nano-technology.'" Proceedings of the International Conference on Production Engineering, Tokyo, 1974, Part II. Japan Society of Precision Engineering).

In 1980, E. Drexler first encountered Feynman's provocative 1959 talk "There's plenty of room at the bottom: an invitation to enter a new field of physics." And in 1986 he independently used the term "nanotechnology" in his book "Engines of creation" (Drexler 1986). In this book E. Drexler suggested the possibility that a nano-sized "assembler" could be able to build a self-copy and copies of other structures of a different complexity and size, including larger structures – or "bottom-up approach" (Vijayakumar et al. 2013). Therefore, Drexler's idea of nanotechnology is frequently

called "molecular manufacturing." Nonetheless, this idea has already been published in science the fiction novel "Autofac" by P.K. Dick 30 years ago (Dick 1955).

A major breakthrough in the development of nanotechnology was the invention of the first scanning tunneling microscope in 1981. This microscope allows imaging surfaces at the atomic level, and the inventors (G. Binning and H. Rohrer) were awarded Nobel Prize in Physics in 1986 for their discovery. Other major discoveries in the field of nanotechnology are the discovery of fullerenes by J. Kroto, R. Smalley, and R. Curl in 1985 and the discovery of carbon nanotubes in 1991 by S. Iijima. In 1999 the first book on nanomedicine ("Nanomedicine" by R. Freitas) was published.

During the first decade of the twenty-first century, 3D nanosystems, networks, and active nanosystems have been developed, and a great concern of the safety of nano-materials and nano-robots has arisen.

Other serious ideas that first arouse in science fiction literature, but nowadays are becoming more and more real, intimately related to the concept of nanotechnology, are the "transhumanism" (graduate merge of humans and machines producing new and more sophisticated creatures that would move humanity to the "next level") and "singularity" (a certain point at which a given mathematical object is not defined or its behavior becomes unpredictable – i.e., not differentiable or infinite; from anthropological and social point of view, this is the probability that at certain point of time, the development of technology will lead to the emergence of unpredictable artificial intelligence with possibly harmful for humanity effects). These ominous predictions made by the science fiction writers more than half a century ago are becoming more and more real today, as the borders between the human and the machine become more and more obscure.

Types of Nano-materials with Proven or Potential Benefits in the Field of Medicine

Different classification systems have been applied to nano-materials according to their size, shape, phase composition, etc. (Nikalje 2015). All nanoparticles have specific physical characteristics (shape, size, surface area, permeability, magnetism) that influence deeply their properties and make them very different from other larger-scale materials (Ventola 2012a). The size of all nanoparticles, by definition, is between 0.1 and 100 nm. This small size allows them to pass through biological membranes and improve drug delivery, improves their solubility, and increases their bioavailability and circulation time within the living body. It also increases the total surface of the administered material (i.e., increases the reactivity, solubility, and bioavailability, increases conjugation properties with electrostatic surfaces or other larger molecules of nanoparticles. Still, the increased permeability and bioavailability of nanoscale materials carries the risk of penetration and accumulation within certain tissues and cells and oncogenesis. Nanoparticles can have different shapes (tubes, spheres, hemispheres, cones, wires, discs, cylinders, etc.) and be solid, porous, or hollow. Therefore, nanoparticles can transport substances to and within the living cell (e.g., for targeted drug delivery, imaging, regeneration, and repair).

Nanoparticles possessing magnetic properties can be used as targeted carriers of biologically active substances as directed by a magnetic field, as MRI contrast media, or for targeted tumor lysis mediated by their magnetocaloric effect (Guo et al. 2018).

Several major types of nanoparticles suitable for medical use with specific properties have been described, including metallic nanoparticles, dendrimers, liposomes, nano-somes, nano-pores, carbon nanotubes, fullerenes, nanocrystals/quantum dots, nano-shells, nano-wires, nano-bubbles, paramagnetic nanoparticles, and nano-bombs; these structures may be combined to form nano-robots and even structures mimicking living cells (i.e., respirocytes and microbivores) (Emerich and Thanos 2003; Guo et al. 2018; Nikalje 2015; Sarfaraz et al. 2018; Surendiran et al. 2009; Vijayakumar et al. 2013).

The major types of nano-materials used in contemporary medicine are presented in Table 1.

Table 1 Major types of nano-materials used in contemporary medicine (Bhattacharya et al. 2012; Emerich and Thanos 2003; Guo et al. 2018; Gupta and Dinda 2018; Idrees 2015; Sarfaraz et al. 2018; Surendiran et al. 2009; Ventola 2012a, b; Vijayakumar et al. 2013; Wani and Kothari 2018)

Material	Properties	Fields of medical application
Liposomes	Biodegradable, biocompatible, and nonimmunogenic microvesicles	Drug carriers for both hydrophilic and hydrophobic agents (including for gene delivery)
Micelles and solid lipid nanoparticles	Nanoparticles of a "larger" size, containing natural biomolecules that form carrier structures allowing targeted transportation of pharmaceuticals	Targeted treatment Possible genetic transfer
Nano-shells	Tiny spheres coated with different materials. They can transport different agents to the living cell (treatment/prophylaxis and imaging) or absorb infrared radiation and, after being deposited within the tumor cells, give away the heat and burn the tumor without affecting the adjacent normal living cells Gold nano-shells being most extensively studied	After conjugation to antibodies, oligonucleotides, targeting ligands, polymers, or other therapeutic agents, they can transport medications and vaccines After conjugation contrast agents or isotopes, they can assist imaging tumors or other lesions
Quantum dots (nanocrystals)	Small light-emitting nanocrystals (e.g., Cd/Zn selenides) with semiconductive properties (2–10 nm corresponding to 10–5 atoms). Obey quantum laws of quantum confinement. Glow when stimulated by UV light (the wavelength depending on the size of the crystal). More stable than traditional dyes – i.e., they can be used to replace biopsy investigations In combination with MRI, they can produce images of tumors	Imaging of specific DNA fragments Imaging of tumor cells and whole tumors Imaging of tumor vascularization "Staining" of cells and tissue structure, as a parallel to biopsy Ultrasound contrast medium
Dendrimers	Branched polymers, biocompatible and biodegradable, used as nano-sized containers and transporters. Consist of a central "core" (container), branches (interior dendritic, or tree-like, structure), and surface with functional groups on it	Targeted drug delivery (i.e., in anticancer treatment) and delivery of contrast agents in MRI Gene delivery Biosensors
Fullerenes	Carbon-based carrier nanostructures in the form of hollow spheres, tubes, ellipsoids, etc. Stable to heat, superconductive properties. Inorganic fullerenes – similar to carbon-containing – but lack C-atoms; contain MoS_2, WS_2, TiS_2, NbS_2; stable to weight	Drug delivery systems
Nano-wires	Wires 40–50 nm in diameter, as long as desired Superconducting (YBCO), semiconducting (Si nano-wires, GaN, InP), metallic (Ni, Pt, Au), insulating $(Si)_2$, TiO_2) Molecular nano-wires – repeating molecular units (organic – DNA) or inorganic (containing Mo, S, and I)	Biosensors Functional MRI and PET scanning
Nanotubes	Carbon-based nanotubes that can: 1. Transport substances within the living cell via endocytosis 2. Carry radioisotopes to target sites in order to create an image of or destroy cancer cells 3. Absorb and emit near-infrared light and	Drug delivery systems Imaging studies Cancer treatment Imaging Nano-robotic devices Reparation and regeneration

(continued)

Table 1 (continued)

Material	Properties	Fields of medical application
	destroy tumor cells 4. Have near-infrared photoluminescence properties and visualize cancer cells 5. Be stimulated by light and move and create nano-robotic for cell and DNA reparation and regeneration	
Nano-electro-mechanical sensors (NEMS, cantilevers)	Nano-mechanical devices that detect the forces, motion, mechanical properties, and masses that emerge in biomolecular level A surface coated with bioreceptor that recognizes the target analyte and bends in response. The transducer transforms the mechanical response into recognizable electrical signal	Biosensors Biorecognition
Magnetic nanoparticles	Metal (Au, Ag, Co, Ni, Mn, Zn), metal oxide (γ-Fe_2O_3 and Fe_3O_4, $CoFe_2O_4$, $Mn0.6Zn0.4Fe_2O_4$, $Mn_3Zn7Fe_2O_4$, $Mn0.6Zn0.4Fe_2O_4$), and metal alloy (FeCo, FePt); ferrite nanoparticles have a stronger magnetism and a higher relaxation rate and are used in MRI. Nonvirulent and nonimmunogenic. Large specific surface area for carrying a large amount of DNA fragments, drugs, and modified compounds (after modification can be used as vector). Most modified magnetic nanoparticles are biocompatible. And some magnetic nanoparticles are superparamagnetic. Magnetic nanoparticles can produce thermal effect under the action of alternating magnetic field (tumor thermotherapy). Magnetic nanoparticles can be used for magnetic separation (under the action of the magnetic field, they can separate biomolecules). Most extensively studied – Fe_2O_3 and Fe_3O_4 nanoparticles	Vector for targeted treatment Medical imaging (MRI) Thermodestruction of tumors and non-tumor structures Separation of biomolecules
Nano-bombs	Nanoparticles that can destroy certain cells and structures via induction of hyperthermia or the targeted delivery of antineoplastic agents Also used for imaging – deposition within certain tissues and generation of a detectable signal after stimulation	Cancer treatment Imaging
Nano-pores	Wafer-like structures with high density of pores that allow entry of lower-molecular-weight substances (oxygen, glucose, insulin) to pass through but stop larger molecules, such as immunoglobulins. Can stop certain molecules or sequences. Can protect the graft after transplantation while assuring proper nutrition Can differentiate DNA strands based on differences in base pair sequences. Can differentiate purines from pyrimidines Improve longitudinal resolution for base pair	Post-transplantation graft protection DNA sequencing

(continued)

Table 1 (continued)

Material	Properties	Fields of medical application
	identification Can be used for genome sequencing	
Nano-bubbles	Nanoscale bubbles that are stable at room temperature and within the human body form microbubbles that can transport pharmaceutical agents and genes or perform sonothrombolysis when combined with ultrasound	Drug and gene delivery Sonothrombolysis
Respirocytes	Hypothetical nano-devices acting as erythrocytes with higher capacity to deliver oxygen and carbon dioxide, surface sensors and regulating system that alter the uptake of carbon dioxide and the release of oxygen as required	Artificial red blood cells
Microbivores	Hypothetical nano-devices acting as leukocytes, expected to have higher efficacy. Theoretically can clean the blood of bacteria in septicemia	Artificial white blood cells
Nano-robots	Nano-sized devices for dynamic follow-up and molecular manipulation of tissues, cells, and cellular structures	Diagnostics and treatment Artificial organs (?)

Interaction of Nanoparticles with Biological Molecules

Nanoparticles correspond and match with natural molecules and functional systems within the living body, and therefore they can actively interact with biological systems (Idrees 2015). As the majority of animal cells are within the range of 10–20,000 nm, nanoparticles and nano-sized devices can enter the living cell and subcellular structures (organelles) and interact with intracellular molecules, such as proteins and ribonucleic acids (DNA and RNA). Nanoscale devices can both detect and possibly cure cellular defects by correcting subcellular defects (e.g., via interaction with intracellular biopolymers such as proteins and ribonucleic acids, with receptor and enzymes) and can be used for active monitoring of cellular processes, (sub)cellular and tissue reparation and regeneration. One should not forget that at these tiny-scale sizes, the characteristics of matter change significantly with domination of quantum effects and significant changes in chemical reactivity that may lead to the occurrence of new and unpredictable effects and properties (Idrees 2015). Nanoparticles have been used as "carriers" of biologically active molecules (antibodies, vaccines, anticancer agents, etc.), where the core of the new nano-biomaterial is formed by the nanoparticles and is covered by inert material (i.e., silica) and then by a linker molecule, and finally the biologically active structures are attached. Nano-materials can also be used to cover and to bind biomolecules, and after transportation to the living cells by the biomolecules (i.e., in this case the carrier is the biomolecule), the targeted nanoparticles may detect and affect the cell. In other words, nanoparticles may be used for the detection and destruction of damaged cells (including neoplastic) after being targeted to these cells by a carrier biomolecule. Moreover, magnetic nanoparticles can be used as carriers, MRI contrast agents, and for the induction of magnetic hyperthermia (Guo et al. 2018).

Areas of Application in Medicine

As in all fields of human life, nanotechnologies have found promising new applications in medical practice – for diagnostic, therapeutic, and prophylactic purposes. Table 2 represents the major

Table 2 Nanoparticle size and applications in medicine (Idrees 2015; Nikalje 2015)

Type of nanoparticle	Size (nm)	Use
Carbon nanotubes	Diameter 0.5–3 Length 20–100	Detection of DNA changes and/or protein biomarkers
Dendrimers	<10	Controller drug release Imaging
Nanocrystals/quantum dots	2–9.5	Improve drug solubility Detect cancer cells Detect mutant DNA fragments Tumor and lymph node visualization
Nano-shells	Various	Tumor imaging Tumor ablation
Nano-wires	Various	Sensing of proteins and chemicals (biomarker and mutant DNA detection) Detection of gene expression products
Nanoparticles	10–100	Contrast agents (MRI and ultrasound) Targeted drug delivery Permeation enhancers Detection of apoptosis and angiogenesis
Liposomes, micelles, emulsions	Various	Drug delivery Liposomes are nontoxic!

uses of nanoparticles in medicine, and Table 3 presents the benefits of nano-sized materials for the contemporary medical practice.

Diagnosis

Nano-materials offer the unique opportunity of noninvasive, fast, and inexpensive in vitro and in vivo diagnostics, even in real time, for nontoxic imaging studies and for the simultaneous diagnostic and therapeutic approaches (the so-called theranostics – targeted diagnostic approach combined with immediate therapeutic intervention, for instance – visualization of tumor cells using magnetic nanoparticles with subsequent magnetism-induced thermal ablation or visualization of the tumor using antibody-bound gold nano-shells with subsequent irradiation with infrared light and thermal ablation). NEMS can be used for precise and noninvasive in vivo sensitizing. Moreover, the tiny-sized nanoparticles permit precise and fast DNA sequencing, in vivo staining and visualization, and targeted imaging of damaged cells and tissues while decreasing the need of biopsy. Therefore, nanotechnologies give us the change to perform both super-targeted screening in high-risk groups and large mass-screening programs for at population level.

The nano-wires also permit detection of pathological changes in remote and inaccessible areas, such as the central nervous system, and detection of alterations in the small blood vessels and nerve fibers that are hard to evaluate using the existing techniques. Moreover, they are capable of detecting tumor antigens located on or within remote tumor cells.

Magnetic and luminescent nanoparticles offer noninvasive in vivo imaging without the risk of renal toxicity with high sensitivity and specificity.

Probably the most impressive breakthrough based on nanotechnologies in contemporary diagnostics is that in molecular diagnostics, nanotechnologies allow detection/sequencing and reparation of DNA changes, even single-nucleotide alterations. Moreover, tiny nano-based quasi-robot systems are capable of correcting the defects. These astonishing new discoveries even allow the construction of new DNA molecules for biomedical and biocomputer researches, such as nano-sensors, nano-electronic and bioelectronic devices, and DNA computation (Zahid et al. 2013).

Table 3 Fields of application and benefits of nano-materials in medicine (Bhattacharya et al. 2012; Emerich and Thanos 2003; Guo et al. 2018; Gupta and Dinda 2018; Idrees 2015; Sarfaraz et al. 2018; Surendiran et al. 2009; Tasciotti et al. 2016; Ventola 2012a, b; Vijayakumar et al. 2013; Wani and Kothari 2018; Yadav et al. 2018; Yambe 2009; Zahid et al. 2013)

Field of application	Benefits
Diagnostics	
Imaging	Magnetic and luminescent nanoparticles for contrast enhancement Contrast-medium carriers Nano-wires allowing noninvasive detection of problems within the central nervous system and other dangerous-to-investigate sites Less invasive and nontoxic imaging. Real-time and early detection Inexpensive mass screening Theranostics
Molecular diagnostics	Nano-probes Less invasive diagnostics, giving information on molecular level with the opportunity to correct the defect Inexpensive mass screening
Treatment	Targeted anticancer treatment with antineoplastic drugs, enzymes/enzyme inhibitors, radiation, thermal ablation, gene therapy, DNA reparation/DNA transfer Lower dose, lower systemic availability, faster response Less toxic or nontoxic for the adjacent tissues/cells and the whole body Anti-infectious treatment (tuberculosis, leishmaniasis, antifungal agents) Ag-containing nanoparticles serving as antimicrobial "scaffold" Mechanisms to overcome therapeutic resistance in infections and in neoplastic diseases Neuroregeneration and reparation (Alzheimer's and Parkinson's diseases). Epilepsy – preventing seizures
Vaccines	Delivery and stabilization of vaccines (against HBV, staphylococci, etc.)
Regeneration and reparation	Wound healing – biocompatible wound healing material, Ag-containing dressings and creams/solutions, chitosan, Cu-containing nanoparticles Glutathione and collagen nanoparticles for cosmetic purposes
Nano-robotics	A nano-sized device for dynamic follow-up and molecular manipulation of tissues, cells, and cellular structures, as a parallel to viruses and bacteria living within our body Must transmit data and receive commands and should be able to repair or correct living structures or processes The simultaneous use of nano-photonic and nanotube-based technologies allows DNA manipulation, and larger and more complex nano-robots/artificial organs are expected to emerge
Transplantology and prosthetics	Targeted and controlled delivery of immunosuppressive medications, preservation of graft function, achievement and preservation of tolerance Imaging Implantable drug delivery systems Nano-engineered prosthetics Development of artificial organs

Treatment

Nanotechnologies are applied in many fields of treatment, including anti-infectious medications (against tuberculosis, fungi, and leishmania), anticancer medications, wound healing and cosmetics, artificial fabrics and tissues, vaccines, dentistry, neuroprotection and neuroregeneration, artificial cells and organs, and nanorobotics (Emerich and Thanos 2003; Gupta and Dinda 2018; Nikalje 2015; Sarfaraz et al. 2018; Surendiran et al. 2009; Tasciotti et al. 2016; Ventola 2012a, b; Vijayakumar et al. 2013; Wani and Kothari 2018; Yadav et al. 2018; Yambe 2009; Zahid et al. 2013).

Nanoparticles can be used for targeted drug delivery offering higher specificity, higher bioavailability, lower dose, and lower incidence of

both systemic and local side effects (i.e., increasing cost-effectiveness). Different types of nanoparticles are used for targeted drug delivery, including liposomes, micelles, dendrimers/nanopolymers, nano-pores, nano-shells, NEMS, etc. Still, their toxicity and safety for the human body and for the environment remain unclear, and further research is required.

Nanoparticles are widely used as carriers of anticancer drugs, such as paclitaxel and doxorubicin. Newly designed nanoparticles are called "minicells" (Nikalje 2015). They are composed of the biomembranes of mutant bacteria and carry different types of antineoplastic medications. After being engulfed by the tumor cells, these nanoparticles are capable of destroying the tumor. Nano-porous materials can also carry different medications and offer the benefit of prolonged release. Tolerogenic nanoparticles have also been developed – after loaded with certain antigens (e.g., myelin) that can be introduced to the human body and induce tolerance to this antigen, thus decreasing the autoimmune response against the same substance.

Another field is the antibiotic delivery and antibiotic resistance (Zn oxide nanoparticles can decrease antibiotic resistance and increase antibiotic effect of ciprofloxacin). Nanoparticles have been used to dissolve thrombi (both in combination with ultrasound and as carriers of anticoagulant substances). Nanoparticles have been used as carriers of nucleic acids (including gene transfer), peptides, etc.

For vaccine delivery, nanoparticles have several important advantages (especially liposomes!): they are inert, their small size permits them to cross biological barriers, and they can be targeted to specific organs. This is particularly important, especially in the development of vaccines against viral pathogens. Moreover, one should not forget that viruses themselves represent natural nanoparticles that become "alive" after entering the host cell and exploiting the host life, supporting and reproducing intracellular systems.

In neurodegenerative disorders, nanoparticles can be used for targeted drug delivery to the damaged cells or areas that otherwise remain hidden behind the blood-brain barrier. Different types of nanoparticles have been investigated, including liposomes, dendrimers, nanogels, emulsions, polymeric and solid lipid nanoparticles, and nano-suspensions. In Parkinson's disease, nanoparticles are investigated as drug carriers to specific brain areas (Nikalje 2015) aimed at improving the patient's condition and quality of life, without being able to improve the prognosis.

The same strategies are under investigation for central nervous system tumors, HIV-induced involvement of the central nervous system, and Alzheimer's disease. In the latter, investigations are also aimed at removal of amyloid precursors and depositions.

In ophthalmology, nanoparticles can be used for diagnosis (measurement of intraocular pressure), treatment (ocular infections and retinal degeneration), and prevention (prevention of scarring and development of secondary glaucoma, of eye dehydration, etc.).

In surgery, nano-techniques can be used for visualization of tumors, for vascular repair, for tissue repair and removal, wound dressings and textiles with antimicrobial properties, etc.

Nanoparticles can affect the immune cells and the immune and allergic response and can therefore be used as drug carriers in autoimmune and allergic diseases. The question concerning the possibility for triggering an autoimmune disease (for instance, by activating complementary cascade or by altering the properties of self-antigens, such as proteins and DNA) remains unanswered.

In transplantation, nanoparticles can be used for drug delivery, for induction and maintenance of donor tolerance, and for diagnostic purposes (including detection of rejection).

A new field of nanomedicine is the development of nano-based prosthetic materials and artificial organs (biocomputer-based systems, incorporating the properties of the living organism and of the computer sensoring and responding systems). The investigations in this field have started with the development of artificial red and white blood cells that are not applicable in the clinical practice due to their unpredictable accumulation and destruction in the spleen. The nanosensors and the opportunities for the development

of nano-based-guided synthesis of specific DNA molecules are a promising new area of investigation.

Gene therapy is among the newest areas of investigation, using nano-based techniques. Multiple investigations, aimed at treatment of genetic diseases (including diabetes, alpha-1-antitrypsin deficiency, cystic fibrosis, and other diseases), are held all over the world. Nanotechnologies are used for the synthesis, vectoring (transfer), and targeting of DNA. These techniques are expected to provide a cure for multiple genetic diseases. Still, they carry the risk of improper and/or wrongly positioned insertion of the DNA fragment and unpredictable further consequences, including oncogenesis.

Pharmacokinetical and Pharmacodynamical Characteristics of Nanoparticles

Pharmacokinetics (PK) is what the living body does to a foreign agent (drug, substance, toxin, etc.) when it enters the body, and pharmacodynamics (PD) is what the agent does to the body (Bhattacharya et al. 2012). The PK and PD profiles of nano-materials are difficult to predict, because of their tiny-scale size and the huge changes in their chemical, mechanical, electromagnetic, and optical properties that happen in the nanoscale size and during their interactions with the living structures. Moreover, the accumulation of nanoparticles within the living body is hard to predict which makes the wide use of nano-materials dangerous. Nano-materials have increased absorption and bioavailability compared to their micro- and macro-analogues (because of their smaller size and free penetration through biological barriers), but their elimination is difficult to predict and therefore is thoroughly investigated. Three known factors that determine the probability of accumulation of nanoparticles are their size, charge, and hydrophilic or hydrophobic nature (Bhattacharya et al. 2012). The size of nanoparticles determines the risk of accumulation: <3 mm accumulate in a nonspecific manner within the living tissues, 3–8 mm are eliminated by the kidneys (especially dendrimers and other nano-polymers), 30–80 mm accumulate in the lungs and well-vascularized tissues, and those >80 nm accumulate within the liver and the spleen (Bhattacharya et al. 2012). The charge of nanoparticles determines their binding to plasma and tissue proteins, distribution, and their renal clearance. It also determines their immunogenicity and propensity to change normal proteins and biomembranes. And last but not least, hydrophobic particles tend to accumulate in parenchymal organs. Another important factor that determines the PK profile of nanoparticles is their carrier and cargo (i.e., the molecules they are bound to). Another confounding factor is the fact that certain cargos in nanoparticles can be released after the action of a specific triggering factor (targeted drug release) or are bound to an agent that decreases release (the so-called slow-release formulas), undergo significant recirculation within the human body (e.g., carbon nanotubes), or are inert and can undergo significant recirculation within the food chain (excretion by the human body, followed by liberation in the environment, uptake by other organisms, and eventually reentering the human body many, many times) (Bhattacharya et al. 2012).

One should not forget that at the nanoscale, small changes of structure and conjugation of different substances lead to large and unpredictable alterations in the behavior of the nanoparticle and therefore in the PK and PD profiles of the nano-material.

To make the long story short, the PK and PD profiles of many nanoparticle-based formulations are not well understood, and because of the nanoscale interactions and changes in the physical and chemical properties of material at these tiny sizes, no extrapolation can be made from the data concerning their micro- and macro-analogues. The carriers and the cargos of nano-materials are crucial for the PK and PD of the nano-material, and even small changes in nanoparticles, carriers, and cargos can lead to significant alterations and formation of new materials with new properties (Wani and Kothari 2018). Moreover, many nano-materials are virtually inert and undergo significant (maybe sometimes even endless)

recirculation within the human body and within the food chain and often tend to accumulate and cause undesirable effects, such as inflammation, induction of immune response, and maybe enhancement or triggering of oncogenesis (Ventola 2012c; Zhang et al. 2017). Nanoparticles are also known to be able to release or trigger the reactive oxygen species that lead to oxidative stress and inflammation and to activate the complement cascade and trigger immune response (Gomez Lopez 2013).

Pharmacogenetics (PG) is a relatively new interdisciplinary field on the borders between pharmacology, genetics, and personalized medicine that evaluates the influence of genetic markers upon the therapeutic response in every individual. It evaluates the role of genetic factors (genetic variations, mutations and polymorphisms, or drug-regulated gene expression and/or epigenetic factors) for the different therapeutic response (i.e., PK profile). Nanotechnologies, particularly nano-pores, can play important role in determining and predicting pharmacogenetic variations in drug metabolism and response by detecting single nucleotide polymorphisms and other genetic variations, as they offer fast and noninvasive DNA sequencing (Bhattacharya et al. 2012).

The toxicological profile of nano-materials remains unclear. Because of the huge changes in the physical and chemical properties of materials at the nanoscale and their multicomponent structure, they have unpredictable toxicity for the living body and for the environment. The main mechanisms of toxicity of nano-materials are associated with the generation of radical oxygen species with subsequent damage of the living structures and inflammatory changes (Lanone and Boczkowski 2006). The interaction with nuclear DNA with the development of subsequent oxidative changes may lead to oncogenesis. On the other hand, the interaction of nano-materials with mitochondrial structures and DNA might further impair cellular metabolism and energy stores.

The interaction with red blood cells may cause hemolysis, and the interaction with platelets and vascular endothelium may precipitate thrombosis.

The accumulation and interaction with liver cells may lead to hepatotoxicity, especially in hepatic accumulation of the nanoparticles. The accumulation within renal structures may lead to oxidative stress and inflammation with subsequent chronic kidney damage and renal failure. As the liver and the kidneys are the two major clearance points of all foreign materials that enter the human body, increasing concern is arising of the hepatic and renal side effects of nano-materials, including oxidative stress, inflammation, and oncogenesis, especially having in mind the increasing use of these materials, their stability, and circulation in the global ecosystem. This issue is very important not only for the human health but for the global safety of all living organisms on our planet (Bhattacharya et al. 2012; McClements and Xiao 2017).

Another serious problem is the lack of reliable methods to assess the toxicity and oncogenicity of nanoparticles, because of the unpredictable properties they may have compared to their macro-analogues (Bhattacharya et al. 2012). Currently we are facing a compelling need for new tools to assess the safety of nanoparticles.

Carbon-based nanotubes are a well-known nano-material, used for diagnostic and therapeutic purposes. Nonetheless, these nanoparticles are quite stable and tend to accumulate in the living body causing oxidative stress and chronic inflammation and changes resembling asbestosis (Bhattacharya et al. 2012). Quantum dots are also composed of toxic elements that can accumulate and harm the human body (Bhattacharya et al. 2012).

Cytotoxic drugs for cancer treatment and in organ transplantation are successfully delivered using modern nanosystems, but after excretion in the environment, they remain stable and may be incorporated by other organisms and undergo prolonged circulation within the ecosystem causing mutagenic and oncogenic effects. New drug delivery systems with decreased toxicity are being developed in response to this issue.

Nanocrystals (quantum dots) and metal- and silica-based nanoparticles can also initiate oxidative, inflammatory, and cytotoxic alterations in the living body, and their safety is still to be evaluated.

Moreover, all metal-containing nanoparticles may cumulate in the human body and cause chronic intoxications (Bhattacharya et al. 2012). Nano-polymers (dendrimers) can cause changes in cell interaction and activation but are known to have low immunogenicity and pro-inflammatory effects (especially the anion-carrying ones).

A serious problem represents the effect of targeted (especially cytotoxic drug carrying) nanoparticles on adjacent and remote tissues and cells (the so-called "off-target" effects) (Bhattacharya et al. 2012). This issue remains to be solved.

Safety and Ethical Issues: To "Nano" or Not to "Nano"?

With the increasing use of nano-materials in all fields of science, including medicine, the question of their safety becomes more and more pressing. They have multiple benefits, but, like a double-edged sword, they carry multiple and sometimes unpredictable and serious risk not only for the patient and the producing workers but for the ecosystem in general. Despite their wide application and the indisputable benefits for the modern food and energy industry, environmental protection, electronics, and medical care, the safety of nanoparticles remains unclear (Table 4), because of several serious problems (Anderson et al. 2016; Bhattacharya et al. 2012; Lanone and Boczkowski 2006; McClements and Xiao 2017; Prodanov 2017; Ventola 2012c; Zhang et al. 2017):

- Insufficient experience with nanoparticles
- Unpredictable physical and chemical properties in vivo because of the significant changes in the characteristics of the materials in the nanoscale with domination of quantum effects and appearance of new and unexpected characteristics
- Significant stability
- Insufficient data on their cumulation in the human body and circulation in the environment after excretion
- Unknown dose-response relationship and dose limitations in vivo
- Limited data on their physical, chemical, and toxicological properties and changes within the ecosystem
- Insufficient in vitro and in vivo experimental data
- Insufficient data on occupational exposure and hazards
- Lack of adequate markers for the evaluation of toxicity, dose, overdose, etc. – it remains unclear which markers are best, i.e., particle size, number, concentration, mass, etc.

According to their safety profile, nano-materials are divided in five major categories: A (no significant health risk), B (slight hazard and toxicity), C (moderate hazard), D (serious hazard), and E (severe hazard) (Prodanov 2017). Carbon-based nanotubes are known to belong to group E, because of their insolubility, cumulation, and toxic and DNA-damaging effects.

Another safety concern, besides the health and environmental risks, is the *preservation of our own self*. It remains unknown whether all modern nanoparticle-containing biosensors, especially when reaching the central nervous system or being able to change and control human DNA or brain activity, can be used for illegal or immoral purposes, such as mind control, eugenics, malevolent changes in human genome, etc. In other words, the nanoparticles are bringing once again the question whether we have reached the point at which full control upon the human body and own self (i.e., DNA) has come? Another serious question, especially concerning nano-prosthetics, artificial organs, and DNA-reparation techniques, is who covers the expenses; does every person deserve these cutting-edge new high-tech services? And what happens if the human body cannot tolerate these new technologies and the devices cannot be extracted without additional health risks? In the presence of biocompatible nano-based devices, who is human and who is not; where is the boundary between the human and the technology? Are the newly build DNA molecules and biocomputer systems alive, or are they merely a technological product or a machine?

Table 4 Advantages and disadvantages of nano-materials (Anderson et al. 2016; Bhattacharya et al. 2012; Gomez Lopez 2013; Prodanov 2017; Ventola 2012c; Wani and Kothari 2018; Zhang et al. 2017)

Advantages	Disadvantages
Fast and cheap in vitro and in vivo diagnostics	Adverse effects profile and toxicology are not well understood and unpredictable
High selectivity and specificity in diagnostics (DNA sequencing, specific DNA, RNA, protein and other targets, possibilities for specific and more stable dying of certain structures vs. conventional biopsy evaluation, real-time diagnostics, nontoxic and specific contrast media, etc.)	Unpredictable interactions with the living cells and structures due to changes in the physical and chemical properties of the materials at the nanoscale and possible domination of quantum effects, unknown magnetic and paramagnetic properties, and electroconductivity
Noninvasive diagnostics	Unpredictable PK and PD profiles. Carriers and cargos significantly change PK and PD
Selective and nontoxic imaging techniques	Generation of radical oxygen species
Targeted (highly specific) drug and radiation (isotope) delivery with minimal toxic effects – both systemic and for the adjacent tissue	Complement activation with subsequent inflammatory and/or autoimmune response, unpredictable oncogenic risk
Improved bioavailability of the therapeutic agent – i.e., lower doses and reduced adverse effects	Endothelial toxicity (particularly on cerebrovascular endothelium)
Targeted thermal ablation	Unknown risks or accumulation in parenchymal organs
Possibilities for PG evaluation (DNA sequencing)	Unknown risks of recirculation within the living body
Opportunities for theranostics – targeted diagnostic approach combined with immediate therapeutic intervention	Unknown effects on the environment and risks of circulation of unknown duration within the ecosystem

These questions have found no answers, and we should be extremely cautious with each and every new invention and technology, carefully weighting the advantages and risks, because we are entering an era when the boundaries between the macromorphological and the quantum worlds and between the human and the technology are becoming more and more obscure and we are facing the risk of losing and even destroying our human self. This "patent age of new invention" (Lord GG Byron (1824) Don Juan, I, 132) may literally bring us to the stars, but unfortunately it may lead us to our end.

References and Further Reading

Anderson DS, Sydor MJ, Fletcher P, Holian A (2016) Nanotechnology: the risks and benefits for medical diagnosis and treatment. J Nanomed Nanotechnol 7:4–5

Bhattacharya S, Alkharfy KM, Janardhanan R, Mukhopadhyay D (2012) Nanomedicine: pharmacological perspectives. Nanotechnol Rev 1:235–253

Dick PK. Autofac. In: Galaxy Magazine, November 1955

Dick PK. The android and the human. In: SF Commentary #31, December 1972

Drexler KE (1986) Engines of creation: the coming era of nanotechnology. Anchor Books, Doubleday

Emerich D, Thanos CG (2003) Nanotechnology in medicine. Expert Opin Biol Ther 3(4):655–663

Feynman R (1959) Engineering and science. California Institute of Technology

Gomez Lopez A (2013) Chapter 44: Nanotechnology and autoimmunity. In: Anaya JM, Shoenfeld Y, Rojas-Villarraga A et al (eds) Autoimmunity: from bench to bedside. El Rosario University Press, Bogota, pp 727–738

Guo T, Lin M, Huang J et al (2018) The recent advances of magnetic nanoparticles in medicine. J Nanomater 2018:1–8, Article ID 7805147. https://www.hindawi.com/journals/jnm/2018/7805147/

Gupta YK, Dinda AK (2018) Nano-pharmaceuticals in medicine. Proc Indian Natl Sci Acad 84(1):255–266. http://www.insajournal.in/insaojs/index.php/proceedings/article/view/470

Idrees M (2015) Role of nanotechnology in medical sciences: a review. Internat J Innov Drug Discov 5 (1):14–24. http://www.ijidd.com/File_Folder/14-24(ijidd).pdf

Lanone S, Boczkowski J (2006) Biomedical applications and potential health risks of nanomaterials: molecular mechanisms. Curr Mol Med 6(6):651–663

Lord GG Byron (1824) Don Juan, I, 132

McClements DJ, Xiao H (2017) Is nano safe in foods? Establishing the factors impacting the gastrointestinal

fate and toxicity of organic and inorganic food-grade nanoparticles. Sci Food 1:6–18
Milbum C (2010) Nanotechnology in the age of posthuman engineering. Science as science fiction. In: Nanovision. Engineering the future. Duke University Press, North Carolina, pp 19–59
Nikalje AP (2015) Nanotechnology and its application in medicine. Med Chem 5(2):81–89
Prodanov D (2017) Management of health risks related to the use of engineered nanomaterials. An analogy to biosafety. Biomed Rev 28:100–104
Sarfaraz S, Bano T, Fatima W (2018) Nanotechnology and its therapeutic application – a review. MOJ Bioequiv Availab 5(1):24–27
Surendiran A, Sandhiya S, Pradhan SC, Adithan C (2009) Novel applications of nanotechnology in medicine. Indian J Med Res 130:689–701
Taniguchi N (1974) On the basic concept of 'nano-technology'. In: Proceedings of the international conference on production engineering, Tokyo, 1974, Part II. Japan Society of Precision Engineering
Tasciotti E, Cabrera FJ, Evangelopoulos M et al (2016) The emerging role of nanotechnology in cell and organ transplantation. Transplantation 100:1629–1638
Ventola CL (2012a) The nanomedicine revolution. Part 1: emerging concepts. P&T 37(9):512–525
Ventola CL (2012b) The nanomedicine revolution. Part 2: current and future clinical applications. P&T 37(10): 582–591
Ventola CL (2012c) The nanomedicine revolution. Part 3: regulatory and safety challenges. P&T 37(11):631–637
Vijayakumar R, Agarwal R, Jagannathan S et al (2013) Application of nanotechnology in medicine. In: Navani NK, Sinha S (eds) Nanotechnology series. Volume 7: Diagnostics and therapeutics. Studium Press LLC, Houston, pp 89–100
Wani KA, Kothari R (2018) Nano technology in medicine and future implications: a mini review. J Nanomed Nanotechnol 9:497–499
Yadav HKS, Alsalloum GA, Al Halabi NA (2018) Chapter 14. Nanobionics and nanoengineered prosthetics. In: Grumezescu A (ed) Nanostructures for the engineering of cells, tissues and organs. Elsevier, Oxford, pp 513–587
Yambe T (2009) Artificial Organs with Nanotechnology and Development of the New Diagnosis Tool. 167–176. https://www.semanticscholar.org/paper/Artificial-Organs-with-Nanotechnology-and-of-the-Yambe/22555b5c39995c4df7c4b5a8c07752a6287f759b
Zahid M, Kim B, Hussain R et al (2013) DNA nanotechnology: a future perspective. Nanoscale Res Lett 8(1): 119–131
Zhang WK, Gu HW, Li XJ et al (2017) The dark side of "the force" – lipid nanoparticles enhance the oncogenesis of diethylnitrosamine and result in liver cancer in mice. Nanomedicine 13(2):701–711. https://www.ncbi.nlm.nih.gov/pubmed/27729235