Nanobiotechnology and Its Application in Nanomedicine: An Overview

1

Trinayan Deka, Malay K. Das, Sanjoy Das, L. Ronibala Singha, and Punamjyoti Das

Abstract

Nanomedicine is the application of nanobiotechnologies to medicine. This chapter highlights the recent trends and applications of nanobiotechnology in emerging fields of nanodiagnostics, nanotherapeutics, and nanotheranostics including clinical nanomedicine.

Keywords

Applied nanobiotechnology · Nanomedicine · Nanodiagnostics · Nanotherapeutics · Nanooncology · Nanocardiology

1.1 Introduction

The term nanotechnology is derived from the Greek word "nano" that means "dwarf" (short man). The term "Nano" means very tiny in size, the scale 10^{-9} m or less. All natural materials and systems have their roots at the nanoscale. The basic material for any living organism, i.e., DNA itself has a nano size. Nanotechnology is the science that deals with materials of nano size range. The most emerging field of science and technology is nanobiotechnology that brings together biology, chemistry, physics, and many areas of engineering, biotechnology, and medicine [1]. Nanobiotechnology has been evolved as an entirely new scientific and technological area from the fusion of nanotechnology and biotechnology. It reflects the demanding importance of nanoscience and nanotools in the generation of novel biomaterials for use in tissue engineering, nanosensors used in diagnostics, nanopores that facilitate the passage of single molecules for DNA sequencing,

T. Deka (✉) · M. K. Das · S. Das · L. R. Singha · P. Das
Drug Delivery Research Laboratory, Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh, Assam, India

M. K. Das, Y. V Pathak (eds.), *Nano Medicine and Nano Safety*,
https://doi.org/10.1007/978-981-15-6255-6_1

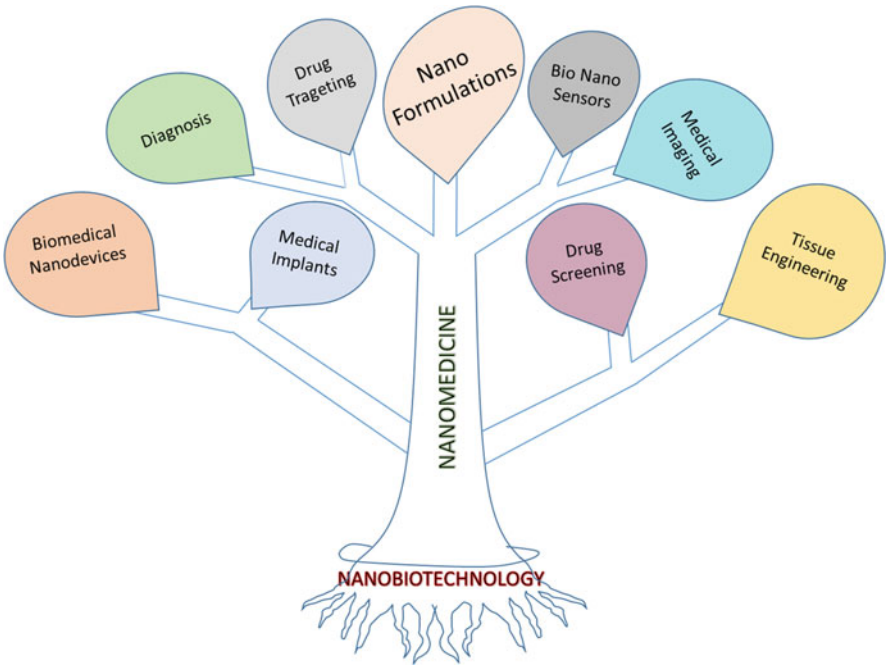

Fig. 1.1 Emerging of nanomedicine by application of nanobiotechnology

nanomaterials for application in imaging single molecules or cells, and devices for therapeutic application [2–5]. By integrating innovative applications of nanotechnology into modern biological issues, many approaches of life sciences are being developed by nanobiotechnology [6].

One of the most elegant emerging fields of applied nanobiotechnology is nanomedicine. Nanobiotechnology has its vast application in different branches of medical science. Tissue engineering, advance medical imaging, clinical diagnosis, nano drug formulation, nanobiosensors are some of the important areas where nanobiotechnology plays a leading role (Fig. 1.1).

The use of nanobiotechnology to revolutionize the medical fields is being highly focused by the scientist. The basic physiological mechanisms of an organism occur at molecular level, i.e., in the nano scale. Understanding different molecular level mechanisms related to physiological changes leads to development of new ideas in the medical perspectives. Drug targeting at molecular level, use of nanosensors, nanopores, quantum dots are some of the significant examples of recent development in nanomedicine [7–10]. It plays a vital role in advanced biology and medical analysis notably within the development of potential targeted delivery systems with lower drug toxicities and higher efficiencies. It has applications in almost each medical branch like neurological disorders (nanoneurology), eye diseases (nanoophthalmology), cardiovascular disorders (nanocardiology), cancer (nanooncology), diseases of skeletal system (nanoorthopedics), and infectious

diseases. Although the application of engineering to drugs seems to be a comparatively recent trend, the basic nanotechnology approaches for medical application dates back to several decades [11–15]. Nanomedicine can likewise be viewed as a refinement of sub-atomic medication and coordinates in genomics and proteomics to encourage the improvement of customized medication. Nanobiotechnology affects the advancement of nanomedicine both legitimately just as by improving different trains, for example, the delivery of nanopharmaceuticals and atomic diagnostics. Similar advancements encourage the improvement of personalized medication corresponding to nanomedicine [7]. Nanotechnologies can expand the limits of current molecular diagnostics and empower purpose of care diagnostics, theranostics, and advancement of personalized medication [16, 17].

1.1.1 Advantages of Nanomedicine

Nanomedicine is being applied to design site specific drug delivery, new techniques for diagnosis and imaging. The advantages of nanomedicine can be categorized into the benefits of nanotherapeutics, nanodiagnostics, and nanotheranostics [16–19] (Table 1.1). This chapter highlights the application of nanobiotechnology in different fields of nanomedicines. Diagnostic, therapeutic, and clinical application of nanomedicines including recent patents are also discussed.

Table 1.1 Advantages of nanomedicine

Advantages of nanomedicine		
Nanotherapeutics	Nanodiagnostics	Nanotheranostics
• Increases drug absorption for effective treatment • Increases drug retention time for higher efficacy • Useful to minimize the amount of active drug for treatment • Provides site specific drug delivery • Helps to deliver drug across blood–brain barrier • Reduced drug toxicity	• Greater optical and magnetic features facilitate effective color coding and labeling of biomarkers for diagnosis • Detection of disease at very early stage made possible by molecular diagnostics • Fast and more accurate detection • Helps to identify the target site for therapy	• Capable of diagnosis and delivery of therapy to the diseased cells • Provides the capacity for personalized medicine

1.2 Application of Nanobiotechnology in Nano Medicine

1.2.1 Diagnosis

Conventional diagnoses for most of the diseases are done by physical examination of symptoms. As the symptom may take time to appear, treatment for those illnesses may have lost their effectiveness. It would be convenient and effective if a disease can be detected at the earliest state of its occurrence. Molecular diagnosis plays a notable role to identify pathogens and diseased cells at very early stage of disease with no symptoms. Nanobiotechnology alters the way of diagnosis by improving sensitivity and better efficacy. Major nanodiagnostics application of nanobiotechnology includes nanobiosensors, biochips and microarrays, nanopore technology, biobarcode, nanoparticle based imaging and labeling, nanoproteomic based diagnosis [20]. Most of the nanodiagnostics technologies are in clinical use and still many are at their development phase.

1.2.1.1 Nanobiosensors

It is one of the most hopeful, concise systems consisting of a biological element (responsible for sampling), and a physical element or transducer (transmitting sampling results for further processing). Detecting an analyte using a transducer by utilizing biochemical reaction to quantify the amount of analyte is the working principle of biosensors [21]. For instance, carbon nanotubes (CNTs) show appropriate electrochemical properties for label-free and multiplexed point-of-care biosensitivity. These were effectively utilized to identify ions, metabolites, and protein biomarkers [22, 23]. They had been used for detection of prostate cancer [24]. CNT-based optical nanobiosensors have been effectively utilized for the determination of immunoglobulins, surface-enhanced Raman spectroscopy (SERS) based biomedical imaging, and phototherapy [25, 26]. Aptamer-AuNPs hybrid frameworks have been showed useful for the identification of specific tumor cells [27, 28]. Comparable hybrid frameworks have been used for combined in vitro imaging and photothermal treatment in oral cancer epithelial cells [29]. Quantum dots (QDs) based lab-on-chip, multiplexed sandwiched immunoassay has been utilized to recognize various lung cancer related biomarkers, for example, carcinoembryonic antigen (CEA), cytokeratin 19 pieces (CYFRA21-1), and neuron-explicit enolase (NSE) in biological fluid [30]. QD based nanosensor was in a nuclease-enzyme-based amplification approach for fluorescence resonance energy transfer (FRET)-based detection of femtomolar concentrations of miRNA [31]. Electrochemical molecularly bioimprinted siloxane biosensor has been utilized for ultra-sensing of gemcitabine as a lung cancer chemotherapy medication [32]. AuNRs modified by ssDNA probes of cadF gene have been developed for precise detection of *Campylobacter jejuni* and *Campylobacter coli* [33]. AuNPs conjugated mesoporous silica-graphene oxide nanoconstructs were effectively utilized for optical bioimaging in colorimetric tumor cell diagnosis [34]. Silicon nanowires (SiNWs) were utilized in sensors as field effect transistors (FETs).

FET-SiNWs have been appeared to detect numerous prostate cancer biomarkers, for example, PSA (prostate-specific antigen) at very early stage [35].

1.2.1.2 Biochips/Microarray

These are nanoscale devices (normally made of glass or silicon base) to coordinate various processes for DNA/protein analysis. These chips are highly sensitive to interact with cellular constituents. Receptor-functionalized nanomotors are capable to isolate biological targets, for example, pancreatic cancer cells and *E. coli* from biological samples [36, 37]. Protein microarrays have been used in analysis of protein level in colon carcinoma cells with exposure to ionizing radiation [38, 39]. This protein analysis helps in the differentiation of the protein level in normal cells compared to premature and metastatic cancer cells [40]. Protein microarray-based analyses of protein–protein interaction and IgE immunoassay for allergy diagnosis have been reported [38, 41, 42].

1.2.1.3 Nanopore Technology

A nanopore is a pore of nanometer size. It comprises a pore-forming protein or as a pore in silicon or graphene. It has been well reported to be used in DNA sequencing. Working principle is the detection of the ionic current passing through it as a voltage is applied across the membrane [43, 44]. Label-free detection of post-translational modifications of protein has been achieved by using single-cell biological nanopore and has tremendous potential for disease diagnosis and cell biology [45]. Bacterial lower respiratory tract infections using nanopore sequencing has been reported as rapid and potential clinical diagnosis tool to replace culture diagnosis [46]. It is applied for cancer diagnosis and treatment through the identification and accurate estimation of MicroRNA (miRNA—cancer biomarkers) and the determination of aberrant DNA methylation as a robust biomarker in cancer. It offers, utilizing MinION stage (Oxford Nanopore Technologies), a viable technique for quick, genome-wide screening of salmonoid RNA virus, with significant potential applications for diagnostics and details investigation concerning the origins and spread of disease outbreaks [47].

1.2.1.4 Biobarcode

Nanoparticle based biobarcode assay is an ultrasensitive and powerful strategy for the determination of biological targets, for example, proteins and nucleic acids. It works on two target specific probes: Magnetic micro beads (MMB) bearing biological probe to identify the target and the second gold nanoparticles (AuNPs) bearing target binding molecule, called biobarcode (an oligonucleotide) [48–51]. The biobarcode method has been successfully used for rapid and reliable detection of amyloid-derived diffusible ligands (ADDL) in cerebrospinal liquid (CSF) for the clinical diagnosis of Alzheimer's disease [52], *E. coli* O157:H7 microbes by means of AuNP labeling and inductively coupled plasma mass spectrometry (ICP-MS) [53], hepatitis C virus (HCV) core antibodies utilizing a TaqMan probe [54]. This method was reported to be potential diagnostic tool for the detection

of PSA [55], the *Vibrio cholerae* O1 OmpW gene [56], and *Staphylococcus aureus* protein A [57].

1.2.1.5 Nanoparticle Based Imaging and Labeling

Nanotechnologies offer various opportunities for improving existing and designing of new imaging methods. Nanoparticles of perfluorohydrocarbons coated with a lipid layer have been reported as an ultrasonic contrast agent [58]. Iron oxide NPs have been clinically applied as MRI contrast agent, for example, superparamagnetic nanoparticles [59], ultra-small SPIO improves MRI for imaging cerebral ischemic injuries and dextran-coated iron oxide nanoparticle improves MRI visualization of intracranial tumors [60, 61]. The fluorescent in situ hybridization (FISH) combined with conventional fluorescence microscopy and fluorescence confocal microscopy have been successfully used to localize abnormal gene related to a disease and to diagnose and differentiate infected erythrocytes from normal erythrocytes [9, 62, 63]. Surface-enhanced Raman scattering (SERS) is generally applied in the detection of small quantity of circulating tumor cells, RNA, nucleic acid, lipids, and proteins present in blood samples [64–69]. It is also used in cancer diagnosis. The single-photon emission computed tomography (SPECT) and positron-emission tomography (PET) have been reported for radiotracer-based targeted in vivo imaging [70].

1.2.1.6 Nanoproteomic Based Diagnosis

Nanoproteomics can reveal critical information related to rare cell populations, hard-to-obtain clinical specimens, the cellular heterogeneity of pathological tissues, and disease biomarkers. These information help in early diagnosis of a disease and monitoring of disease progression. Magnetic nanospherical probes functionalized with antibodies were utilized to recognize anti-HSA antibody [71]. Identification of target autoantibody GDC glutamate decarboxylase (Type 1 diabetes) was successfully accomplished by utilizing supramolecular nanoprobes [72]. AuNP or europium NP-based bio-barcode identification approach utilized for signal intensification of HIV-1 p24 immunoassay [73]. Sol–gel immobilized nanostructure zinc film was utilized for *Neisseria gonorrhoeae* identification [74]. Serum small extra vesicles proteome of tuberculosis patients showed typical deregulation and consequently, could be helpful for designing alternate host-directed therapeutic interventions [75]. The sputum proteomics study helps to separate active TB from non-TB patients with moderate accuracy [76].

1.2.2 Therapeutics

Today nanoformulation plays a leading role in drug delivery and development. Due to several advantages like high efficacy, site specific delivery over conventional drug therapy, nanotherapeutics is now highly focused for achieving health benefits. Polymeric nanoparticles, liposomes, nanogels, *si*RNA, dendrimers, and gene drug delivery are some of the highly anticipated nanobiotechnology used in therapeutic nanomedicine application. Over the past few decades, the US FDA has approved

100 nanomedicine formulations [77]. This shows that nanotechnology is playing an immense role in today's biomedical science [78, 79].

1.2.2.1 Polymeric Nanoformulation

The polymeric nanoparticles are fabricated from synthetic and/or natural polymers. The synthetic polymers are preferred over natural one due to their good availability with higher purity, batch to batch reproducibility, and controlled release behavior for the entrapped drug(s) [80]. Some examples of biodegradable and non-biodegradable polymers commonly used in the preparation of polymeric nanoparticles are polylactide (PLA), poly lactide-co-glycolide, copolymers (PLGA) and poly (-ε-caprolactone), polyacrylates, and poly (methyl methacrylate) [81]. Both hydrophilic and hydrophobic drugs can be encapsulated into polymeric nanoparticles by emulsion solvent evaporation, double emulsion solvent evaporation technique, or other suitable methods. A few of the popularly marketed polymeric nanoparticles are Decapeptyl®, Gonapeptyl Depot®, Enantone Depot®, and Abraxane [82, 83].

1.2.2.2 Liposomes

Liposome based drug delivery systems enhance the therapeutic indices of various drugs through alterations in their pharmacokinetics and pharmacodynamics. A few liposome products have become commercially available for the management of various cancer and fungal infections. For examples, Doxil® for the treatment of ovarian cancer and AIDS-related Kaposi's sarcoma [84], DaunoXome® for the management of advanced HIV-associated Kaposi's sarcoma [85]. A few more commercial liposome products are Depocyt® by SkyPharma Inc., Myocet® by Elan Pharmaceuticals, Mepact® by Takeda Pharmaceutical, Marqibo® by Talon Therapeutics [86–88], and Onivyde™ by Merrimack Pharmaceuticals, Inc. [86–89]. For fungal infections, the US FDA approved Amphotec® and Ambisome® in 1996 and 1997, respectively [90, 91].

1.2.2.3 Nanogels

A nanogel is a nanoparticle composed of a hydrogel—a crosslinked hydrophilic polymer network. Various bioactive compounds such as DNA, proteins, and drugs can be encapsulated in polymeric mesh for drug delivery for various biomedical applications [92, 93]. The preparation methods include micro-molding and photolithographic methods, continuous microfluidics, and free radical polymerization techniques [94]. Chitin nanogel based clobetasol (anti-psoriatic drug) exhibited strong cytotoxicity towards THP-1 and HaCaT cell lines by MTT assay [95]. Sane Care Nanogel, Zyflex Nanogel, Augen Nanogel Eye-care Gel, Skin Perfect Brightening Nanogel, and Oxalgin Nanogel formulation are commercially available [96].

1.2.2.4 siRNA

Small interfering RNA (siRNA), sometimes known as short interfering RNA or silencing RNA, is a class of double-stranded RNA. It is an exciting new tool in molecular biology and the next frontier in molecular medicine [97–99]. The therapeutic advantages of siRNAs for treatment of viral infection, dominant disorders,

cancer, and neurological disorders show great promise. Gold nanorod and trimer of N-acetylgalactosamine (GalNAc) have been reported as carrier for the delivery of siRNA [100–103]. In another study, siRNA targeting Beclin1 was conjugated to ferric–cobalt electro-magnetic nanomaterial (CoFe2O4@ BaTiO3; MENP-siBeclin1) to deliver siRNA into the brain. This novel drug delivery system was effective against HIV-1 infection following on-demand release of siRNA using an in vitro human BBB model [104]. Anticancer siRNA therapeutics has no or negligible side effects as compared to chemotherapeutics. Scientists have tried to target undruggable oncogenes like k-RAS or c-MYC siRNA in mouse model to develop RNAi based therapeutics [105]. siRNAs have been used against BCR/ABL transcripts induced apoptosis [106]. siRNAs have also been used to target K-RAS transcripts carrying the valine-112 oncogenic mutation (K-RASV112) [107]. SphK1 siRNA or JSI-124 showed strong pro-inflammatory effects on the progression of ulcerative colitis, which may be the therapeutic target for its treatment [108].

1.2.2.5 Dendrimers

Dendrimers are three-dimensional, globular hyper branched polymeric nanoarchistructures. Arginine terminated peptide dendrimers, along with sonophoresis improved the transdermal penetration of ketoprofen [109]. The most widely used dendrimers for pharmaceutical uses are poly-propyleneimine (PPI, AstromolR, DAB) [110] and polyamidoamine (PAMAM; Starburst) dendrimers [111]. The multifunctional dendrimers can carry cancer cell specific molecule, anticancer drug and molecule that recognizes the signals of cell death. Dendrimers are also capable for on-demand drug release within the cancer microenvironment [112–114].

1.2.2.6 Gene Drug Delivery

Gene delivery is the process of introducing foreign genetic material, such as DNA or RNA, into host cells. Genetic material must reach the nucleus of the host cell to induce gene expression. It is essential in gene therapy of human genetic diseases. The gene therapy is a promising therapy for inherited disorders, viral infection, and cancers. DNA-based gene delivery systems have been carried out for lentivirus, poxvirus, adenovirus, adeno-related virus, retrovirus, human foamy virus (HFV), and herpes virus [115]. RNA-based gene delivery systems have been done for HIV with lenti-viral vectors-adjusted CD 34(+) cells in patients experiencing transplantation for AIDS-related lymphoma [116]. In case of cancer, the cytokine immune-gene therapy is a promising strategy [117–119]. The previous literatures report on the development of gene delivery carriers. For examples, the cationic non-viral lipid-based gene carriers “lipoplexes” [120, 121], biodegradable poly (ethyleneimine) for plasmid DNA delivery [122], branched poly (ethyleneimine)-cholesterol water-soluble lipo-polymers [123], and polyethylene glycol-grafted poly (L-lysine) as polymeric gene carriers [124, 125] have been developed.

1.2.2.7 Other Nanoformulations

Nanoparticulate drug delivery systems can alter the PK/PD of poorly soluble drugs by increasing their solubility and bioavailability. Drugs loaded in NPs can be protected against external environment making them less sensitive to physical/chemical changes due to photo-oxidation [126–128]. US FDA approved nanocrystal drug formulations for target specific delivery, dose reduction, and enhanced safety profile. For examples, Tricor (fenofibrate, AbbVie), Emend (Aprepitant, Merck), and MAT2501 nanocrystal (Amikacin) [129–131]. Drugs can also be encapsulated into lipid and/or polymer core to alter their PK/PD properties [132, 133]. For examples, resveratrol loaded lipid-core nanocapsules (RSV-LNC) for targeting colon cancer [134] and ciprofloxacin loaded SLNs for better antibacterial activity [135]. Various delivery routes such as oral, dermal, pulmonary, ocular, and rectal routes have been investigated for the administration of nanocapsules [136–141]. Some iron oxide nanodrugs have been approved by US FDA for iron replacement therapies. For examples, Venofer (iron sucrose infusion, American Regent, Inc.), Ferrlecit (sodium ferric gluconate complex in sucrose infusion, Sanofi-Aventis U.S.), Infed (iron dextran infusion, Actavis Pharma), and Dexferrum (iron dextran infusion, American Regent, Inc.) indicated for anemia associated with chronic kidney disease [130]. There are also colloidal gold bound tumor necrosis factor and TNF-bound colloidal gold for anticancer effects [131].

1.2.2.8 Nano Surgery

Nanobiotechnology has significant application in the field of surgery. The development of surgical nanorobot is a significant achievement in the field of surgery. It can act as a semi-autonomous on-site surgeon inside the body guided by a human surgeon. Surgical procedures are performed through various functions such as pathology, diagnosing and correcting lesions by nanomanipulation via coded ultrasound signals, coordinated by an on-board computer and a human surgeon [142]. In femtosecond laser surgery, femtolaser is considered as a pair of nanoscissors by vaporizing tissue locally while leaving adjacent tissue unharmed [143]. Proteolytic liposomal NPs of collagenase were reported to enhance periodontal remodeling of the oral connective tissues that replaced surgical blades [144]. Nanorobotic microbivores have been developed for spying and removing unwanted pathogens from bloodstream [145].

1.2.2.9 Medical Implants

Medical implants are devices or tissues that are placed inside or on the surface of the body as prosthetics or for drug delivery or to control physiological functions or for giving support to body parts. Previous literatures showed that a significant development has been done in the field of medical implants using nanobiotechnology. Titanium spinal implants with surface modification through the addition of titanium oxide/zirconium nanoparticles have shown increased bone formation compared to conventional smooth implants [146]. Cervical cages modified with silicon nitride nanoparticles have shown multiple biomechanical advantages and commercially available [147]. The nanoLOCK™ by Titan Spine technology has been found to

induce a higher osteogenic and angiogenic growth factors than with traditional titanium polyether-ether-ketone cages [148]. Additionally, arthroplasty implants [149], orthodontic implants [150], dental nanorobots [151], and dental implants [152] have also been reported in the literatures. Some commercially available medical implants include Nano TiteTM (Bicon LLC, Boston, USA), Nano TiteTM (Biomet 3i, Palm Beach Gardens, USA), OSSEANTM (IntraLock International, Boca Raton, FL, USA), and Osseo SpeedTM (Astra Tech, AB, Mölndal, Sweden) [153].

1.2.3 Clinical Advances and Patents

Currently, the approval process for nanomedicines in humans is regulated by the US FDA, and is essentially the same as that for any other regulated drug, device, or biologic [77]. As of October 2019, 68 clinical trials including the term "nano" were listed as "recruiting" or "active" on ClinicalTrials.gov. Likewise, 165 clinical trials including the term "liposome" were listed [154]. Both diagnostic and therapeutic nanomedicine those are in clinical trials or recently patented are listed in Tables 1.2 and 1.3.

1.3 Challenges for Nanobiotechnology in Nanomedicine

The use of nanobiotechnology to nanomedicines is being expanding and developed day by day. However, numerous difficulties have also been faced by the researcher, industry, and regulators for doing as such [156]. Characterization of novel nanocompounds for their safety and toxicity is one of the major difficulties in nanomedicine development. Huge efforts have been given to discover how structure of nanoparticles and their properties like charge, size, shape, surface coats, and so on interact with living body system [129]. Lack of specific protocols for assessing of nanomedicines at the physicochemical and biological level influence their development [157]. US FDA has published guidelines regarding the importance of nanomaterial characterization [129]. The Nanotechnology Characterization Laboratory (NCL), set up by the National Cancer Institute, has additionally published guidelines about innovative platforms for the development of nanodrugs for cancer treatment [156]. Reports have been released in regard to the tendency of certain NPs to show toxicity at molecular, cellular, and tissue level [158]. Biological toxicities of NPs include oxidative stress, inflammation, immunotoxicity, genotoxicity, neurotoxicity, and carcinogenicity [159]. The harmful properties of NPs might be used positively for surgical removal of diseased tissues and cancer immunotherapy. Additionally, the toxicity of NPs can be reduced through surface coating with hydrophilic polymers to improve cell viability [160]. Cost for the development and regulatory approval of nanoformulations is other challenge, which is difficult to compensate for low selling nanomedicine. The withdrawal of nanomedicines from the market post FDA approval may be due to the toxicity issues. For examples,

Table 1.2 Recent nanomedicines in clinical development [154]

Name	Description	Condition/disease	Phase	Clinical trial no	Sponsor
Zinc oxide nanoparticles	Antibacterial effect of laser diode and zinc oxide nano particles in dental cavity disinfection	Dental caries	–	NCT03478150	Cairo University
Nano-crystalline hydroxyapatite silica gel	Clinical and radiographic evaluation of nano-crystalline hydroxyapatite silica gel in comparison with open flap debridement for management of periodontal intrabony defects	Chronic periodontitis	–	NCT02507596	Cairo University
Nano polymer-free sirolimus-eluting stents	Evaluation of the safety, efficacy, and deliverability of the combo bio-engineered sirolimus-eluting stent versus the nano polymer-free sirolimus-eluting stents in the treatment of patients with de novo stenotic lesions of native coronary artery	Coronary arteriosclerosis	–	NCT02542007	OrbusNeich
BCMA nano antibody CAR-T	Evaluation of the safety and efficacy of BCMA nano antibody CAR-T in the treatment of multiple myeloma	Relapsed and refractory multiple myeloma	I	NCT03661554	The Pregene (ShenZhen) Biotechnology Company, Ltd
Aminolevulinic acid nano emulsion	Comparison of three photosensitizers, hexylaminolevulinate (HAL), and aminolevulinic acid nano emulsion (BF-200 ALA) to methylaminolevulinate (MAL) in photodynamic therapy of superficially growing basal cell carcinomas	Carcinoma, basal cell	II	NCT02367547	Joint Authority for Päijät-Häme Social and Health Care
Ultrasmall superparamagnetic iron oxides (USPIO)of ferumoxtran-10	Evaluation of the diagnostic accuracy of an USPIO contrast agent (ferumoxtran-10) in combination with 7 tesla MRI to detect lymph node metastases in rectal and breast cancer	Rectal neoplasms Breast neoplasms	III	NCT02751606	Radboud University

(continued)

Table 1.2 (continued)

Name	Description	Condition/disease	Phase	Clinical trial no	Sponsor
Nano-crystalline hydroxyapatite	Evaluation of the histomorphometric study of nano-crystalline hydroxyapatite (nano bone) with lovastatin in the preservation of the tooth socket	Bone loss	II	NCT03981601	Islamic Azad University, Tehran
USPIO nanoparticles	Investigation of inflammation of cranial and meningeal arteries during pharmacologically induced migraine attacks, using ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles and black blood imaging (BBI) MRI	Migraine headache Migraine without aura	–	NCT02549898	Danish headache center
Anti-CD19 CAR-T cells injection	Evaluation of the safety and clinical activity of anti-CD19 chimeric antigen receptor T cells (KD-019 CAR-T) infusion in the treatment of relapsed/refractory B-cell lymphoma and B-cell acute lymphoblastic leukemia	B-cell lymphoma B-cell acute lymphoblastic leukemia	I	NCT03854994	Yan'an Affiliated Hospital of Kunming Medical University
Ceramide nanoliposome	A dose escalation study of ceramide nanoliposome in patients with advanced solid tumors	Carcinoma solid tumors	I	NCT02834611	Keystone Nano, Inc
Nano-albumin bound paclitaxel	Testing of a combination of chemotherapy of carboplatin, nano-albumin bound paclitaxel, and durvalumab against surgically resectable squamous cell carcinoma of the head and neck	Carcinoma, squamous cell Oral cancer Oropharynx cancer Larynx cancer Lip cancer Esophageal cancer	II	NCT03174275	UNC Lineberger Comprehensive Cancer Center

NanoKnife LEDC system	Evaluation of irreversible electroporation (IRE) therapy works in treating patients with breast cancer. IRE kills tumor cells by electrical impulses creating nanopore on the cell membrane and inducing target cell death	Breast cancer	–	NCT02340858	Fuda Cancer Hospital, Guangzhou
Nanomicellar curcumin	Determining the effects of supplementation of nanomicellar curcumin on glycemic control, serum lipid profile, blood pressure, and anthropometric measurements in patients with metabolic syndrome	Metabolic syndrome	–	NCT03534024	National Nutrition and food technology institute
Nanostructured titanium dental implant "KONTACT N"	Evaluating the clinical outcome of dental implants "Kontact N"; and the effects of its nanostructured surface on the osseointegration and secondary stability without increasing the rate of peri-implantitis	Implant-supported fixed prosthesis	–	NCT03582657	Biotech dental
Liposomal amphotericin B	Comparison of the pharmacokinetic exposure to liposomal amphotericin B between critically ill patients and non-critically ill (hematology) patients in an early and late exposure day	Hematological patients	IV	NCT03529617	Universitaire Ziekenhuizen Leuven
Irinotecan hydrochloride liposome injection (LY01610)	Evaluation of the safety and tolerability, the maximum tolerated dose (MTD), and the dose limited toxicity (DLT) of LY01610 monotherapy and combine with 5-Fu in patients with advanced solid tumors	Advanced solid tumor	I	NCT04088604	Luye Pharma Group Ltd.

(continued)

Table 1.2 (continued)

Name	Description	Condition/disease	Phase	Clinical trial no	Sponsor
Polyethylene glycol liposome doxorubicin	Clinical application of polyethylene glycol liposome doxorubicin (PLD) in primary lymphoma	Lymphoma, non-Hodgkin; Hodgkin disease	IV	NCT02526823	Shandong Provincial Hospital
MPER-656 liposome vaccine	Evaluation of the safety and immunogenicity of an HIV-1 gp41 MPER-656 liposome vaccine in healthy, HIV-uninfected adult participants	HIV infections	I	NCT03934541	National Institute of Allergy and Infectious Diseases (NIAID)
Liposomal bupivacaine	Enhanced recovery with liposomal bupivacaine in orthognathic surgery	Pain, postoperative	IV	NCT03844451	University of Texas at Austin
Ethosomal and liposomal preparations of anthralin	Formulation and clinical evaluation of ethosomal and liposomal preparations of anthralin in psoriasis	Psoriasis vulgaris	IV	NCT03348462	Assiut University
Oxiconazole nitrate SLNs loaded gel	Clinical assessment of oxiconazole nitrate solid lipid nanoparticles loaded gel	Tinea fungal diseases	I	NCT03823040	Minia University
Docetaxel-polymeric micelles	Evaluation of the effects and safety of first line docetaxel-PM and oxaliplatin weekly administration chemotherapy for the participants with inoperable or metastatic esophageal squamous cell carcinoma	Esophagus squamous cell carcinoma (SCC) Metastatic cancer	II	NCT03585673	Sung Yong Oh

Table 1.3 Recent US FDA approved nanomedicines [155]

Name	Type	Indication	Year
Esperoct	Antihemophilic factor (recombinant), glycopegylated-exei	Use to treat and control bleeding in adults and children with hemophilia A	2019
Jivi	Antihemophilic factor [recombinant] PEGylated-aucl	Use in previously treated adults and adolescents (12 years of age and older) with hemophilia A (congenital factor VIII deficiency)	2018
Vyxeos	Liposomal combination of daunorubicin, and cytarabine	Treatment of adults with newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC)	2017
Onivyde	Irinotecan liposome injection	Combination with fluorouracil and leucovorin, for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy	2015
Marqibo	Vincristine encapsulated in sphingomyelin/cholesterol liposomes	Treatment of adolescent young adult with Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia	2012
Exparel	Bupivacaine liposome injectable suspension	Administration into the surgical site to produce postsurgical analgesia	2011
Ozurdex	Intravitreal implant containing dexamethasone in the Novadur solid polymer sustained-release drug delivery system	Treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)	2009

Feruglose and Resovist. Hence, phase 4 post-marketing pharmacovigilance is the major concern to further assess the safety of nanomedicine [161].

1.4 Conclusion and Future Aspects

Nanotechnology provides innovative nanodevices and nanosystems those are much smaller than a human cell. Such tools can be used at molecular and cellular levels to kill cancer cells or take over the function of subcellular organelles. Nanodiagnostics will enable routine detection of single particles of viruses or bacteria in minuscule samples. Nanobiotechnology will give nanodevices to look at tissues in minute details. Biosensors those are smaller than a cell would provide us an interior check out of cellular operation. With lab-on-chip utility using nanobiochips, routine check of diagnostic parameters of patients will come to a precise and fast effective theranostic measure. Research is increasing daily to find out newer drug delivery options, newer targeting strategies for medicinal products by the use of nanobiotechnology. Successful implementation of liposomal carrier system, Doxil^{R},

in drug market is a land mark of nanomedicine that inspires industry and regulators to bring forward many more nanodrug formulations for human use. Increasing scenario of the clinical trials and FDA approved nanoformulation represent the growth of awareness utility and knowledge in this area. Such trends in nanoverse will lead to hand to hand use of medical application in the near future.

Nanomedicines have shown nice potential to handle clinical needs in various diseases. However, toxicity and ethical problems with nanomedicine are the major challenges. Fortunately, with the outburst of public and scientific awareness of nanobiotechnology, there is a detail discussion on these ethical and toxicological issues. The potential applications provided by nanotechnology for diagnosis, prevention, and treatment of diseases are presently terribly broad. Therefore, to pursue the sensible application of nanomedicine, there is a demand of straightforward approaches, and systematic development in conjunction with creativeness and visionary power.

Acknowledgement The authors are grateful to the Indian Council of Medical Research (ICMR), Government of India, for offering Senior Research Fellowship to Trinayan Deka to pursue his research works in the Department of Pharmaceutical Sciences, Dibrugarh University, India. S. D acknowledges the Dibrugarh University Research Fellowship (DURF) to carry out this research works.

Conflict of Interest The authors declare there is no conflict of interest. All the tables and figures are original and self-made.

References

1. Navalakhe RM, Nandedkar TD (2007) Application of nanotechnology in biomedicine. Indian J Exp Biol 45:160–165
2. Sahoo SK, Parveen S, Panda JJ (2007) The present and future of nanotechnology inhuman health care. Nanomed Nanomed 3:20–31
3. Drabu S, Khatri S, Babu S, Verma D (2010) Nanotechnology: an introduction to future drug delivery system. J Chem Pharm Res 2:171–179
4. Whatmore RW (2005) Nanotechnology-should we be worried? Nanotechnol Percep 1:67–77
5. Ramachandran R, Shanmughavel P (2010) Preparation and characterization of biopolymeric nanoparticles used in drug delivery. Indian J Biochem Biophys 47:56–59
6. Thrall JH (2004) Nanotechnology and medicine. Radiology 230:315–318
7. Jain KK (2007) Applications of nanobiotechnology in clinical diagnostics. Clin Chem 53:2002–2009
8. Halberstadt C, Emerich DF, Gonsalves K (2006) Combining cell therapy and nanotechnology. Expert Opin Biol Ther 6:971–981
9. Jain KK (2005) Nanotechnology in clinical laboratory diagnostics. Clin Chim Acta 358:37–54
10. Jain KK (2005) Nanotechnology-based lab-on-a-chip devices. In: Fuchs J, Podda M (eds) Encyclopedia of diagnostic genomics and proteomics. Marcel Dekkar, New York, pp 891–895
11. Rizzo LY, Theek B, Strom G, Kiesslig F, Lammers T (2013) Recent progress in nanomedicine: therapeutic, diagnostic and theranostic applications. Curr Opin Biotechnol 24 (6):1159–1166
12. Lee VC (2012) The nanomedicine revolution—part 1. Pharm Therap 32:512–517

13. New research offers breakthrough in nanotechnology, University of Sheffield. https://www.sheffield.ac.uk/news/nr/nanotechnology-nuclear-magnetic-resonance-1.174327
14. Suri SS, Fenniri H, Singh B (2007) Nanotechnology-based drug delivery systems. J Occup Med Toxicol 2:16
15. Sahoo SK, Parveen S, Panda JJ (2007) The present and future of nanotechnology in human health care. Nanomed Nanotechnol Biol Med 3:20–31
16. Moffatt S (2016) Nanodiagnostics: a revolution in biomedical nanotechnology. MOJ Proteomics Bioinform 3(2):00080
17. Han M, Gao X, Su JZ (2001) Quantum-dot-tagged microbeads for multiplexed optical coding of biomolecules. Nat Biotechnol 19(7):631–635
18. Saini R, Saini S, Sharma S (2010) Nanotechnology: the future medicine. J Cutan Aesthet Surg 3:32–33
19. Kim TH, Lee S, Chen X (2013) Nanotheranostics for personalized medicine. Expert Rev Mol Diagn 13(3):257–269
20. Rajasundari K, Ilamurugu K (2011) Nanotechnology and its applications in medical diagnosis. J Basic Appl Chem 1(2):26–32
21. Kubik T, Kubik KB, Sugisaka M (2005) Nanotechnology on duty in medical applications. Cur Pharma Biotechnol 6:17–33
22. Zhu Z (2017) An Overview of carbon nanotubes and graphene for biosensing applications. Nano-Micro Lett 9(3):25
23. Ijeomah G, Obite F, Rahman O (2016) Development of carbon nanotube-basedbiosensors. Int J Nano Biomater 6(2):83–109
24. Silva PMS, Lima ALR, Silva BVM, Coelho LCBB, Dutra RF, Correia MTS (2016) Cratylia mollis lectin nanoelectrode for differential diagnostic of prostate cancer and benign prostatic hyperplasia based on label-free detection. Biosens Bioelectron 85:171–177
25. Williams RM, Lee C, Galassi TV et al (2018) Noninvasive ovarian cancer biomarker detection via an optical nanosensor implant. Sci Adv 4(4):1–11
26. Dong J, Salem DP, Sun JH, Strano MS (2018) Analysis of multiplexed nanosensor arrays based on near-infrared fluorescent single-walled carbon nanotubes. ACS Nano 12 (4):3769–3779
27. Azizah N, Hashim U, Gopinath SCB, Nadzirah S (2017) A direct detection of human papillomavirus 16 genomic DNA using gold nanoprobes. Int J Biol Macromol 94:571–575
28. Jiang Y, Shi M, Liu Y et al (2017) Aptamer/AuNP biosensor for colorimetric profiling of exosomal proteins. Angew Chem Int 56(39):11916–11920
29. Yin D, Li X, Ma Y, Liu Z (2017) Targeted cancer imaging and photothermaltherapy via monosaccharide-imprinted gold nanorods. Chem Commun 53(50):6716–6719
30. Liu L, Wu S, Jing F et al (2016) Bead-based microarray immunoassay for lung cancer biomarkers using quantum dots as labels. Biosens Bioelectron 80:300–306
31. Wang Y, Howes PD, Kim E et al (2018) Duplex-specific nuclease-amplified detection ofmicroRNA using compact quantum dot–DNA conjugates. ACS Appl Mater Interfaces 10:28290–28300
32. Shoja Y, Kermanpur A, Karimzadeh F, Ghodsi J, Rafati AA, Adhami S (2019) Electrochemical molecularly bioimprinted siloxane biosensor on the basis of core/shell silver nanoparticles/EGFR exon 21 L858R point mutant gene/siloxane film for ultra-sensing of gemcitabine as a lung cancer chemotherapy medication. Biosens Bioelectron 145:111611
33. Shams S, Bakhshi B, Tohidi MT, Behmanesh M (2019) A sensitive gold-nanorods-based nanobiosensor for specific detection of *Campylobacter jejuni* and *Campylobacter coli*. J Nanobiotechnol 17(1):43
34. Maji SK, Sreejith S, Mandal AK, Ma X, Zhao Y (2014) Immobilizing gold nanoparticles in mesoporous silica covered reduced graphene oxide: a hybrid material for cancer cell detection through hydrogen peroxide sensing. ACS Appl Mater Interfaces 6(16):13648–13656
35. Reimhult E, Höök F (2015) Design of surface modifications for nanoscale sensor applications. Sensors 15(1):1635–1675

36. Balasubramanian S, Kagan D, Jack Hu CM et al (2011) Micromachine-enabled capture and isolation of cancer cells in complex media. Angew Chem Int Ed 50:4161–4164
37. Wang J, Gao W (2012) Nano/microscale motors: biomedical opportunities and challenges. ACS Nano 6:5745–5751
38. Sreekumar A, Nyati MK, Varambally S et al (2001) Profiling of cancer cells using protein microarrays: discovery of novel radiation-regulated proteins. Cancer Res 61:7585–7593
39. Amonkar SD, Bertenshaw GP, Chen TH et al (2009) Development and preliminary evaluation of a multivariate index assay for ovarian cancer. PLoS One 4(2):e4599
40. Walter G, Bussow K, Lueking A, Glokler J (2002) High-throughput protein arrays: prospects for molecular diagnostics. Trends Mol Med 8(6):250–253
41. Bao YP, Wei TF, Lefebvre PA, An H, He L, Kunkel GT (2006) Detection of protein analytes via nanoparticle-based bio bar code technology. Anal Chem 78:2055–2059
42. Jambari NN, Wang X, Alcocer M (2017) Protein microarray-based IgE immunoassay for allergy diagnosis. Methods Mol Biol 1592:129–137
43. Akeson M, Branton D, Kasianowicz JJ, Brandin E, Deamer DW (1999) Microsecond time-scale discrimination among polycytidylic acid, polyadenylic acid, and polyuridylic acid as homopolymers or as segments within single RNA molecules. Biophys J 77(6):3227–3233
44. Bayley H (2009) Membrane-protein structure: piercing insights. Nature 459(7247):651–652
45. Restrepo-Pérez L, Wong CH, Maglia G, Dekker C, Joo C (2019) Label-free detection of post-translational modifications with a nanopore. Nano Lett 19(11):7957–7964
46. Charalampous T, Kay GL, Richardson H et al (2019) Nanopore metagenomics enables rapid clinical diagnosis of bacterial lower respiratory infection. Nat Biotechnol 37(7):783–792
47. Gallagher MD, Matejusova I, Nguyen L, Ruane NM, Falk K, Macqueen DJ (2018) Nanopore sequencing for rapid diagnostics of salmonid RNA viruses. Sci Rep 8:16307
48. Nam JM, Wise AR, Groves JT (2005) Colorimetric bio-barcode amplification assay for cytokines. Anal Chem 77:6985–6988
49. Nam JM, Thaxton CS, Mirkin CA (2003) Nanoparticle-based bio-bar codes for the ultrasensitive detection of proteins. Science 301:1884–1886
50. Yin HQ, Jia MX, Shi LJ et al (2011) Nanoparticle-based bio-barcode assay for the detection of bluetongue virus. J Virol Methods 178:225–228
51. Byung KO, Jwa MN, Seung WL, Mirkin CA (2005) A fluorophore-based bio-barcode amplification assay for proteins. Small 2:103–108
52. Georganopoulou DG, Chang L, Nam JM et al (2005) Nanoparticle based detection in cerebral spinal fluid of a soluble pathogenic biomarker for Alzheimer's disease. Proc Natl Acad Sci 102 (7):2273–2276
53. Li F, Zhao Q, Wang C, Lu X, Li XF, Le XC (2010) Detection of *Escherichia coli* O157:H7 using gold nanoparticle labeling and inductively coupled plasma mass spectrometry. Anal Chem 82(8):3399–3403
54. Yin HQ, Ji CF, Yang XQ et al (2017) An improved gold nanoparticle probe-based assay for HCV core antigen ultrasensitive detection. J Virol Methods 243:142–145
55. Zhang K, Lv S, Lin Z, Li M, Tang D (2018) Bio-bar-code-based photoelectrochemical immunoassay for sensitive detection of prostate-specific antigen using rolling circle amplification and enzymatic biocatalytic precipitation. Biosens Bioelectron 101:159–166
56. Narmani A, Kamali M, Amini B, Kooshki H, Amini A, Hasani L (2018) Highly sensitive and accurate detection of Vibrio cholera O1 OmpW gene by fluorescence DNA biosensor based on gold and magnetic nanoparticles. Process Biochem 65:46–54
57. Amini A, Kamali M, Amini B et al (2019) Bio-barcode technology for detection of Staphylococcus aureus protein a based on gold and iron nanoparticles. Int J Biol Macromol 124:1256–1263
58. Dayton PA, Ferrara KW (2002) Targeted imaging using ultrasound. J Magn Reson Imaging 16 (4):362–377

59. Weissleder R, Elizondo G, Wittenberg J, Rabito CA, Bengele HH, Josephson L (1990) Ultrasmall superparamagnetic iron oxide: characterization of a new class of contrast agents for MR imaging. Radiology 175(2):489–493
60. Maeda M, Kuroda CS, Shimura T, Tada M, Abe M, Yamamuro S (2009) Magnetic carriers of iron nanoparticles coated with a functional polymer for high throughput bioscreening. J Appl Phys 99:98–103
61. Atanasijevic T, Shusteff M, Fam P, Jasanoff A (2006) Calcium-sensitive MRI contrast agents based on superparamagnetic iron oxide nanoparticles and calmodulin. Proc Natl Acad Sci U S A 103:14707–14712
62. Choolani M, Ho SS, Razvi K et al (2007) FastFISH: technique for ultrarapid fluorescence in situ hybridization on uncultured amniocytes yielding results within 2 h of amniocentesis. Mol Hum Reprod 13(6):355–359
63. Esposito A, Choimet JB, Skepper JN et al (2010) Quantitative imaging of human red blood cells infected with Plasmodium falciparum. Biophys J 99(3):953–960
64. Stosch R, Henrion A, Schiel D, Guttler B (2005) Surface-enhanced Raman scattering based approach for quantitative determination of creatinine in human serum. Anal Chem 77 (22):7386–7392
65. Lin D, Feng S, Pan J et al (2011) Colorectal cancer detection by gold nanoparticle based surface-enhanced Raman spectroscopy of blood serum and statistical analysis. Opt Express 19 (14):13565–13577
66. Feng S, Chen R, Lin J et al (2010) Nasopharyngeal cancer detection based on blood plasma surface-enhanced Raman spectroscopy and multivariate analysis. Biosens Bioelectron 25 (11):2414–2419
67. Chen Y, Chen G, Feng S et al (2012) Label-free serum ribonucleic acid analysis for colorectal cancer detection by surface-enhanced Raman spectroscopy and multivariate analysis. J Biomed Opt 17(6):067003
68. Lin J, Chen R, Feng S et al (2011) A novel blood plasma analysis technique combining membrane electrophoresis with silver nanoparticle-based SERS spectroscopy for potential applications in noninvasive cancer detection. Nanomedicine 7(5):655–663
69. Wang X, Qian X, Beitler JJ et al (2011) Detection of circulating tumor cells in human peripheral blood using surface-enhanced Raman scattering nanoparticles. Cancer Res 71 (5):1526–1532
70. de Barros AB, Tsourkas A, Saboury B, Cardoso VN, Alavi A (2012) Emerging role of radiolabeled nanoparticles as an effective diagnostic technique. EJNMMI Res 2(1):39
71. Colombo M, Ronchi S, Monti D, Corsi F, Trabucchi E, Prosperi D (2009) Femtomolar detection of autoantibodies by magnetic relaxation nanosensors. Anal Biochem 392:96–102
72. Lee SH, Lee H, Park JS et al (2007) A novel approach to ultrasensitive diagnosis using supramolecular protein nanoparticles. FASEB J 21:1324–1334
73. Tang S, Hewlett I (2010) Nanoparticle-based immunoassays for sensitive and early detection of HIV-1 capsid (p24) antigen. J Infect Dis 201:59–64
74. Ansari AA, Singh R, Sumana G, Malhotra BD (2009) Sol–gel derived nano-structured zinc oxide film for sexually transmitted disease sensor. Analyst 134:997–1002
75. Arya R, Dabral D, Faruquee HM et al (2019) Serum small extracellular vesicles proteome of tuberculosis patients demonstrated deregulated immune response. Proteomics Clin Appl 14 (1):e1900062
76. Bishwal SC, Das MK, Badireddy VK et al (2019) Sputum proteomics reveals a shift in vitamin D-binding protein and antimicrobial protein Axis in tuberculosis patients. Sci Rep 9:1036
77. Etheridge ML, Campbell SA, Erdman AG, Haynes CL, Wolf SM, McCullough J (2013) The big picture on nanomedicine: the state of investigational and approved nanomedicine products. Nanomed Nanotechnol Biol Med 9(1):1–14
78. Dilnawaz F, Acharya S, Sahoo SK (2018) Recent trends of nanomedicinal approaches in clinics. Int J Pharm 538(1–2):263–278

79. Ragelle H, Danhier F, Preat V, Langer R, Anderson DG (2017) Nanoparticle-based drug delivery systems: a commercial and regulatory outlook as the field matures. Expert Opin Drug Deliv 14(7):851–864
80. Panyam J, Labhasetwar V (2003) Biodegradable nanoparticles for drug and gene delivery to cells and tissue. Adv Drug Deliv Rev 55:329–347
81. Zhang Z, Tsai PC, Ramezanli T et al (2013) Polymeric nanoparticles-based topical delivery systems for the treatment of dermatological diseases. Wiley Interdiscip Rev Nanomed Nanobiotechnol 5:205–218
82. Lherm C, Muller RH, Puisieux F et al (1992) Alkylcyanoacrylate drug carriers: cytotoxicity of cyanoacrylate nanoparticles with different alkyl chain length. Int J Pharm 84:13–22
83. Cortesi R, Esposito E, Luca G et al (2002) Production of lipospheres as carriers for bioactive compounds. Biomaterials 23:2283–2294
84. Barenholz YC (2012) Doxil®—the first FDA-approved nano-drug: lessons learned. J Control Release 160:117–134
85. Petre CE, Dittmer DP (2007) Liposomal daunorubicin as treatment for Kaposi's sarcoma. Int J Nanomedicine 2:277–288
86. Glantz MJ, Jaeckle KA, Chamberlain MC et al (1999) A randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal methotrexate in patients with neoplastic meningitis from solid tumors. Clin Cancer Res 5:3394–3402
87. Rodriguez M, Pytlik R, Kozak T et al (2009) Vincristine sulfate liposomes injection (Marqibo) in heavily pretreated patients with refractory aggressive non-Hodgkin lymphoma. Cancer 115:3475–3482
88. Drummond DC, Noble CO, Guo Z, Hong K, Park JW, Kirpotin DB (2006) Development of a highly active nanoliposomal irinotecan using a novel intraliposomal stabilization strategy. Cancer Res 66:3271–3277
89. Hong K, Drummond DC, Kirpotin D (2016) Liposomes useful for drug delivery. U.S. Patent No. US20160030341 A1, 4 February 2016
90. Walsh TJ, Yeldandi V, McEvoy M et al (1998) Safety, tolerance, and pharmacokinetics of a small unilamellar liposomal formulation of amphotericin B (AmBisome) in neutropenic patients. Antimicrob Agents Chemother 42:2391–2398
91. Boswell G, Buell D, Bekersky I (1998) AmBisome (liposomal amphotericin B): a comparative review. J Clin Pharmacol 38:583–592
92. Soni G, Yadav KS (2016) Nanogels as potential nanomedicine carrier for treatment of cancer: a mini review of the state of the art. Saudi Pharm J 24:133–139
93. Jung T, Kamm W, Breitenbach A et al (2000) Biodegradable nanoparticles for oral delivery of peptides: is there a role for polymers to affect mucosal uptake? Eur J Pharm Biopharm 50:147–160
94. Oh JK, Drumright R, Siegwart DJ et al (2008) The development of microgels/nanogels for drug delivery applications. Prog Polym Sci 33:448–477
95. Panonnummal R, Jayakumar R, Sabitha M (2017) Comparative anti-psoriatic efficacy studies of clobetasol loaded chitin nanogel and marketed cream. Eur J Pharm Sci 96:193–206
96. Sharma A, Garg T, Aman A et al (2016) Nanogel-an advanced drug delivery tool: current and future. Artif Cells Nanomed Biotechnol 44:165–177
97. Mitsuyasu RT, Merigan TC, Carr A et al (2009) Phase 2 gene therapy trial of an anti-HIV ribozyme in autologous CD34+ cells. Nat Med 15:285–292
98. Prasad PN (2003) Introduction in biophotonics. Wiley, New York
99. Petrocca F, Lieberman J (2011) Promise and challenge of RNA interference-based therapy for cancer. J Clin Oncol 29:747–754
100. Foster DJ, Brown CR, Shaikh S et al (2018) Advanced siRNA designs further improve in vivo performance of GalNAc-siRNA conjugates. Mol Ther 26:708–717
101. Springer AD, Dowdy SF (2018) GalNAc-siRNA conjugates: leading the way for delivery of RNAi therapeutics. Nucl Acid Therapy 28:109–118

102. Nair JK, Willoughby JLS, Chan A et al (2014) Multivalent N-acetylgalactosamine-conjugated siRNA localizes in hepatocytes and elicits robust RNAi-mediated gene silencing. J Am Chem Soc 136:16958–16961
103. Bonoiu AC, Mahajan SD, Ding H et al (2009) Nanotechnology approach for drug addiction therapy: gene silencing using delivery of gold nanorod-siRNA nanoplex in dopaminergic neurons. Proc Natl Acad Sci U S A 106(14):5546–5550
104. Rodriguez M, Kaushik A, Lapierre L, Dever SM, El-Hagel N, Nair M (2017) Electro-magnetic nano-particle bound Beclin1 siRNA crosses the blood-brain barrier to attenuate the inflammatory effects of HIV-1 infection in vitro. J Neuroimmune Pharmacol 12(1):120–132
105. Bäumer S, Bäumer N, Appel N et al (2015) Antibody-mediated delivery of anti-KRAS-siRNA in vivo overcomes therapy resistance in colon cancer. Clin Cancer Res 21:1383–1394
106. Wilda M, Fuchs U, Wossmann W, Borkhardt A (2002) Killing of leukemic cells with a BCR/ABL fusion gene by RNA interference (RNAi). Oncogene 21:5716–5724
107. Brummelkamp T, Bernards R, Agami R (2002) Stable suppression of tumorigenicity by virus-mediated RNA interference. Cancer Cell 2:243–224
108. Liu J, Jiang B (2019) Sphk1 promotes ulcerative colitis via activating JAK2/STAT3 signaling pathway. Hum Cell 33:57–66
109. Manikkath J, Hegde AR, Kalthur G et al (2017) Influence of peptide dendrimers and sonophoresis on the transdermal delivery of ketoprofen. Int J Pharm 521:110–119
110. Duncan R, Izzo L (2005) Dendrimer biocompatibility and toxicity. Adv Drug Deliv Rev 57:2215–2237
111. Tomalia D, Baker H, Dewald J et al (1985) A new class of polymers: starburst-dendritic. Polym J 17:117–132
112. Mody V (2010) Dendrimers in medicine. Chron Young Sci 1:31–32
113. Understanding cancer series: nanodevices. Available from http://www.cancer.gov/cancertopics/understandingcancer/nanodevices/page21
114. Becker A. A student's view of nanotechnology. Available from http://www.nanoscience.cam.ac.uk/schools/articles/nanostudent.pdf
115. Augusta G, Gonçalves R, de Melo R, Paiva A (2017) Gene therapy: advances, challenges and perspectives. Einstein 15(3):369–375
116. DiGiusto DL, Krishnan A, Li H et al (2010) RNA-based gene therapy for HIV with lentiviral vector-modified CD34(+) cells in patients undergoing transplantation for AIDS-related lymphoma. Sci Transl Med 2(36):36–43
117. Choi IK, Li Y, Oh E, Kim J, Yun CO (2013) Oncolytic adenovirus expressing IL-23 and p35 elicits IFN-ɤ-and TNF-α-co-producing T cell-mediated antitumor immunity. PLoS One 8(7): e67512
118. Hernandez-Gea V, Toffanin S, Friedman SL, Llovet JM (2013) Role of the microenvironment in the pathogenesis and treatment of hepatocellular carcinoma. Gastroenterology 144:512–527
119. Baban CK, Cronin M, O'Hanlon D, O'SullivanG C, Tangney M (2010) Bacteria as vectors for gene therapy of cancer. Bioeng Bug 1(6):385–394
120. Ginn SL, Amaya AK, Alexander IE, Edelstein M, Abedi MR (2018) Gene therapy: clinical trials worldwide to 2017: an update. J Gene Med 20(e3015):1–16
121. Huli-Curtis SL, Uusi-Kerttula H, Jones R, Hanna L, Chester JD, Parker AL (2016) Evaluation of CD46 re-targeted adenoviral vectors for clinical ovarian cancer intraperitoneal therapy. Cancer Gene Ther 23:229–234
122. Ahn CH, Chae SY, Bae YH, Kim SW (2002) Biodegradable poly(ethylenimine) for plasmid DNA delivery. J Control Release 80:273–278
123. Wang DA, Narang AS, Kotb M, Gaber AO, Miller DD, Kim SW, Mahato RI (2002) Novel branched poly(Ethylenimine)-cholesterol water-soluble lipopolymers for gene delivery. Biomacromolecules 3:1197–1202
124. van der Meel R, Vehmeijer L, Kok RJ, Storm G, van Gaal EV (2015) Ligand targeted particulate Nano-medicines undergoing clinical evaluation: current status. In: Prokop A, Weissig V (eds) Intracellular delivery III. Springer, Cham, pp 163–200

125. Ginn SL, Amaya AK, Alexander IE, Edelstein M, Abedi MR (2018) Gene therapy clinical trials worldwide to 2017: an update. J Gene Med 20:3015
126. Havel HA (2016) Where are the nanodrugs? An industry perspective on development of drug products containing nanomaterials. AAPS J 18(6):1351–1353
127. Bansal S, Bansal M, Kumria R (2012) Nanocrystals: current strategies and trends. Int J Res Pharmaceut Biomed Sci 3:406–419
128. Bruchez M Jr, Moronne M, Gin P et al (1998) Semiconductor nanocrystals as fluorescent biological labels. Science 281:2013–2016
129. Bobo D, Robinson KJ, Islam J et al (2016) Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date. Pharm Res 33(10):2373–2387
130. Farjadian F, Ghasemi A, Gohari O, Roointan A, Karimi M, Hamblin MR (2019) Nanopharmaceuticals and nanomedicines currently on the market: challenges and opportunities. Nanomedicine (Lond) 14(1):93–126
131. Caster JM, Patel AN, Zhang T, Wang A (2017) Investigational nanomedicines in 2016: a review of nanotherapeutics currently undergoing clinical trials. Wiley Interdiscip Rev Nanomed Nanobiotechnol 9(1):1
132. Kim D, Kim E, Lee J et al (2010) Direct synthesis of polymer nanocapsules: self-assembly of polymer hollow spheres through irreversible covalent bond formation. J Am Chem Soc 132:9908–9919
133. Kobobothamasu P, Kanumur H, Ravur N et al (2012) Nanocapsules: the weapons for novel drug delivery systems. Bioimp 2:71–81
134. Feng M, Zhong LX, Zhan ZY et al (2017) Enhanced antitumor efficacy of resveratrol loaded nanocapsules in colon cancer cells: physicochemical and biological characterization. Eur Rev Med Pharmacol Sci 21:375–382
135. Shazly GA (2017) Ciprofloxacin controlled-solid lipid nanoparticles: characterization, in vitro release, and antibacterial activity assessment. Biomed Res Int 2017:1–9
136. Pinto JF, Muller RH (1999) Pellets as carriers of solid lipid nanoparticles (SLN) for oral administration of drugs. Pharmazie 54:506–509
137. Dingler A, Blum RP, Niehus H et al (1999) Solid lipid nanoparticles (SLNTM/Lipopearls TM) a pharmaceutical and cosmetic carrier for the application of vitamin E in dermal products. J Microencapsul 16:751–767
138. Videira MA, Almeida AJ, Botelho MF et al (1999) Lymphatic uptake of radiolabelled solid lipid nanoparticles administered by the pulmonary route. Eur J Nucl Med 26:1168–1168
139. Cavalli R, Gasco MR, Chetoni P et al (2002) Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin. Int J Pharm 238:241–245
140. Sznitowska M, Gajewska M, Janicki S et al (2001) Bioavailability of diazepam from aqueous-organic solution, submicron emulsion and solid lipid nanoparticles after rectal administration in rabbits. Eur J Pharm Biopharm 52:159–163
141. Souto EB, Müller RH (2008) Cosmetic features and applications of lipid nanoparticles. Int J Cosmet Sci 30:157–165
142. Freitas RA Jr (2005) Current status of nanomedicine and medical nanorobotics. J Comput Theor Nanosci 2:1–25
143. Drexler KE (1992) Nanosystems molecular machinery, manufacturing and computation. Wiley, New York
144. Zinger A, Adir O, Alper M et al (2018) Proteolytic nanoparticles replace a surgical blade by controllably remodeling the oral connective tissue. ACS Nano 122:1482–1490
145. Freitas RA Jr (2005) Microbivores: artificial mechanical phagocytes using digest and discharge protocol. J Evol Technol 14(1):54–106
146. Hsu WK, Goldstein CL, Shamji MF et al (2017) Novel osteobiologics and biomaterials in the treatment of spinal disorders. Neurosurgery 80(3S):S100–S107
147. Ganau M, Holly LT, Mizuno J, Fehlings MG (2018) Future directions and new technologies for the management of degenerative cervical myelopathy. Neurosurg Clin N Am 29 (1):185–193

148. Olivares-Navarrete R, Hyzy SL, Slosar PJ, Schneider JM, Schwartz Z, Boyan BD (2015) Implant materials generate different peri-implant inflammatory factors: poly-ether-ether-ketone promotes fibrosis and microtextured titanium promotes osteogenic factors. Spine 40 (6):399–404
149. Gusić N, Ivković A, VaFaye J et al (2014) Nanobiotechnology and bone regeneration: a mini-review. Int Orthop 38(9):1877–1884
150. Serra G, Morais L, Elias CN et al (2013) Nanostructured severe plastic deformation processed titanium for orthodontic mini-implants. Korean J Couns Psychother 33(7):4197–4202
151. Ure D, Harris J (2003) Nanotechnology in dentistry: reduction to practice. Dent Update 30:10–15
152. Rathi S, Verma A (2018) Nanoscale modifications of dental implants: an emerging trend. Int J Appl Dental Sci 4(2):149–153
153. Bressan E, Sbricoli L, Guazzo R, Tocco I, Roman M, Vindigni V et al (2013) Nanostructured surfaces of dental implants. Int J Mol Sci 14(1):1918–1931
154. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/results?term=nano&Search=Apply&recrs=a&recrs=d&age_v=&gndr=&type=&rslt=
155. Centre Watch. https://www.centerwatch.com
156. Sainz V, Conniot J, Matos AI et al (2015) Regulatory aspects on nanomedicines. Biochem Biophys Res Commun 468(3):504–510
157. Elsaesser A, Howard CV (2012) Toxicology of nanoparticles. Adv Drug Deliv Rev 64:129–137
158. Wolfram J, Zhu M, Yang Y et al (2015) Safety of nanoparticles in medicine. Curr Drug Targets 16(14):1671–1681
159. Ventola CL (2017) Progress in nanomedicine: approved and investigational nanodrugs. P&T 42(12):742–755
160. Pathak YV (2019) Surface modification of nanoparticles for targeted drug delivery. Springer, Cham
161. D'Mello SR, Cruz CN, Chen ML, Kapoor M, Lee SL, Tyne KM (2017) The evolving landscape of drug products containing nanomaterials in the United States. Nat Nanotechnol 12:523–530