

Chapter 10

Engineered Nanoparticles: Are They an Inestimable Achievement or a Health and Environmental Concern?



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Abstract Inorganic particles often exhibit novel and outstanding properties as their size approaches nanosize dimensions. The synthesis of these nanoengineered materials with specific composition, architecture, and functionality, and their uses in diverse fields, are changing paradigms. In this chapter we highlight the application of a lot of nanoparticles in biology, medicine, and biomedical engineering, and some concerns regarding human and environmental health are also discussed. There are two approaches to nanoparticle development and application for health care purposes: the bottom-up (science-driven) approach and the top-down (regulation-driven) approach, but neither of these has been able to demonstrate health care benefits without toxicological side effects. Consequently, nanoparticle toxicity has to be assessed, and the standardization of techniques should be set by scientists and decision makers worldwide. Cutting-edge knowledge regarding the interactions between nanoparticles and human health has to move forward, but environmental quality and social welfare must also be ensured.

Keywords Biocompatibility and toxicity · Current challenge · Drug delivery · Environment pollution · Human disease · Modern medicine · Molecular diagnostics · Sustainable development

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1 Introduction

Engineered nanoparticles are intentionally designed with at least one dimension ranging from 1 to 100 nm, and they are produced to be applied in several fields such as environmental remediation, materials science, catalysis, electronic devices, cosmetics, pharmaceuticals, biomedicine, energy, and food production (Angeli et al. 2008; Logothetidis 2012; Nie et al. 2007; Qu et al. 2013; Rashidi and Khosravi-Darani 2011; Shi et al. 2010; Smith et al. 2013; Song and Kim 2009; Sozer and Kokini 2009). Among the various existing nanomaterials, inorganic nanoparticles are especially important for current developments because they exhibit novel properties as their size approaches the nanometer scale ($1 \text{ nm} = 10^{-9} \text{ m}$), such as superconductivity (Iijima 2002; Shi et al. 2012), superparamagnetism (Vatta et al. 2006), ultrahardness (Lamni et al. 2005), thermal resistance (Miyake et al. 2013), optical performance (Kelly et al. 2003), anticorrosive properties (Hamdy and Butt 2007), photocatalytic properties (Evanoff and Chumanov 2005; Tong et al. 2012), and antibacterial properties (Chen and Chiang 2008), which are some of the most commonly used properties.

Inorganic nanoparticles can be easily synthesized, characterized, and industrially produced; they can also be quickly integrated into several applications (Baker et al. 2005; Evanoff and Chumanov 2005; Gehrke et al. 2015; Hwang et al. 2000; Piccinno et al. 2012). This is possible by controlling the shape, size, and structure of their inorganic core, and selectively linking active molecules to the nanoparticle surface, allowing them to interact with different biological materials or environmental systems.

In this context, because of the various properties and effects of inorganic nanoparticles on the materials' surface, human and environmental organisms can easily be exposed to them through respiration, ingestion, or the dermal route (Reidy et al. 2013; Tinkle et al. 2003), with potential side effects and various implications for health and safety. Actually, many investigations have studied the toxicity of inorganic nanoparticles in cell lines and animal models; nevertheless, their conclusions have often been contradictory, with results depending on controlled conditions (Alt et al. 2004; Braydich-Stolle et al. 2005; Hussain et al. 2005; Kathiresan et al. 2009). Therefore, there is a lack of comprehensive regulation and no assessment framework to manage the complete life cycle of nanomaterials, from their manufacture to their distribution, storage, exposure/dosage, and final disposal (Fig. 10.1). To address this concern, appropriate *in vivo* toxicological studies should be performed to identify, evaluate, and regulate human and environmental exposure limits and disposal before use of nanoparticles is scaled up into commercial products (Liu and Jiang 2015). Additionally, in a complex system, biological interactions such as immune responses, absorption, and agglomeration—as well as physicochemical properties such as particle size, shape, surface charge, concentration, stability, surface chemistry, and storage time (León-Silva et al. 2016)—must be considered for understanding of the complete toxicity mechanisms and determination of ecotoxicological potential.

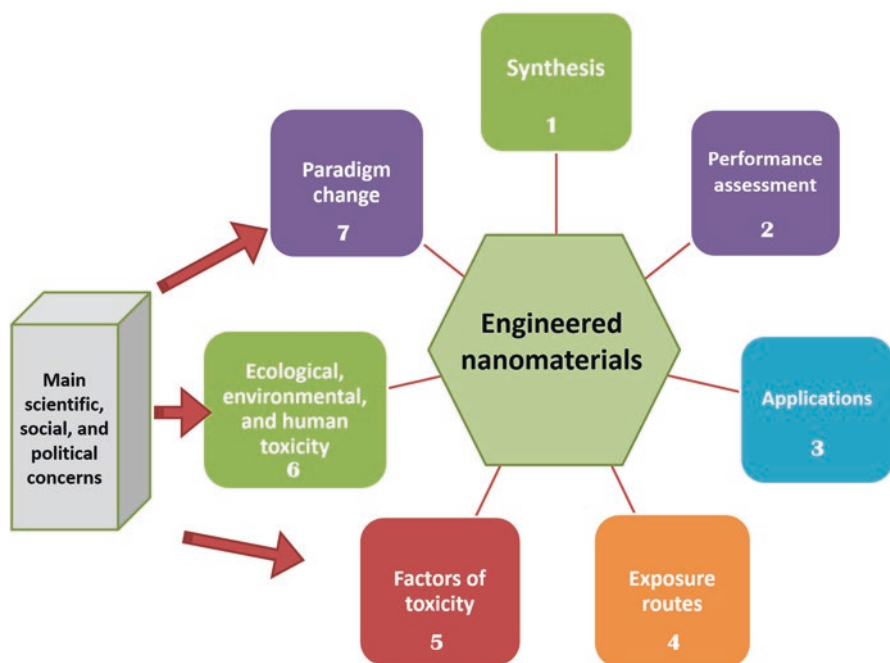


Fig. 10.1 Production and uses of engineered nanoparticles, and the main concerns regarding them

2 Nanoparticles in Biology, Medicine, and Biomedical Engineering

Within the diverse application areas of nanotechnology, biological sciences (including biomedical engineering and medicine) have benefited considerably from the introduction of nanomaterials in the preventive branch of medicine and in prevention of biological complications. Nanotechnology has become a powerful tool for treatment and diagnosis applications (Angeli et al. 2008; Shenava et al. 2015; Shi et al. 2010). With the addition of the unique properties of inorganic nanoparticles to cells, diseases may be managed or cured at the appearance of the first symptoms. In other words, diagnosis of illness could become more precise and accurate, avoiding severe complications (Marchesan and Prato 2013). Additionally, nanomaterials are helpful in the transport of medicines to specific parts of the body, making possible the alteration of damaged cells and transformation of genes, to improve the function of specific cells (Panyam and Labhasetwar 2003).

Certain subdisciplines of nanomedicine such as ethics, drug delivery, and genetics (Fig. 10.2) need to define the current “state of the art” so that we can advance toward cutting-edge knowledge. However, areas such as toxicology, the legal framework, and sustainable development have to be taken into account.

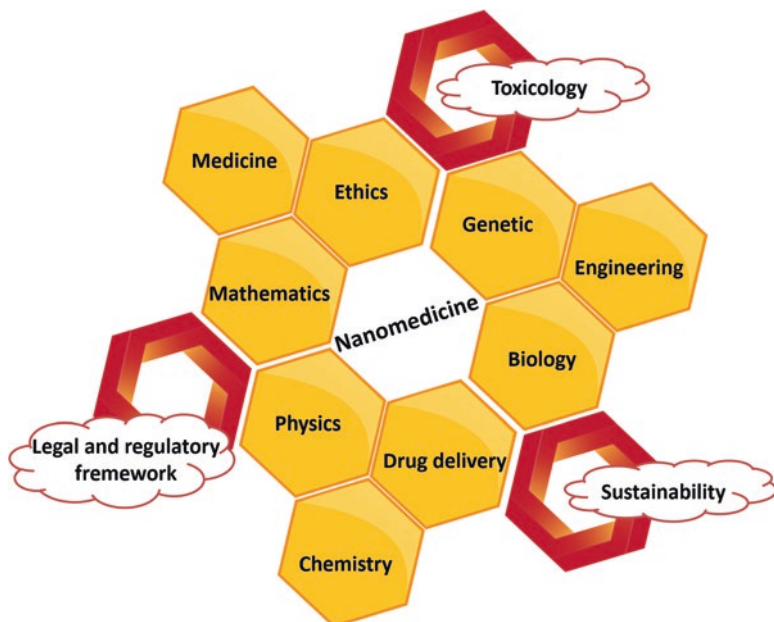


Fig. 10.2 Nanomedicine and its subdisciplines. The red hexagons highlight three strongly related areas that are seldom taken into account

Despite their different material properties, it has been found that mixing of some elements with nanoparticles increases their biological effects. Inorganic materials with cores composed of noble and magnetic metals (e.g., Au, Ag, Pt, and Pd), including their alloys and oxides (e.g., Fe_3O_4 , Co, CoFe_2O_4 , FePt, and CoPt), as well as semiconductors (e.g., CdSe, CdS, ZnS, TiO_2 , PbS, InP, and Si) and compound nanostructures, have shown vast potential for application in many different areas of biomedicine such as gene therapy, drug delivery, tracking agents, regeneration of cells, diabetes and cancer healing, hyperthermia treatments, labeling, magnetic resonance imaging (MRI), and transmission electron microscopy (TEM) imaging (Bai et al. 2007; Chen and Schluesener 2008; Gong et al. 2007; Hwang et al. 2000; Krzyzewska et al. 2016; Nie et al. 2007; Sotiriou et al. 2011; Sperling et al. 2008).

As a result of the increasing functionality of inorganic nanomaterials, more than 1000 research articles have been published in the Web of Science within the last 5 years (<https://apps.webofknowledge.com.access.biblioteca.cinvestav.mx>), using a wide variety of nanoparticles, particularly silver, gold, palladium, platinum, silica, quantum dots, iron oxide, zinc oxide, and metal fluorides (Dastjerdi and Montazer 2010; Ladj et al. 2013; Sekhon and Kamboj 2010) (Table 10.1). For example, silver nanoparticles are commonly used to provide enhanced opportunities for drug delivery (Panyam and Labhasetwar 2003). Also, nanocrystalline quantum dots are used for applications in biomedical imaging and electro-optical devices (Bera et al. 2010). Additionally, gold nanoparticles are used for bioseparation, cancer therapy,

Table 10.1 Principal properties of inorganic nanoparticles and their applications in biomedicine

Type of nanoparticle	Property	Application
Iron oxide (FeO), cobalt (Co), nickel (Ni)	Superparamagnetic	<ul style="list-style-type: none"> – Sensor and diagnosis – Drug delivery – Photothermal therapy – Magnetic resonance imaging (MRI) contrast agents
Gold (Au), silver (Ag), palladium (Pd), platinum (Pt)	Antimicrobial	<ul style="list-style-type: none"> – Optical imaging – Photothermal therapy – Antimicrobial coatings – Drug delivery – Biochemical sensing – Cancer treatment
Silicon dioxide (SiO ₂), quantum dots (QD), zinc oxide (ZnO), silica oxide (SiO ₂)	Fluorescence	<ul style="list-style-type: none"> – Energy transfer for sensing and diagnosis – High-resolution imaging
Zinc oxide (ZnO), quantum dots (QD), titanium dioxide (TiO ₂)	Semiconductor	<ul style="list-style-type: none"> – Biosensor – Photobleaching stability – Imaging devices – Detectors

gene delivery, and immunoassay diagnostics (Ghosh et al. 2008; Saha et al. 2012; Sperling et al. 2008). According to Bobo et al. (2016), some key examples of nanomedicines (listed by material category) are polymeric nanoparticles, polymeric micelles, liposomal nanoparticles, protein nanoparticles, inorganic nanoparticles, and crystalline nanoparticles. In this chapter we discuss inorganic nanoparticles such as Ag-NP, Au-NP, Pd-NP, and Pt-NP.

2.1 Silver

Since ancient times, silver has been used against infections and to prevent food spoilage (Suman et al. 2013). Silver nanoparticles (Ag-NP) can be synthesized by several routes and methods to obtain certain characteristics in terms of size, shape, and agglomeration (Panacek et al. 2006). By these processes, Ag-NP acquire unique electrical, optical, thermal, and antifungal properties, which are incorporated into products ranging from photovoltaics to electronics, medical devices, and chemical sensors (Abou El-Nour et al. 2010; Marambio-Jones and Hoek 2010; Nasrollahzadeh et al. 2014). In the biomedical area, Ag-NP are incorporated into a large number of consumer products that take advantage of the antibacterial effects of silver for therapeutic purposes (Prabhu and Poulouse 2012; Shenava et al. 2015). The antibacterial mechanism of silver metal ions works by destroying the cell membrane and bonding the –SH group of the cellular enzymes, then as a consequence of the critical enzymatic decrease, the metabolism changes, inhibiting cell growth until the bacterium dies (Marambio-Jones and Hoek 2010; Prabhu and Poulouse 2012).

The purposes of using Ag-NP in the medical and biomedical fields are to prevent bacterial infections and reduce inflammation. They are used as a coating for, or integrated into, contraceptive devices, female hygiene products, bone cement, wound dressings, surgical instruments, dental fillings, catheters, sutures, prostheses, and bandages (Furno et al. 2004; Silver et al. 2006). Additionally, Ag-NP are used in the treatment of diseases that requires specific drug delivery. Biosensing is another field of Ag-NP application; because of their plasmonic properties, they can detect several disorders and illnesses in the human body, such as cancer (Syed et al. 2013). Moreover, Ag-NP are harnessed in bioimaging for monitoring of dynamic reactions (Sekhon and Kamboj 2010). Also, Ag-NP are impregnated into different surgical instruments, such as dental instruments, or composites. For example, Ahn et al. (2009) used Ag-NP in orthodontic adhesives to increase their strength and resistance, and Furno et al. (2004) and Roe et al. (2008) developed polyurethane catheters with antibacterial coating to prevent infections. Moreover, Alt et al. (2004), Chaloupka et al. (2010), Durán et al. (2007), Li et al. (2006a), and Grunkemeier et al. (2006) integrated Ag-NP into surgical masks, cardiovascular heart valves, bone cements, and dressings for use in artificial prostheses and treatment of wounds, burns, and ulcers for prevention and treatment of bacterial infections.

2.2 Gold

Gold nanoparticles (Au-NP) possess unique optoelectronic properties, high dispersibility, size uniformity, and catalytic properties, which have been utilized in photovoltaics, therapeutics, drug and gene delivery, sensory probes, biosensing, electrical conductors, and catalysis applications, among others (Ghosh et al. 2008; Panyala et al. 2009; Sperling et al. 2008). Additionally, the versatility of the properties of Au-NP enhances the possibility of their use in medical applications such as cancer treatment; through control of the size, shape, and surface of the particles, they can bind cysteine–lysine proteins, causing an antiangiogenic effect, which avoids tumor growth of cancer cells (Huang and El-Sayed 2010; Panyala et al. 2009).

Furthermore, the large surface area of Au-NP allows the possibility for them to be coated with therapeutic agents or antifouling polymers to serve as drug carriers to specific cells (Ghosh et al. 2008). Moreover, gold nanorods and nanoshells have the potential to enhance the contrast of blood vessels, mainly for use in MRI. Also, they can be heated by light, enabling them to eliminate targeted tumors; this process is called photodynamic or hyperthermia therapy (Huang and El-Sayed 2010). Other Au-NP applications in this field include diagnosis of heart diseases through detection of biomarkers and infectious agents (Mieszawska et al. 2013; Panyala et al. 2009). Also, they are used in a variety of sensors for detection of food spoilage or as substrates for chemical bonds (Sperling et al. 2008). Finally, Au-NP can produce dark field array colors, usually employed for biological imaging and probes in TEM (Wang and Ma 2009).

2.3 *Palladium*

Palladium nanoparticles (Pd-NP) are characterized by their catalytic and optical properties, which enable them to be used as a photothermal agent and drug activator. Serious drawbacks of this material are its high cost and its allergenicity in contact with skin, which restrict its application (Larese Filon et al. 2016). Nevertheless, in medicine, Pd-NP are used in dental appliances, as an antibacterial agent, and for cancer and microbial therapy (Adams et al. 2014). Because of their high photothermal efficiency, size, biocompatibility, and numerous applications in combined therapies, Pd-NP have become an attractive alternative for noninvasive cancer treatment. Also, Pd-NP-coated needles are used for treatment of prostate cancer and in choroidal melanoma brachytherapy (Blasko et al. 2000; Dumas and Couvreur 2015; Finger et al. 2002; Saldan et al. 2015).

Additionally, Pd-NP hold promise for use in biosensors; for example, Baccar et al. (2013) developed a chronoamperometric nonenzymatic sensor using various sizes of Pd-NP to detect hydrogen peroxide (H_2O_2) in milk. Also, Kowalska et al. (2013) developed a hydrogen sensor using Pd-NP; this makes use of the selective absorption of hydrogen, which forms palladium hydride. These Pd hydrides possess greater electrical resistance than other metals, allowing design of thick-film hydrogen sensors with increasing electrical resistance. Finally, Pd-NP are used to control water pollutants and emissions, such as emissions of halogenated compounds, and they are also used in the production of fuel cells (Long et al. 2013; Mackenzie et al. 2006).

2.4 *Platinum*

Platinum nanoparticles (Pt-NP) are another type of inorganic nanomaterial, which displays excellent catalytic properties and antioxidant properties. In the biomedical field, Pt-NP are commonly used in consumer products such as cosmetics and supplements (Shibuya et al. 2014). Also, Pt-NP have been shown to have therapeutic efficacy against solid tumors and are used in electrochemical sensors and biosensors (Luo et al. 2006). However, the duration of their clinical use is limited by their side effects such as systemic toxicity and drug resistance (Wang 2010; Zalba and Garrido 2013). In biological and chemical applications, Pt-NP are studied for their capacity to encourage the oxygen reduction reaction, producing water, which is used to oxygenate cells. In other experiments, Pt-NP have been coupled with Au-NP to produce devices capable of following chemical reactions such as oxidation of carbon monoxide (Newton et al. 2015).

Apart from the positive effects of nanoparticles, recent investigations have been performed to control and take advantage of their negative impacts; for example, platinum ions are used as a reservoir to induce DNA damage in cancer cells (Wang 2010). Additionally, Gehrke et al. (2011) evaluated Pt-NP in a human colon

carcinoma cell line (HT29) *in vitro*, concluding that the small size of Pt-NP caused a harmful effect on DNA while cellular glutathione was decreased. Furthermore, Porcel et al. (2010) suggested that the combination of ion radiation with Pt-NP should improve cancer therapy protocols.

2.5 Iron Oxide

Iron oxide nanoparticles (FeO-NP) are one of the most popular and safe nanomaterials used in medicine (Ling and Hyeon 2013). They usually take the form of magnetite (Fe_3O_4) or maghemite ($\gamma\text{-Fe}_2\text{O}_3$) particles, ranging from 1 to 100 nanometers in size. Recent investigations have focused on control of their size, crystalline structure, uniformity, and surface properties. In biomedicine, FeO-NP are commonly used for *in vitro* and *in vivo* diagnostic applications, as well as in hyperthermia, drug delivery, biosensing, and biomedical imaging (Mohapatra and Anand 2010). These uses are possible because of their superparamagnetic properties and biocompatibility, which provide additional stability, allowing separation and purification of biomolecules (e.g., antibodies, proteins, and antigens) and detection of protein and nucleic acids (Ladj et al. 2013; Tuçek et al. 2014). The common use of these nanoparticles in biomedicine is made possible through a chemical modification of their surface chemistry, polymer adsorption, or incorporation into colloidal particles via an encapsulation process. Iron oxides are used as support to capture specific targets such as bacteria or viruses in a microsystem, then, with use of an external magnetic field, they can be separated from the biomolecules simple and quickly, instead of through a conventional filtration and centrifugation process, reducing the time and cost considerably (Rahman and Elaissari 2010).

As a result of these magnetic characteristics, several applications of FeO-NP have been reported. Na et al. (2009) used iron oxide nanoparticles as MRI contrast agents because of their ability to shorten relaxation times in the liver, spleen, and bone marrow. Additionally, Kayal and Ramanujan (2010) coated a magnetite (Fe_3O_4) nanoparticle with polyvinyl alcohol (PVA) to serve as a drug carrier of doxorubicin (DOX), concluding that iron nanoparticles could be a viable option for drug delivery. Moreover, Wahajuddin and Arora (2012), reported the use of maghemite and magnetite as gene carriers for gene therapy in cancer treatments. Finally, Stanley et al. (2012) employed iron oxide nanoparticles as a platform for adjuvants in the activation of cell production.

2.6 Zinc Oxide

Zinc oxide nanoparticles (ZnO-NP) exhibit unique semiconducting, optical, and piezoelectric properties, which are useful in several industrial applications. ZnO nanomaterials have low toxicity and biodegradability; in this context, Schilling

et al. (2010) inferred that there was no conclusive evidence that ZnO-NP pose a phototoxicity or genotoxicity risk to humans. On the contrary, the authors considered that this nanomaterial protected human skin by absorbing ultraviolet (UV) radiation, preventing harmful effects and providing protection against DNA damage. Additionally, ZnO-NP are considered a promising material in cancer treatment and food additives (Wang et al. 2007). In the biological field, they are commonly used in bioimaging probes, degradation of organic compounds, antimicrobial agents, and drug carriers (Padmavathy and Vijayaraghavan 2008). Moreover, in the food industry ZnO-NP have extensive applications because of their antibacterial action against pathogens, improving the effectiveness of food packaging and thereby encouraging their use and development in food nanotechnology (Espitia et al. 2012).

Several features and attractive characteristics of ZnO-NP have made them a promising candidate among metal oxides to be utilized as a successful tool against multidrug-resistant microorganisms and a viable substitute for antibiotics. Finally, ZnO-NP-specific properties have been developed to extend their applications in several fields, particularly in biomedicine and catalysis (Sirelkhatim et al. 2015).

2.7 *Quantum Dots*

Quantum dots (QDs) are semiconductor nanocrystals with three spatial dimensions at the nanometer scale (Bera et al. 2010). Because of their optical properties and distinctive surface, they have been used in detection probes, biomolecule labels, and drug delivery (Rosenthal et al. 2011). QDs can be composed of several materials, including CdSe, CdTe, CdS, ZnS, ZnSe, ZnO, GaP, GaN, GaAs, and InAs. Nevertheless, the most common combination is cadmium–selenium (CdSe). Their photostability and spectral properties enable their use for in vitro and in vivo imaging of a wide variety of cellular processes (Biju et al. 2010; Nida et al. 2008). Furthermore, because of their nanocrystal size (2–10 nm) and semiconductor properties, QDs exhibit nonfluorescent bleaching, which enhances their broader excitation spectra, and they can be used as an alternative to the usual fluorescent molecules (fluorescein and rhodamine) for detection, imaging, and labeling of particles in complex experimental media (Alivisatos et al. 2005; Wu et al. 2003).

In this context, Qi and Gao (2008) applied QDs to cell lines for use as drug carriers. Also, Gui et al. (2014) developed QDs featuring carriers for real-time monitoring of drug release. In both investigations it was concluded that QDs could be a viable tool for fluorescent probes, especially for long-term, multiplexed, and quantitative imaging and detection systems. However, a serious drawback in industrial production of QDs is related to the technique used for their synthesis, which requires controlled conditions and coupling to several surfactants for stabilization and prevention of aggregation, consequently raising the cost of their production (Ladj et al. 2013).

2.8 *Silica*

Silica nanoparticles (Si-NP) are considered the main basis for the development of nanostructures used in bioimaging, biomolecular adsorption, and polymeric materials (Selvan 2010; Tallury et al. 2008). Because of their highly active surfaces, controlled particle size, enhanced water solubility, high colloidal stability, low nonspecific interaction, and biocompatibility, they are used in several medical applications (Zhang et al. 2014a). Biofunctionalization of Si-NP with organic nanostructures such as DNA or antibodies provides controlled release and recognition capabilities for drug delivery, assay labeling, and biosensing applications (He and Shi 2011). Si-NP are also used in the detoxification of lead, cadmium, and mercury in blood, as well as in targeting of cancer cells (Sangvanich et al. 2014). Moreover, Si-NP have been used for drug delivery in biological studies *in vitro*. For example, Mackowiak et al. (2013) demonstrated that mesoporous Si-NP could be used in hydrophobic anticancer drugs. By use of a magnetic nanocrystal coating, silica can be manipulated and monitored inside living cells to target cancerous cells and induce apoptosis, as well as being useful for imaging and therapeutic applications.

Furthermore, Si-NP are mixed with organic materials to create hybrid systems, which combine the functional organic chemistry with the thermal stability of the inorganic structures. Liu et al. (2014) used poly(methyl methacrylate) with SiO₂ as a filler in dental resins. Combination of organic and inorganic materials in biomedical appliances enhances the strength of bone grafts, as well as providing the potential for effective bone regeneration (Wang et al. 2014).

2.9 *Titanium Oxide*

The high strength and fatigue endurance of nanostructured titanium and its alloys make them very attractive for medical applications (Kashef et al. 2011). Titanium oxide (TiO₂) plays a major role in the improvement of health care, especially in cancer treatment and medical implants (Elias et al. 2008; Valiev et al. 2008). Principally because of its photocatalytic activity, high stability, broad-spectrum antibiotic properties, and long-lasting nature (Fu et al. 2005), TiO₂ shows the capability to eliminate cancer cells. Additionally, it is used for cell imaging, biological analysis, antibacterial activity, protection against UV radiation, drug delivery, dental implants, catheters, medical coatings, and environmental purification (Elias et al. 2008; Gong et al. 2007; Li et al. 2006b; Yeung et al. 2009; Yin et al. 2013).

Titanium has better characteristics than other surgical metals, principally because of the formation of a stable passive layer of TiO₂ on its surface. Also, TiO₂ is intrinsically biocompatible and exhibits direct bone apposition (Niinomi 2008). Another important characteristic is its low elastic modulus, which results in less stress shielding and associated bone resorption around orthopedic and dental implants

(Mishnaevsky et al. 2014). Furthermore, TiO_2 is lighter than other surgical materials, and it is used to produce diverse devices on computed tomography (CT) and MRI. In water remediation it is useful for removal of hazardous substances and disinfection. Finally, in the agricultural field, TiO_2 is used to remove residual pesticides and deodorize hydroponic crops (Geetha et al. 2009).

2.10 Other Nanoparticles

2.10.1 Cobalt

Cobalt nanoparticles (Co-NP) play a major role in the medical field because of their magnetic properties, with promising applications in imaging as a contrast agent for MRI, drug delivery of cancer therapies, catalysis, optics, microelectronics, and biological sensors (Ogunlusi et al. 2012). Xu et al. (2008) coated graphitic carbon with magnetic Co-NP shells, generating thermal cellular damage to induce cancerous cell death, creating the possibility to apply this therapy to other biological systems for successful tumor treatment in clinical applications. In this context, Rutnakornpituk et al. (2002) used Co-NP in silica spheres as carriers for their application in ophthalmic surgery. Finally, Sathya et al. (2016) investigated the effects of cobalt nanotubes in theranostic applications, concluding that cobalt nanotubes could serve as heat mediators for in vivo hyperthermia and MRI applications.

2.10.2 Copper

Copper nanoparticles (Cu-NP) have potentially very useful properties such as superconductivity, electron correlation effects, and spin dynamics. Thus, Cu-NP have diverse applications in several fields, being useful in supercapacitors, solar cell batteries, biosensors, nanofluids, photodetectors, superhydrophobic surfaces, gas sensors, solar energy conversion, and field emission emitters. They are also useful for removal of arsenic and organic pollutants from wastewater (Zhang et al. 2014b). Additionally, Cu-NP can improve fluid viscosity and enhance thermal conductivity (Garg et al. 2008). Furthermore, copper oxide crystal structures exhibit a narrow band gap, which gives them useful photocatalytic and photovoltaic properties, coupled with photoconductive functionality (Shaabani et al. 2014; Zhang et al. 2014a). Cu-NP also have bactericidal properties for use in medical applications against a range of bacterial pathogens, including methicillin [meticillin]-resistant *Staphylococcus aureus* (MRSA) and *Escherichia coli*, with minimum bactericidal concentrations (Ren et al. 2009).

2.10.3 Cerium Oxide

Notably, cerium oxide nanoparticles ($\text{CeO}_2\text{-NP}$) have attracted the attention of researchers because of their antioxidant potential and biocompatibility, showing adequate protection of cells against damage caused by increased formation of reactive oxygen or nitrogen species (Karakoti et al. 2010). The protective effects of $\text{CeO}_2\text{-NP}$ have been used for cardioprotection, reduction of chronic inflammation, wound healing, neuroprotection, cancer treatment, and ocular treatment (Kim and Hyeon 2013). Chigurupati et al. (2013) showed that the antioxidant properties of cerium reduce tumor growth in ovarian cancer treatment. Moreover, Pagliari et al. (2012) showed that cerium nanoparticles represented a promising tool to control oxidative stress in isolated cardiac progenitor cells.

3 Concerns Regarding Human and Environmental Health

Recently, there has been increasing interest in nanoscience and nanotechnology worldwide, because of their enormous potential for development of new products and applications with improved performance and new functionalities. It has to be remembered that nanotechnology is an emerging field for production of nanoscale products/devices with more efficient reactivity and larger surface areas than their bulk forms. These unique attributes of nanoparticles offer immense potential for their application in almost all scientific and technological areas. However, while nanoscience and nanotechnology might revolutionize a number of industrial and consumer sectors, there are uncertainties and knowledge gaps regarding the toxicological effects of these emerging sciences (Table 10.2). It has to be stated that although nanoparticle research has been ongoing for more than 30 years, the development of methods and standard protocols required for their safety and efficacy testing for human use is still a work in progress. Additionally, there are still no protocols or regulatory and legal frameworks worldwide for protection of human and environmental health.

Uncontrolled release of nanoparticles or nanomaterials in the environment can harm the abundance and diversity of biotic ecosystem components such as microorganisms, plants, or animals. Additionally, these materials may also affect some abiotic components such as soil moisture, temperature, and nutrient availability. Because these particles have a higher surface area to volume ratio than their bulk forms, nanoparticles are highly reactive and effective in their actions. The attributes of these nanomaterials are very similar to those of their parent chemical species. Thus, active involvement of these materials in various biological, physicochemical, and biochemical processes in the environment may be detrimental to ecological systems. A few metal nanoparticles such as TiO_2 , ZnO , AgO , CuO , and Fe_2O_3 are well known for their toxicity and antimicrobial activities when present in excessive amounts (Fernández-Luqueño et al. 2014; Kumari and Singh 2016; León-Silva et al. 2016).

Table 10.2 Human health and environmental concerns

Concern	Novel research	Reference
Exposure	<ul style="list-style-type: none"> – Potential routes of exposure have been elucidated, including inhalation, dermal, oral, and parenteral – Additionally, toxicity has been studied at lungs, skin, kidneys, or genitals, in order to determine the nanomaterials dose-response 	Stern and McNeil (2008); Van Broekhuizen et al. (2012)
Harmful effects	<ul style="list-style-type: none"> – Different inflammatory and oxidative effects can generate cytotoxicity or genotoxicity potencies in experimental systems – In consequence several studies suggest that cytotoxicity and genotoxicity also depend on size, shape, concentration, stability, superficial charge, and time exposure of the nanoparticles 	Asharani et al. (2009); Kim et al. (2009); Krzyzewska et al. (2016)
Economic viability	<ul style="list-style-type: none"> – Purity compounds, low process yields, and hi-tech infrastructure could complicate their large-scale manufacturing – Cost-effective evaluation 	Şengül et al. (2008); Tian et al. (2012)
Normalization and regulation	<ul style="list-style-type: none"> – No clear standards for workers and final consumer protection – No international regulation policies or assessments frameworks, in order to standardize the use and production of nanomaterials 	Kulinowski and Lippy (2011); Schulte et al. (2014); Renn and Roco (2006)
Final disposal	<ul style="list-style-type: none"> – Elaboration and implementation of recollection protocols after used – Further investigations about the long-term toxicity in human health and environment – A complete evaluation of their life cycle impacts is required 	Keller et al. (2013); Miseljić and Olsen (2014)
Scientific dissemination	<ul style="list-style-type: none"> – Communication with society about safety information and the latest toxicological investigations made in nanomaterials is currently scarce, creating barriers in the diffusion, acceptance, and growth of this sector 	Helland and Kastenholz (2008)

In recent years, inorganic nanoparticle use, especially use of magnetic iron oxide materials for imaging, has been a particular focus, and their impacts on human cell and tissue functions pose compelling safety and toxicity concerns (Hofmann-Amttenbrink et al. 2015) (Fig. 10.3). According to Hofmann-Amttenbrink et al. (2015), assessments of the influences of their particle size, morphology, and surface charge, and the resulting interfacial protein adsorption in their interactions with tissues, uptake by lymphatic or blood components, and correlations with toxicity or safety risks have certainly provided no consensus to date; thus, in vitro methods and

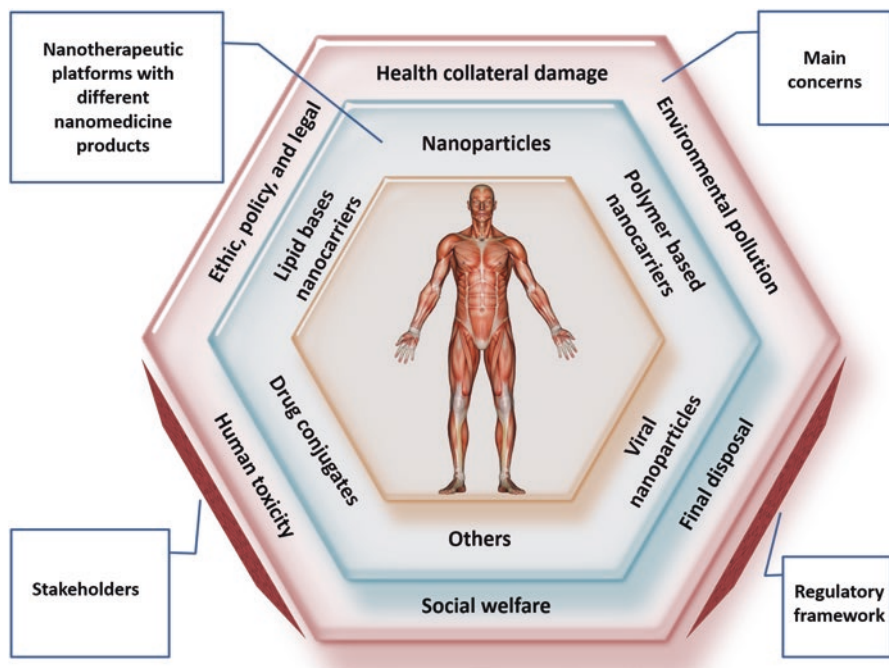


Fig. 10.3 Nanotherapeutic platforms with different nanomedicinal products and the main concerns regarding use of nanomedicine. Stakeholders are not able to work about that because they have limited knowledge of the problem. Therefore, many countries throughout the world have not implemented suitable regulatory frameworks

preclinical models to produce such correlations for human use currently lack validation and standards. Hence, without accepted approaches for assessing safety, translation of nanomaterials and nanoparticles as marketable biomedical products may prove to be challenging (Hofmann-Amttenbrink et al. 2015; León-Silva et al. 2016).

According to Hofmann-Amttenbrink et al. (2015), the many variations in reported investigations—often with only vague descriptions of materials and preparation, storage, and analytical certification methods—prevent robust scientific comparisons of the diverse published results on seemingly related inorganic particle chemistries. Additionally, industrial standards are lacking for these systems: relevant legal guidelines and important definitions remain vague, but also a lack of legal and regulatory frameworks regarding nanomaterials, nanoparticles, and nanodevices is common worldwide. Nanoparticles offer a wealth of opportunities for developing innovative products with applications in biomedicine, pharmaceuticals, and food processing, among other applications, which may bring important benefits to industry and consumers. However, negative effects caused by exposure, use, and final disposal of products using Ag-NP may include DNA damage, gene perturbation, and metabolic changes, with toxicity varying depending on the size, shape, size

distribution, exposure, and concentration in the environment. Therefore, it is important to address the compelling needs for improved and standardized assessments of inorganic nanoparticles and their toxicity in various biomedical uses, for coherence between scientific developments and corresponding health and safety regulations, and for definition of the necessary prerequisites for implementing and enforcing such regulations. These concerns have led to the following three key issues (Hofmann-Antenbrink et al. 2015):

1. *Nanoparticle properties and characterization methods:* The sizes and shapes of inorganic nanoparticles, their physicochemical properties and, most importantly, their surface and interfacial properties in biological milieu that result in formation of ubiquitous adsorbed protein corona on particle surfaces are proposed as critical parameters to measure. Importantly, these properties should be verified and monitored to correlate and control their interactions with living systems throughout the entire product life cycle.
2. *Toxicity assessment:* Despite global proliferation of engineered nanoparticle research and production, reliable, validated, high-throughput, and standardized methods are still needed for rapid assessment of nanoparticle toxicity in various environmental conditions, human routes of exposure, dosing of cell cultures, and in vivo biological conditions. Correlations of in vitro cell and protein exposure result in in vivo host responses that are often uncertain and unpredictable for use in risk–benefit analysis. Furthermore, to date, there is not current consensus, validation, or standardization of the preclinical in vivo experiments and models necessary to best mimic a given dose–exposure situation for these nanoparticles in formulations appropriate for human use.
3. *Regulation:* Government policies governing nanomaterial production and occupational exposure, environmental release, commercial product stewardship, and human exposure remain a critical part of the entire product life cycle of nano-enabled products. Policy formulation and implementation must enable creation of clear guidelines to govern interactions between nanomaterial researchers, developers, and regulatory bodies to collaboratively facilitate responsible transfer of research results assessing toxicity (if any) to ensure product safety for industrial and medical users. This should be a living, dynamic engagement: research and development in nanotechnologies/nanoparticles for biomedical products are continuously evolving. New details of nanoparticle properties and toxicity, with their associated implications for benefits and risks, are continually mentioned in scientific reports, as well as in consumer digests in the public media. The associated evolving legal aspects surrounding these issues must also be considered and appropriate measures taken to provide both stability via responsibility to industrial developers for their future markets and also safety to the consumer in terms of appropriate use and exposure.

At present, the most significant concerns involve risk assessment, risk management of engineered nanomaterials, risk communication and, of course, fraud (Resnik and Tinkle 2007). As the science and technology of nanomedicine forge ahead, ethics, policy, and the law are struggling to keep up. It is important to

proactively address the ethical, social, and regulatory aspects of nanomedicine to minimize its adverse impacts on the environment and public health—and also to avoid a public backlash.

Rapid growth in nanotechnology toward the development of nanomedicinal products holds great promise to improve therapeutic strategies against some common and terminal diseases. According to Bobo et al. (2016), a nanomedicine is a therapeutic or imaging agent that uses a nanoparticle to control the biodistribution, enhance the efficacy, or reduce the toxicity of a drug or biological agent. It has to be recognized that nanomedicinal products represent an opportunity to achieve sophisticated targeting strategies and multifunctionality, but the challenges faced in using nanomedicinal products and translating them from the preclinical level to the clinical setting must also be understood. Bobo et al. (2016) identified 51 nanomedicines approved by the US Food and Drug Administration (FDA) and 77 products in clinical trials. While the FDA-approved materials are heavily weighted toward polymeric, liposomal, and nanocrystal formulations, there is a trend toward development of more complex materials comprising micelles or protein-based nanoparticles, and also the emergence of a variety of inorganic and metallic particles in clinical trials. It has to be taken into account that some nanoparticles used as medicines have been approved by the FDA but subsequently withdrawn from the market (Bobo et al. 2016). However, nanoparticles have gained much interest as a specific and sensitive tool for diagnosis of bacterial, fungal, and viral diseases (Shaan et al. 2016).

In recent years there has been exponential growth in publications focusing on “cancer + nanoparticles.” According to Web of Science®, in 2017 alone, 13,711 manuscripts were published regarding “cancer* + nano*,” but only 2995 manuscripts were published regarding “cancer* + nano* + toxic*,” i.e., there is enough evidence that nanoparticles may have the ability to heal some diseases, but some doubts have arisen, e.g., nanoparticles may heal some diseases, but won’t they cause collateral damage? Also, could people who have been healed by nanomedicine suffer an aftermath? (Fig. 10.3).

According to Hofmann-Amttenbrink et al. (2015), considering the current situation and future needs regarding nanoparticles in medicine, a general picture may be constructed, taking into account the following:

1. Improved methodology and testing tools are needed to characterize nanomaterials from the research stage to marketable versions and throughout the product life cycle, covering the diverse manifestations and impacts of these materials on both human health and on the environment.
2. The assessment of possible risks should be harmonized between the main stakeholders worldwide.
3. Researchers working on nanomaterial-based products for industry and medicine should adopt a common approach to safety and toxicology testing, distinct in certain aspects from traditional testing of new soluble drugs. This is especially important for nanomedicinal products based on inorganic nanoparticles, for which conventional toxicological knowledge is often insufficient in routine pharmaceutical toxicology testing (Hofmann-Amttenbrink et al. 2015). Nanoparticle

assays and their outcomes are not comparable with soluble molecule-based product assessments and must be treated differently.

4. Improvements in regulation of nanomaterials, especially nanoparticles, are necessary to address current ambiguities in industries that avoid use of “nanobranding” in their nanomaterial-containing products if it is not specified as a marketing instrument.
5. Several current nanomedicinal products are based on reinvention or adaptation of formulation strategies for existing poorly soluble or insoluble drugs that show improved performance when encapsulated in lipid vehicles (i.e., liposomes) or protein complexes, or in nanocapsules and organic (polymer) nanoparticles.

In order for us to take advantage of nanotechnology in medical applications, the properties of nanoparticles should be known and their behavior must be identified under various conditions. The success of nanoparticles in healing or reducing the discomforts caused by chronic diseases may be affected by their physicochemical properties, size, shape, and surface chemistry, which can characterize their biodistribution, pharmacokinetics, and biocompatibility (Yadollahpour 2015). In characterization and control of the physicochemical properties of magnetic nanoparticles (MNPs), synthesis and coating processes play a crucial role. Various structural models for MNPs have been proposed, each of which has its own advantages and drawbacks for medical applications in clinical settings. In order for us to propose new MNPs and elucidate their behaviors in a living body, high-tech methods are needed. Considering the recent advances in synthesis of NPs, as well as biotechnological advances, we can expect clinical uses of MNPs in different fields of medicine in the near future.

Nanocomposite scaffolds combining biopolymers and nanosized bioresorbable fillers such as calcium phosphates (CaPs) have great potential in tissue engineering and regenerative medicine (TERM) because of their ability to mimic the structural and mechanical properties of native tissues. Natural polymers are appealing because of their different degradation rates, while CaPs offer the required osteoconductivity and biocompatibility features (Pina et al. 2015). In addition, research efforts in designing an ideal nanocomposite material for repair and regeneration of damaged/diseased tissues have revealed the promise of nanocomposites comprising collagen, gelatin, silk fibroin, chitosan, alginate, hyaluronic acid, gellan gum, derivatives such as natural polymeric matrices, and hydroxyapatite (HAp) and β -tricalcium phosphate (β -TCP, a high-temperature phase of CaPs) as bioactive fillers.

Nanocomposites from natural polymers and CaPs have nanofeatured structures such as a large surface area and enhanced porosity, which are essential for appropriate cellular adhesion, proliferation, and differentiation. Furthermore, they can be functionalized with bioactive molecules and stem cells to enhance tissue healing/regeneration. In vitro cell culturing in three dimensions, using perfusion bioreactor systems, may be also applied to produce mature tissues. Such dynamic systems can provide an optimal environment for convectively transporting nutrients to cells and removing metabolites, with appropriate mechanical stresses to guide cell growth and proliferation, and extracellular matrix production.

However, an entire natural nanocomposite scaffold, mimicking the hierarchical structure and morphology of bone while performing a temporary function, has not yet been developed. Still, silk fibroin and collagen biopolymers combined with CaPs have shown great promise in preclinical studies (Pina et al. 2015). It has to be noted that these scaffolds are still at the stage of research and development, lacking application in clinical surveys. Future developments of this kind of nanocomposite for tissue repair and regeneration, aimed at clinical applications, should be devoted to clear understanding of the nanocomposite–tissue interactions, optimization of their composition and hierarchical structure for long-term service, and the related mechanical strength, especially the fatigue limit under periodic external stress. Furthermore, the use of these nanocomposites for therapeutic effects and drug delivery, combined with differentiated or undifferentiated autologous cells, should be thoroughly investigated (Pina et al. 2015).

Nanoparticles have also been used in imaging technology for vascular pathology, where high specificity and a practically universal target range make antibodies natural candidates for nanoparticle targeting (Annappagada 2015). The key applications of antibody targeting of imaging nanoparticles have been summarized by Annappagada (2015). However, although numerous attempts at antibody targeting of nanoparticles have been made, the fundamental obstacles in the path of this approach include the large size of the antibody molecule (700 kDa), the expense of raising the antibodies, their relative instability, and the potential for immune reactions unless the antibodies are humanized. The large size raises significant problems with accelerated clearance and makes the masking–unmasking approach difficult to practice (Annappagada 2015). Nanoparticle-based imaging technologies for vascular pathologies are at various stages of development, ranging from early investigations to clinical trials, but are not yet at the commercial stage. However, several targeted and untargeted nanoparticle imaging agents are currently in development, and the future is bright for nanoparticle-enabled imaging of vascular pathologies (Annappagada 2015).

According to Bonifacio et al. (2014), nanosized drug delivery systems for herbal drugs could potentially enhance their biological activity and overcome problems associated with plant medicines. However, significant challenges remain for implementation of clinically viable therapies in this field. Trials of novel methods to control the interactions of nanomaterials with biological systems represent some of the current challenges involved in translating these technologies into therapies. Other new challenges in the development of nanotechnology-based drug delivery systems include the feasibility of scaling-up processes to bring innovative therapeutic techniques to the market quickly, the possibility of obtaining multifunctional systems to fulfill several biological and therapeutic requirements, probing the targeting efficiency of nanoparticles, and satisfying international standards for their toxicology and biocompatibility (Bonifacio et al. 2014). It has to be noted that nanotechnology-based drug delivery systems have been well studied and documented in recent years. Reviews regarding this topic have been published by Calixto et al. (2016), da Silva et al. (2016), Fonseca-Santos et al. (2015), and Gidwani and Vyas (2015), among others.

According to the above, there are strong scientific teams working very hard worldwide to determine the appropriate uses of nanoparticles in medicine and related knowledge areas. However, the toxicological potential of nanoparticles has scarcely been studied. To take advantage of nanotechnology in medical applications, the properties of nanoparticles must be well known and their behavior must be identified under various conditions. Also, it has to be noted that new treatments based on nanoparticles or other nanotechnological developments must be validated and backed by internationally recognized organizations. Unfortunately, regulatory frameworks regarding nanotechnology are lacking in many countries.

4 Current Challenges

It is widely acknowledged that nanotechnologies will contribute to shaping future growth and our lives. However, because of their peculiar features, there are some concerns that the innovation generated by these technologies may be linked to risks and societal implications that could challenge their use. The need for research and innovation in response to these issues is unavoidable to fulfill the expectations raised by these technologies (Mantovani et al. 2016). The key to the fulfillment of these expectations is the Responsible Research and Innovation (RRI) approach of the European Commission, i.e., the development of products, processes, and services that are safe and respectful of the fundamental ethical and social needs and expectations. According to Mantovani et al. (2016), the European Commission has made RRI a cornerstone of Horizon 2020 to support European research in the years 2014–2020. The Horizon 2020 Specific Programme describes the aim of Part V—“Science with and for Society” (SWAFS)—as follows: “The aim is to build effective cooperation between science and society, to recruit new talent for science and to pair scientific excellence with social awareness and responsibility.” Figure 10.4 shows some human values and technological or scientific considerations that should be taken into account to build nanoparticles without unwanted effects. Taking into account the aim stated by Horizon 2020, scientists should work in nanomedicine considering not only the health benefits but also bearing in mind the ethical, social, economic, and environmental concerns, i.e., scientists should go to the cutting edge to solve problems and to shape a sustainable future, but never with money and the fame as the only interests.

A little-studied topic is the nanotoxicology of nanoparticles and their final disposal, as well as remediation techniques when nanoparticles are released into the environment. Application of physicochemical processes for removal of these nanoparticles from soil and water may not be feasible due to lack of cost-effectiveness and eco-friendly nature of the process. There is the need for the development of eco-friendly and sustainable bioremediation technology that is cost-effective, eco-friendly, and target specific. Successful phytoremediation technology and recovery of nanoparticles from water and soil are still remote dreams. There are urgent needs

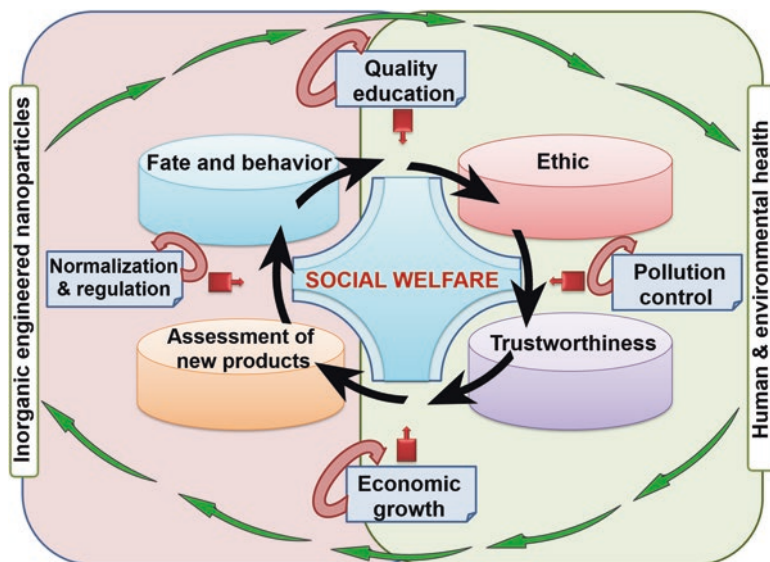


Fig. 10.4 Human values and technological or scientific considerations that should be taken into account to build nanoparticles without unwanted effects. These criteria should be considered before nanoparticles are marketed

not only for assessment of the ecological risk and consequences caused by nanoparticles but also for thorough understanding of their environmental fate.

In addition, there are specific challenges for some scientific teams. According to Vizirianakis et al. (2016), the existing tumor heterogeneity and the complexity of cancer cell biology critically demand powerful translational tools to support interdisciplinary efforts aiming to advance personalized cancer medicine decisions in drug development and clinical practice. In this sense, science has to lead with development of physiologically based pharmacokinetic (PBPK) models to predict the effects of drugs in the body and facilitate the clinical translation of genomic knowledge and implementation of *in vivo* pharmacology experience with pharmacogenomics. This would unequivocally empower the scientific capacity to make personalized drug dosage scheme decisions for drugs, including molecularly targeted agents and innovative nanoformulations, i.e., to establish pharmacotyping in prescribing. In this way, the applicability of PBPK models to guide individualized cancer therapeutic decisions of broad clinical utility in nanomedicine in real time and at a low cost should be developed (Vizirianakis et al. 2016). The necessity for combined efforts within the scientific borders of genomics, medicine, and nanotechnology to ensure significant benefits and productivity in nanomedicine and personalized medicine interventions must be noted. It has to be stated that there are also other challenges regarding nanomaterials which, after they are used, will be released into the environment (Table 10.3).

Table 10.3 Main challenges that nanomaterials most face currently and their potential applications

Challenge	Actual situation	Recent developments	References
Sustainable energies	<ul style="list-style-type: none"> – Energy demand is forecast to increase by 50% for 2025 – 60% of energy depends on fossil fuels – More than 1.6 billion people have no access to electricity 	<ul style="list-style-type: none"> – Development of more efficient fuel cells with solid oxide nanostructures electrodes – Enhance hydrogen storage capacity using carbon nanotubes – High-efficiency photovoltaic solar cell with mesoporous oxides 	Jiang (2012); Conserve Energy Future (2017); Schlapbach and Züttel (2001); Lee et al. (2012)
Provide potable water	<ul style="list-style-type: none"> – About 1.1 billion people do not have access to safe water – More than 2.4 billion humans lack sanitation facilities – 80% of developing world diseases are waterborne with an estimate of 3.4 million deaths 	<ul style="list-style-type: none"> – Disinfection and microbial control using AgNP, carbon nanotubes, and TiO₂ – Detection and adsorption of recalcitrant contaminants with metal oxide nanoparticles 	Qu et al. (2013); Gehrke et al. (2015)
Enhance human health	<ul style="list-style-type: none"> – 30% of worldwide deaths are due to HIV/AIDS, Ebola, and Avian Flu – Approximately cancer kills over 500,000 people and 1.5 million are diagnosed annually in the United States 	<ul style="list-style-type: none"> – Prompt diagnostics, biosensing, bioimaging, and drug delivery are some examples of the use of AgNP, AuNP, and TiO₂ for medical applications – AgNP are used for cancer treatment taking advantage of their potential to modify DNA 	Marambio-Jones and Hoek (2010); Furno et al. (2004); Silver et al. (2006)
Preservation and improvement of the environment	<ul style="list-style-type: none"> – There are more than 500 million cars in the world and by 2030 the number will rise to one billion – CO₂ concentrations have increased the greenhouse effect 	<ul style="list-style-type: none"> – Strong, lightweight polymers are used for automobiles to reduce fuel consumption – Nanoscale zeolites, metal oxides, carbon nanotubes, and enzymes are used for in situ remediation – Reduction of greenhouse gases emission 	Paul and Robeson (2008); Karn et al. (2011); Samimi and Zarinabadi (2012)

The current challenges regarding nanoparticles in medicine have a wide scope, but the main difficulties relate to current concerns regarding (1) the stage of research and development of nanomedicine; (2) environmental pollution; (3) the lack of real applications; (4) the ethical, social, and regulatory aspects; (5) translation of these technologies into therapies; and (6) recovery of nanoparticles from water and soil after treatment.

5 Conclusion

In order for us to take advantage of nanotechnology in medical applications, the properties of nanoparticles must be understood and their behavior must be identified in various conditions in accordance with international regulatory frameworks. The success of nanoparticles to heal or reduce the discomforts caused by chronic diseases may be affected by their physicochemical properties, size, shape, and surface chemistry, which can characterize their biodistribution and pharmacokinetics, as well as their biocompatibility. Moreover, it has to be noted that nanocomposite scaffolds are still at the research and development stage, lacking application in clinical surveys. Trials of novel methods to control the interactions of nanomaterials with biological systems represent some of the current challenges involved in translating these technologies into therapies.

Additionally, there is potential for growth in the use and study of clinical nanoparticles, which will continue to be a productive and challenging field for academics, industry, clinicians, and regulators. As the science and technology of nanomedicine forge ahead, ethics, policy, and the law are struggling to keep up. It is important to proactively address the ethical, social, and regulatory aspects of nanomedicine to minimize its adverse impacts on the environment and public health—and also to avoid a public backlash.

Removal of accidentally or unintentionally released nanoparticles from the environment is crucial for maintaining sustainable ecosystem function. However, successful remediation technology for recovery of nanoparticles from water and soil is still a remote dream.

The discussion regarding the possibilities for transdisciplinary collaboration between medical science, environmental science, social science, and humanities needs to go on and make such collaboration a reality. Nanomedicine entails strong challenges that can only be addressed by transdisciplinary scientific teamwork. No area of knowledge in isolation can provide adequate solutions to the long list of diseases and discomforts that people suffer worldwide.

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