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# Nanomedicine: The next-generation therapeutics

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## Abstract

Recently, nanotechnology has garnered enormous attentiveness in medicine, as it addresses numerous issues associated with the conventional therapeutic strategies such as poor pharmacokinetics, lack of targeting ability, and systemic toxicity. Nanoparticles-based formulations have been utilized in various areas of biomedicine, which are of particular interest in drug delivery, imaging and diagnostic platforms, implants, vaccines, and tissue engineering due to their attractive physicochemical properties and biocompatibility. Herein, this article focuses on the insights concerning the impact of nanotechnology on the development of pharmaceutical products, which will emerge as a next-generation therapeutic platform and are envisioned to have a potential impact on public health. In addition, we highlight the existing challenges and prospects for their translation from bench to clinical practice.

## Background

The current state-of-the-art of fabrication of materials using nanotechnology has attracted increasing interest from researchers in various fields for designing the innovative materials with exceptional performances [1,2]. In addition, this technology is of particular interest with not only exploring new applications but also adding flexibility to the existing systems [3,4]. This field involves the engineering and application of materials greater than atomic scale (approximately 100 nm size or less in one of the dimensions) [5], and has created enormous scope for their application in many areas such as biomedical field, agriculture, electronics, and energy production as well as storage [6, 7]. The resultant ultra-small components of materials display a wide range of physicochemical properties such as electronic (interplay between charge transfer), magnetic, mechanical (high strength, toughness, ductility, and potential superplasticity), morphological (size, shape, and surface), and optical (refractive indices, photo-active effects, and color) [1,2,7,8]. These properties of nanoparticles can be altered and attain control over them by changing the synthetic conditions based on the requirement. More often, the aforementioned attractive properties of nano materials may exist either in the intermediate or final form of the designed construct [9].

The integration of this innovative technology with life science is one such exciting field, i.e., nanomedicine, that has opened a new paradigm for a wide range of biomedical applications [4]. It is envisioned that the resultant products of nanomedicine will lead to the development of better devices for the treatment of a wide-range of diseases with high specificity and efficacy [1]. In addition, this technology can also be used to design nanodevices or carriers for the enhancement of the therapeutic efficacy of the existing active pharmaceutical agents. To achieve this, the key components of nanotechnology, i.e., nano-sized particles are used as carriers, where a large variety of nanoparticles that replicate dimensions and some functions of the biological molecules, which facilitate their accumulation in the tissues (enhanced permeation and retention (EPR) effect in cancer) and easy adsorption in the targeted cells [1,10]. The clas-

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sic examples of nanoparticles include, organic-based materials such as liposomes, polymeric nanoparticles, protein constructs, nucleic acid nanostructures, carbon-based materials like carbon dots and nanotubes, fullerenes and graphene, and inorganic nanostructures such as iron oxide nanoparticles (IONPs), layered double hydroxides (LDHs), gold-based nanostructures, mesoporous silica nanomaterials (MSNs), and up-conversion nanomaterials (UCNPs) [4,10-21]. These different constructs possess attractive physicochemical properties based on their morphological attributes such as structure, shape, and size [1]. Moreover, these properties can be altered by changing the morphological attributes depending on their application [10]. The most predominant aspects of the biomedical field where these nanoconstructs are considered necessary are drug delivery, imaging or diagnostics, and tissue engineering (**Figure 1**) [2,4,10,22].

## Drug Delivery

Ideally, choosing a safe and effective delivery system in medicine to convey the right amount of drug to the right position and release them in a controlled fashion at the desired site is an essential pre-requisite for the delivery of potent therapeutic agents, for example, chemotherapeutic agents [11]. As most of the chemotherapeutic agents are hydrophobic; they could be delivered better by using a nanoparticle-based carrier [1]. In addition, the tremendous progress has evidenced the advancements in the development of several strategies for the delivery of drugs by using nanoparticles [13,16,20]. These carriers offer many attractive features over conventional therapeutic agents such as improvement in pharmacokinetics of the drugs, controlled delivery along with on-demand releasing ability of multiple drugs via co-delivery, surpassing drug resistance, better protection of drugs in harsh environments (high level of proteases, extreme pH conditions) in the body, targeted delivery to specific site, either tissue or cell for improved efficacy, and reduced adverse effects [1,3,4,6,13,17,18,21]. Other exciting features include high mobility and long circulation half-life, exceptional stability, high biocompatibility, biodegradability, rapid clearance, high drug loading capacity due to the high surface area [3,4,6,13,17,18,21]. The advent of nanotechnology has created a significant impact on this field for the development of various kinds of nanoparticles to enhance the release efficiency by creating on-demand release by taking advantage of environmental stimuli such as pH, temperature, and intracellular molecules and external triggers like light, magnetic field, and others, avoid premature release or low release ability for better therapeutics [13,18]. The aforementioned nanoparticles are underway of development for the advancement of carriers with high efficacy and decreased toxicity. For a better therapeutic efficacy, targeting ligands are attached to the nanoparticles to deliver the active therapeutic cargo at the right position by offering the advantages such as the ability to reduce the off-target effects, target the specific cell population and convey the payload to the target site [16,18,20,21]. Recently, this has become an exciting approach, which has gained enormous attention and applied for most of the nanocarriers intended for drug delivery [18,20]. The classic examples of targeting ligands that are immobilized on the nanoparticles include folic acid, cell surface peptides, and RGD peptide, which can detect the cell-surface receptors and internalized to deliver the drug cargo with minimal side effects [1,6,7,10]. Further advancements have been made in the development of sub-organelle targeting ligands, which include specific molecules such as Transactivator of transcription peptide, pentamethiniumsalts and nucleotides, that target mitochondria and nucleus [23-26].

Despite the success and advantages, nanoparticle-based drug delivery systems face several challenges or limitations that are required to be addressed to translate them from bench to clinical practice. First, the delivery efficiency of targeted nanoparticles for improved therapeutics is facing negative consequences, in which the administered nanoparticles predominantly smaller than 5.5 nm are engulfed by phagocytic system i.e., network of spleen and liver, and then excreted by renal system, leading to reduced accumulation in targeted cells and corresponding lower delivery efficiency [27]. This could be addressed by exploring the interactions between the nanoparticles and biological systems from mouse to human model [27]. Second, accelerated blood clearance (ABC) phenomenon, certain approaches have been utilized to overcome the recognition of nanoparticles by phagocytic system, for example, stealth effect, which is predominantly intended to confer the invisibility of nanoparticles [28,29]. This approach has been highly acknowledged for increasing blood circulation time of nanoparticles and has been applied for more than 30 years. However, upon repeated administration, an unexpected pharmacokinetic behavior, i.e., ABC phenomenon has been observed in animal species due to enhanced accumulation in liver. Optimization of formulation to abrogate this effect is required to augment the in vivo performance of nanocarriers and this has been explicitly discussed elsewhere [28]. Third, in addition to treatment efficiency, the toxicity of nanomaterials should be addressed before their translation from bench to clinics [2,30]. In general, the toxicity of any drug formulation is defined as the amount of substance that provoke the generation of undesired biological responses and lead to damage of tissues, organs and eventually death. It should be noted that bio-behavior of nanomaterials is different compared to their bulk counterparts [2]. The behavior of nanoparticles in the biological environment depends on their physicochemical attributes such as size, surface charge, chemical functionalities, lattice, and their interaction with the biological membranes [2,30]. In addition, the toxicity depends on the administered dose of the material, which is different with different nanoparticle-based formulations. Though the administered dose is appropriate and safe, the physicochemical attributes may drive them to severe aggregation, which leads to toxicity issues. Another important aspect of nanotoxicity is related to compatibility issue of nanoparticles. Most of these synthetic constructs exert incompatibility with the biological tissues with varying degrees of incompatibility. However, deep analyses on the nanotoxicity and incompatibility yet remain to be accomplished. It is obligatory that these issues have to be solved to accelerate the clinical translation of nanomedicine.

## Imaging/Diagnostics

Imaging techniques by using nanomaterials can be preferred to diagnose and monitor various diseases by enabling the non-invasive assessment of the extent of disease [31]. Engineered nanomaterials with different contrast agents are utilized for the detection via visualization of biological tissues using various sophisticated imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and fluorescence imaging. Amongst all, CT imaging is generally not a nanoparticle-based imaging modality, but it typically uses non-ionic contrast IV and barium, iodine or gastrograffin based oral contrastcompounds for maximum sensitivity [10]. The use of nanomaterials as contrast agents in medicine involves the anatomical and functional evaluation of tissues by localizing them and yield high

contrast. More often, various nanoparticles with intrinsic optical properties such as gold nanoparticles (GNPs), nanodiamonds, IONPs, and others such as UCNPs are used in different imaging techniques such as CT and MRI. However, the potential toxicity of these nanomaterials is the limiting factor that plays a crucial role in their translation to clinics. In addition, various other contrast agents like indocyanine green, loaded in nanocontainers, for example, MSNs and LDHs have been used as versatile image able agents, which are highly sensitive and accuracy for imaging owing to their degradability, and biocompatibility [4,17]. Out of all, paramagnetic agents such as iron oxide and gadolinium-based agents are highly efficient contrast agents with T1 and T2 relaxivity. However, the poor biocompatibility of these agents should be considered before taking them into account for clinical studies. In a few cases, these agents were also incorporated in nanocarriers for better imaging performance [10,13].

### Tissue Engineering

Tissue engineering (TE) has gathered an attracted interest due to the increase of the demand for organ replacement therapies and a shortage of donated organs [2,21,32,33]. The integration of nanotechnology with the tissue engineering field has offered enormous potential and opportunities for the functional progress and the restoration of tissues [34]. In addition, the tremendous progress in the past few decades has evidenced the advancements of various methods of nanotechnology in developing versatile biomaterials for a better understanding of the molecular mechanisms relevant to the nano-bio-interface, i.e., interactions between cellular surface components of the extracellular matrix (ECM) and innovative nanomaterials [2,8,35,36]. In the past few decades, much research has been focused on the development of biomimetic tissues along with the 3D environment at an arbitrary gauge, i.e., macroscale and microscale (biomimetic 3D scaffolds as tissues). Very recently, the focus has been narrowed down to elucidate the facts behind the molecular mechanisms at the nanoscale and creating the artificial tissue substitutes with better control over the tissue environment [2]. These nano-sized materials at molecular level play a crucial role in tissue maturation and significant functional improvement and became an efficient alternative to overcome the challenges of biomimetic scaffolds such as inadequate cell migration into scaffolds, limited electrical coupling at the gap junctions of cells and others [2]. Currently, extensive varieties of nanomaterials have been utilized alone or by encapsulating them in biomimetic 3D constructs like polymeric scaffolds or hydrogels to mimic the electrophysiological and morphological features of native tissues for a better regenerative outcome owing to their biocompatibility and attractive physicochemical properties [9,35,37,38]. In this framework, various nano-sized assemblies include carbon-based materials such as carbon nanotubes (CNTs), and graphene oxide (GO), gold-based structures such as GNPs, and gold nanorods (GNRs), IONPs, and polymeric carriers (PCs), which are of particular interest for improving the regenerative outcome through cell growth and differentiation and delivery of therapeutic cargo [39-43]. In addition, these nanoconstructs exert other tasks such as propagating electrical impulses in engineered cardiac tissues (ECTs) for myocardium regeneration due to their electronic architecture. Indeed, these nanoconstructs-integrated ECTs offer enormous opportunities for the functional improvement and structural restoration of tissues [2]. Numerous efforts have been expended to evaluating the efficiency of nanoparticles in 3D tissue substitutes relevant to the therapeutic efficacy and addressing the toxicity issues [44,45]. For example, nanomaterials first-in-man(NANOM-FIM) long-term clinical outcome trial for atheroprotective management has demonstrated that the bioengineered nanoparticles have shown no signs of significant toxicity in the group of patients and have shown lower risk on cardiac health [46].

In recent times, nanoelectronics has gained increasing interest from researchers in the development of electronic interfaces with tissues for recording the electrophysiological activities of organs like heart and brain [2,47,48]. Though in its infancy, we believe that the progress of well-organized nano electronics is envisioned for the regulation of tissue growth.

### Therapeutic Application

Ideally, the nanoparticle-based delivery systems should convey the active drug cargo safely to the desired site by overcoming numerous extracellular barriers during the conveyance [49]. To address this, various improvements have been made in the past decade by utilizing different strategies such as shielding with inert polymers like polyethylene glycol (PEG), for the improvement of in vivo delivery of drugs. However, PEGylation of nanoparticles for stealth effect has certain limitations in their performance in vivo upon sytemic adminsitration, for example, ABO clearence. Further advancements have been made in addressing the limitations for their utilization in vivo via modifing the PEG moiety, manipulating the physicochemical properties of PEG, changing the adminsistraton regimen, and encapsulation of immunosuppressive agents in the formulation such as doxorubicin [28]. Another strategy of therapeutic application is by immobilizing targeting ligands such as folic acid, RGD peptide, and cell surface peptides, which can detect the cell-surface proteins and delivery the active drug cargo. Attaching these ligands to the surface of nanoparticle significantly improves the internalization of nanoparticles specifically by cells and reduces the adverse effects. However, the nanoparticle formulation should be optimized such that the delivery efficiency should meet the requirements to convey the optimal dose to the target site. Many polymeric nanoparticles-based drug delivery systems that have entered clinics and currently a considerable number are at preclinical stages of development [1,4]. In the past decade, numerous formulations based on chemotherapeutic agents such as paclitaxel, doxorubicin, daunorubicin, cytarabine, vincristine sulfate, and asparaginase have been approved by United States Food and Drug Administration (US-FDA) and several others are currently under clinical investigation [1,4]. The examples of nanoparticle-based formulations in clinical use or under clinical investigation include liposome, dendrimers, cyclodextrin protein-drug conjugates and hydrogels and various inorganic nanoparticles such as GNPs [1,10]. Recently, one of the classic examples of nanoparticles includes ultra-small multimodal silica nanoparticles (Cornell dots or C dots) got approved by the FDA for targeted molecular imaging of cancer[50].

### Conclusions

In summary, this reviewed data has given the insights of nanoparticles for biomedical applications, highlighting the use of various nanoparticles and their attractive properties and advantages over conventional systems. These attractive properties of nanoparticles have enabled them for their utilization in various biomedical applications, which are of particular interest in drug delivery, diagnostics via imaging and tissue engineering. Despite the substantial improvements in the development of nanoparticle-based drug delivery systems, there are still a few critical challenges that are required to be addressed before they enter clinics such a better understanding of the complexity of

the architecture, safety, and toxicity for their potentially widespread applications. In addition, the challenges associated with the bulk production of nanoparticles need to be addressed for batch-to-batch reproducibility. At the outset based on technological advancements and the accumulated knowledge in the past few decades, we envision that shortly, nanoparticle-based products will revolutionize the pharma industry for various ailments. In addition, further advancements in medicine are anticipated for the development of personalized nanotherapeutics with highly sophisticated designs as the next generation healing platform.

## Figures

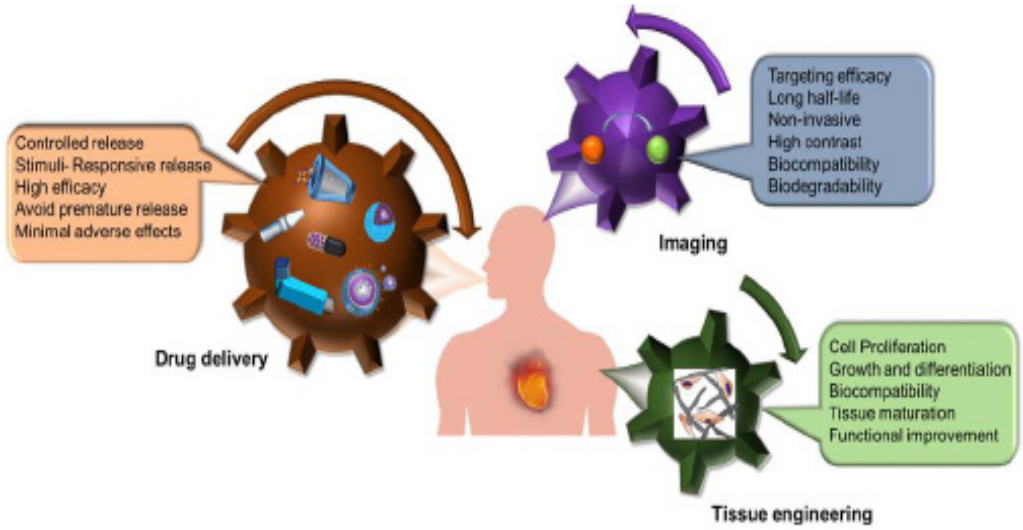


**Figure 1:** Schematic illustration showing the application of nanotechnology in the areas of the biomedical field and the listed beneficial characteristics.

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