Functionalized Targeted Theranostic Nanomedicines

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Abstract

Nanotechnology has a substantial impact on the development of both therapeutic and diagnostic agents in the health sector. Nanocarriers were widely explored for therapeutic purpose by scientific community due to its unique ability to improve the solubility, bioavailability, and cellular uptake of active pharmaceutical ingredients. Nowadays, nanomedicines became more popular for its ability to serve as carrier to get imaging of various biological systems or deliver the image-guided treatment options in treatment of various life-threatening diseases. Clinically effective formulations that combine treatment and diagnostics are widely attractive at the nexus of these two paradigms: This notion, recently termed as nanotheranostic, is significantly important for the ligand decorated nanocarriers, which accumulated at diseased area more potentially and can give customized or image-guided treatment. Numbers of theranostic nanoparticles with various

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combination of imaging agents and therapeutic agents were thoroughly investigated in past few years. These include, for example, liposomes; polymeric nanoparticles; micelles; drug conjugates and complexes; dendrimers; vesicles; micelles; core-shell particles; microbubbles; and carbon nanotubes. The current chapter gives detailed overview of various imaging techniques that are usually used in clinical setups along with recently explored theranostic nanocarriers and regulatory obstacles behind its commercialization.

Keywords

Nanomedicines · Theranostic nanoparticles · Imaging agents · Quantum dots · Diagnostic techniques

Abbreviations

AuNPs	Gold nanoparticles
GO	Graphene oxide
MRI	Magnetic imaging resonance
NIR	Near infrared
PDT	Photodynamic therapy
PEG	Polyethylene glycol
PET	Positron emission tomography
PLA	Polylactic acid
PTT	Photothermal therapy
SPIONs	Superparamagnetic iron oxide nanoparticles

1.1 Introduction

There is a tremendous demand in clinical trials for addressing differences in drug responsiveness induced by genetic diversity in large patient populations. Therefore, as a result, tailored treatment is the current strategy for resolving this issue (Moghimi et al. 2005). Hood invented the Predictive, Personalized, Preventive, and Participatory (P4) approach to medicine. Personalized medicine is predicated on collecting unique data from an individual's cells or biomolecules regarding their illness, health status, and therapeutic response (Hood 2013). Personal medicine or precision medicine can be defined as, "a customized medical care based on the detailed study of genomic, epigenetic changes and other data to treat the disease in best possible way" (National Research Council (US) Committee on A Framework for Developing a New Taxonomy of Disease 2011). The vast pharmacokinetic diversity of drug has opened the doors for personalized medicine in treatment of life-threatening diseases. Because of the unique characteristics of personalized medicine, it has gained considerable attention (Kim and Nie 2005). Numerous techniques, including genomics,

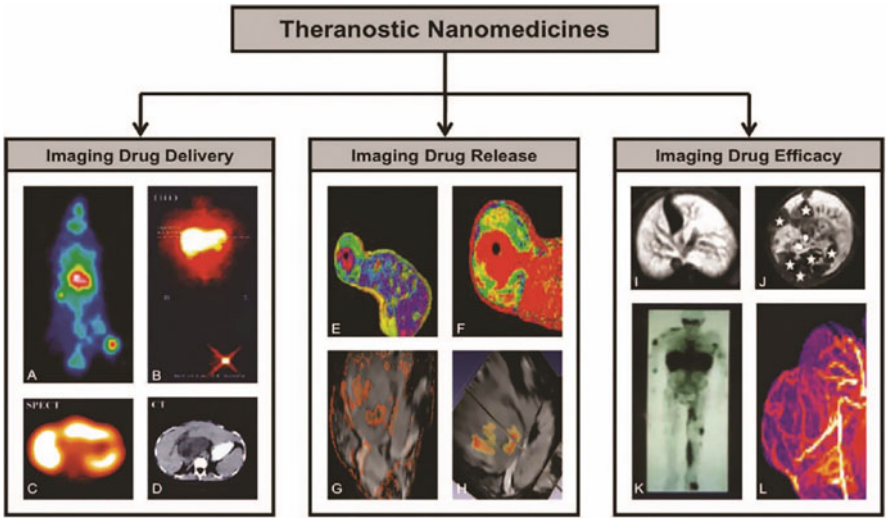

Fig. 1.1 Applications of theranostic nanomedicine formulations (Adapted with permission from Lammers et al. (2011))

proteomics, and metabolomics, can be used to decode and collect data at the molecular level for a person. Over the last few decades, the traditional Evidence-Based Medicine paradigm has transitioned steadily toward an individualized or customized medicine system. In general, the main objective behind the phase IV clinical trial was to optimize the medications for a large group of population in conventional treatment strategy. But the newer approaches focused on the individual's genetic peculiarities, which not only minimize the side effects associated with conventional medicines but also improve the therapeutic outcome. Additionally, real-time monitoring of pharmacokinetics of drug and pathological conditions will give insights for future planning of treatment strategy. This provides chance to manage the dosage of medications so that therapeutic response will get better and side effects will decrease (Lammers et al. 2012).

In the realm of medical science, nanotechnology has developed a distinct position. Due to their unique physical and chemical attributes, nanomaterials imparted the desired characteristics like large surface area for improving the solubility of lipophilic drugs; ease of functionalization will provide better cell uptake and side specific delivery of drug, high loading capacity, etc. This enables them to be applied in a broad range of technological disciplines. Theranostics is a term that refers to a method that combines diagnostic and therapeutic aspects. The concept of tailored nanomedicine lies at the heart of nanotheranostic. In 2002, Funkhouser coined the term "Theranostics," which includes therapeutic as well as imaging moieties in a single carrier to track the unwanted disposition of drug or its carrier and side effects associated with it (Moghimi et al. 2005). After it is injected into the body, the pharmacokinetics and pharmacodynamics can be tracked using theranostic materials. There was an initial focus on cancer treatment, but it has now been

broadened to other life-threatening diseases as well, which include autoimmune disorders such as type 1 diabetes, cardiovascular diseases, inflammatory diseases, and many more (Gollavelli and Ling 2014). Figure 1.1 showed the various applications of theranostic nanocarrier system. It is possible to perform both treatment and diagnosis simultaneously using tailored multifunctional theranostic nanomaterials, such as magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET) scans, or fluorescence imaging. Smart and new biomaterials will steadily improve the theranostic efficacy of nanoparticles (Choi et al. 2011).

Therapy is the process of resolving a problem following its discovery. The methods used will differ according to the patient's condition. Effective treatments strategy for cancer includes radiation therapy, immunotherapy, chemotherapy, targeted therapy, stem cell therapy, and surgery. Conventional therapy approaches have numerous disadvantages like toxicity to normal cells, lengthy processing times, high dosage requirements including nonspecific targeting, etc. (Gollavelli and Ling 2014). The major side effects associated with chemotherapy include neurotoxicity, immune system suppression, hair loss, fatigue, muscle pain, headache, etc. This showed the requirement of development of more precise and effective dosage form, which significantly reduces the dose of anticancer agents by lowering the unwanted disposition of drug and increasing the cellular uptake at tumor site (Li et al. 2014). Nanotherapeutics have potential to precisely target the infection location; they reduce undesirable side effects, increase effectiveness, and improve patient compliance and prognosis. This chapter discussed in detail the importance of theranostic nanocarrier and various imaging techniques along with various therapeutic and imaging agents, along with novel nanocarrier explored to get theranostic application in treatment of various life-threatening diseases.

1.2 Design of Nanotheranostic

Nanotheranostic is a term that referred as combination of nanotechnology, diagnostics agent, and therapeutic moiety. Several scientific fields have put significant efforts in developing theranostic nanomedicines during the past several years.

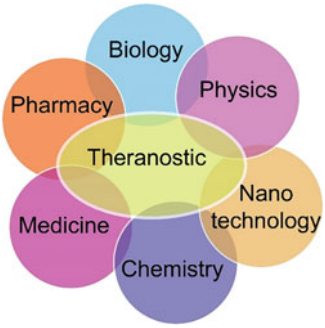

Fig. 1.2 Schematic representation of the highly interdisciplinary field of nanotheranostics

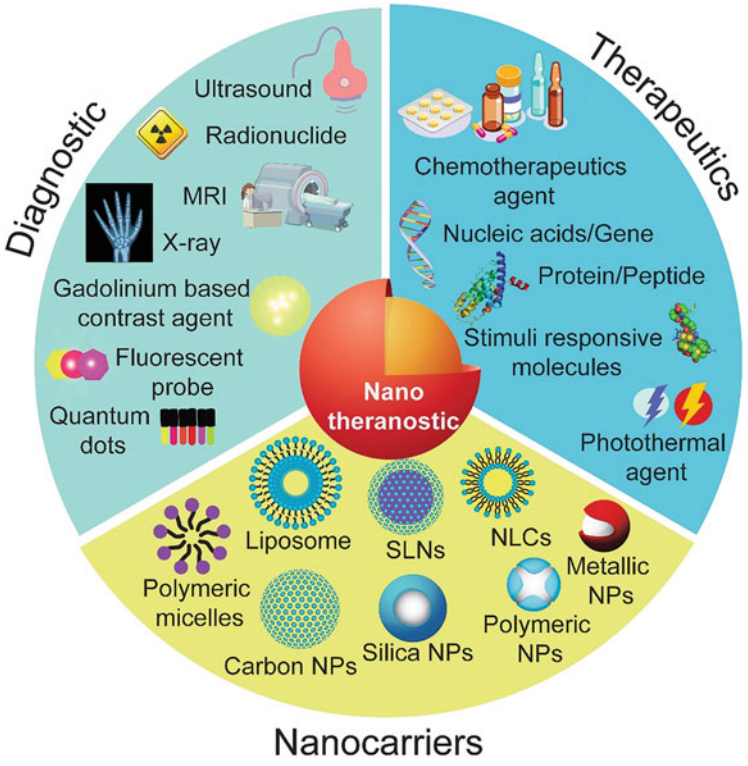

Fig. 1.3 Schematic representation of nanotheranostic system

New and exciting applications for nanotheranostic-based nanomedicines are the results of this collaboration (Akhter et al. 2013; Bukhari et al. 2021; Ahmed et al. 2022). As shown in Fig. 1.2 theranostic is an interdisciplinary approach, which required sincere involvement of a pharmacist, pharmacologists, a medicinal chemist, and other technical personnel.

There are three primary components to nanotheranostic agents: a therapeutic drug, an imaging agent, and a carrier that envelopes both. This theranostic system is targeted explicitly by connecting the ligands to carrier molecule. Figure 1.3 depicts a straightforward schematic illustration of a nanotheranostic system.

1.3 Therapy in Nanotheranostic

1.3.1 Drug Therapy

There are a lot of things that make it hard for drugs to get to the sites they need to go, like anatomical barriers, cellular membranes, blood-brain barriers, nuclear membranes, physiological barriers, and chemical and physical barriers (Lammers

et al. 2012; Bai et al. 2015). Nanotechnology plays an integral part in the rapidly expanding field of personalized medicine by clubbing therapeutic and diagnostic functions in a single system (Kim et al. 2013; Akhter et al. 2011). As nanocarrier-based delivery systems have the ability to deliver the drug directly to the desired site, thus reducing the dose and frequency of medication (Bai et al. 2015; Ahmad et al. 2013, 2015). Additionally, cytotoxicity associated with the plain drug also decreases significantly upon its entrapment inside ligand decorated nanocarrier due to selective delivery to diseases site sparing normal cells. Cisplatin, 5-fluorouracil, carboplatin, bleomycin, dactinomycin, paclitaxel, topotecan, vinblastine, doxorubicin, etoposide, mercaptopurine, and other chemotherapeutics are commonly employed as therapeutic drugs in nanotheranostic system for treatment of cancer (Ali et al. 2011).

1.3.2 Gene Delivery

Gene delivery includes transfer of specific gene to the infected cells of human body to treat the specific disease. One such approach is RNA interference (RNAi), which includes usage of siRNA (small-interfering RNA) or miRNA (micro-RNA) to reduce the expression of physiologically overexpressed proteins. Circulating miRNA is an important biomarker of cancer (Wan et al. 2012). Due to siRNA's low stability and inadequate distribution to target cells, its therapeutic potential is restricted. Inhibition of overexpressed miRNA and its reconditioning were the two major objectives behind the RNAi treatment (Muthiah et al. 2013). To overcome the challenges affiliated with the in vivo delivery of genes, Kenny et al. developed theranostic siRNA attached PEGylated nanoparticles. These magnetic resonance sensitive nanoparticles were used in combination with fluorescent markers to get the image-guided delivery of siRNA in tumor. In vivo administration of this formulation in tumor-bearing mice resulted in a significant decrease in tumor growth (Kenny et al. 2011). Overall, gene delivery is a novel approach to treat a range of diseases, but its high cost and lack of stability limit its application in clinical application.

1.3.3 Photodynamic Therapy

Historically from very ancient time phototherapy was used for treatment of various skin and other diseases; for instance, vitiligo was treated by applying plant extract of *Ammi majus L.*, followed by exposing them to sunlight (Hönigsmann 2012). Nowadays, development of focusable carbon arc torch to cure the lupus vulgaris by Danish physician Niels Finsen made the phototherapy popular, again (Gøtzsche 2011). Photodynamic therapy (PDT) can be used in the treatment of a wide range of malignant as well as non-malignant disorders. Photosensitizers are used in PDT to absorb light energy and transfer it to surrounding cells, resulting in the formation of reactive oxygen species inside the cells, which can eventually lead to cell death (Bai et al. 2015). In PDT, photosensitizing agents absorb lights at a specific wavelength

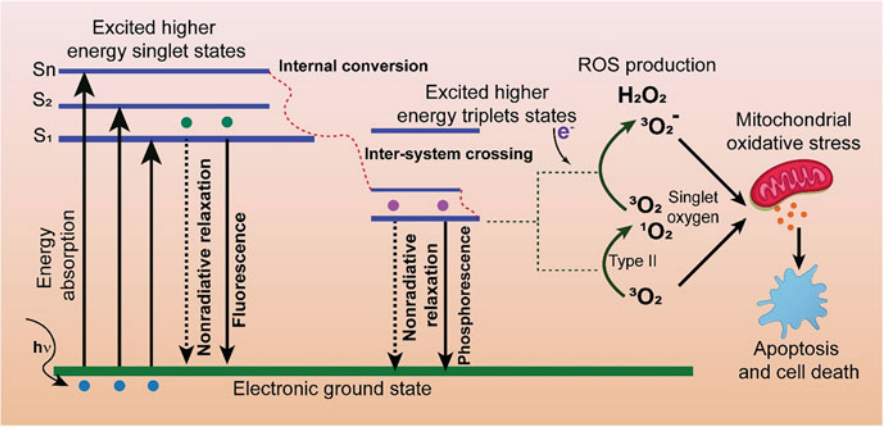

Fig. 1.4 Schematic representation of photosensitizer associated ROS generation and its role in causing apoptosis of cancer cells

and convert molecular oxygen present inside the cytoplasm of cells to singlet oxygen, which cause apoptosis of tumor cells (Paszko et al. 2011). Examples of photosensitizing agents used in PDT include napthalocyanines, photofrin, phorphine, phthalocyanine derivatives, and chlorins (Gollavelli and Ling 2014; Li et al. 2014; Allison et al. 2004). Figure 1.4 showed the photochemical reaction as per Jablonski's rule. In the case of a photosensitizer material, an excited electron crosses over the other molecules instead of coming to its ground or low energy state, which may produce hydrogen peroxide or superoxide as shown in Fig. 1.5. This hydrogen peroxide or superoxide was able to kill the tumor cells by damaging nucleus or cell organelles like mitochondria, resulting in cell death (Calzavara-Pinton et al. 2007). However, these types of photosensitizing agents tended to stay in the human body for longer period of time, which made the patients more susceptible to sunlight. To avoid any unwanted phototoxicity, patients were advised to stay in a dark environment (Zhao and He 2014). The ligand decorated theranostic nanocarriers can make the PDT safe as well as effectively improving the cellular uptake in diseased cells.

1.3.4 Photothermal Therapy

Photothermal therapy (PTT) is also called heat ablation technique, which uses light radiation to generate heat within the tissue (Gellci and Mehrmohammadi 2014). Heat is a highly effective weapon for destroying tumor cells. However, inducing a moderate temperature of 41–50 °C in the body for a brief period (5–10 min) without damaging normal tissue is a challenging task. PTT uses the near infrared (NIR) light waves to get the better tissue penetration and a photosensitive agent with good light absorbing capacity. PTT can selectively kill the pathologic cell upon excitation of photosensitizing agent by NIR light by converting the resonance energy of

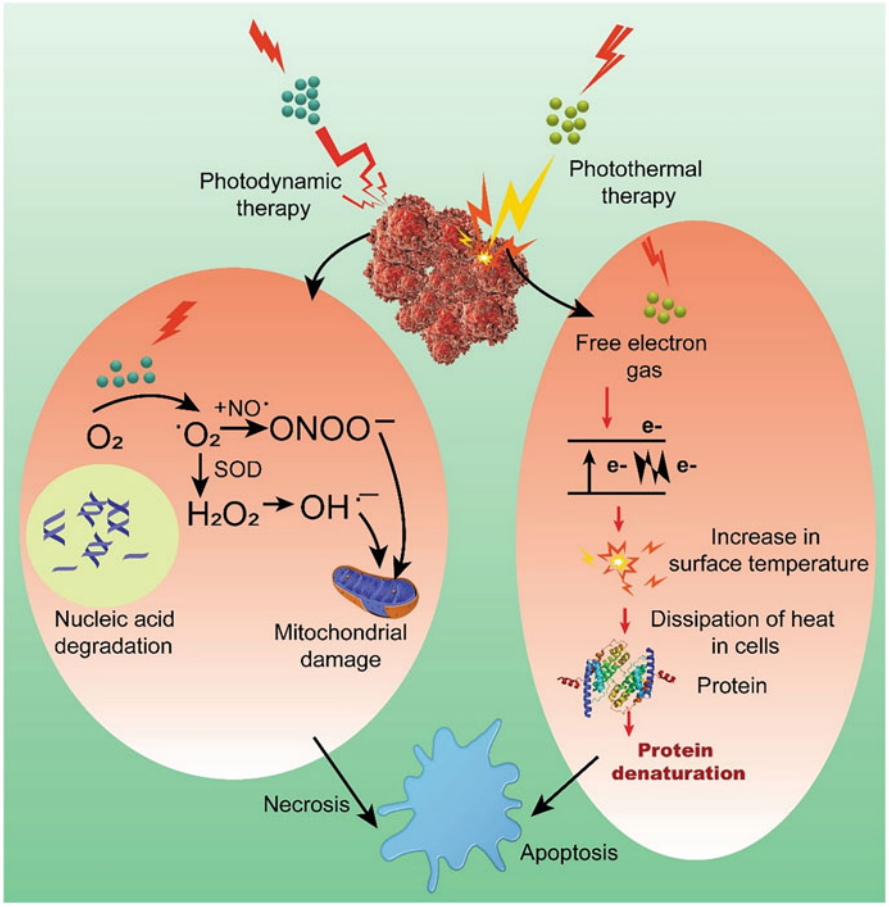

Fig. 1.5 Schematic representation of PTT and PDT using nanotheranostic

electromagnetic rays into heat production as shown in Fig. 1.5. This heat causes the irreversible changes in tumor cells by cellular mutilation (Gellci and Mehrmohammadi 2014). However, use of PTT in clinical practice is very limited due to its no specificity in identification between malignant and non-malignant cells. Clear demarcation between diseased and non-diseased cell is important to protect the normal body cells. To overcome this problem, ligand decorated nanotheranostic agents were explored in recent years. Due to its ability to significantly improve the cellular uptake at diseased tissue, side effect associated with unwanted disposition of photosensitizing agents was reduced significantly, and its therapeutic potential will improve (Huang et al. 2021; Liu et al. 2020; Dheyab et al. 2021). Such types of nanomaterials along with suitable targeting ligands were preferable for the clinical application of PTT.

Many interesting theranostic nanomaterials are made from noble metals such as gold. Gold nanoparticles (AuNPs) were widely explored for the PTT due to its low toxicity and easy renal clearance (Akhter et al. 2012). Gold has been the most extensively studied PTT agent, which showed promising results in treatment of various cancers in many research articles.

1.4 Nanotheranostic for Imaging

Theranostic agents must contain some imaging agents to provide in vivo diagnosis. Many approaches are being investigated to meet these goals using various materials. Nanotheranostic can be imaged using a variety of techniques such as optical imaging, nuclear imaging, CT, MRI, PET, and ultrasound (Fig. 1.6) (Debbage and Jaschke 2008; Janib et al. 2010). Each technique has its own advantages and disadvantages, which are discussed in the following subsections.

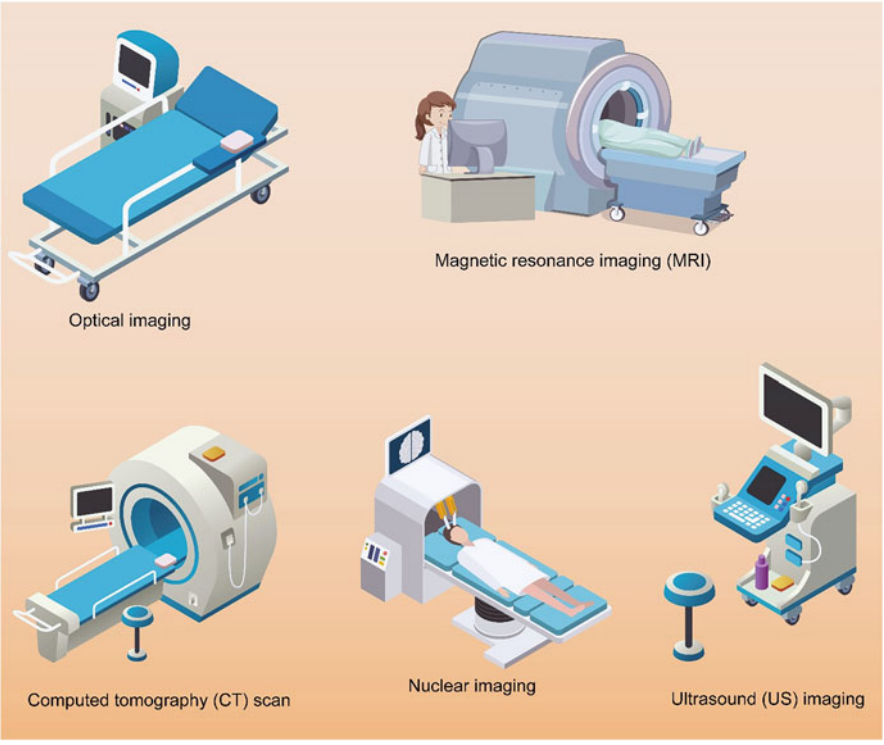

Fig. 1.6 Typical molecular imaging instruments

1.4.1 Optical Imaging

Optical imaging is the cost-effective and most widely used imaging technique in preclinical studies. It has proven helpful for non-invasive, sensitive, real-time molecular recognition and imaging investigations. Photons generated by bioluminescent or fluorescent probes are used in optical imaging (Janib et al. 2010; Sarbadhikary et al. 2021; Jain and Zhong 2022). It offers advantages over other imaging modalities in that it is relatively inexpensive to detect low-energy photons; also, the visible to near-infrared (NIR) light spectrum gives excellent spatial resolution without the use of ionizing radiation (Janib et al. 2010). To get the better resolution optical imaging can be integrated with other imaging agents such as PET or MRI. Bioluminescence and fluorescence imaging are the two most commonly explored technique in tumor diagnosis and image-guided surgery, in vivo (Lim et al. 2020). Metal nanoparticles can also be used in nanotheranostic to provide anticancer therapy with fluorescence imaging. For example, silver nanoparticles with strong metal enhanced fluorescence are helpful for cell imaging (Li et al. 2015a). Unfortunately, this modality has limited application in biological system due to poor tissue penetration. Additionally, fluorescence imaging is sensitive to noise due to heme groups (λ_{max} 560 nm), protein (257–280 nm), and even water (around 900 nm) (Debbage and Jaschke 2008). However NIR probe due to its identical structural properties could improve the efficiency due to good tissue penetration capacity.

1.4.2 Magnetic Resonance Imaging

The precession movement given by hydrogen nuclei of water within the applied magnetic field is the basis for the MRI signal (Janib et al. 2010; Richard et al. 2008). This modality produced a high-quality cross-sectional image of the body in any plane using radiofrequency pulses and a controlled magnetic field (Anani et al. 2021; Zhou et al. 2021). All hydrogen atoms align and become excited along the applied external magnetic field after the application of radiofrequency. The wire coils in the MRI unit will capture the energy released by the excited atoms, and with the aid of a computer system, the MRI mapping will be performed. The relaxation process, which takes place when the nuclei return to their initial aligned condition, can be used to produce an image (Li et al. 2015a). MRI contrast agents helped in reducing the relaxation parameters to increase the tissue differentiation. MRI contrast agents can be divided as paramagnetic agents, such as manganese or gadolinium, and superparamagnetic agents like iron core or manganese core polymeric matrix, which were considered as better MRI contrast agents (Avasthi et al. 2020; Bonnet and Tóth 2021; Xiao et al. 2016).

Due to its great spatial resolution and sensitivity, MRI is frequently used to diagnose solid and brain tumors, which is regarded as the most efficient and non-invasive imaging technology. It has superior spatial resolution when compared to other imaging techniques. However, it has low sensitivity. To compensate, relatively large contrast agent concentrations are needed to provide a discernible

signal. Concerns about accumulation and toxicity have arisen due to the use of high dosages of these contrast agents, which has become a substantial issue for Gd (III) complexes. While Gd (III) provides more excellent contrast for tumor and vascular imaging, sluggish excretion and toxicity from long-term accumulation may limit its clinical application.

1.4.3 Computed Tomography

A CT scan employs computer processing to build cross-sectional images from a series of X-ray images obtained from various angles around the body. The capacity of CT to differentiate tissues is dependent on the degrees of X-ray attenuation, and the attenuation coefficient depended on the electron density and atomic number of the tissues. Absorption differences between identification of air, fat, and bone depended on the absorption differences, and produced high contrast images of anatomical components (Janib et al. 2010; Weissleder 2002). The CT contrast agents that are currently available have a low molecular weight and exhibit quick extravasation as well as clearance. However, macromolecular and nanoparticulate agents may be more suited for vascular CT imaging because of their long-lasting presence in the blood (Janib et al. 2010). Most CT contrast research is focused on solid nanoparticles or liposomes containing iodinated molecules since these ingredients are required in high concentrations (Cormode et al. 2009).

1.4.4 Ultrasound Imaging

In ultrasound imaging, a transducer (probe) is used to convert the electrical energy into mechanical energy based on the piezoelectric effect. A thin layer of gel was applied over the skin to transmit the ultrasound waves generated by transducer (Janib et al. 2010). This ultrasound imaging approach is well established, non-invasive, adaptable, and commonly utilized in human clinical imaging modalities as a diagnostic tool (Janib et al. 2010; Zhou et al. 2020). Because of the advantages of real time, portable, non-ionizing, and deep tissue-penetrating abilities, Ultrasound has already become a widely demanded approach for tumor diagnosis due to advantages like portable machinery, real time imaging and deep tissue imaging abilities (Zhou et al. 2020; Frinking et al. 2000).

Furthermore, the advent of US contrast agents has accelerated its use in diagnosis and treatment of various diseases (Campbell 2006). Microbubble-based ultrasound imaging offers good contrast effect, which is the need for in vivo imaging. Additionally, it can function as an efficient delivery mediator of genes and medications for treating tumors by affecting cellular membranes and vascular endothelial integrity in the case of an excessive collapse of microbubbles at high-pressure amplitude (Papachristodoulou et al. 2019; Xu et al. 2017). Furthermore, these gas-filled microbubbles have poor stability and a short half-life due to the materials used and the process used to produce them (Zhou et al. 2020). Nanotheranostic agents have

some eye touching features like ultrasmall size and ability to bind specific receptors to target cells or tumor microenvironments with prolonged circulation time and high stability (Ahmad et al. 2013, 2020, 2021; Akhter et al. 2012). Tremendous possibilities available behind the development of novel theranostic agents to treat life-threatening diseases attract lots of scientists to research in this particular area (Bajwa et al. 2015; Jain et al. 2015a). Such nanotheranostics carriers are discussed in the following sections.

1.5 Different Types of Nanotheranostics

The "theranostics" word is referred to systems that can be both applied as therapeutics and imaging agents. Ideally, a nanotheranostic should be designed in such a way that it could circulate for a longer duration in the biological system, depict desired release as per the requirement, have target specificity and ability to deliver the drug and theranostic agent in desired concentration at target site, and have imaging ability and a larger target to background ratio.

Based on nanoplatform used in design of nanotheranostics, nanotheranostics could be classified into two categories. One is inorganic theranostic, where inorganic materials are used as theranostics like superparamagnetic iron oxide, gold, carbon

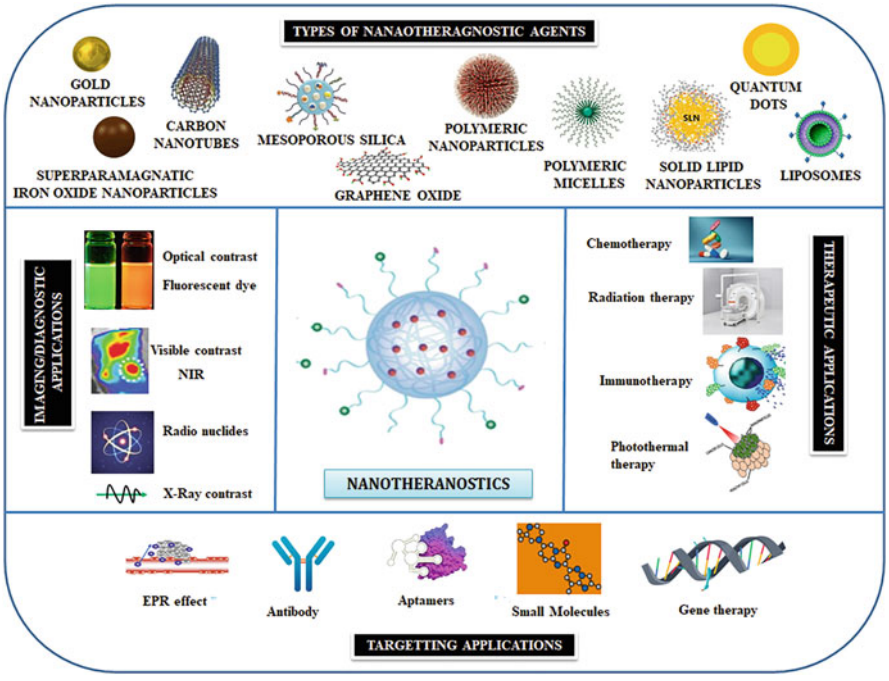

Fig. 1.7 Types and applications of nanotheranostics

nanomaterials, graphene oxide, quantum dots, etc. Another category is organic nanotheranostics in which organic materials like polymeric nanoparticles, polymeric micelles, liposome, lipids, etc. are used. We have shown different nanotheranostic systems graphically in Fig. 1.7 along with their three main biomedical applications, i.e., therapeutic delivery, diagnostic/imaging applications, and targeted delivery of bioactive if we modify or engineer the nanotheranostics with targeting ligands/moieties also depicted in Fig. 1.7. Additionally, the summary of recently researched nanotheranostic agents is showcased in Table 1.1.

Inorganic nanocarriers have offered wide range of benefits due to their properties like diverse surface chemistry, controllable structures, large surface area, and tunable optical characteristics in delivery of therapeutic and diagnostic agents. Furthermore, research work published in last decade proved the efficiency of inorganic nanoparticles as theranostic agents (Feliu et al. 2016).

1.5.1 Superparamagnetic Iron Oxide Nanoparticles

SPIONs are the particles of submicron size, consisting of iron oxide core, which imparts them magnetic properties under influence of external magnetic field. The colloidal stability of SPIONs is improved by either surface functionalization or surface coating with suitable polymeric or non-polymeric capping agents such as carboxymethyl cellulose, chondroitin sulfate, starch, chitosan, etc. (Sun et al. 2019; Mallick et al. 2015, 2016). SPIONs can be used as efficient multimodal nanotheranostics carrier due to its small size, good biocompatibility, ability of surface functionalization, sensitivity, and their capacity to be used as multimodal contrast agent (Cai et al. 2020). The FDA authorized "Ferumoxides," the first SPION-derived MRI contrast agent, in 1996. Several iron oxide nanoparticles, notably "Feridex" and "Feraheme," have so far obtained confirmation for use in clinical settings (Wahsner et al. 2019). Iron oxide nanoparticles capped with specific polymers have shown ability to serve as efficient contrast agents in ultrasound/MRI (Sun et al. 2019).

SPIONs are used as multimodal MRI contrast agent for imaging of brain cells, liver cells, lung cells, heart cells, etc. (Yoon et al. 2017; Reczyńska et al. 2020; Dao et al. 2017). Conjugation of SPIONs with aptamers has been explored for colorectal and prostate cancer therapy and imaging. High-intensity MRI signals were observed from tumor area upon intravenous administration of aptamer conjugated SPIONs. Scientists have also observed that SPIONs were metabolized into non-toxic iron ions in in vivo experiments (Jalalian et al. 2013; Wang et al. 2008). Cai et al. developed ultrasmall SPIONs coupled with phenothiazine-based NIR fluorescent dye and evaluated for Alzheimer's disease. The SPION coupled with novel theranostic agents showed strong binding with Aβ species as well as an enhancement of fluorescence in the NIR window. They were highly stable in bovine serum with low cytotoxic effect toward human neuroblastoma cells. The in vivo NIR fluorescence and MRI images showed a big difference between double transgenic mice and wild-type control mice. Histological staining in slices of brain confirmed the specific

Table 1.1 Summary of few nanotheranostic agents explored for biomedical applications

S. no.	Types	Functionalization	Targeted disease	Imaging technique	References
1.	Superparamagnetic iron oxide nanoparticles (SPIONs)	SPIONs-aptamer bioconjugates	Cancer	MRI	Jalalian et al. (2013)
2.	SPIONs	Chitosan-coated SPION	Cancer	Ultrasound/ MRI	Sun et al. (2019)
3.	SPIONs	Chondroitin sulfate-capped SPIONs	Cancer	MRI	Mallick et al. (2016)
4.	Ultrasmall SPIONs	Phenothiazine-based near-infrared (NIR) fluorescent dye	Alzheimer's disease	NIR	Cai et al. (2020)
5.	Ultrasmall SPIONs	Epirubicin (EPI)-loaded ultrasmall SPIONs with poly (aspartic acid) graft copolymer	Cancer	MRI	Yoon et al. (2017)
6.	Gold antennas	Cetuximab loaded in gold nanoantenna	Tumor	Raman spectroscopy	López-Lorente (2021)
7.	Hollow gold nanocages	Ac-Glu-Glu-Cys-NH_2 tripeptide-linked AuNPs loaded with cisplatin Pt (II)	Cancer	NIR	Xiong et al. (2018)
8.	Carbon nanomaterials	Functionalized fullerene with cytokine interleukin-13 encapsulated	Cancer	MRI	Li et al. (2015b)
9.	Nanodiamonds	Human serum albumin-based biopolymer (polyethylene glycol) coating (dcHSA-PEG)	Brain targeting	Fluorescent dye	Moscariello et al. (2019)
10.	Polymeric nanoparticles	Poly (vanillin oxalate) nanoparticles	Hepatic ischemia/ reperfusion (I/R) injury	H_2O_2	Kang et al. (2016)
11.	Polymeric nanotheranostics	Autofluorescence polymer polyethylene imine-polylactide (PEI-PLA)	Angiogenesis and tumor cell growth	Polymer with NIR dye	Shao et al. (2019)
12.	Liposome	PEG-coated and folate-PEG-coated	Cancer	^{159}Gd	Siafaka et al. (2021)

binding of nanoparticles to Aβ plaque. The SPION coupled with novel theranostic agents blocked the seeding-mediated aggregation with an IC_{50} of 11.7–32.1 ng/mL, which is much better than observed in phenothiazine-based small molecules (Cai et al. 2020). Also, the research published in last few years confirmed that conjugation of SPIONs with antibodies, ligands, polymers, folic acid, PEG, or peptide gave promising results of radiosensitivity in ovarian cancer, cervical cancer, and breast cancer (Fakhimikabir et al. 2018; Zhang et al. 2016; Song et al. 2018; Pan et al. 2018).

Excellent blood–brain barrier permeability of SPIONs without disturbing other brain cells under low radio radiofrequency field is an important feature in brain imaging. Phenothiazine-based and PEGylated ultrasmall SPIONs worked as novel theranostics agents for amyloid plaques in Alzheimer's disease (Dao et al. 2017; Yallapu et al. 2010). Next generation SPIONs act as a Trojan horse (administered intravenously) for the delivery of therapeutic drugs to cancers. Recently, ultrasmall SPIONs working as a multimodal contrast agent have been recognized as a promising material for development of nanotheranostic carriers due to its good biocompatibility and high sensitivity (Chen et al. 2022). SPIONs have tremendous potential to study the in vivo behavior of nanocarriers, as they are inherently holding the MRI contrast agents.

1.5.2 Gold

AuNPs have been widely explored for applications as imaging agents, drug delivery carrier, for targeted delivery, theranostics, etc., because they are capable of conjugating and delivering drugs and bioactive molecules (ligands) to targeted cells. AuNPs were an attractive alternative amidst various inorganic systems exploited by research community due to their high surface-area-to-volume ratio, unique and tunable optical properties, as well as easy surface functionalization along with high loading capacity of biomolecules. When AuNPs are in contact with a biological medium, they may rapidly be coated with nonspecific serum proteins. This process has been known as the *corona effect*. To diminish corona effect AuNPs were frequently coated with PEG (Albertini et al. 2019; Groysbeck et al. 2019) or multilayer coating of albumins (Achilli et al. 2022).

In addition to this, AuNPs can be explored for the PDT, PTT, and photoacoustic treatments. Therefore, we can use AuNPs in various fields, e.g., bioimaging (Demiral et al. 2021; Nicholls et al. 2016), targeted delivery of therapeutics (García et al. 2022; Li et al. 2018), and plasmonic PTT (Ali et al. 2022; Taylor et al. 2022). Demiral et al. formulated PEGylated AuNPs by attaching cell penetration enhancer D-α-Tocopherol succinate to detect and treat drug-resistant micro tumors through PTT by using verteporfin as photosensitizer. The theranostic system was not only used for drug delivery and imaging in vitro/vivo, but it can also be used for other fluorescence-based biological and medical purposes. Covalent attachment of ligand and imaging agent to the system makes the theranostic agent work better against tumors, and observed to be the most promising candidate, causing 4 times as many

cells to die. The cell studies showed that the theranostic agent improves the apoptosis process in 61% of the cells (Demiral et al. 2021).

Gold nanocarriers involved in diagnosis, therapeutic, and theranostic application showed different morphology such as spherical, nanorods, nano shells, hollow nanocages, nanoantenna, nanoplates, nano prisms, etc. (López-Lorente 2021; Xiong et al. 2018; Vines et al. 2019; Gharatape and Salehi 2017). Gold-based nanotherapeutics can be remodeled for tumor microenvironment for targeting by changing unfavorable therapeutic conditions into therapeutically accessible by imparting them different external (temperature, laser, or ultrasound) and internal (pH, enzymes, and glutathione) stimuli responsive drug release mechanisms (Mohapatra et al. 2021; Rajendrakumar et al. 2018). AuNPs have inherent property to provide catenate sites for coating or conjugation of various active pharmaceutical ingredients, ligands, proteins, and imaging agents, which provide immense potential to use AuNPs as nanocarrier in biological system.

1.5.3 Carbon Nanomaterials

Carbon allotropes such as nanodiamonds, carbon nanoparticles, fullerenes, carbon nanotubes, graphene, etc., have tremendous potential to serve as delivery carrier due to their unique physiochemical properties, chemical nature, handy fabrication, facile surface modification, thermal stability, optical properties, great mechanical strength, and electrical conductivity (Kaur et al. 2016). Researchers already explored carbon-based nanomaterials as theranostics nanocarrier in image-guided treatment of cardiovascular diseases and cancer (Alagarsamy et al. 2021; Gao et al. 2019).

Nanodiamonds have an octahedral architecture (size 5–50 nm), known for its unique properties like low toxicity, stable fluorescence, easy functionalization, and intrinsic biocompatibility (Qin et al. 2021). Similarly, carbon nanotubes have a unique architectural form of fullerene (cylindrical fullerene) broadly classified into single-walled carbon nanotubes and multi-walled carbon nanotubes. They are highly ordered, pseudo-one-dimensional carbon allotropes that can easily penetrate various cells to deliver the drugs or bioactive molecules (Augustine et al. 2017).

Fullerenes have lots of free active groups on its surface, which provide them immense potential for functionalization (Shi et al. 2014). Li et al. formulated surface functionalized fullerene with cytokine interleukin-13, and encapsulated Gadolinium, to increase the intracellular uptake of anticancer agent. When this fullerene was attached to an interleukin-13 peptide, this hydrophilic nanoparticle showed a better uptake in human brain cell lines (U-251 GBM). These results support the idea that the positively charged (amino)-I nanoparticle has a stronger charge attraction for human brain cellular endocytosis on the metallofullerene cage surface (Li et al. 2015b).

A wide range of carbon-based materials provide good fluorescence and less toxicity compared to the organic dyes, although their cytotoxicity-related concerns and poor knowledge regarding pharmacokinetic behavior limit their commercial application.

1.5.4 Graphene Oxide

Graphene oxide (GO) is a form of graphene that has been oxidized, widely explored in biotechnology and medicine field to treat cancer, drug delivery, and easy penetration through cells. GO also has many physical and chemical properties, such as a nanoscale size, a large surface area, and an electrical charge (Esmaeili et al. 2020). GO is more hydrophilic compared to graphene, hence showed more solubility and colloidal stability in aqueous media. GO-based nanocarriers can also be explored as antimicrobial agents due to their dose-dependent cytotoxicity and bactericidal activity. Although GO was toxic to living cells and organs, which makes it hard to use in the biomedical field, surface functionalization of GO decreases the toxicity significantly. Two graphene-based materials, GO and reduced GO nanosheets, which significantly inhibited the *E. coli* bacterial growth were reported by Kumar and co-workers (Kumar et al. 2019).

GO nanoparticles were explored for the non-invasive bio-imaging and targeted therapy (Syama and Mohanan 2019) due to their unique advantages such as low cytotoxicity, tunable optical properties, high photostability, brightly emissive for high-contrast imaging, and facile surface functionalization for specific targeting (Dong et al. 2018). GO as fluorescence probe is highly suitable for fluorescent probe, due to its advantages like biological compatibility, resistance to photobleaching, and efficient light emission (Esmaeili et al. 2020). More advancement in GO nanoparticles was performed to improve its hydrophilicity and subsequently the in vivo circulation time by attaching the low molecular weight PEG. Results of the in vivo study showed improved blood circulation time and lowered cytotoxicity (Ghosh and Chatterjee 2020). To make the most of the benefits of nanotechnology and to reduce the risks to human health, it is important to figure out the molecular targets involved in toxicity and to weigh the pros and cons of GO.

Nanomedicine can be formulated using varieties of organic materials, which majorly include carbohydrates, proteins, lipids, and synthetic or semi-synthetic polymers. The commonly used nanoparticles are discussed in the following subsections.

1.5.5 Polymeric Nanoparticles

Polymeric nanoparticles are widely explored due to their easy availability, cost effectiveness, sustained type drug release pattern, and inertness. Commonly used polymers for formulating theranostics nanoparticles are chitosan, gelatin, albumin, sodium alginate, poly (lactic-co-glycolic acid), PLA, poly-glutamic acid, etc., used very promisingly for delivering the drug to cardiovascular and central nervous systems (Kang et al. 2016). Shao and co-workers formulated the triple-collaborative nanotheranostics nanocarrier for combining the therapeutic benefits of anti-angiogenesis, RNA interference, and PTT using PLA as polymer. In vitro cell line study showed self-fluorescence activity and significant increase in cellular uptake (Shao et al. 2019). Chio et al. made chlorin e6, a second-generation photosensitizer

and camptothecin-loaded polymeric nanoparticles that were decorated with hyaluronic acid-grafted monomethoxy PEG for imaging and treating triple negative breast cancer. In vitro cell line studies with MDA-MB-231 cells showed that hyaluronic acid-grafted monomethoxy PEG-based nanoparticles were taken up much more rapidly than nanoparticles without a coating. The therapeutic effectiveness was measured by putting free and camptothecin-loaded nanoparticles into MDA-MB-231 cells for 6 h and then emitting a 670 nm laser on them. The results showed that nanoparticles killed 28% of the cells while same concentration of camptothecin has killed 12% of cells (Choi et al. 2015). Polymeric nanoparticles have been explored widely for theranostic application, and due to the inertness of polymers, it provided stable nanoparticles for treatment of various diseases.

1.5.6 Polymeric Micelles

Polymeric micelles are self-assembled aggregated colloidal nano-constructs of amphiphilic polymers with a core-shell structure. These have been used as versatile carriers for delivery of diagnostic agents and drugs. They have gained immense popularity due to their unique features such as smaller size, good solubilization properties, easy surface functionalization, biocompatibility, longevity, enhanced permeation and retention effect, good encapsulation efficiency, high stability (in vitro and in vivo), and the ability to accumulate into tumor through compromised vasculature. The core of the micelles are formed by various amphiphilic copolymers including di-block, triblock, as well as graft copolymers of PEG, poly-L-aspartic acid, poly(2-hydroxyethyl-L-aspartamide), etc. (Kang et al. 2016). Gregoriou and his team used a single emulsification-based approach to make resveratrol-loaded micelles from pluronic F127 block copolymer and D—tocopheryl PEG succinate. This was done to improve cellular uptake and get more desirable pharmacokinetics for breast cancer treatment. Cellular uptake studies were performed on MCF-7 and MDA-MB-231 cells; 4 h cellular uptake data showed significantly higher cellular uptake by MDA-MB-231 cells compared to MCF-7 cells (Gregoriou et al. 2021). Micelles were widely explored for their simplicity and easy modification capacity. Results published regarding the theranostics micelles in scientific literature have potential to give therapeutic and image-guided treatment to patients.

1.5.7 Liposome

Liposomes are one of the widely accepted, biocompatible, biodegradable lipidic nanocarriers and first approved nanocarrier by FDA. Easy preparation, feasibility to scale up, biocompatibility, ability to load hydrophilic, as well as hydrophobic drugs and easy surface functionalization (PEG or vitamins) established it as a superior nanocarrier. Recently, liposome was explored for various applications of in vivo imaging through optical, MRI, PET, CT, PDT and PTT, etc., by scientific community (Lee and Im 2019).

Skupin-Mrugalska et al. formulated liposomes by using lipid derivatives of gadolinium (III) diethylenetriaminepentaacetic acid salt, which can also serve as MRI contrasting agent and a photosensitizer agent zinc phthalocyanine. This hybrid nanocarrier was capable to kill cancer cells by PTT as well as diagnosis through MRI. Confocal microscopy images showed the internalization of nanohybrid inside the fibroblast cells (Skupin-Mrugalska et al. 2018). Lozano et al. made a nanotheranostic system for TNBC using doxorubicin and indocyanine green loaded monoclonal antibody decorated PEGylated liposomes that target the mucin1 receptor. In vivo monitoring of this antibody-coated nanotheranostic formulation showed that the liposomes quickly gathered in a tumor model, unlike the non-targeted formulation (Lozano et al. 2015).

There are numbers of liposomal products currently in the market as well as in clinical trials, which impart them immense value to develop as novel commercial product. But clinical application of theranostic liposomes or other nanocarriers requires detailed clinical studies regarding their behavior in biological system, metabolism profile, toxicological studies, and many more. Although few theranostic-based nanocarriers are currently under clinical trials, outcomes of such clinical studies will guide researchers in the future.

1.6 Regulatory Aspects

Nanomedicine has been a massively explored research area worldwide, due to its ability to improve therapeutic outcome of active pharmaceutical ingredients by transforming polymers, lipids, carbohydrates, etc., into nanocarriers, ligand decorated nanocarriers, inorganic nanoparticles, dendrimers, and quantum dots (Jain et al. 2015b; Ojha et al. 2021). However, most of the regulatory authorities do not have clear regulatory guideline for the marketing approval of nanomedicine, which restricts the easy translation of nanomedicine and creates a lack of clarity for research institutes and manufacturer in development of novel nanocarriers (Sainz et al. 2015).

There are lots of challenges in preparation of clear regulatory guidelines for nanomedicines. For instance, (1) at physiological level nanomedicine demonstrated contrasting pharmacokinetic behavior compared to small drug molecules, (2) unavailability of clear evidence regarding its penetration through blood-brain barrier due to its small size, which may compromise the normal brain function; (3) another problem was associated with nanomaterial is explanation of the accumulation of nanoparticles in high blood perfusion containing organs upon systemic administration, and (4) lack of standard nanotoxicology tests cumulatively limits the translation of nanomedicine from bench to bed (Hejmady et al. 2020). Furthermore, insufficient and ununified regulatory guidelines (like different interpretations of definition and classification of nanomedicine in different countries) made regulatory approval of nanomedicine more stringent and time-consuming. One of the major concerns was scale up of laboratory batches at commercial level, and stability throughout its shelf life also created muddle in regulatory approval. Genotoxicity

and environment-related concerns have further aggregated, which required separate guideline and analytical tests for regulatory clearance (Foulkes et al. 2020).

Besides all these regulatory-related problems, more than 50 nanomedicines were already deployed in the market till date, and this number raises steadily (Sarwal et al. 2019). Most of the regulatory authorities do not consider nanomedicine harmful but choose to evaluate and provide approval on case-to-case bases. In recent time many regulatory authorities have created committee or declared some sort of guidelines to make the regulatory approval process easy. For example, the US Food and Drug Administration has formed a task force and a "Nanotechnology Interest Group." The task force noticed that the current regulatory guidelines were broad enough to ensure the safe production of nanomedicines, which can go to the preclinical and clinical trials. But no specific points were discussed about the clinical evaluations (Nanotechnology Task Force 2022). Similarly, the European Union and the healthcare product authority of the United Kingdom have established a European nanomedicine characterization laboratory for providing constantly refined intellectual results in preclinical studies of nanomedicine to manufacturers and regulatory authorities. Furthermore, few of the health-related government agencies of the United States and European Commission have introduced a project titled "REFINE" to set the criteria for regulatory approval of nanomedicine with their objective "Development and validation of new analytical or experimental methods." To set the definite criteria for manufacturing of nanomedicine, the Department of Science and Technology, Government of India, has also prepared a draft. This contained the three-tier governance framework to regulate the nanomedicine (Foulkes et al. 2020).

It was now clear toward the regulatory authorities present worldwide that a proper set of guidelines is a must for smooth approval of nanomedicine and for guiding the manufacturers as well as health workers for development of new nanomedicines. Academicians, clinicians, manufacturers, and regulatory personnel should combinedly form a defined set of criteria, which will make approval process for nanomedicine easy.

1.7 Conclusion

The current chapter discussed in detail the various ligand decorated nanotheranostic drug delivery carrier. Various imaging techniques like fluorescence, PET, CT, MRI, etc., used for in vivo imaging were also explored. The novel techniques like PTT and PDT have opened the new door for the treatment of various life-threatening diseases like cancer. Also, the numerous research articles published by scientific community proved the efficiency of ligand decorated theranostic nanocarrier for the treatment of cancer, infectious diseases, and neurodegenerative diseases. Some of the ligand decorated nanocarriers have also entered the initial stage of clinical trials, which proved the importance and feasibility of this type of nanocarriers in clinical applications.

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