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Nanotechnology in Healthcare: Applications and Challenges

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Abstract

In this era of nanoscience, advances of nanotechnology have led to the creation of new generations of nanostructures, each characterized by their explorative utilization in various types of applications in biomedicine and bio-engineering. These applications are expected to significantly improve the diagnosis and therapeutic aspects of many diseases. The materials have been explored and reported as components of biosensors and as very efficient drug delivery platform. Though, few nano-materials have been reported to be used in clinical medicine, but not coherently effective. This could be because of nano-toxicity which is a potential limitation for its use in biological system. A brief description on the development of nanostructure for biomedical application over the years in terms of new materials and understanding of their interaction with the body, may lead to better biocompatible nanostructures.

Keywords: Nanotechnology; Health care application; Nanotoxicity; Challenges

Introduction

Nanotechnology and science of nanomaterials provide apt potential in engineering of materials and at present is the enormously growing and developing scientific technology. It is defined as the study of controlling, manipulating and creating systems based on their atomic or molecular specifications [1]. As stated by the US National Science and Technology Council, the essence of nanotechnology is the ability to manipulate matters at atomic, molecular and supra-molecular levels for creation of newer structures and devices [2]. Generally this science deals with structures sized between 1 to 100 nanometer (nm) in at least one dimension and involves in modulation and fabrication of nanomaterials and nanodevices. It has been endured as an area of intense scientific research in various fields like optical, electronic and biomedical fields. Bacterial cells, plant cells and mammalian cells which are more than 100 nm size can easily engulf or internalize the particulates of nano-size like viruses (75-100 nm), proteins (5-50 nm), nucleic acids (2 nm width) and atoms (0.1 nm). If we compare a single human hair diameter (50 μm) to 1 nm nanofibre, hair will be 50,000 times larger than the size of 1 nm [3]. The great visionary late Nobel Physicist Richard P Feynman first designed the idea of molecular manufacturing in 1959. The legendary scientist who first suggested that devices and materials could someday have atomic specifications and that this development path cannot be avoided [4]. For years this science have engaged scientist in exploring the very unique physico-chemical properties of nanoparticles.

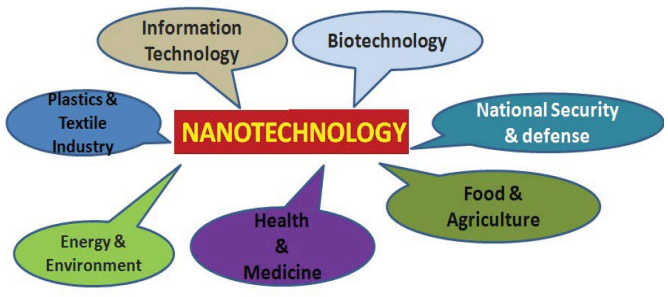

Figure 1: The diagram depicts the applications of nanotechnology in various research fields. Nanotechnology spans many areas like biotechnology, national security and defense, food and agriculture, information technology, aerospace, plastics and textile industries, energy and environment, cosmetics and health and medicine (Figure 1). In this review, the health care benefits and risks of nanomaterials would be enlightened along with their limitations and challenges for their applications in medicine.

Perspectives of Nanotechnology

Applications in Medicine and Health

Nanotechnology has potential to remarkably affect the diagnostic and therapeutic approach for a disease. The unparallel sensitivity and performance, enhanced durability and flexibility, unique physic-chemical properties of nano-materials, have been exploited in medical diagnosis (Table 1) for early detection of diseases, in target approached clinical therapy (Table 2) and in regenerative medicine for reconstruction of damaged tissues.

Medical diagnostics

The entire world has witnessed the phenomenon revolution in biosensors towards Point-of-care testing by glucometer for blood glucose monitoring. It has developed from very primitive enzyme based method to amperometric based principle and further development of reverse iontophoresis method. The technique has evolved from invasive procedure to non-invasive monitoring, from *in-vitro* diagnosis to *in-vivo* monitoring of blood glucose.

Similarly many nano-devices and nano-biosensors have been innovated to monitor the bio- molecules, at a very low concentration resulting in detection of disease at an early stage. They can be a novel and powerful tool for cancer detection system. The traditional diagnostic modalities are unable to detect tumors in their initial stage and more imprecise in differentiating benign from malignant stage. Compared to the conventional methods, novel nanoparticles (NPs) are capable of yielding selective imaging of affected areas.

Clinical therapy and drug delivery systems

The innovative NPs not only act as efficient imaging agents for identifying the diseased tissues but are also ideal carriers to deliver anticancer drugs and other therapeutic drugs at the target site with optimum proficiency and minimum collateral damage to the

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Nanomaterial	Use and its Principle	References
Graphene oxide	Detect very low level of cancer cells (3-5 cancer cells/ml blood)	Yoon et al. [5]
Single-walled Carbon nanotubes (SWNT)	Monitor blood nitric oxide level in inflammatory diseases. It uses the principle of fluorescent signal	Iverson et al. [6]
Silver based nanoparticle and Raman dye-labeled DNA hairpin probes	Targets specific markers in infections. Uses the principle of SERS (surface – enhanced Raman Scattering)	Wang et al. [7]
Nanoflares (first genetic based approach for detecting cancer cells from blood)	Enable live cell detection of intracellular mRNA. It is based on the principle of fluorescence.	Halo et al. [8]
Iron oxide nanoworm particles coated with proteases (matrixmetalloproteases, cathepsins) for early detection of cancer	It can home to a tumor and interact with cancer proteins to produce thousand of biomarkers which can be detected in patient's urine by mass spectrometry.	Kwong et al. [9]
Target specific magnetic nanoparticles	It allows real-time monitoring the glioblastoma multiforme microvesicles in blood. The are detected by a miniaturized, hand-held device.	Shao et al. [10]
NanoVelcro chip – anti-EpCAM antibody coated silicon nanowwires overlaid with polydimethylsiloxane	To detect and isolate the circulating tumor cells. It utilizes the principle of laser micro-dissection (LMD).	Lu et al. [11]
Silver nanorod array substrate	On-chip separation and detection of biological agents like bacteria and viruses in blood, urine, saliva and food. It uses the principle of surface enhanced Raman spectroscopy (SERS).	Negri et al. [12]
Gold nanoparticles coated with influenza A specific antibodies.	To detect the influenza virus in sample. It is based on the principle of dynamic light scattering (DLS).	Driskell et al. [13]
Gold nanoparticles modified with monoclonal anti-hemagglutinin antibody (mAb)	For detection of influenza A virus in blood. It utilizes the principle of colorimetric immunosensing.	Liu et al. [14]
Nanoparticles that form clumps	To detect presence of cancer biomarker like Prostate specific antigen and viral markers like p24 in low HIV viral load.	de la Rica et al. [15]
μQLIDA (microfabricated Quantum dot-linked immune-diagnostic assay)	In-vitro diagnostic test for detecting nanomolar concentration of myelopeoxidase (MPO). It is an economic and fast detecting immunofluorescence sensor with the capability of 2 μl of analyte solution and detecting nanomolar concentration of MPO or other analytes.	Yu et al. [16]
Silicon quantum dots and fluorescent nanodiamonds	These are ultra-stable, biocompatible and nontoxic luminescent nanoprobes. It can be an ideal diagnostic tool for long-term bioimaging and also a non-toxic vector for drug delivery.	Montalti et al. [17]
Iron-oxide magnetic nanoparticles coated with peptide (poly-dopamine)	To locate cancerous cells clusters during Magnetic Resonance Imaging (MRI) and photothermal cancer therapy using near-infrared laser irradiation.	Wu et al. [18]
[^{18}F]-FAC family of positron emission tomography imaging agents	Tumors responsive to chemotherapeutic drugs appear as bright images in PET scans.	Braas et al. [19]
Nano-MRI agent	Bind to $a_v\beta_3$-integrin found on the surface of newly developing blood vessels	Liu et al. [20]
Gold nanoparticle based molecular diagnostic platform	Under FDA approved nanosensor for genetic test for warfarin sensitivity. It allows testing for other genetic targets	Lefferts et al. [21]

Table 1: Nanomaterials used in biosensing of analytes for early diagnosis of specific diseases.

Nanomaterial	Use and its Principle	References
Biomimetic nanosponge	For detoxification treatment	Hu et al. [23]
Nano-composite film of carbon nanotubes (CNTs)	For non-invasive ultrasound therapy. It converts light to sound and generate high pressure sound waves to disrupt cells. It is also called 'Invisible knife for non-invasive therapy.	Baac et al. [24]
Gold/Bismuth based nanoparticles	To concentrate radiation used in radiation therapy to treat cancer tumors.	Cooper et al. [25]
Poly(ethylene oxylated) single-walled carbon nanotubes	Maintains brains blood circulation.	Alqathami et al. [26]
SWNT functionalized with HER2 antibody	For selective destruction of breast cancer cells	Bobadilla et al. [27]
GRGDS-NPs (copolymer of poly(lactic-co-glycolic acid) and poly-ε-L-lysin with polyethylene glycol terminated with arginine-glycine-aspartic acid) based targeting ligands	These are novel hemostatic NPs administered intravenously to activates the clotting process and reduce bleeding due to trauma.	Xiao et al. [28]
Fidgetin-like 2 (FL2) small interfering RNA (siRNA) nanoparticles	FL2, the regulator of cell migration is targeted by the nanoparticle encapsulated siRNA, to promote wound closure and regeneration.	Shoffstall et al. [29]
Fullerene nanoparticles	Reduce allergic reactions	Charafeddine et al. [30]
Carbon nanotube based nanofiber scaffold	Cardiac tissue engineering	Ryan et al. [31]
Thymosin β4 coated poly (ε-caprolactone) nanoscaffolds	The coated nanoscaffolds, stimulates growth and differentiation of cardiomyocytes into functioning cardiac tissue and thus have potential for cardiac replacement after any cardiac event.	Oh et al. [32]
BIND-014, a prostate specific membrane antigen (PSMA)-targeted NP containing docetaxel	Used in chemotherapy naïve metastatic castrate with refractory solid tumors	Kumar et al. [33]
siRNA encapsulated in a cyclodextrin based nanoparticle	To inhibit the key enzyme production in cancer cells	Mita et al. [34]
Gelatin nanoparticles as acarrier for osteopontin (OPN)	Given intranasally for treatment of ischemic stroke	Davis et al. [35]
Nanoparticles poly (D,L-Lactitide-co-glycolide)-(PLGA-) based polymer	Carrier for insulin delivery in diabetic patients	Kanasty et al. [36]
Monodisperse microgels consisting of chitosan matrix, enzyme nanocapsules and recombinant human insulin	The microgels with enzyme nanocapsules monitor insulin release and basal blood sugar level in type 1 diabetes mellitus.	Joachim et al. [37]
Nanocrystalline silver	Antimicrobial agent for treatment of wounds	Verma et al. [38]
Bioreducible polycations-polymer of Polyethylenimine (PEI)	pDNA carrier with endosomal escape function	Gu et al. [39]

Table 2: Nanomaterials used for clinical therapy in various diseases.

neighboring healthy tissues. The therapeutic modality is now being shifted towards intracellular molecular targets rather than the cell itself. Intracellular delivery of such gene-encoding DNAs, gene- silencing small interfering RNAs or recombinant proteins can be achieved by utilizing biocompatible packing materials. The packaging scaffold usually used are liposomes or bacterial toxins or viral NPs, but usually they get degraded and cleared off early from the circulation or may not reach to the potential target site. Recent developments in bioreducible polymers have gained more attention in as they are amenable to molecular programming through sensors that can respond to the changes in ion concentrations in the micro- environment and thus can differentiate between extracellular and intracellular sites [22].

Tissue growth and regenerative medicine

Researches in tissue regenerative medicine aims in developing implants or scaffolds capable for delivering drugs, growth factors, hormones for tissue repair. They provide sustained delivery of bioactive molecules to support survival, infiltration and proliferation of cells for tissue engineering. The expected outcome of such treatment modality is to have complete tissue replacement and functional recovery. Extracellular matrix formation is enhanced by using CNT, nanowires and nanoparticles. Biomimetic hydrogels are used as controlled biomolecule delivery of growth factors to expedite bone regeneration [40-42]. The nanofilled composites provide better compressibility, tensile strength and flexure strength compared to traditional composite microparticles. Crosslink agent composed of partially hydrolyzed polyacrylamide (HPAM) and nanocrystalline hydroxyapatite (nHAp) can be a novel scaffold for osteochondral repair [43]. Chodritin sulfate nanoparticles (CSnps) within the scaffold of chitin blended with poly(butylenes succinate) have been used for skin repair in wounds [44]. It provides superior aesthetic sense as it is biodegradable, biocompatible and forma a porous layer for better nutrient exchange. Polyethylene glycol-based hydrogel scaffold are aid in retention and growth of transplanted heart cells in myocardial infarction [45]. Glass slide coated with garphene oxide film stimulate the adhesion and osteogenic differentiation of human adipose-derived stem cells [46]. Collagen, chondroitin-6-sulfate, chitosan and laminin matrix, together have been demonstrated to support islet function *in-vitro* and allow islet survival and post-transplantation vascularization [47]. Systemic understanding of the interaction between the cells and the *in-vivo* microenvironment at nanoscale level can abet for better designing and fabrication of biomimetic scaffolds.

Toxic Outcomes of Nanostructures

Nanotechnology is now regarded the double edged sword. One edge depicts for potential health benefits and the other for potential health risks. Nanotechnology provides numerous advantages such as high performance, reduced size, mass and power consumption, POC testing and improved reliability and robustness. In order to explore the characteristic physicochemical properties of these nanostructures, the toxicity aspect is overlooked. They elicit unique and unpredictable biological responses, as discussed below, because of their tunable properties.

Size, shape and surface area of the nanomaterial

Because of their nanoscale size, these particles are easily accessible to the vital cells and organs. They interact with the host cell and remain adhered to the surface or internalize by translocation or by receptor mediated endocytosis. Intracellularly also they may alter the cellular metabolism by interacting with the subcellular organelles. The surface area 'o' the particle increases with decrease in particle size and the ratio of surface to total atoms or molecules increases exponentially as the particle size decreases. Ivask et al. had explained about "size-dependent: biological effects of silver NPs. In his study, silver NPs of <10 nm in comparison to NPs >10 nm, proved to be more toxic because of their higher intracellular bioavailability [48].

Shape dependent toxicity has also been reflected in different studies based on carbon nanotubes, nanorods, nanospheres, silicas, copper, gold and many more. In a comparative study of copper oxide (CuO) nanorods to CuO nanospheres by Kennedy et al. results indicated that the higher surface area of nanorods released more ions and therefore more toxic [49]. Yet optimizing the synthetic methodology, unique properties may be enhanced with minimal adverse reactions. Almodarresiyeh et al. in their studies devised a new methodology to synthesize rod-like zincoxide (ZnO) nanoparticles in presence of polymers (polyethylenimine and hexamethylenetetramine). These NPs of ZnO have a wide band gap semiconductor with large excitation energy that favors its suitability to be used in optoelectronic devices [50-52].

Solubility of NPs in the biological media

The solubility of the nanomaterials in a medium is affected by its particle dispersion and agglomeration state, which in turn is influenced by its size and surface ratio. Thus the reciprocal action between the particle and its solvent also a determining factor for toxicity of NPs. Hamilton et al. illustrated the greater toxic effect of longer TiO_2 nanofibers (15 mm) in comparison to shorter fibers because the longer fibres are insoluble in lung fluids and remain in lungs for longer time which initiates inflammatory response by the alveolar macrophages [53].

Yang et al. reported in his study that silver NPs dissolved in lower ionic strength resulted in greater toxicity than the same NPs in a higher ionic strength [54]. TiO_2 or ZnO exhibits different diameters in different biological milieu and thus toxicity differs accordingly.

Surface chemistry (charge/surface coatings)

Surface charge of a NP is also a major determinant factor for its interaction with the biological environment. As per Dejaguin-Landau-Verwey-Overbeek (DLVO) theory, stability of particles is determined by the net electrostatic surface interactions of the particles and the Van der Waals forces. As depicted in a study by Stebounova et al. polymer-coated silver NPs with higher surface charge were more stable than the silver NPs with unspecified coatings in simulated lung fluid [55]. Park et al. suggested that negatively charged silica (SiO_2) NPs had more toxic effect compared to weakly negatively charged silica NPs. Articles have revealed significant cellular uptake of positively charged SiO_2 owing to their enhanced opsonisation by plasma proteins. SiO_2 also induce intracellular reactive oxygen species (ROS) generations and exert their toxic effect by oxidative stress [56].

Composition and degree of purity

Nanomaterials are composed of heavy metals with known toxicity such as Cadmium Selenide (CdSe) NPs are toxic to rat liver and renal cells [57], carbon based NPs cause lung tumors [58] and iron containing NPs are toxic to nerve cells [59].

Liu et al. in their study provided evidences for genotoxic and cytotoxic effects of cadmium sulfide (CdS) on renal cells, liver cells, spermatozoon and tested organs [57].

Harper et al. assessed the impact of synthesis method and purity on the biocompatibility of peptide-capped gold-glutathione (Au-GSH) NPs. The study displayed significant morbidity and mortality for Au-GSH-$(Trp)_2$ purified by dialysis. The toxic effects were also significant

for Au-GSH-$(His)_2$ synthesized by either dialysis or ultracentrifugation whereas Au-GSH-$(Met)_2$ manifested least toxicity. A prudent synthesis protocol can yield high degree purity for NPs and show improved biocompatibility [60].

Aspect ratio dependent toxicity

It is seen that toxicity is directly proportional to the aspect ratio (ratio of highest to the lowest dimension considered the particles are of similar size). NPs with high aspect ratio include nanotubes, nanowires and nanorods whereas low aspect ratio seen in spherical, oval, cubic forms [61]. Asbestos fibers longer than 10 microns cause lung cancer, those of 5 micron size lead to mesothelioma in lungs whereas fibers of 2 microns with asbestosis. The longer asbestos fibers are degraded perpendicularly and made shorter and cleared by the macrophages. Smaller fibers are cut longitudinally generating more of smaller diameter fibres which are more difficult to be removed. However slow clearance of degraded particles would lead to accumulation of the longer fibers in the alveoli inducing inflammatory changes. Long aspect ratio of SWCNT has been signoificantly associated with pulmonary toxicity when compared to the spherical amorphous carbon black particles [62].

Aggregation state of NPs

Aggregation is an ubiquitous phenomenon among all NPs and mediate cellular uptake of bio-molecules. Albanese et al. investigated uptake of transferrin-coated gold NP aggregate on different cell lines. The aggregates reduced the uptake via receptor-mediated-endocytosis in HeLa and A549 cells. In contrast, foe MDA-MB-435 cells, the aggregates internalized independent of transferring receptor via unknown mechanism. The study predicted that NP aggregate bring about multiple cellular responses [63]. Tripathy et al. demonstrated about the effects of particle size and aggregation of ZnO nanoparticles. Smaller aggregates tend to have higher dissolution rate and cellular uptake resulting in ROS generation and induction of cellular apoptosis [64].

Antigenicity of NPs

Nanoparticles can be antigenic themselves and the immunogenicity depends on their physicochemical properties. They can be opsonized by plasma proteins and result in activation of complement cascade. As reported by Trynda-Limiesz et al. nab-paclitaxel in pigs evoked immunological type of response when compared to albumin control [65]. Abrams et al. documented that liposomal siRNA delivery vehicle LNP201 induced cytokine release (cytokine storm) typical of unregulated innate immune response [66].

Challenges for Nanotechnology

Although nanotechnology is a very rapidly growing field, still the product availability is far away from reach because of various hurdles at different stages of development. The barriers for growth, as enumerated below, if overcome can bring about revolutionary changes in the field of health care and medicine.

Lack of knowledge NP components and their characteristics

There are numerous varieties of nanostructures, with different compositions and actions. The *in-vitro* and *in-vivo* physicochemical phenomenon of these NPs are not well understood. Hence identifying the right nanomaterial for the intended indication is crucial. PEI is being recognized as an excellent cargo for intracellular nucleic acid targeting. Nonetheless, it is also regarded as a significant cytotoxic agent. Owing to its higher proficiency in drug delivery, methods have been devised to reduce its toxicity by crosslinking low molecular weight PEI to dithiodipropionic acid di(N-succinimidyl ester) [22].

Lack of uniformity of toxicity

Nanomaterials of different composition, size or shape may be toxic to a different set of cells at different set of exposure conditions. The target cell and the target moieties for toxicity varies with the composition, size, shape, charge, aggregation, coating and solubility of nanoparticles. CNTs at 400 μg/ml are cytotoxic to human T-cells, 3.06 μg/cm^2 on alveolar macrophages whereas cell cultures exposed to 3.8 μg/ml do not reveal any cytotoxicity [22].

Lack of standardization in model systems and test assay

There is no good *in vivo* model to elucidate the physical, chemical and biological behavior precisely. It is difficult to validate the results of interplay of NPs with cells as the outcome varied with different set of cells even if the test assay conditions remain same.

Lack of standard synthesis protocol

Production of nanomaterials utilizes numerous synthetic reagents which are also toxic. Efficient synthetic pathway must be developed with avoidance to use of precarious pollutants. Prudent use of synthetic material and comply with safety guidelines can ensure for yield of high purity and better biocompatible nanoparticle.

Lack of efficient analytical tools

Nanotechnology deals with nanoscale structures, hence novel analytical methods need to be developed to acquire the nanomaterial description precisely such as particle size, surface charge, surface chemistry, crystalline state, aggregation state and its distribution. New innovations in metrological technology requisite to predict the behavior of nanoparticle in biological media.

Lack of understanding of impact on biological system

Impact on health and safety issues still unclear in terms of cellular or organ toxicity, genotoxic or carcinogenic. These materials are small enough to be inhaled and the particles accumulate in lung alveoli to induce inflammatory changes or carcinogenic effect. This would be of prime concern because the workers will be under threat of occupational hazard.

Lack of *in-vivo* monitoring systems

Substantial infrastructure for *in-vivo* analysis of the nanomedicines, inability to monitor multiple probes and patients need to be admitted for analysis, are the major factors that preclude optimization of the biological activities.

Lack of standardized safety guidelines

Due to complex nature of nanomedicines and their multiform toxicity, it is difficult to outline a particular safety guideline for a particular nanoparticle. To provide a safety protocol, empirical evidence and extensive pre-clinical testing is mandatory.

Lack of well trained workforce

High energy consumption due to which production cost is very high and restricted accessibility to people. This is a major hindrance for the goal to be achieved for POC testing to the remote areas.

It is the need of the hour to ensue towards efficient production of nanostructures 'Safe by Design', through green chemistry, optimizing standard protocols for synthesis, production and clinical testing. In shaping of 'Green Nanotechnology', contribution and involution of scientific personnels, persons from governmental sector, industrial and workforce representatives is required in order to modulate the

set of rules so that the occupational and health promotional benefits outweighs the cost and risk factors [67].

Conclusion

Nanotechnology offers the ability to build large numbers of products that are incredibly powerful. Nanomedicines and nanodevices are in their early stages of development. The development processes are heavily interwined with biotechnology and information technology, making its scope very wide. Nanotechnology based products are capable of overcoming the limitations of traditional methods. But, the major challenges are yet to prevail over its toxicity, environmental hazards, production cost and accessibility to the un-reachable at far-off areas.

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