Nanotechnology and Nanomedicine: Going Small Means Aiming Big

Mahesh Kumar Teli[1], Srinivas Mutalik[2] and G.K. Rajanikant[1,*]

[1]*School of Biotechnology, National Institute of Technology Calicut Calicut 673601, India,* [2]*School of Pharmacy, Pharmacy Australia Centre of Excellence (PACE), The University of Queensland, Woolloongabba, Brisbane, QLD 4102, Australia.*

Abstract: Nanotechnology is an emerging branch of science for designing tools and devices of size 1 to 100 nm with specific function at the cellular, atomic and molecular levels. The concept of employing nanotechnology in biomedical research and clinical practice is best known as nanomedicine. Nanomedicine is an upcoming field that could potentially make a major impact to human health. Nanomaterials are increasingly used in diagnostics, imaging and targeted drug delivery. Nanotechnology will assist the integration of diagnostics/imaging with therapeutics and facilitates the development of personalized medicine, i.e. prescription of specific medications best suited for an individual. This review provides an integrated overview of application of nanotechnology based molecular diagnostics and drug delivery in the development of nanomedicine and ultimately personalized medicine. Finally, we identify critical gaps in our knowledge of nanoparticle toxicity and how these gaps need to be evaluated to enable nanotechnology to transit safely from bench to bedside.

Keywords: Nanotechnology, nanomedicine, personalized medicine, nanodiagnostics, nanomaterials, nanotoxicology.

INTRODUCTION

Since the land mark lecture by eminent Nobel Laureate Richard Feynman in 1959 entitled "There's plenty of room at the bottom", the concept of nanotechnology has been influencing all different fields of research involving chemistry, physics, electronics, materials science and biomedical science [1]. This concept led to the new paradigm that size and shape govern the functions of materials. This differentiates the 'Nanoscience' from other technologies, which have some facets at the nanosize range. National Science Foundation and the National Nanotechnology Initiative define nanotechnology as understanding and technological applications of materials and assemblies at the nanometric scale (1-100 nm), where unique phenomena such as optical, magnetic, electronic and structural properties not seen with macromolecules enable novel applications [2].

At the nanometer scale, the physical, chemical and biological properties of nanomaterials are fundamentally different from those of individual atoms, molecules and bulk materials [3]. They differ significantly from other materials due to two major principal factors: the increased surface area and quantum effects. A larger surface area usually results in more reactive chemical properties and also affects the mechanical or electrical properties of the materials. At the nanoscale, quantum effects dominate the behaviors of a material, affecting its optical, electrical and magnetic properties. By exploiting these novel properties, the main purpose of research and development in nanotechnology is to understand and create materials, devices and systems with improved characteristics and performances.

Typical Approaches for Synthesis of Nanomaterials

The approaches for synthesis of nanomaterials are commonly categorized into top-down approach, bottom-up approach and hybrid approach.

A. Top-down Approach

This approach starts with a block of material and reduces the starting material down to the desired shape in nanoscale by controlled etching, elimination and layering of the material [4]. For example, a nanowire fabricated by lithography usually contains impurities and structural defects on the surface. One problem with the top-down approach is the imperfections of the surface structure, which may significantly affect the physical properties and surface chemistry of the nanomaterials [4]. Further, some uncontrollable defects may also be introduced even during the etching steps. Regardless of the surface imperfections and other defects, the top-down approach is still important for synthesizing nanomaterials.

B. Bottom-Up Approach

In a bottom-up approach, materials are fabricated by efficiently and effectively controlling the arrangement of atoms, molecules, macromolecules or supramolecules [5]. The synthesis of large polymer molecules is a typical example of the bottom-up approach, where individual building blocks, monomers, are assembled into a large molecule or polymerized into bulk material. The main challenge for the bottom-up approach is how to fabricate structures which are of sufficient size and amount to be used as materials in practical applications. Nevertheless, the nanostructures fabricated in the bottom-up approach usually have fewer defects, a more homogeneous chemical composition and better short and long range ordering.

C. Hybrid Approach

Though both the top-down and bottom-up approaches play important roles in the synthesis of nanomaterials, some technical problems exist with these two approaches. It is found that, in many cases, combining top-down and bottom-up methods into an unified approach that transcends the limitations of both is the optimal solution [6]. A thin film device, such as a magnetic sensor, is usually developed in a hybrid approach, since the thin film is grown in a bottom-up approach, whereas it is etched into the sensing circuit in a top-down approach.

One area of nanotechnology application that holds the promise of providing great benefit for society is in the area of medicine. Given the nanoscale functional components of living cells, it was foreseeable that nanotechnology would be applied in medicine, giving rise to 'Nanomedicine'. Nanomedicine (a part of nanotechnology) is an interdisciplinary research area integrating biology, chemistry, engineering and medicine with the intention of delivering a valuable set of research tools and clinically helpful devices for disease diagnosis, prevention, and treatment [7]. Because of the unique characteristics like superparamagnetic or fluorescent properties, and small size comparable to biomolecules, nanostructured materials are being emerged as novel biomedical imaging,

*Address correspondence to this author at the Assistant Professor, School of Biotechnology, National Institute of Technology Calicut, Calicut 673601, India; Tel: +91-9495204863; Fax: +91-495-2287250;
Email: rajanikant@nitc.ac.in

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diagnostic and therapeutic agents for the future biomedical field [8] (Table **1**). Moreover, the conjugation of targeting moieties on the surface of the multifunctional nanomaterials gives them specific targeted imaging and therapeutic properties [9]. Nanoparticles and nanodevices under investigation for imaging and drug/ gene delivery applications are quantum dots, nanoshells, nanospheres, dendrimers, paramagnetic nanoparticles, liposomes and carbon nanotubes [10]. In this review, we summarized important applications of nanotechnology in medicine with more emphasis on diagnostics, imaging, drug delivery and finally on personalized medicine.

NANOTECHNOLOGY FOR CYTOGENETICS AND DIAGNOSTICS

Cytogenetics which is a part of molecular diagnostics has mainly been used to describe the chromosome structure and to identify abnormalities related to diseases [11]. Localizing specific gene probes by fluorescent *in situ* hybridization combined with conventional fluorescence microscopy has reached its limit and molecular cytogenetics is now enhanced by nanotechnology [12]. Endothelial progenitor cells taken from human umbilical cord blood and labeled with perfluorocarbon nanoparticles (200 nm) could be detected by MRI [13]. Further, superparamagnetic iron-oxide nanoparticles are emerging as an ideal probe for noninvasive cell tracking [14].

Combining advances in related fields such as nanotechnology, biotechnology and pharmaceutics, nanomedicine offers the potential to move from a 'one-size-fits-all' approach to 'one more individually tailored' for higher efficacy [15]. For diagnosis, this translates to recognition and characterization of very early (even pre-symptomatic) non-invasive disease providing assessment. One of the early applications of nanotechnology in MRI was the use of paramagnetic iron oxide particles. When taken up by healthy hepatocytes, these particles could help to distinguish between normal and cancerous liver cells [16]. Similarly, substantial success in nanotechnology-enabled molecular imaging has been made in all imaging modalities including optical, nuclear, ultrasound and computed tomography [17-24]. For example, carbon nanotube based X-ray device that emits a scanning X-ray beam composed of multiple smaller beams while also remaining stationary will enable the construction of smaller and faster X-ray imaging systems for medical tomography such as CT scanners, which produce higher-resolution images [25]. Another study reported the feasibility silica nanospheres as contrast-enhancing agents for ultrasonic imaging [26].

Because of the small dimension, most of the 'nanodiagnostics' fall under the broad category of nanobiochips and nanoarrays [27]. Nanotechnology-on-a-chip is a new paradigm for total chemical analysis systems [28]. Protein nanobiochips can detect traces of proteins in biological fluids that are not detected by conventional immunoassays. Nanobiosensors based on nanotechnology are portable and sensitive detectors of chemical and biological agents, which are useful for point-of-care testing of patients. Gold particles (~13 nm) attached with small pieces of DNA can detect millions of different DNA sequences simultaneously [29]. Quantum dots are inorganic fluorophores with potential applications for cancer diagnosis [30] Fig. (**1**). Viral diagnosis is another application of quantum dots. For example, current respiratory syncytial virus detection methods are not sensitive enough and are moreover time consuming. However, antibody-conjugated nanoparticles rapidly and sensitively detect respiratory syncytial virus and estimate relative levels of surface protein expression [31].

Nanotechnology also has an impact on improving our understanding of the nervous system and developing new treatments for neurological disorders [32]. For instance, with the help of platinum nano-wires and blood vessels as conduits to lead the wires, neuroscientists have successfully detected the activity of individual neurons lying close to the blood vessels [33]. Iron oxide nanoparticles can outline not only brain tumors under MRI but also other lesions in the brain that may otherwise have not been noticed [34]. Further, iron oxide nanoparticle coated with biocompatible polymer and tagged with chlorotoxin (tumor-targeting agent) and a fluorophore, has been shown to cross the blood-brain barrier and specifically target brain tumor [35]. Quantum dot technology has been used to gather information about how the central nervous system environment becomes inhospitable to neuronal regeneration following injury or degenerative events [36].

NANOTHERAPEUTICS

Unfortunately, early diagnosis is meaningless if not coupled with effective therapy. Developing effective drug delivery systems is a major challenge for pharmaceutical companies since nearly half of the drugs are poorly soluble in water, which is an essential factor for drug effectiveness. Incorporating a drug molecule into nanoparticles not only improves its bio-availability, bio-compatibility and safety profiles but also facilitates targeted transport, immune evasion and favorable drug release kinetics at the target site and thus maximizing patient compliance [37]. In this connection, nanotechnology is moving from being used in 'passive structures' to 'active structures' in medical field, through more targeted drug therapies or "smart drugs" by conjugation of specific ligands to nanocarriers or to aptamers [38]. Nanotechnology is particularly useful for the delivery of biomolecules such as genes, proteins or stem cells. These new nano-drug therapies have been reported to be more effective than traditional therapies but also have been shown to cause fewer side effects [39]. There are a number of advantages with nanoparticles in comparison to microparticles; particularly, nanoparticles can advance through the blood stream without depositing or occluding the microvasculature. Nanoparticles can circulate in the body and penetrate tissues such as tumors. In addition, they can be taken up by the cells through natural means such as endocytosis [40]. Nanotechnology improves the drug-effectiveness by the following approaches:

- Minuscule particle size increases the surface area, thereby enhancing the rate of dissolution.
- Novel nanoparticle formulations with improved stability and shelf-life.
- Development of nanoparticle formulations for improved absorption of insoluble compounds/ macromolecules enables improved bioavailability and release rates, potentially reducing the amount of dose required and thereby decreasing the side effects.
- Nanoparticle formulations having sustained release profiles can improve patient compliance with drug/dosage regimens.
- Ligand conjugated nanoparticles for targeted drug delivery.

Few nanotechnology-based products are already approved for the treatment of cancer. Examples include: Doxil (a liposome preparation of doxorubicin) and Abraxane (paclitaxel in nanoparticle formulation) [41,42]. Many of these already commercialized products are not available directly to the consumer. Instead, they are exploited by drug discovery scientists and physicians in need of better imaging techniques and as prescriptions to treat particular kinds of illness (Table **2**). Other example is gold nanoparticles which offer a novel class of selective photothermal agents to destroy the malignant cells. The capability of gold nanoparticles to detect cancer was presented previously [43,44]. Similarly, immunotargeted nanoshells (engineered to both scatter light in the near-infrared range facilitating optical molecular cancer imaging and to absorb light) enable selective destruction of targeted carcinoma cells through photothermal therapy [45]. Hence, it would be possible now to design an 'all-in-one' active agent that can be used for noninvasive cancer detection and destruction. This exclusive technique has a potential in molecularly targeted

Table 1. Recent Approaches in Different Areas of Nanomedicine

Therapeutic areas	Description	References
Nanodiagnostics		
• Magnetic nanoparticles	Label choice is made so that its interaction with the analyte gives a magnetic signal to be used and the detection is done by magnetometer. **Example:** Water-dispersible oleic acid-Pluronic-coated iron oxide magnetic nanoparticle loaded with doxorubicin.	[16, 75, 87, 88]
• PEBBLE nanobiosensors	Probes Encapsulated by Biologically Localized Embedding (PEBBLE) nanosensors consist of sensor molecules entrapped in a chemically inert matrix by a microemulsion polymerization process that produces spherical sensors in the size range of 20 to 200 nm. **Example:** Gadolinium (MRI contrast agent) incorporated PEBBLEs for brain tumor MRI imaging.	[89-91]
• Nano-scale cantilever arrays	Microscopic, flexible beams resembling a row of diving boards - are built using semiconductor lithographic techniques. Such micron-sized devices, comprising many nanometer-sized cantilevers constructed as part of a larger diagnostic device, can provide rapid and sensitive high-throughput detection of proteins, DNA, RNA and whole-cell for a broad range of applications ranging from disease diagnosis to analytical chemistry. **Example:** Nanocantilever biosensors, Atomic force microscope cantilevers reagentless biosensors that detect restriction endonucleases with the application of a magnetic field.	[92-94]
Nanotherapeutics		
• Targeted drug delivery systems	Nanoparticle based drug delivery system with consideration of specific target, desired pharmacokinetic profile and route of administration. **Example:** Polymeric nanoparticles (Abraxane), Dendrimers (polyamidoamine dendrimer/methotrexate complex), Carbon nanotubes (Carbonnanotubs/methotrexate).	[95-97]
• Theranostics	Engineered nanoparticles possessing both diagnostic and therapeutic potentials. **Example:** Trastuzumab (nanoparticle conjugated with the anti-HER2 monoclonal antibody), Plasmonic nanobubbles (gold nanoparticle-generated transient photothermal vapor nanobubbles).	[98-100]
• Lipoplexes	Spontaneous self-assembly of anionic nucleic acids with cationic lipids as ordered aggregates in order to achieve effective systemic delivery of therapeutic genes to humans. **Example:** PEGylated lipoplexes with extended residence time in the circulation.	[101-103]
Reconstructive surgery		
• Nanoscaffolds for tissue engineering.	Nanoscaffold constructs mimicking cellular matrices to guide tissue repair and replacement. **Example:** Polymeric nanofiber matrix, Single-walled carbon nanotubes (SWNTs) for the growth of artificial bone material, Degradable poly(-caprolactone) scaffold.	[104, 105]
• Implants	Durable rejection-resistant artificial tissues and organs. **Example:** Peptide nanofiber scaffold for brain repair and axon regeneration.	[106, 107].
• Nanolaser surgery	Laser microsurgery for ablation and repair of tissues. Nanolaser spectroscopy to study very small biological structures. Nanolasers for biphotonic detection of cancer in single cells. **Example:** Femtosecond laser nano-surgery.	[108, 109]
Nanorobotics		
• Surgical nanobots	Miniaturized robots (nanobots) programmed to perform routine surgical procedures. **Example:** Respirocyte, Spherical nanorobot intended to function as an artificial erythrocyte.	[110, 111]
Implants and Prosthetics		
• Prosthetics and implants	Nanotechnology based prosthetics and implants for biomedical applications. **Example:** Carbon nanofiber (CN)-reinforced polycarbonate urethane (PU) composite as orthopedic prosthetic devices, Polypyrrole implants suitable for neural prosthetics.	[112, 113]

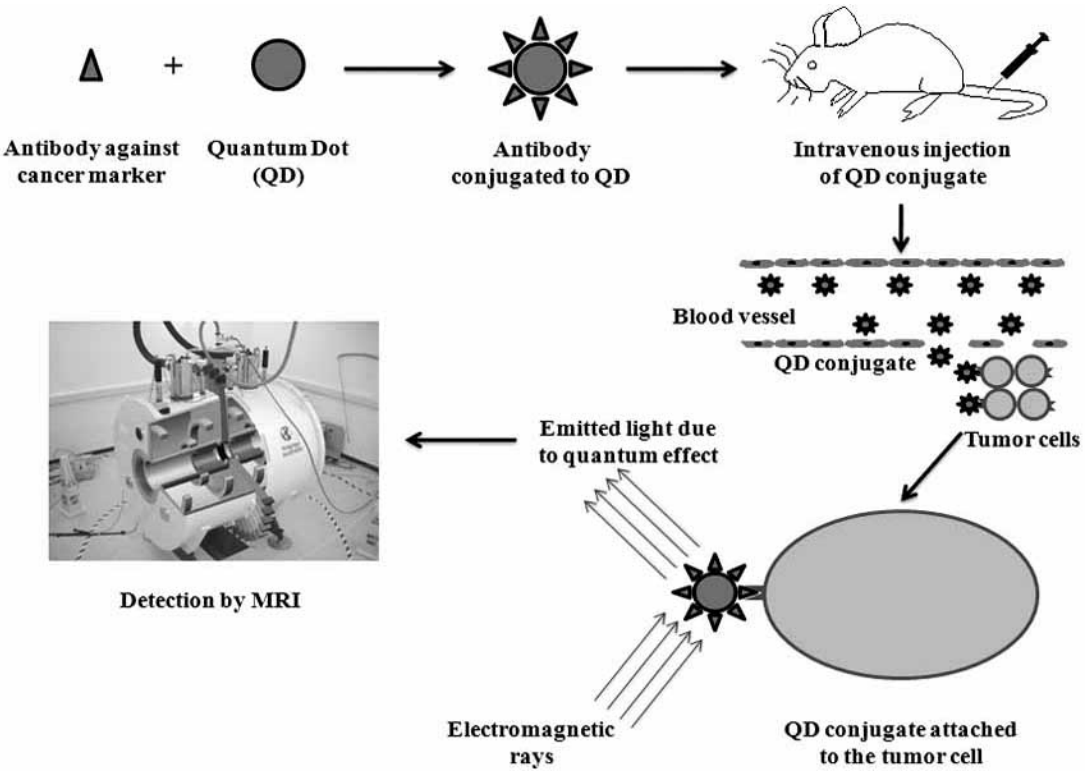

Fig. (1). Molecular targeting and *in vivo* MRI imaging of tumors using quantum dot-antibody conjugate.

Table 2. Commercialized Nanotechnology Products for Various Biomedical Applications

Therapeutic Area	Trade Name	Company	Description of the Product
Appetite Stimulant	Megace® ES	Par Pharmaceutical Companies, Inc. (USA)	• For stimulation of appetite. • Uses Elan's NanoCrystal technology to improve the rate of dissolution and bioavailability of the original megesterol acetate oral suspension.
Cancer	Abraxane™	American Pharmaceutical Partners, Inc., USA	• For advanced breast cancer. • Albumin-bound form of paclitaxel (Mean particle size: ≈ 130 nm).
	Doxil®	ALZA Corporation, USA	• For refractory ovarian cancer and AIDS-related Kaposi's sarcoma. • Lipid nanoparticles that incorporate a PEG coating.
	Emend®	Merck & Co., Inc., USA	• Anti-nausea formulation for chemotherapy patients. • 80/125 mg of aprepitant formulated as NanoCrystal drug particles.
Cholesterol Lowering	TriCor® .	Abbott Laboratories, USA	• TriCor® employs Elan's NanoCrystal Technology for easy administration.
Imaging	Qdot Nanocrystals	Invitrogen Corporation, USA	• Nanometer-scale atom clusters containing a semiconductor material (cadmium mixed with selenium/tellurium) coated with an additional semiconductor shell (zinc sulfide) to improve the optical properties of the material.
	TriLite™ Technology	Crystalplex Corporation,USA	• Alloyed nanocrystal (40-50 nm) aggregates of 8-12 individual nanocrystals functionalized with carboxyl groups.
Medical Tools	EnSeal Laparoscopic Vessel Fusion System	SurgRx, Inc., USA	• Indicated for surgical hemostasis. • An electrode consisting of nanometer-sized conductive particles embedded in a temperature-sensitive material. • Each particle acts like a discrete thermostatic switch to regulate the amount of current that passes into the tissue area.

(Table 2) Contd….

Therapeutic Area	Trade Name	Company	Description of the Product
	TiMESH	GfE Medizintechnik GmbH, Germany	• Indicated for laparoscopic and open surgery. • Has an ideal surgical mesh property along with biocompatibility, resistance to infection and the ability to be recognized by the body as a solid titanium implant.
	Acticoat®	Smith & Nephew, Inc., USA	• Based on a patented nanocrystalline technology for safe bactericidal concentrations of silver.
	SilvaGard™	Technology AcryMed, Inc., USA	• Nanoformulation containing antimicrobial silver nanoparticles in solution form.
Bone Replacement	Vitoss	Orthovita, USA	• Porous scaffold for bone defects and to increase resorption and new bone growth.
	Zirconium Oxide	Altair Nanotechnologies, Inc., USA	• Zirconium oxide in nano-sized range for dental applications including fillings and prosthetic devices.
Diagnostic Tests	CellTracks®	Immunicon Corporation, USA	• Magnetic ferrofluid nanoparticle conjugated to antibodies against circulating tumor/endothelial cells.
	NanoChip® Technology	CombiMatrix Corporation, USA	• Provides an open platform for electronically addressing biotinylated samples, hybridizing complementary DNA reporter probes and applying stringency to remove un-bound and nonspecifically-bound strands after hybridization.
	Microarrays	CombiMatrix Corporation, USA	• Semiconductor based microarray technology for rapid analysis of samples and detection of disease.
Hormone Therapy	Estrasorb™	Novavax, Inc., USA	• Micellar nanoparticle drug-delivery platform employed to deliver therapeutically effective dose of 17β estradiol.
Immuno-suppressants	Rapamune®	Wyeth, USA	• Immunosuppressant formulation indicated for the prophylaxis of organ rejection in renal transplants.

photothermal therapy *in vivo*. In this regard, Nanoshells (e.g., AuroShell™ by Nanospectra Biosciences Inc.) are in commercial development for the targeted destruction of various cancers. In addition to this, novel nanoparticles incorporated with molecular sensors to respond to physical or biological stimuli (like changes in pH, redox potential or enzymes) would make most effective drug delivery systems [46].

Another significant role of nanotechnology in the management of infections is the use of nano-formulations to improve the activity of known bactericidal agents. The bactericidal properties of some agents are detectable only in nanoparticulate form. These formulations are made of simple and nontoxic metal oxides such as magnesium oxide and calcium oxide in nanocrystalline form, carrying active forms of halogens. The examples include $MgO.Cl_2$ and $MgO.Br_2$. When these ultrafine powders came in contact with vegetative cells of *Escherichia coli*, *Bacillus cereu*s or *Bacillus globigii*, over 90% of cells were killed within a few minutes. The aluminum oxide or copper oxide nanoparticles have also been reported to exhibit significant antimicrobial activity [47,48]. Silver nanoparticles have been incorporated in commercial preparations for wound care to prevent infection [49,50]. A simple molecule from a hydrocarbon and an ammonium compound, diacetylene amine salt, has also been used to create a unique nanotube structure with antimicrobial capability [51].

Some drug delivery devices are implanted in the body for release of therapeutic substances *in vivo*. The lining of these devices can be improved by nanotechnology [52]. For example, drug release kinetics can be controlled by polymeric surface coated microcapsules by: (a) diffusion of the drug through a polymeric coating, (b) degradation of biodegradable polymer coating, releasing the core drug material [53]. A self-assembling perforated microcontainer could serve as a delivery system for medications/ cells and can be tracked easily by MRI [54].

Drug delivery to the CNS is a challenging task and most of the nanotechnology based strategies are aimed at overcoming a major hurdle in drug delivery to the brain i.e. the blood-brain barrier [39]. Nanoparticles like dendrimer could potentially carry out multiple tasks in a predefined sequence, which is very important in the delivery of drugs across the blood-brain barrier Fig. (**2**). A significant amount of research in this area has been spent exploring methods of nanoparticle-mediated delivery of antineoplastic drugs to tumors in the central nervous system. For example, radiolabeled polyethylene glycol coated hexadecylcyanoacrylate nanospheres targeted and accumulated in a rat gliosarcoma [55]. However, this method is not yet ready for clinical trials, due to the accumulation of the nanospheres in surrounding healthy tissue. Some studies have shown that nanotechnology can facilitate neuroprotection. Water soluble derivatives of buckminsterfullerene (C60) derivatives are a unusual class of nanoparticles having potent antioxidant properties [56]. Robust neuroprotection against excitotoxic, apoptotic and metabolic insults in cortical cell cultures has been demonstrated by the use of carboxyfullerenes [57,58]. Besides therapeutic drugs, several genes are also being introduced to cells using nanotechnology. A variety of nanoparticles including nanoliposomes, gelatin nanoparticles, calcium phosphate nanoparticles, dendrimers and other nanostructures have been used for nonviral gene delivery [59-61].

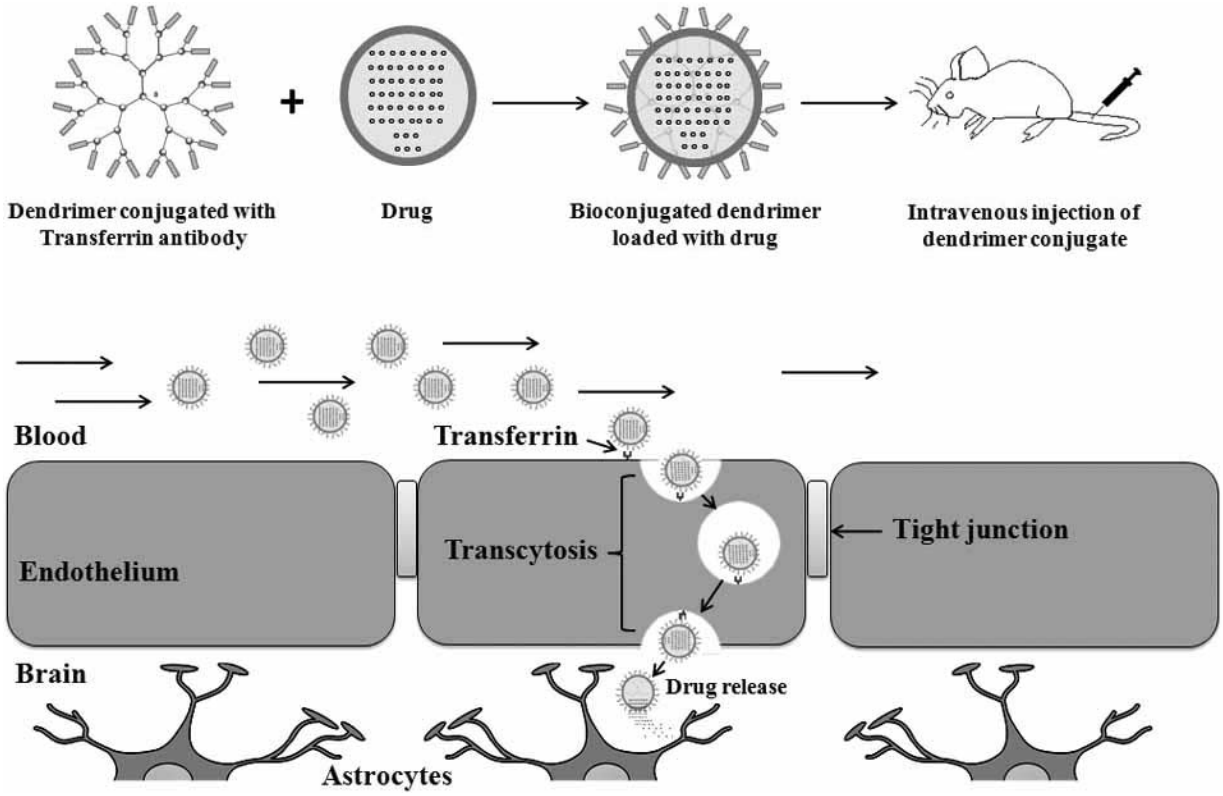

Fig. (2). Dendrimer-antibody bioconjugate as nanocarrier for targeted drug delivery system across blood brain barrier.

Nanotechnology is well suited to optimize the promising outcomes already accomplished in cell transplantation [62]. The small size of nanomaterial construct provides countless options to label, transfect, visualize and monitor cells/tissues used in transplantation. Neural progenitor cells encapsulated in self-assembled peptide amphiphile nanofibers facilitated the growth of nerve cells in tissue cultures [63].

Nanodevices like carbon nanotubes for targeted delivery of anticancer drugs at the specific tumor site have been reported [64]. The potentials of nanotechnology can also be employed in the construction of artificial cells, enzymes and genes. Currently, in the treatment of anemia and infections, encapsulated nanodevices like respirocytes, microbivores and probes have better applications [65]. Thus, by looking into all these facts, nanotechnology is spreading its wings to address the key problems in the field of medicine in the present scenario.

Theranostic Nanoagents

The ability to develop agents integrating multiple functionalities in particular, the combination of diagnostic and therapeutic moieties (theranostic nanoagents), is one of the major advantages of nanomedicine. Theranostic nanomaterials have ultimate clinical utility in the concurrent diagnosis and treatment of any ailment. Besides, they provide feedback mechanisms to define the location, release or efficacy of the incorporated therapeutic agent. Also, the combination of imaging and therapeutic moieties enables the multimodal investigation of agent biodistribution. Nasongkla and colleagues have reported the synthesis of pH-sensitive polymeric micelles containing superparamagnetic iron oxide nanoparticles and an anticancer drug, doxorubicin, which were targeted to $\alpha_v\beta_3$-integrin via cyclic RDG moieties [66]. Magnetofluorescent iron oxide nanoparticles have also been employed as a delivery vehicle for a number of theranostic constructs, including those used in light activated and siRNA-based therapies [67-69]. Bhatia and colleagues have investigated a number of methodologies for the targeted delivery of siRNA using quantum dots [70,71].

Despite this enthusiasm, theranostic nanoparticles also encounter substantial challenges. One dilemma that is immediately experienced in the formulation of these nanoagents is the need to adjust the mismatch between the doses required for imaging and therapy. The most extreme example would be the case of a radionuclide-labeled theranostic nanoparticle. For comparison, the imaging dose of ^{18}F fluorodeoxyglucose is 0.5-1 μg/kg bodyweight (with a maximum of 9.3 μg/kg bodyweight), whereas the standard dose of doxorubicin is 2 mg/kg [72]. If combined within the same nanoscaffold, it is likely the patient would not receive the therapeutic dose of doxorubicin at the maximum allowable dose of ^{18}F. On the contrary, theranostic nanoagents formulated for MRI using gadolinium may require up to 100 mg/kg of the gadolinium chelate (based upon the clinical dose of Magnevist) in order to ensure adequate contrast. To avoid acute toxicity, the loading percentages of the therapeutic entities would thus have to be reduced, thereby decreasing the potency of each nanoparticle. The most direct solution to this problem is the use of materials that are essentially applicable for both imaging and therapy, such as gold nanoshells and nanorods, which can be detected by optical coherence tomography or MRI. The efficacy of these nanoagents may be further augmented by the addition of affinity ligands (antibodies, peptides or aptamers) or even small molecules. This results in higher target-to-background ratios and decreased systemic toxicity.

One final but often neglected challenge is that theranostic nanoagents will only be employed in particular situations, as it is not essential to administer imaging agents every time a patient receives therapy. One caution to this statement lies in the utility of probes that are activated upon delivery of the therapeutic agent. For example, Bagalkot *et al.* have described the synthesis of a bifluorescence-resonance energy transfer construct based upon a quantum dot-aptamer conjugate [73]. When loaded with doxorubicin, the construct is nonfluorescent. Upon localization within target cells,

the chemotherapeutic is released and the probe regains its fluorescence, allowing for the monitoring of drug delivery.

Although a plenty of theranostic nanoagents have been reported, comparatively few have been investigated for in vivo efficacy, delaying the dissemination of knowledge into the larger nanomedicine community as to the types of designs that demonstrate utility. This may be attributed to a lack of access to the relevant animals models or robust collaborations with expertise in the appropriate fields.

NANOTECHNOLOGY AND PERSONALIZED MEDICINE

Traditional medical practice depends on standards of care based on epidemiologic studies of large cohorts, which is not always applicable to a specific individual. Hence, physicians generally take into account of specific characteristics—such as age, gender, weight, diet and environment—when evaluating an individual patient. Recognizing that patients respond differently to treatments, they routinely use diagnostic tests to learn more about the patient's disease and choose specific treatment options and drug dosages based on the results of those tests, as well as the patient's family medical history, comorbidities and lifestyle factors. However, it is only recently that science has begun to give physicians understanding of individual patient or disease differences at the molecular or genetic level, enabling them to tailor treatment even more effectively. Contemporary emerging molecular profiling technologies like genomics, proteomics, metabolomics and transcriptomics coupled with genetic tests are facilitating the development of fresh conceptual approach called personalized medicine. The United States Congress defines personalized medicine as “the application of genomic and molecular data to better target the delivery of health care, facilitate the discovery and clinical testing of new products, and help determine a person's predisposition to a particular disease or condition”. It is anticipated that personalized medicine will allow physicians to focus their attention on factors specific to an individual patient to provide individualized care [74].

Nanotechnology can also make important contributions to personalized medicine through refinement of various technologies used for diagnosis and therapeutics as well as interactions among these [74] Fig. (**3**). One example of application of nanotechnology in improving cancer management is as follows: alphanubeta3-targeted paramagnetic nanoparticles have been applied for noninvasive detection of very small areas of angiogenesis associated with nascent melanoma tumors [75]. Metal particle was used to enhance the contrast in conventional MRI scans when the growth of newly forming blood vessels is still invisible to conventional MRI. The surface of each particle tagged with an antibody that attaches to newly forming blood vessels that are present at tumor sites, enabling the detection of sparse biomarkers with molecular MRI *in vivo*. Early detection by such means can potentially increase the effectiveness of treatment, particularly in case of melanoma. Another advantage of this approach is that the same nanoparticle used to detect the tumors can be used to deliver stronger doses of anticancer drugs directly to the tumor site without systemic toxicity [76]. The nanoparticle MRI would enable physicians to more readily evaluate the effectiveness of the treatment by comparing MRI scans before and after treatment. This fulfills some of the important components of personalized cancer therapy: early detection, combination of diagnostics with therapeutics (theranostics) and monitoring of efficacy of therapy. As indicated by the term "theranostics," its promise consists in the fusion of therapy and diagnostics. As diagnostic capabilities improve, one might come up with treatments well before a disease manifests itself symptomatically. Ideally, diagnosis and treatment could be performed in a single step through a monitoring process. Hence, multifunctionality is the key advantage of nanoplatforms. Targeting ligands, imaging labels and therapeutic drugs can all be integrated into the nanoplatform to enable for targeted molecular imaging and personalized

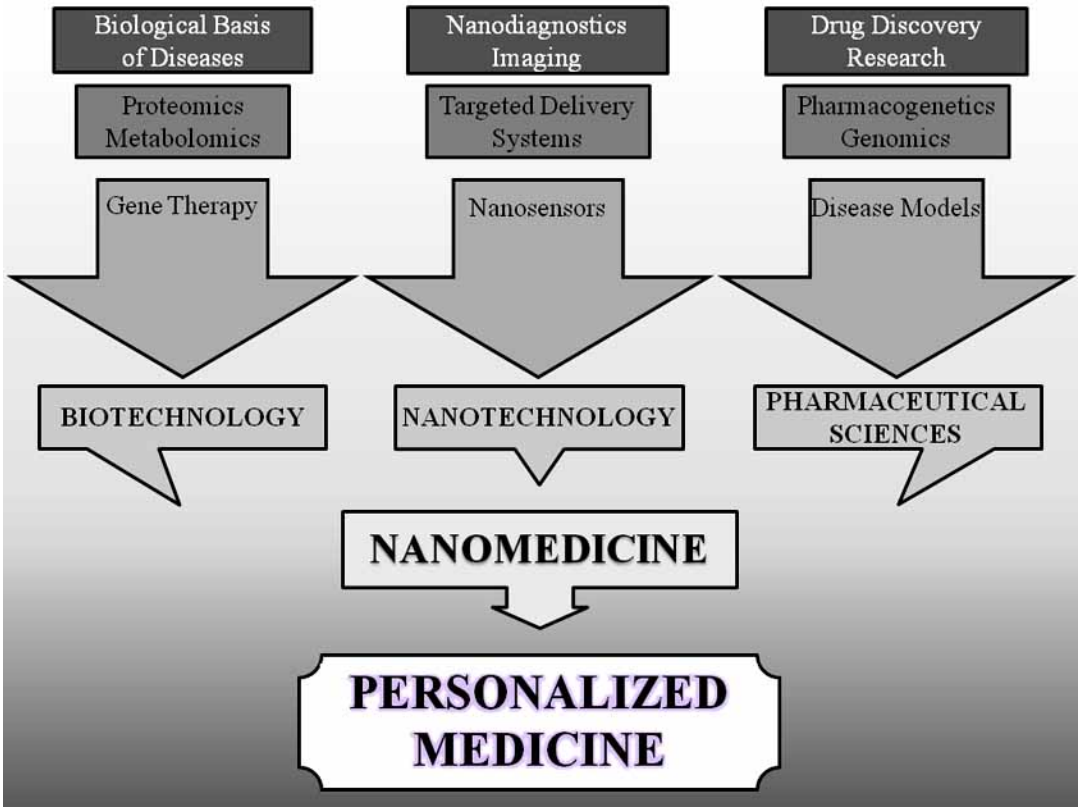

Fig. (3). Flowchart showing the emergence of personalized medicine from nanotechnology and related disciplines.

medicine (15). Both nanomedicine and personalized medicine would interact, develop and play a significant role in moulding the future of medical practice since they already exist in the present medical practice although not specifically allocated as specialties of medicine [77].

Problems with Current Nanotechnology

A. Drug Loading

The loading efficiency of a drug is one of the most important parameters in developing many nanotechnology based drug delivery systems. The volume of a drug reservoir in a nano-sized drug carrier is extremely limited in comparison to macro drug delivery systems. For example, conventional micellar nanoparticles (e.g., PEG-b-PLG micelles) composed of diblock copolymers can hold a maximum of only 20-30% (weight of drug/total weight of carrier) of a hydrophobic drug. The drug loading into polymeric micelles is simply based on hydrophobic interactions between a hydrophobic drug and a hydrophobic polymer block forming the micelle core and thus the drug loading is limited. The loss of a drug during the loading process is also not negligible. One approach that can be utilized to overcome this problem is the concept of hydrotropic polymers that are prepared from monomers having hydrotropic properties for a selected therapeutic agent [78].

B. Stability and Storage

Depending on its chemistry and morphology, a polymer will absorb some water on storage in a humid atmosphere. Absorbed moisture can initiate degradation and a change in physicochemical properties, which can in turn affect the performance in vivo. Storage conditions may thus be critical to the shelf life of a polymeric nanoparticle formulation. The presence of oligomers, residual monomer or remaining polymerization catalysts or solvents may impair the storage stability, catalyzing moisture absorption or degradation. The incorporation of drug may also affect the storage stability of a polymer matrix. To maintain absolute physicochemical integrity of degradable polymeric drug delivery device, storage in an inert atmosphere is recommended [79].

Stability of polybuty1cyanoacrylate nano-suspensions was examined by measuring particle sizes and size distributions over a period of two months in hydrochloric acid, phosphate buffered saline (PBS) and human blood serum. When stored in acidic medium, nanoparticles were found to be stable for at least two months while those stored in PBS agglomerated and showed increase in their polydispersity index. When added to human blood serum, nanoparticles were found not to agglomerate, remaining stable in size for at least five days. Thus instead of lyophilization, which potentially poses problems with reconstitution, acidic storage can ensure stability in certain cases [80].

C. Complexity of Nanocarriers

Efforts to develop more efficient and multifunctional drug carriers have caused more complicated nanotherapeutic agents. Integrating multiple components in a single nanosized carrier, however, requires multiple chemical synthetic steps and multiple formulation processes. Such multiple procedures inevitably lower the yield and increase the cost of production. Complex systems also have more variables in their physicochemical properties, which make it more difficult to predict the fate and action mechanism of the systems after they are administrated into the human body.

D. Characterization Challenges for Nanopharmaceuticals

Nanomaterials might have chemical, physical, magnetic, electric, optical or biological properties different from their large counterparts. The characterization of nanoparticles poses a challenge to developers as well as regulators in terms of these properties. Validated assays are important for detecting and quantifying nanoparticles in tissues and medical products and how physical characteristics may impact product quality and performance [81].

E. Purity of Nanoparticles

Purification and size-based separation of nanoparticles are some of the challenges in the preparation of well-defined materials. Diafiltration shows considerable potential for the efficient and convenient purification and size separation of water-soluble nanoparticles, allowing for the removal of small-molecule impurities and for the isolation of small nanoparticles from larger nanostructures in a single process [82].

F. Toxicity Issues

The unique properties such as small size (<100 nm), relatively high surface-to-volume ratio, quantum dot effect and reactivity of nanoparticles, whilst likely to benefit many aspects of our lives, are also a cause of concern as their possible impact on human health is not known. In addition to risks from use of the nanomedicine products, there are also concerns about the occupational and environmental risks associated with the manufacture and disposal of nano-drugs and nano-devices. Hence, understanding and resolving the issues related to toxicity and environmental impact of nanomaterials are becoming the growing concern for nanotechnologists [83,84]. Although nano-constructs are becoming highly promising technology, many features of nanomaterials may also contribute negatively on the environment and human health [84]. While nanotechnology offers improved circulating half-life, greater surface area and other benefits for a drug molecule, it may lead to new and yet unknown constraints. As the drug retention time increases, time required for drug clearance from the body will also be prolonged. Accordingly, some nanoparticles might be retained in the body not only for days, but potentially for years. In such cases, the safety profile of the nanomaterials such as metal nanoparticles, metal-oxide nanoparticles, quantum dots, fullerenes and fibrous nanomaterials which were found to induce chromosomal fragmentation, DNA strand breakages, point mutations, oxidative DNA adducts and alterations in gene expression becomes a major concern [85] Fig. (**4**). Because of these unresolved yet serious issues, nanotoxicology has emerged as an integral part of nanotechnology research field. Thus, the issue of whether nano-drugs and devices present unique risks, and what type of testing is required to demonstrate their safety, remains an open and unresolved issue.

CONCLUSION

Nanotechnology is a growing field that is potentially altering the ways to treat diseases through novel and advanced diagnostic and therapeutic methods. Using nano-constructs, these advances yielded the potential for very early diagnosis coupled with highly effective targeted therapy, which ultimately led towards the concept of personalized medicine. Although nanotechnology and nanomedicine have been found to be promising areas, significant challenges still exist in promoting these fields into clinically feasible therapies. Nanomedicine has to be properly and systematically addressed and there has to be a clear positive benefit-to-risk ratio that will accompany the clinical implementation of products and procedures based on nanotechnology. Many scientific authorities have concluded that nanotechnology products may exhibit unique toxicological properties that may not be predicted from the toxicological assessment of the bulk version of the same material [83]. Another main problem encountered in testing nanoparticles for human toxicity is the lack of appropriate standardized protocols. Most nanomedical products, whether they be a drug, device, biologic or combination of any of the above, must be demonstrated to not only be effective but also safe before they will be approved for patient use. Thus, regulatory agencies (FDA) should develop the data, testing methods, appropriate standardized protocols for toxicity studies and regulatory requirements that will be needed to ensure the efficacy and safety of nanomedical products. Such requirements should also detect any toxicity in the required clinical studies even if caused by a novel mechanism unique to nanotechnology. To understand and resolve issues related

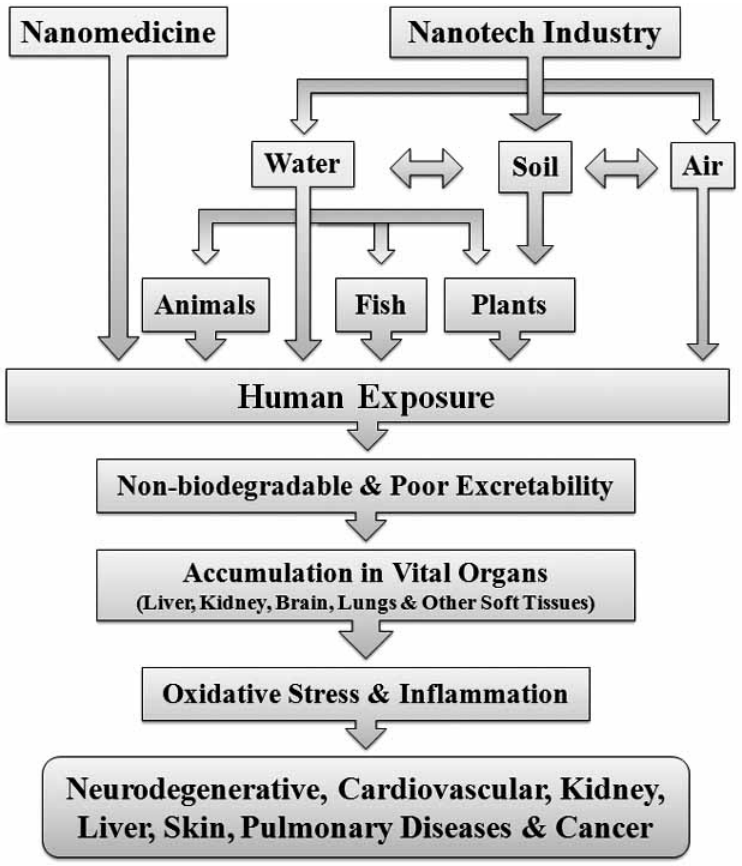

Fig. (4). Flowchart depicting the potential human health risks associated with nanoparticle exposure.

to toxicity and environment, nanomaterials must be evaluated on a particle-by-particle basis and their rational characterisation strategy must include both *in vitro* and *in vivo* pharmacokinetic (absorption, distribution, metabolism and excretion tests), physicochemical and toxicological studies [86]. However, because of toxicity and environmental issues associated with nanotechnological products and as we are continuously exploring nanotechnology for biomedical applications, it is indispensable for us to ensure that the nanotechnologies developed for human use are safe.

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