Chapter 2
Nanomedicine: Insight Analysis of Emerging Biomedical Research and Developments

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2.1 Scope of Nanomedicine

The concept of "nanomedicine," first put forth by Freitas in 1993, was used to describe the observations, control, and treatment of biological systems of human physiology at molecular level using nanodevices and nanostructures (Freitas, 2000). With advances in research, nanomedicine (NM) has evolved to enable the diagnostics, therapeutics, and prevention of various disorders and ailments. The wide-ranging applications of nanotechnology (NT) in different industrial advancements are attributed to the novel physicochemical properties of nanoparticles (NP) like smaller size and larger size: charge ratio enhancing their efficiency when compared to other larger compounds. Numerous examples of NT can be enlisted in the field of drug design and delivery, owing to the superior specificity toward target molecules, larger size: charge ratio, reduced toxicity toward nonspecific tissues, use of "green synthesis" techniques, and so on. But on the downside, the physicochemical properties of nanoformulations have certain drawbacks like alterations to pharmacokinetics of absorption, distribution, metabolism, and elimination, the potential to cross biological barriers and persistence in human body and environment. NPs are predominantly utilized in medical applications in three areas, i.e., nanodiagnosis, nanotherapy (drug delivery), and regenerative medicine in addition to theranostics. Nanoformulations have recently been applied in treating neuropathic pain and are being tested in clinical trials, in addition to few of these formulations that have obtained FDA approval for commercialization (Ventola, 2017). Novel properties of NM include integration of effective molecules that otherwise

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possess high toxicity, utilization of multiple mechanisms of action, maximization of efficiency, reduction in dosage and toxicity, and enabling controlled and targeted drug delivery combined with site-specific release. NP possesses high surface area: volume and consequently a high particle surface energy. This renders them more reactive and enables them to readily absorb biomolecules like proteins, lipids, and so on (Soares et al., 2018). Organic NPs have been known to be easily degradable into their elemental forms, thus eliminating any cytotoxic effects, and in animal trials they have been proven to be tolerable (Kuthati et al., 2020). Hence, NM encompassing a thorough understanding of pathology and diagnostics will provide efficient and effective ways to alleviate problems associated with diagnostic and therapeutic techniques.

2.1.1 Nanomedicine: R&D in Prophylaxis

Nanovaccines (NVs) are made up of polymers, macromolecules, and metals and they can be designed to interact with immune cells like B cells, phagocytic cells, etc. (Zaheer et al., 2021). Some NPs can carry antigens or immunostimulatory molecules encapsulated or as a structural element of the particle itself; however, the majority of NVs have antigens of interest coated on their surface, which allows for direct interaction with B-cell receptors (Facciola et al., 2019). In recent times, the rate of virus mutations is so high, and thus rapid development of vaccines is necessary against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Compared to nucleic acid vaccines, subunit vaccines have less safety concerns and they also showed good results in clinical trials (Chen et al., 2020). In a recent study, biodegradable silica NP encapsulated with CpG (cytosine-phosphate-guanine oligodeoxynucleotide) and coated with genetically engineered cell membrane, containing SARS-CoV-2 receptor binding domain (RBD), was used as a vaccine. After extensive studies, the specific vaccine was administered to mice to initiate immunization. After receiving this NV, they exhibited strong immune defenses and high titers of SARS-CoV-2 neutralizing antibodies. Also, using a flash nanocomplexation technique, the mass production of this vaccine was possible (Chen et al., 2022).

Another study was done by designing a nasal NV which can be inhaled against COVID-19. This vaccine to a greater extent mimics the structure of SARS-CoV-2 and promotes better mucosal immunity (Zheng et al., 2021). The vaccines which brought us hope in the midst of COVID-19 pandemic were BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna). Lipid NPs were used in these two vaccines as nanocarriers. These nanocarrier-based vaccinations demonstrate the significance of NT and the power of nanoscale delivery systems to shield payloads from deterioration and to deliver drugs directly to cells (Khurana et al., 2021). In another study, gold NPs were used as an antigen carrier and also as an adjuvant of recombinant S protein (spike protein) present in the spikes of SARS-CoV virus. Gold NP adjuvanted protein showed a very high immune response (IgG) (Sekimukai et al., 2020).

Even after the century-old BCG vaccination routine, TB remains as one of the topmost infectious diseases. In a study, BCG-primed mice were immunized with Ag85B CD4+ T cells, coated in peptide nanofibers (PNFs). After the immunization there was a steep increase in antigen-specific T cells along with resident memory (Trm) and effector memory (Tem) cells and also cytokines (Megan et al., 2022). An intranasal vaccine was developed against *Mycobacterium* based on a goal to create mucosal protection and thus prevent the infection at the site of entrance. In this study polymeric nanocapsules (NCs) were used with a chitosan polymer shell and an oily core. A Toll-like receptor-7 (TLR-7) Imiquimod, which is an immunostimulant, was encased in the oily core, and a fusion protein made with two antigens was expressed in the NC surface. This study was successful after trials in mice but prior immunization with BCG showed heightened immune response was observed (Diego et al., 2022). Johne's disease caused by *M. avium* subsp. *paratuberculosis* affects ruminants and is a major reason for economic losses in the dairy industry. A novel polyanhydride NP-based vaccine was designed against this bacterium with a core composed of cell lysate and culture filtrate. Immunization in mice was successful with no inflammatory lesions and sizable increase in T cell responses, cytokines, etc. (Thukral et al., 2020).

Infections caused by *Pseudomonas aeruginosa* are challenging because of the drug resistance these strains exhibit. Engineered mesoporous silica nanospheres (MSNs) containing cytosolic and membrane antigens from PAO1, which is a drug-resistant *P. aeruginosa* strain, were used as vaccines without any additional adjuvants. The vaccine showed a notable increase in humoral and cellular immune response in mice and protected them from drug-resistant *Pseudomonas* (Guo et al., 2022). Influenza is a persistent health hazard that causes high morbidity and mortality rate. Due to frequent changes and drifts in antigens, the efficacy of vaccines is limited to only 10–60%. A biepitope NV was discovered recently, which showed full protection against H3N2 and H1N1 viruses. The vaccine contained two conserved epitopes (M2e and CDhelix) expressed on the ferritin surface. Subcutaneous injection in mice with this vaccine showed a rise in humoral and cellular response (Qiao et al., 2022).

The Zika virus spreads through the bite of infected *Aedes* mosquitoes and this disease is creating a threat to humans, leading to epidemics. Therefore, the efficient development of vaccines is a challenge. In a recent study, a self-assembling NV was constructed with complete protection against Zika virus infection. zEDIII, a Zika virus envelope protein domain III, was expressed on recombinant human heavy chain ferritin NPs (rHF). Without any adjuvants, this zEDIII-rHF vaccine showed a remarkable upshoot in both humoral and cellular immune responses in mice. Another advantage of this vaccine is that it does not counteract with the dengue virus-2, thus overcoming the antibody-dependent enhancement (ADE) problem, which was a safety issue in Zika virus development (Rong et al., 2022). To better tackle infectious diseases and malignancies, NVs can enhance targeted delivery, antigen presentation, stimulation of the body's innate immunity, strong T cell response, and safety. Various modes of NV strategies against superbugs have been explored (Santhosh et al., 2022). Future objectives of ideal NVs include more logical design, enhanced antigen loading, extended functionalization, and targeted administration (Das & Ali, 2021).

2.1.2 Nanomedicine: R&D in Diagnostics

The use of NPs help address the quantum confinement effect. This is demonstrated with the blue shift with widerenergy gaps and more discrete energy levels, increasing the distance between the ground state and the excited state (Malhotra & Ali, 2018). They can be visualized by acting as probes or being labeled as probes while frequently acting as biosensors due to antigen-antibody reactions, allowing the diseases to be identified in the primitive stages on the basis of their biochemical markers. Based on sizes, NPs can be classified as zero-, one-, two-, and three–dimensional particles. A zero-dimensional particle includes quantum dots and metal NPs; one-dimensional particle includes nanomaterials made of metals like gold, palladium, etc.; A zero-dimensional particle includes quantum dots and metal NPs; one-dimensional particle includesnanomaterials made of metals like gold, palladium, etc.; two-dimensional particles which are bifacial, includes oneside on the nanoscale and the other in macro scale and three-dimensional particle includes bulk NPs composed of individual nanoblocks. As mentioned earlier, several modifications can be made to the NPs for them to be visualized or for them to act as biosensors. The fact that they have a large surface area makes them ideal candidates for the immobilization of larger biomolecules and as efficient biosensors. Microfluidic analyses have revealed that, by virtue of the association with groups complementary to the target biomolecules, NPs can be quite efficient. For the synthesis of these bioparticles, a signal transducer, bioreceptor, a signal processor, a site to display, and biocompatibility of the parts are essential. Precisely designed NPs can detect a multitude of diseases at initial stages itself, even with only a miniscule amount of the target binding biomolecule.

Meanwhile, NPs with high contrast can be efficient when it comes to functional and molecular imaging. NPs of sizes ranging from 5 to 100 nm are highly efficient when it comes to visualization for diagnostic purposes (Kiessling et al., 2014). Being of smaller size and capable of bonding to functional groups, they are more specific and have less noise during visualization. They have a long half-life and can be efficiently transported through the reticuloendothelial system, which helps in locating the disease or tumor site. Liposomes, iron oxide NPs, and gold NPs are examples of efficient contrast agents, supporting visualization at a nanoscale. Quantum dots are semiconductors which upon exposure to UV light shift to a higher energy level, demonstrating optical and electronic properties which can be visualized, aiding in diagnosis. They help to redimension the magnitude of the scale, allowing for ease in diagnosis at a molecular level. Iron oxide and other metal NPs can be put into resonance with the magnetic NPs. Interesting properties of iron oxide NPs however are superparamagnetic characteristic and low toxicity, making them ideal for diagnosis as well as treatment. This indicates that they display magnetic properties upon exposure to an external magnetic field allowing for MR-based imaging (Thorek et al., 2006). By increasing the specificity and precise synthesis of NPs, multimodal imaging using various techniques such as optical, MRI, CT, and PET is possible, some of which are listed in Table 2.1.

Table 2.1 Applications of nanoparticles in the molecular diagnostics of diseases

Sl no	Disease name	Disease biomarker detected	Type of nanoparticle	Method of visualization	Reference
1.	HIV	CD4+ cells produced during the infection	Nanobiosensor like NPs and QDs	Biosensor that allows for real-time ligand-receptor interaction	Farzin et al. (2020)
2.	Sepsis	C reactive protein and procalcitonin	Metal, magnetic, or lipid-based NPs	Colorimetric & electrochemical detection and magnetic separation respectively	Lim et al. (2021)
3.	Coronary artery disease	Fibrin deposition accompanied with tissue factor	Metallic-like iron oxide NPs	In vivo by ultrasound and in vitro by MRI	Lanza and Wicklin (2003)
4.	SARS-CoV-2 2	Presence of the N gene in the virus	Gold NPs with oligonucleotide dual-function biosensor	Plasmonic photothermal effect and localized surface plasmon resonance (LSPR) sensing transduction	Talebian et al. (2020)
5.	Traumatic brain injury	Plasma levels of ubiquitin-C-terminal hydrolase-L1 (UCH-L1)	Gold NPs	By high-resolution microscope or by fluorescence microscope or Raman spectroscopy	Liao et al. (2012)
6.	Alzheimer's	Aβ peptides τ (Thr181 and Thr231) proteins in varied levels between CS fluid	Iron oxide NPs	PET to view amyloid plaque, MRI for visualization of alpha beta aggregation along with morphological and structural modification	Luo et al. (2020)
7.	Brain tumor	Uptake of particle CD11b + cells and primary tumor cells	Multimodal NP CLIO-Cy5.5	Fluorescence and MRI	Kumar and Das (2017)
8	Cardiovascular disease	Myoglobin and cardiac tropin 1	NDs in HsGDY	Real-time detection through label-free visualization	Wang et al. (2021)

2.1.3 Nanomedicine in Therapeutics

Physicochemical characteristics such as particle size (>100 nm), shape (rod, sphere, wire, sheets), and chemical composition enable these nano-sized compounds to attain their function (Yetisgin et al., 2020). Since nanodrugs can move through the blood vessels and lymphatic vessels throughout the body, they can easily bind to the target site. Major goals in nanomedical research are (i) targeted drug delivery, (ii)

site-specific drug delivery, and (iii) designing of biocompatible nanocompounds (Bawarski et al., 2008).

2.1.3.1 Nanomedicine in Drug Delivery

NM can be delivered intracellularly through oral, buccal, intravenous, and subcutaneous routes (Sultana et al., 2022). Intracellular transport of NM facilitates its absorption, diffusion, and excretion. NM coated with surfactants and polymers degrades after the NM is absorbed by the cell surface (Patra et al., 2018). NPs coupled with proteins or antibodies open at the specific tight junctions where the permeability of the drug is easier. Anticancer drugs capped with NPs are also studied to bind with the target sites making the drug release and treatment easier (Liu et al., 2021). The enhanced permeability and retention property of the NP help them to transmit the NM directly at the target tissues by combining with polysaccharides, antigens, enzymes, or peptides. Internal and external stimuli also trigger some of the NP which helps in releasing the drug at the target site. Magnetic and electric fields developed by the NP also release the drugs to gather at the target site for target-specific action (Mullner, 2022).

2.1.3.1.1 Polymer-Based Nanoparticles

Biodegradable polymers include natural polymers like chitosan, alginate, gelatin, and albumin and synthetic polymers like poly D,l-lactide (PLA), poly D,l glycolide (PLG), polylactide-co-glycolide (PLGA), etc. The wide availability and the stability of the biopolymeric NP together with the body fluids is a characteristic of polymeric NP. The therapeutic agents will be coated at the surface of the polymer, and on entering the body fluids, the drugs will be released and the polymer degrades to monomers and polymers further leading to adsorption (Naki & Aderibigbe, 2022). NP coated with polyethylene glycol (PEG) is widely studied to increase the circulation of NP through blood. Polymer-based NP includes dendrimers, polymeric NP, micelles, drug conjugates, protein NP, and nanogels. The main disadvantages of polymeric NP include its high cost, complex preparation method, and agglomeration in blood streams (Ebhodaghe, 2022).

(a) Dendrimers—Dendrimers are nano-sized artificial macro molecules designed by a combination of a large number of functional groups with a dispersed structure (Marwah et al., 2022). Biological properties like nontoxicity, stability, self-assembling, electrostatic interaction, solubility, etc., make them compatible in the field of NM. Dendrimers also have the property of controlled drug delivery, making them a potential platform for drug delivery. Dendrimers are used in transdermal drug delivery and gene delivery. Dendrimers functionalized with vitamins, proteins, and antibodies improve biocompatibility further increasing site-specific drug delivery (Seidu et al., 2022).

(b) Micelles—Polymeric micelles are spherical shell-shaped NPs formed by self-assembly of polymers in aqueous solution (Jhaveri & Torchilin, 2014). The small size (30–100 nm), shapes (cylindrical, spherical, bilayer), and solubility property make the polymeric micelles a good candidate for drug administration. Polymeric micelles act as an efficient drug carrier for poorly water-soluble drugs. Advantages of micelles include reduced side effects of the drug encapsulated, easy to scale up the preparation, longer circulation time due to hydrophobic moieties, etc. A drawback of polymeric micelles is the sudden rupture of the micelles due to low molecular weight, where the drugs are released before reaching the target site. Thermosensitive micelles are used in drug delivery where structural changes occur due to thermal stimuli leading to the release of drug (Khot et al., 2022).

(c) Protein NP—Natural bio-molecules such as proteins are used as an alternative for polymers in developing nanodrug formulation (Habibi et al., 2022). The biocompatible, biodegradable, availability in natural environment, easy synthesis process, and cost-effectiveness of the proteins gives the advantage of using them in drug delivery. Protein NPs are delivered intracellularly through endocytosis. Different proteins including silk protein fibroin, human serum albumin, gelatin, legumin, lipoprotein, ferritin, etc., are used as nanocarriers (Li et al., 2022). Protein NPs are used to deliver genetic materials, anti-cancer drugs, growth factors, etc. Compared with other NPs, protein NPs are nontoxic and enable targeted drug delivery to tissues and organs. NMs from natural compounds are also studied for the treatment against cancer, diabetes mellitus, neurodegenerative diseases, etc., which has to studied further. Proteins and peptides of therapeutic importance are clustered to form nanoclusters for drug delivery (Danielsen et al., 2022).

(d) Nanogel—NGs are cross-linked polymeric NP or hydrogels with 3-D property, which are used as drug carriers (Shah et al., 2020). NGs are highly stable, permeable, and environment friendly. NGs encapsulated with hydrophilic or hydrophobic drugs can produce responses to temperature pressure and to stimulus. NGs encapsulation includes conjugation, self-assembly, physical entrapment, etc. NGs doped with ligands are developed for achieving targeted drug delivery where the ligands directly bind to the protein at the target site. Drug release from the NGs includes diffusion, ion movements, pH, and thermosensitive techniques (Sindhu et al., 2022).

(e) Nanofibers—Nanofibers are developed using electrospinning techniques and are studied for its therapeutic application (Odularu, 2022). The fundamental principle of NPs is that higher the surface area of the drug carrier, faster is the drug dispersal. Polymers coated with therapeutics are woven as fibers and are used in wound healing as the drug is having direct contact with the wound and healing occurs. Antifungal nanofibers are also used in wound healing function. Table 2.2 shows the use of different types of NP in therapeutics.

Table 2.2 Application of polymeric nanoparticles in therapeutics

Types of Nanoparticles	Size	Compounds used for therapeutics	Application	References
Dendrimers	1–5 nm	Poly(amidoamine) dendrimer Tryptophan-rich peptide dendrimer	Antibacterial activity Tumor therapy	Chauhan et al. (2020)
Micelles	>100 nm	Micelles with polyesteramide and poly(urea-urethane) PEGylated uricase micelles	Anticancer therapeutics Treatment of gout	Majumder et al. (2020)
Drug conjugates	>100 nm	Polyethylene glycol with cisplatin, carboplatin PEG-Embelin conjugate	Cancer-targeted drug delivery Antidiabetic, anti-inflammatory	Manandhar et al. (2021)
Protein nanoparticles	>100 nm	Gelatin nanoparticles Gliadin nanoparticles	Anti-cancer drugs, anti-AIDS drugs, antimalarial drugs Gastric diseases	Kianfar (2021)
Nanogels	>100 nm	Alginate (ALG) nanogel Paclitaxel nanogel	Antitumor activity Hepatocellular carcinoma Chemo immunotherapy	Yin et al. (2020)
Nanosponges	>1 μm	Curcumin nanosponges	Tumor treatment	Tiwari and Bhattacharya (2022)

2.1.3.1.2 Lipid-Based NPs

Lipid-coated NPs are considered more efficient than polymeric NP. Physiological and biodegradable lipids carriers are used as nano-safe carriers of drugs. Surface modification of the lipid NP using carbohydrates is also used in drug delivery technology (Gagliardi et al., 2021). Lipid-based NPs are used for the delivery of various biomolecules like enzymes, hormones, ribozymes, nucleic acids, and mRNAs.

(a) Solid-lipid NPs—Solid-lipid NPs have solid matrices ranging in size from 1 to 1000 nm. They are spherical, pellet, rod, or anisotropic in shape (Hamid & Manzoor, 2020). Lipid NPs are studied extensively in gene delivery, cancer therapy, protein, peptide therapy, etc. They are studied as oral drug delivery systems where rifampicin, isoniazid, and pyrazinamide-loaded nanodrugs for tuberculosis and camptothecin and tamoxifen for cancer are examples (Shirodkar et al., 2019). Lipid NPs are also studied in brain drug delivery where the particles easily pass through the blood-brain barrier. Solid-lipid NPs containing cationic lipids serve as a reservoir for hydrophobic drugs and the positively charged lipids enable cellular intake of drugs, which helps in blood-

brain penetration. Drug leakage, drug storage, and crystallization of the NP are the major drawbacks.

(b) Liposomes—These are vesicles made of one or more phospholipid bilayer with an aqueous pore at the center. Liposomes are nontoxic and biodegradable with a size of 100 nm to 5 μm (Lamichhane et al., 2018). The phosphor lipid layers of the liposomes are arranged in an order that both hydrophobic and hydrophilic molecules can bind to the liposomes. The most important advantage of liposomes is to bind itself with the cell membrane and release the drug into the cytoplasm which can be used for targeted drug delivery. Another advantage of liposomes is that more than one type of drug can be attached with the different layers of liposomes. Liposomes coated with drugs are studied to travel through the blood-brain barrier and release the drug at the target site (van der Koog et al., 2022). Liposomes are studied extensively for their therapeutic application for brain-targeted drug delivery, as vaccines, and in cancer diagnostics.

(c) Exosomes—These are extracellular vesicles of 30–150 nm size and are found in breast milk, saliva, urine, and blood (Pegtel & Gould, 2019). The vesicles isolated from the body fluids are studied to improve targeted drug delivery since the cells have an advantage over immune systems. Exosomes are studied to deliver drugs for autoimmune disease, cancer, and tissue regeneration.

(d) Virus-like particles—VLPs are nonreplicative, noninfectious proteins originated from viruses (Tornesello et al., 2022). Virus-like particles encapsulate molecules like nucleic acid and other drug compounds for drug delivery application. Hepatitis B virus cores are highly efficient NPs ranging from 30 to 34 nm in diameter for drug delivery. VLP vaccines were studied against Epstein-Barr virus-related cancer, cancer caused by T-lymphotropic virus, and cancer caused by human HPV.

2.1.3.1.3 Nonpolymeric Nanoparticles

(a) Carbon Nanotubes—CNTs are made of carbon compounds having tubular structure with a particle size of 1 nm in diameter and 100 nm in length. CNT is formed as multiwalled, single-walled nanotubes and C60 fullerenes (Kazemzadeh & Mozafari, 2019). The nanotubes enter cells by endocytosis or through insertions in cell membranes. C60 fullerenes are studied for their ability to protect mitochondria as they release free radicals, which is considered a positive property to use them as an agent for targeted drug delivery (Kaur et al., 2019). CNTs are studied for their ability to deliver antibiotics, antiviral drugs, and cancer drugs. Surface-functionalized nanotubes are used to deliver therapeutic materials at specialized target sites.

(b) Metallic NPs—Metallic NPs (1–100 nm in size) made of gold, iron, nickel, cobalt, and its oxides are synthesized with an outer functional group so that the therapeutic agent can be bound to the functional group (Kovács et al., 2022). Since these compounds have magnetic properties, they are used for diagnostic purposes. Many such NPs have been explored as having multiple modes of

antibacterial activity too (Sarojini & Jayaram, 2021). Gold NPs are widely used in cancer therapy and diagnostics as they are relatively less cytotoxic and targeted to tumor tissues to kill cancer cells using its photothermal therapeutical characteristics which in response to light or magnetic stimuli were studied for controlled drug release (Clasky et al., 2021).

(c) Quantum dots—These are NPs with 2–10 nm in diameters and are made with a semiconducting material (Campbell et al., 2021). They are made of inorganic core and aqueous outer shell. The outer shell is used to conjugate biomolecules. Quantum dots are highly toxic on exposure to UV light or aqueous regions which is considered as a major drawback in therapeutic research.

(d) Silica-based NPs—Silica NPs have high surface area, have larger pore size ranging from 2 to 50 nm, are biodegradable, and exhibit aqueous dispersal property, which make them a good drug carrier (Trzeciak et al., 2021). Poorly water-soluble drug camptothecin (cancer drug) incorporated with silica mesoporous NPs was used for targeted drug delivery resulting in apoptosis of cancerous cells. Mesoporous silica NPs are biocompatible with high loading capacity with targeted drug delivery capacity.

2.2 Nanoparticles in Cancer Diagnosis

Early-stage detection is of paramount significance for successful cancer therapy, which can lead to a drastic reduction in cancer-related mortality (Zhang et al., 2019). The large surface area and volume ratio make NPs an excellent material for cancer detection compared to bulk material. Due to their adaptability and affordability, NT-based solutions are presently being created and developed as a viable tool for real-time cancer diagnosis and detection (Chen et al., 2018). NPs can be easily surface functionalized with functional groups, making cancer diagnosis more efficient (Chaturvedi et al., 2018). Figure 2.1 shows some of the applications of biosensors in the field of medicine.

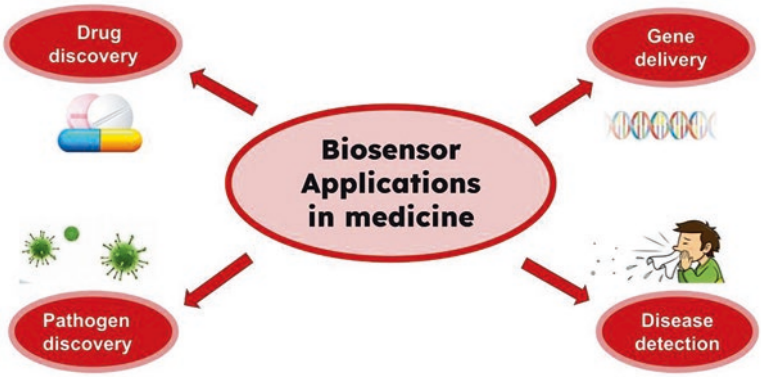

Fig. 2.1 Applications of biosensors in the field of medicine

2.2.1 Nanoparticles in Bioimaging/Biosensing

Early disease identification and development of novel treatments are made possible by biosensing and bioimaging techniques, which enable researchers to visualize the internal structures and investigate the physiological processes of living systems at molecular level (Pu, 2019). They are particularly useful for examining the dynamics of tumor progression by locating tumor sites, characterizing cell phenotype, and visualizing key biological processes using cell composition and other indicators inside the tumor microenvironment (Chung et al., 2021). An analyte-binding input modality and a detectable output modality are both included in a biosensor (Yur et al., 2021). Optical imaging (fluorescence (FL), two-photon FL, and Raman imaging) (Berckman & Chen, 2020), PET/SPECT (positron emission tomography/single-photon emission computed tomography) (Cui et al., 2018), MRI (magnetic resonance imaging) (Wu & Huang, 2017), PAI (photoacoustic imaging) (Lemaster & Jokerst, 2017), and multimodal imaging CT (computed tomography) represent some of the molecular imaging techniques currently adopted using NPs (Lin et al., 2016). Each bio-imaging strategy is distinct and has its own set of benefits and drawbacks. As a result, single imaging will not meet the requirements. To overcome the issue a series of modulation imaging for visualization is being researched (Rostami et al., 2019). Biomedical imaging probes based on inorganic NPs have been intensively researched as a potential alternative to conventional molecular imaging probes. They have better adaptability in terms of enhanced multimodal, stimuli-responsive, and targeted imaging performance. Revolutionary findings in the field of imaging probes have led to excellent molecular and subcellular bioimaging (Kim et al., 2018).

2.2.2 Nanoparticles in Drug Delivery

One important area of NT with many potential applications in the field of cancer research is the delivery of drugs and the targeting of malignant cells using a variety of nano-based biomaterials (Limeres et al., 2019). The drug nanocarrier system is versatile as it enhances cancer treatment efficiency, selectively raises the number of drugs accumulated within target tumor cells, and reduces therapeutic agent toxicity in neighboring cells. Nanocarriers are highly soluble, capable of transporting a wide range of medications, have an expanded surface area, and can be used for a variety of delivery methods (Khodabandehloo et al., 2016). The difficulty for the drug delivery system is to deliver drug molecules exactly at the target region without harming healthy cells (Yaqoob et al., 2020).

Two targeting techniques—active targeting and passive targeting—are used to deliver NPs to the tumor tissue. Enhanced permeation and retention effect (EPR) is the phenomenon in passive targeting. The most promising and efficient method for increasing the specificity of the NPs is termed “active targeting” (Ingle et al., 2017).

Due to their optical, mechanical, electrical, and thermal properties, several carbon-based nanomaterials (CNMs) have recently attracted significant research interest in the development of cancer treatments. They are more biocompatible and safer than metal-based nanomaterials (Kumari et al., 2016). These CNMs can be functionalized, either covalently (chemical bond formation) or noncovalently (physio adsorption), as per the requirement, to make them biocompatible (Clemons et al., 2018).

Photodynamic therapy (PDT) is used to treat abnormal cells in the presence of light. Earlier, Eosin was used as a photosensitizer for tumors which developed cytotoxicity and skin damage. The issue was addressed by introducing hematoporphyrin as a photosensitizing agent, which acts as a carrier too. The superior high mechanical strength, optical properties, low toxicity, and biocompatibility have made carbon-based nanomaterials a potential material in PDT (Bhattacharya et al., 2016). NPs are an effective material in PDT because of their distinctive properties as carriers, sensitizers, energy transducers, or enhancers for reactive oxygen species (ROS) formation. Compared to other therapeutic techniques, PDT is considered less harmful to healthy cells. Metal-organic frameworks are yet another class of nanomaterials used in PDT. These highly flexible hybrid structures are designed from metal ions or clusters using organic linkers. In order to increase blood flow time and improve their ability to target tumors, MOF NPs are loaded and altered (van Straten et al., 2017).

Another technique used for the cancer treatment is photothermal therapy (PTT), in which near-infrared radiations are used. In this therapeutic technique, radiations are used to inflict heat for damaging the cancer cells (Fig. 2.2). PTT uses photothermal

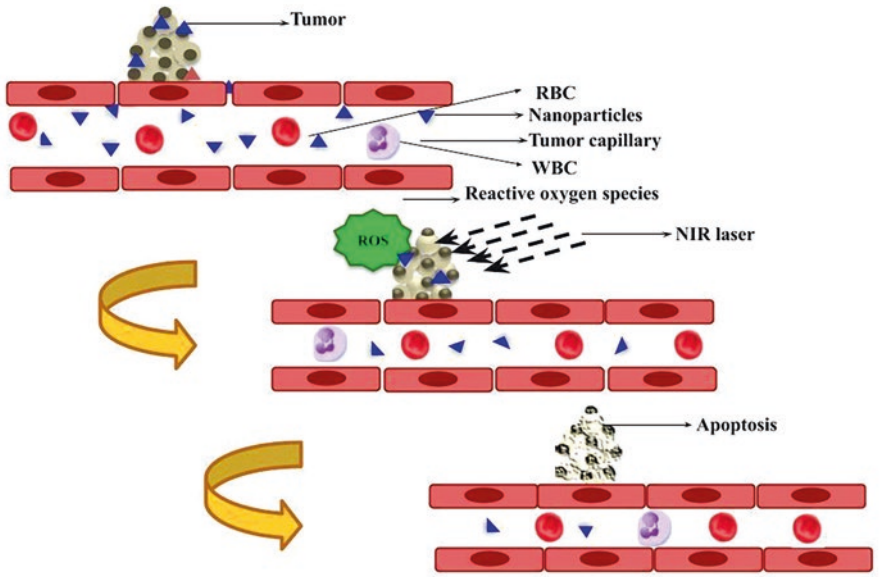

Fig. 2.2 Schematic illustration of PTT mechanism

agents (PTAs) with high PT conversion efficacy to convert light to heat using NIR (Lucky et al., 2015). The anticancer effects of FA-GO/SF (folic acid (FA)-conjugated polyvinyl pyrrolidone functionalized graphene oxides) were improved by the photothermal effect while exposing GO to near-infrared irradiation (Babu et al., 2022). FA-GO transforms it into an anticancer drug carrier capable of pharmacological and photothermal effects. Gold NPs and CNTs have attracted interest recently for potential PTT applications. A two-step reduction technique was used to create the hybrid of gold nanostars and MWCNTs. The biocompatibility of these hybrids exhibited high photothermal efficiency compared to the gold nanostars (Zou et al., 2016).

2.3 Challenges in Nanomedicine R & D

NM has potential advantages such as the delivery of NP-based drugs, vaccine delivery, and cell-based diagnosis. Research and development in this field has greatly enhanced NP-based screening, diagnosis, and treatment of diseases (Kargozar & Mozafari, 2018). However, very few NP-based drugs get clinical approval to use because of challenges at different stages in drug development.

The safety challenges arise when nanotherapeutics interact with the body once it enters the bloodstream, extracellular matrix, cell organelles and cytoplasm. Different NMs require different pharmacokinetic parameters that are very different from the commercially available drugs. Thus, there remains a lack of proper methods and standards to evaluate the safety of nanodrugs. In recent years, researchers are addressing toxicity issues of nanodrugs for human health. These NMs upon interacting with intracellular organelles, proteins, polysaccharides, and enzymes may alter their signaling pathways, complicating the safety issues. Thus, the development of standard tests for toxicity evaluation of NM becomes the need of the hour (Wu et al., 2020; Zhang et al., 2020).

Scale-up issues—For clinical and pre-clinical studies of NM, only a small amount of product is needed; thus, robustness and effectiveness can be maintained in small-scale production of the nanodrugs. On the other hand, large-scale production of nanodrugs shows polydispersity and changes in physical and chemical properties such as drug composition, size, surface charge, crystallinity, and therapeutic outcomes of nanodrugs, thus compromising the stability in manufacturing process. Methods for synthesis and characterization of nanoformulations and upscaling their production remains a time-consuming and costly affair (Metselaar & Lammers 2020; Zhang et al., 2020).

Biological Challenges—First challenge is the increased biodistribution of nanodrugs to target sites such as cells and tissues and reduced accumulation in healthy tissues. Secondly, the interaction between nanodrugs and biological barriers such as cells, skin, organs, etc., may interfere with the drug delivery system thereby, affecting the efficiency and stability of nanotherapeutics. The understanding of nano-bio interactions with the goal of overcoming and transporting the nanodrugs to target sites is the need of the hour. Another problem is the storage of NM leads to loss of its stability. The nanomaterials used in the preparation of NM are usually

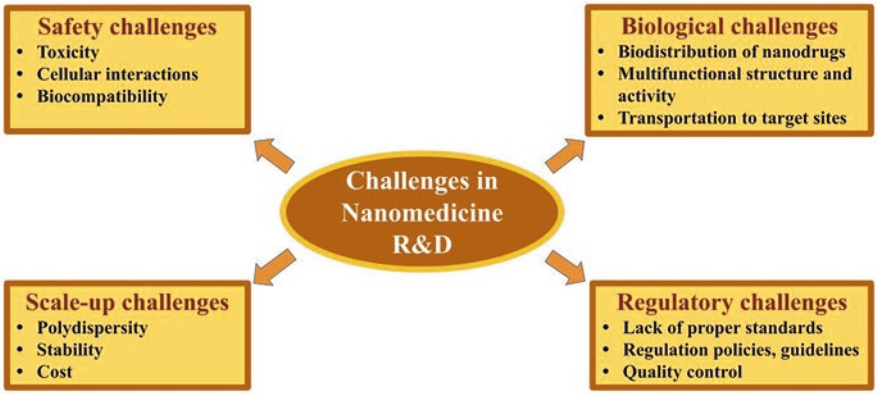

Fig. 2.3 Schematic representation of challenges faced in nanomedicine R&D

biodegradable, so while storing, its property could alter (Wu et al., 2020; Abdel-Mageed et al., 2021).

Regulatory Challenges—Regulations laid down by FDA and EMA (European Medicines Agency) are very different and change from time to time which may affect the approval of nanodrugs, which are in the clinical trial stage. Another obstacle is nanotherapeutics approved in one country do not get approval from other countries. Thus, due to the lack of proper standards and regulation policy, detailed guidelines for proper characterization and quality control for nanodrugs are the major barriers to develop nanotherapeutics (Farjadian et al., 2019). Major challenge in developing cancer-targeted anti-angiogenic NM demands intensive understanding of cancer-related metabolic processes, their interaction with immune cells and body, optimizing pharmacokinetic parameters, and grasping their biodegradative property (Mukherjee et al., 2020). A few of the challenges faced in nanomedicine R&D is depicted in Fig. 2.3.

2.4 Future Perspectives

Recent times have witnessed the emergence of different diseases, many of which have their underlying pathophysiology in the disturbances at the nanoscale levels of genes and molecules (like gene mutations and protein misfolding). The correlation between nanoscale understanding of disease mechanisms, progression, and therapy, with the need for comprehensive knowledge about physicochemical properties of NP, forms the basis of NM for targeted and effective approaches. There exists an additional concern that needs to be resolved to eliminate nonspecific toxicity, i.e., regulating the interaction between NP and the biological environment. Here, considerable importance needs to be given to understand the interactions between the surface of NPs and surrounding biological components and fluids (phospholipids,

vesicles, etc.) that could subsequently affect the pathophysiological responses. This interaction is affected by the composition of NP and nature of the suspending media (solvents, water molecules, salts, etc.) used. Together, there arises variations in the physicochemical properties of NP size, surface area, shape, surface charge, roughness, porosity, conduction states, hydrophobic/hydrophilic nature, and so on. In tandem, these factors will affect the physiological responses brought about by the cells being targeted with these NP (Nel et al., 2009). Small-scale setups enable easy regulation of nanoformulations, but at the larger scale, even slight errors could result in significant changes in physicochemical properties of NP that will impact their efficiency, quality, reproducibility, and safety. Subsequently, these erroneous particles when administered in diagnostics or therapy would elicit inappropriate physiological responses. Hence, in accordance with specific disease pathophysiology, we need to augment the physicochemical properties of NP and tailor them to resolve the disease or diagnostics being targeted. A global consensus aimed toward harmonizing and integrating the regulatory, safety, and scientific protocols of NM will further catalyze the standardization of the usage of NP with maximum reproducibility, safety, efficacy, and specificity.

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