Chapter 1
Nanotheranostics: An Emerging Nanoscience

Bushra Jamil and Mahendra Rai

Abstract Theranostic approaches have been suggested for various ailments, particularly cancer, microbial diseases, AIDS, and many others. This is a kind of personalized treatment where the treatment is guided according to the individual molecular profile or on the basis of biomarker identification. Combination of diagnostics and therapeutic strategy into a single platform can be made possible with the help of nanotechnology. Usually most of the nanomedicines act by increasing bioavailability of the drug, protection from degradation, and controlled biodistribution in the body system. Nanotheranostics thus encompass all those nano stages that can be used for simultaneous detection and treatment of disease by providing better penetration of drugs within the body systems with reduced risks as compared to other conventional therapies. Theranostics offer new and emerging applications of nanotechnology. Nonetheless, the nanocarrier should have the capacity to accommodate multiple agents such as stabilizer, therapeutics, and targeting and imaging moieties.

The pharmaceutical and healthcare industry is the one that has the most benefits of this new and emerging field of nanotechnology. It can also play a key role in the field of molecular biology by the development of molecular sensors or imaging agents for diagnosis and carriers or vehicle development for therapeutic agents. These innovative carriers and agents can make difference in the treatment of cancer, AIDS, cardiovascular diseases, burn wounds, infections, etc. by the development of nanotheranostic diagnostic systems like immunoassays or colorimetric assays and in therapeutic approaches through gene therapy or by biomarker identification and targeting systems.

Keywords Nanotheranostics · Biomarkers · Molecular imaging · Imaging probes · Image-guided therapy · Aptamer theranostics

B. Jamil
Department of DMLS, University of Lahore, Islamabad, Pakistan

M. Rai (✉)
Department of Biotechnology, Nanobiotechnology Laboratory, Amravati, Maharashtra, India

Department of Chemistry, Federal University of Piauí, Teresina, Piauí, Brazil

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Nomenclature

ATP	Adenosine-5′-triphosphate
ADCC	Antibody-dependent cellular cytotoxicity
CDC	Complement-dependent cytotoxicity
cDNA	Complementary single-stranded DNA
CT	Computed tomography
Dox	Doxorubicin
ELISA	Enzyme-linked immunosorbent assay
FA	Folic acid
FDA	Food and Drug Administration
Gd	Gadolinium
GSH	Glutathione
GSSH	Glutathione disulfide
IHC	Immunohistochemistry
ICG	Indocyanine green
MRI	Magnetic resonance imaging
mAbs	Monoclonal antibodies
NPs	Nanoparticles
NIR	Near-infrared spectroscopy
PLA2	Phospholipase A2
PT	Photothermal
PTT	Photothermal therapy
PET	Positron emission tomography
QDs	Quantum dots
ROS	Reactive oxygen species
Si NPs	Silica nanoparticles
SPECT	Single-photon emission computed tomography
ssDNA	Single-stranded DNA
SWNTs	Single-walled carbon nanotubes
SPIO	Superparamagnetic iron oxide
SIPPs	Superparamagnetic iron platinum particles
SPR	Surface plasmon resonance
SELEX	Systematic evolution of ligands by exponential enrichment
USPIO	Ultrasmall superparamagnetic iron oxide
US	Ultrasound

1.1 Introduction

There is a drastic change in the healthcare services in the field of drug delivery, imaging modalities, and diagnosis with the evolution of nanotheranostic, an emerging field of nanotechnology. This new field of nanotechnology aims at combining both diagnostics and therapeutics to bring results that are more prolific in the cure of

diseases (Prabhu and Patravale 2012; Sharma et al. 2019). Nonetheless, nanoparticles (NPs) themselves may also act as multifunctional agents due to their unique properties; for instance, gold (Au) has many unique properties like surface functionalization, plasmon resonances, photo thermal ablation, and ease of detection (Yeh et al. 2012; de Melo-Diogo et al. 2017). Surface plasmon resonance (SPR) is an optical and quantitative detection phenomenon (as the incident light is converted into both scattered and absorbed component. The scattered component gives optical properties and the absorbed portion gives the thermal effect). It is used to determine molecular binding kinetics in real time. It is a label free, highly sensitive detection method and requires a very minute quantity of sample. Whereas the other techniques like ELISA gives only the binding affinity, SPR gives binding kinetics or the on-and-off phenomenon depending upon association and dissociation of molecules. The only problem with plasmon resonant NPs is low sensitivity because of background scattering by cells and tissues (Jain et al. 2007; Khlebtsov and Dykman 2010). The image quality can be improved with photothermal (PT) techniques. In photothermal therapy (PTT) electromagnetic radiation, most often near-infrared (NIR) wavelengths, are used. NIR radiation upon absorption generates heat. This heat kills the surrounding cells. This approach has already been used successfully to not only kill local cancerous cells but also the cancer cells that have been metastasized (Zou et al. 2016). PTT is actually an extension of photodynamic therapy. In photodynamic therapy a photosensitizer (for instance, porfimer sodium) is used. This photosensitizer is injected in blood. All body cells take photosensitizers. However, normal body cell releases photosensitizer more quickly as compared to cancer cell. After 24–72 h most of the photosensitizers are therefore retained only by cancerous cells and when the body is irradiated with laser beam of specific wavelength only cancerous cells are exposed to radiations. Photosensitizer produces reactive oxygen species (ROS) that kills the nearby cells (Shirata et al. 2017). Nonetheless, PTT offers more advantages over photodynamic therapy as it does not require oxygen. The penetration of PTT is better and can be used to cure deep cancer and cancer metastasis as well but the problem with PT techniques is that it requires higher laser-induced temperatures that can be detrimental to cells and molecules (Lukianova-Hleb et al. 2010).

Targeted drug delivery systems may be applied to increase the therapeutic index of the drugs and imaging agents at the targeted site. Nonetheless, the convergence of therapeutics and diagnostics in combination with nanotechnology can play a vital role for personalized and precision medicine where the drug release would be on demand (Vinhas et al. 2015; Silva et al. 2019). Nanotheranostics provide an unprecedented opportunity to integrate various components along with customized therapeutic agents, controlled-release mechanisms, targeting strategies, and reporting functionality for therapeutic detection/visualization within a nano-scaled architecture (Wang et al. 2017a; Sonali et al. 2018) (Fig. 1.1).

In this chapter, the general overview of nanotheranostics and its important components have been discussed. In addition, all the creative approaches being developed for these classes of therapies, imaging modalities, and the recent developments in the field have also been examined. It can be said that nanotheranostic is a promising

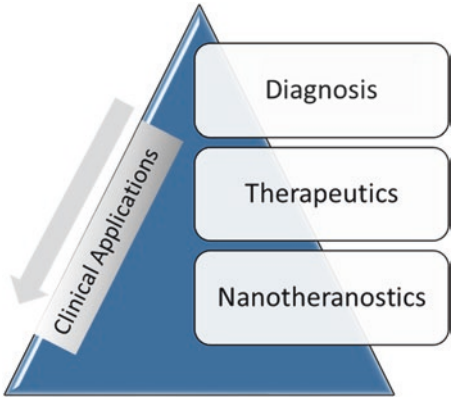

Fig. 1.1 Nanotherapeutics may offer a wide range of clinical and medical applications with less side effects

and emerging field that can offer rapid detection and targeted delivery system, which is rapid and cost-effective with reduced risks. However, there is a need to address some of the limitations related to this field before properly introducing this application in the clinics.

1.2 Nanotheranostic as a Novel Platform

An important component of nanotheranostics is developing a nanocarrier or nano-platform that has the potential to accommodate all requirement of an efficacious theranostic in one system (Kang et al. 2008; Rai and Morris 2019).

Several nanotheranostics platforms have been presented over the past decade. Nonetheless, most frequently used are the traditional ones, namely metal (gold and silver) and silica nanoparticles (Si NPs), liposomes, quantum dots, and composite NPs (Miao et al. 2019; Parchur et al. 2019; Silva et al. 2019; Xu et al. 2019) (Fig. 1.2).

Generally, the physicochemical characteristics (like size, shape, charge, and surface functionalization) of nanoparticles (NPs) determine their fate (Penet et al. 2014). For instance, very small nanoparticles, <20 nm, have rapid body distribution but are also subjected to rapid renal clearance. Whereas larger nanoparticles, >200 nm, are cleared by mononuclear phagocytic system and accumulate in various body organs like liver and spleen (Zhang et al. 2009). The pore size of tight endothelial junction in normal blood vessels is usually <10 nm whereas the size of tight junction in tumor microenvironment is much larger, i.e., >200 nm to 1200 nm. In addition to that, there is no lymphatic drainage in tumor tissues so that nanoparticles cannot escape the tumors; this is enhanced permeability and retention (EPR) effect.

These platforms allow visualization and monitoring of the route taken by the formulation, providing information about delivery kinetics, intra-organ and/or intratumor distribution, and drug efficacy. Using a single NP, it is possible to tune

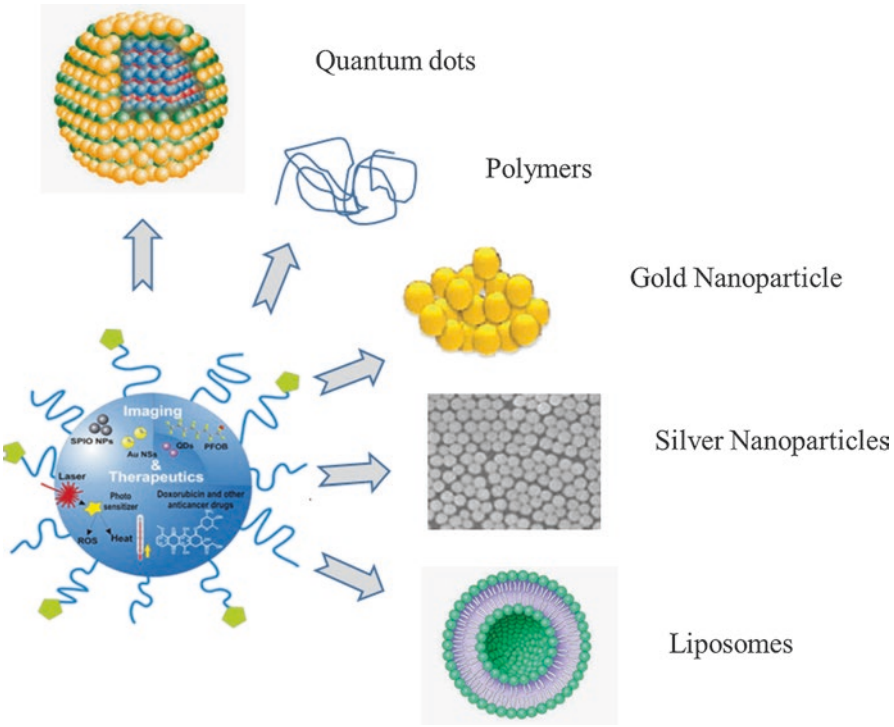

Fig. 1.2 Nano-platforms for developing a successful theranostics

therapy while simultaneously providing for real-time monitoring of disease progression (Vinhas et al. 2015).

Other important components while working with nanoparticles in nanotheranostics are understanding of type of target cells and biomarkers at the target site. Secondly, the route of administration or pathway they will follow to reach their target site (Rajora et al. 2014). Stability of nanoparticles while in the body system (in vivo), i.e., they must resist attack from body's natural immune system till they reach their specific target site and get absorbed. Shape and size of NPs used in theranostics is directly related to their efficacy (Penet et al. 2014). For example, spherical NPs are commonly used in cancer theranostics. Filamentous, rod-shaped, disk-shaped, worm like, or well-shaped, all have different features like drug loading and absorption capacity, circulation time, target uptake, absorption at target site, etc. Similarly, size range is important for the transport and absorption of NPs. Their size may vary from 50 to 200 nm according to Banerjee et al. (2016). They have tested this size range in the intestine. In another study by Loverde et al. (2012), it was found that worm-like NPs with specific probe of PEG-PBD are more effective in cancer treatment.

NPs may target the specific receptor related to the specific cellular microenvironment like hypoxia, pH, and interstitial fluid pressure. For example, lower oxygen

levels can induce cancerous characteristics in the cells and lower pH favors the tumor microenvironment around the cells (Penet et al. 2014). In case of change of interstitial fluid pressure, the passageway for any foreign body can be opened that may allow free influx or efflux in the cell with the change in cellular permeability. The foreign body can be a cancer carrier and may contain any other unwanted marker that may cause changes in the cellular functions with the increase or decrease in the cellular permeability (Wang et al. 2017b). For example, increased permeability may cause loose membranes, which in turn make it difficult to target the vasculature in the cancer microenvironment. Another example is that some of the stromal cells surrounding tumors in the body are cancerous fibroblast or macrophages in nature and can induce uncontrolled proliferation that will lead to cancer development (Rajora et al. 2014). Extracellular matrix can also be a target that can change the mechanical properties of cells and can induce tumor formation promptly (Wang et al. 2017b). Similarly, matrix metalloproteinases are responsible for tumor growth, formation of tumor blood vessels, metastasis, and invasion and are considered a targeted site for tumor detection as they are overly expressed on cancer cells than on normal cells (Yoon et al. 2003).

Nanoparticles have some unique intrinsic properties that lead to its application in functionalization and imaging utility. For example, their specific sizes have strong utility and advantage toward the target site of action, especially in cancer treatment (Rajora et al. 2014). The specific small size supports their blood circulation time over standard chemotherapeutics in vivo and increases the chances of absorption from tumor blood vessels into tumor tissues through tumor vasculature (Penet et al. 2014). Another property that NPs have surface-area-to-volume ratio that is high enough to give loading capacity to imaging probe and targeting ligands in case of cancer therapy is another benefit for them to become nanotheranostics (Loverde et al. 2012). All these features of nanoparticles strongly benefit the field of personalized medicine in diagnosis even based on biomarker identification (Mura and Couvreur 2012). These diversified properties of NPs make them a choice in cancer treatment and management for optimizing treatment strategies and their effects along with targeted diagnosis.

It is strongly observed in past studies that nanoparticles are very useful tools that can play a vital role in early diagnosis and in targeted drug delivery. Nonetheless, human body is not a single compartment, rather a combination of multifaceted and multifarious enzymes, organs, and systems, and every individual is genetically and phenotypically different from all others. Every individual responds to treatment differently, and thus the development of bioresponsive nanotheranostics to cater to the requirement of individual need requires a deep understanding of the pathophysiological features of many distinct types of diseases. The tissue microenvironment in disease is different from healthy tissues like in case of infections and tumors blood flow and pH changes. Consequently, there are many other biomarkers (it's an indicator to show the presence or severity of a disease like antibody for a specific antigen indicates infection) that are specifically expressed in disease tissues. These biomarkers basically provide foundation for personalized treatment (treatments individually tailored to specific patients).

1.3 Biomarkers for Theranostics

Biomarkers can be used synonymously to molecular markers. Although biomarkers are in clinical use since ancient times, nowadays more focus is on development and identification of molecular biomarkers that could diagnose disease accurately at early stages and could predict treatment in response to stimuli and can also be able to predict prognosis. Stimulus for nanotheranostics might be external or internal (Raza et al. 2019).

External stimulus is commonly used as imaging biomarkers. Imaging biomarkers offer several advantages like patient convenience, noninvasive procedure, and highly intuitive. By imaging biomarkers one can get both qualitative and quantitative data. It includes computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), near-infrared spectroscopy (NIR) that responds to magnetic field, temperature, ultrasound, light, or electric pulses (Wilhelm et al. 2016).

Considering the limitations of external stimuli, numerous internal stimulus such as glucose concentrations, pH differences, redox reactions, and other ions/small biomolecules are more efficient for the designing of smart drug delivery systems (Fig. 1.3).

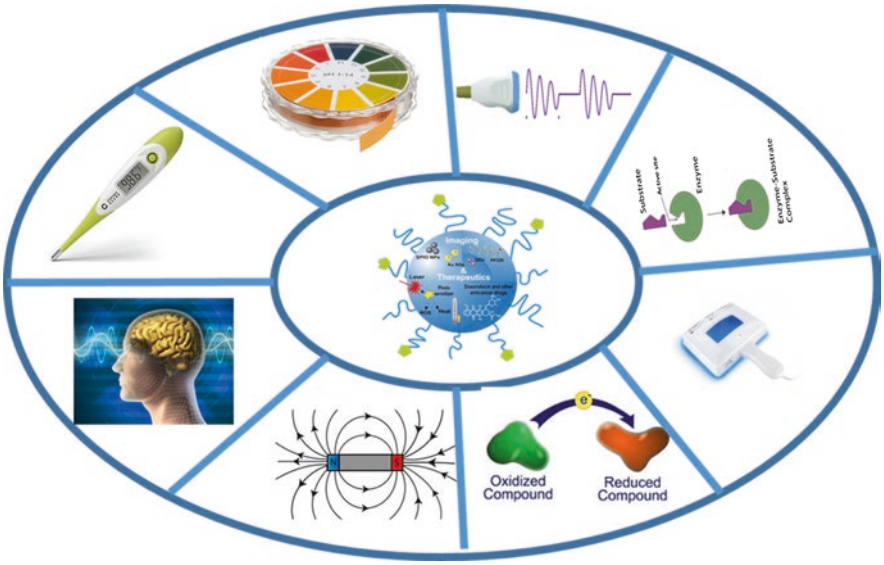

Fig. 1.3 External and internal stimuli for theranostics

1.3.1 Internal Body Signals for Theranostics

1.3.1.1 pH as Stimuli

Among all internal stimuli, pH difference is a most regularly investigated internal body signal for developing targeted theranostics. Tumor microenvironment, infected tissues, ischemia, and rheumatoid arthritis have acidic pH as compared to normal body tissues (Du et al. 2011; Wu et al. 2014; Ju et al. 2016; Fernandez-Piñeiro et al. 2017; Li et al. 2017a). Tumor microenvironment has more energy requirement because of rapid and uncontrolled growth of tumor cells. It results in high lactate and hydrogen ion concentration which reduces the pH to 6.5. It is pertinent to mention that normal body tissues have 7.4 pH. Hence, the difference in pH can serve as a key biomarker for targeting certain disease.

There certainly exist many materials that are sensitive to slight pH differences. Tertiary amines and imidazoles have the property of switching their state after sensing pH difference. They are hydrophobic at pH > 7 whereas hydrophilic at pH < 7. They form agglomerates at higher pH and as the pH drops they release their drug cargo in aqueous environment (Li et al. 2017b). In addition to that, intracellular compartments like endosomes and lysosomes are also acidic in nature having 5.5 and 5.0 pH, respectively. Many endogenous pathogens can therefore be targeted directly by these intracellular vesicles (Wu et al. 2018).

pH-responsive nanomaterials have been used to design sensitive nano-systems for drug delivery as they can stabilize the drug at physiological pH and release the drug when the pH trigger point is reached (Gao et al. 2010; Liu et al. 2014; Eskiizmir et al. 2017).

1.3.1.2 Redox Reactions

Another important stimuli that is used for biomedical appliances is the utilization of oxidation-reduction reactions (Zhang et al. 2017). Glutathione (GSH) naturally exists in the cells and serves as a protective agent to prevent damage caused by reactive oxygen species (ROS). It has the ability to donate electrons and form glutathione disulfide (GSSH) (Fig. 1.4).

In healthy cells the ratio of GSH to GSSH is 90:10 and in disease state this ratio gets disturbed with the increase in the concentration of GSSH. The concentration of GSH to GSSH is called oxidative stress. Oxidative stress is an indicator of many pathological disorders. Redox-responsive polymers sense the presence of ROS and

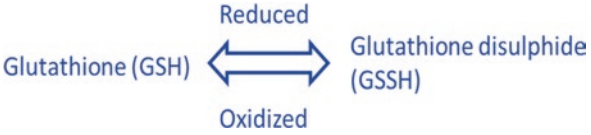

Fig. 1.4 Conversion of glutathione (GSH) to glutathione disulfide (GSSH)

release their cargo where there is high oxidative stress (Iamsaard et al. 2018; Yang et al. 2018). Redox-responsive polymers can be fabricated by incorporating disulfide, diselenide, and boronic ester linkages in the polymers (Huo et al. 2014).

1.3.1.3 Hypoxia

Another important feature of tumor microenvironments is low oxygen pressure, called hypoxia. It is caused by consumption of oxygen by rapidly proliferating cells. The tumor cells adapt to hypoxic environment by their genetic instability. Hypoxia microenvironment is also a marker of angiogenesis, poor prognosis and enhanced tumor aggressiveness and metastasis (Jiang et al. 2018). Likewise, the therapeutic efficiency of radiotherapy also gets reduced because of hypoxia (Hu et al. 2018). However, hypoxia serves as an opportunity to target tumors which have reductive state. Many hypoxia-selective drugs like azobenzene, nitroaromatics, and quinones have been developed to trigger drug release in the absence of oxygen (Wang et al. 2017a).

1.3.1.4 Enzyme-Responsive Nanotheranostic Agents

Enzymes are essential component of all metabolic reactions/processes because of their catalytic properties and their dysregulation leads to many abnormalities and pathological conditions. Enzyme-responsive nanotheranostics can bring more significant and controlled response with small dose by their biocatalytic nature. In addition to that, they also exhibit more specific chemical reactions (Andresen et al. 2010; de la Rica et al. 2012; Popat et al. 2012; Hu et al. 2014). Enzyme-responsive nanotheranostic offers many advantages, such as more selectivity and specificity. Many enzymes like hydrolases, oxidoreductases, proteases, transferases, and phospholipases can be used in nanotheranostics. Phospholipase-based theranostics utilizes the upregulation of phospholipase A2 (PLA2). PLA2 upregulation has been a pathological indicator for multiple kinds of cancers and many other disease processes, including thrombosis, congestive heart failure, inflammation, neurodegeneration, and infectious pathogens (Scott et al. 2010; Hu et al. 2014).

1.3.1.5 Nucleic Acids (i.e., DNAs or RNAs) as Bioresponsive Switches

Nucleic acid sequences (both DNA and RNA) have unique sequences and hence can also be used as reliable biomarkers. These are generally used as fluorophore-labeled single-stranded DNA (ssDNA) in combination with nanoparticles (Xia et al. 2017). In one approach, polymer-coated iron oxide nanoparticles were used and fluorophore-labeled single-stranded DNA (ssDNA) was joined with the nanoparticles (Fig. 1.5). As the system target mRNA inside the cells dye-labeled ssDNA is released from the closed system and produces fluorescence (Lin et al. 2014).

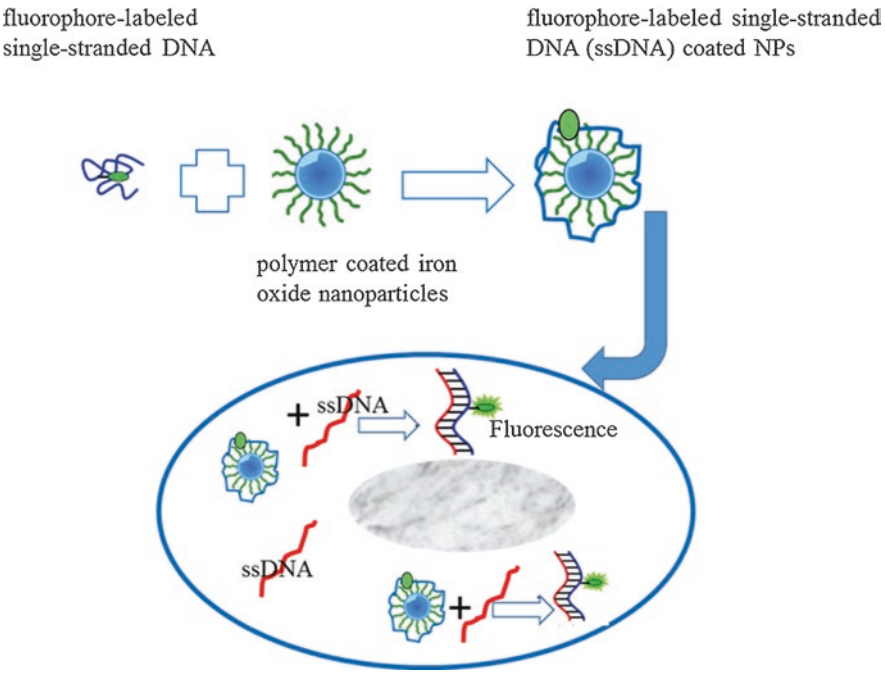

Fig. 1.5 Mechanism of using ssDNA as bioresponsive switch

1.3.1.6 Small Biomolecule-Responsive Theranostics

In addition to specific macromolecules, small biomolecules such as adenosine-5′-triphosphate (ATP) and GSH have also been exploited as biological triggers for stimuli-responsive theranostic applications. ATP is a readily available coenzyme in intracellular environment and is used to provide energy during cellular metabolism. In this regard, Mo et al. (2014) developed a polymeric nano-vehicle comprising an ATP-responsive DNA motif (containing ATP aptamer and its complementary single-stranded DNA (cDNA)) with anti cancerous drug (doxorubicin (Dox)), protein (m-protamine) and hyaluronic acid for "on-demand" release of drugs. The drug was loaded in GC sites of DNA. In the presence of ATP, the doxorubicin was released from DNA motif after conformational changes (Mo et al. 2014; Wang et al. 2017a).

1.3.2 External Body Signals or Molecular Imaging Probes/ Agents Used for Theranostics

Molecular imaging can be defined as "it is the visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems" (Thakur and Lentle 2005; Mankoff 2007). Currently,

many techniques like optical imaging (bioluminescence and fluorescence), magnetic resonance imaging (MRI), nuclear imaging, computed tomography (CT), single-photon emission computed tomography (SPECT), positron emission tomography (PET), and ultrasound (US) are being used for molecular imaging (Mankoff 2007; Janib et al. 2010). CT and MRI are not sensitive enough to detect pathological disease markers at early stages; however, PET can do so. PET can efficiently investigate sophisticated processes like receptor binding, DNA synthesis or enzyme activity, oxygen metabolism and blood flow (Vinhas et al. 2015; Wang et al. 2017a).

Nonetheless, for developing smart bioresponsive nanotheranostics that can monitor drug trafficking and therapeutic efficiency and that can provide an on-demand drug release after sensing the disease progression, more sensitive nanoimaging modalities are required (Kelkar and Reineke 2011).

1.3.2.1 Types of Imaging Probes

Near-Infrared (NIR) Imaging

The electromagnetic spectrum of NIR ranges from 780 to 1700 nm. It is further subdivided into NIR I and NIR II regions. NIR I ranges from 780 to 900 nm and NIR II from 900 to 1700 nm (Fig. 1.6).

- NIR I imaging can be done by two type of dyes, namely,
  - Ujoviridin (indocyanine green)
  - Provayblue (methylene blue)

These two dyes emit short wavelength radiation in NIR I region. Although they are better in terms of tissue penetration as compared to visible probes, they are incompatible with CT and MRI because of photon scattering by tissues.

Imaging in NIR II window is characterized by reduced photon scattering and thus aid in improving image quality with lessened background fluorescence. Two types of NIR II imaging techniques are used, namely NIR II-emission imaging and NIR II-excitation imaging.

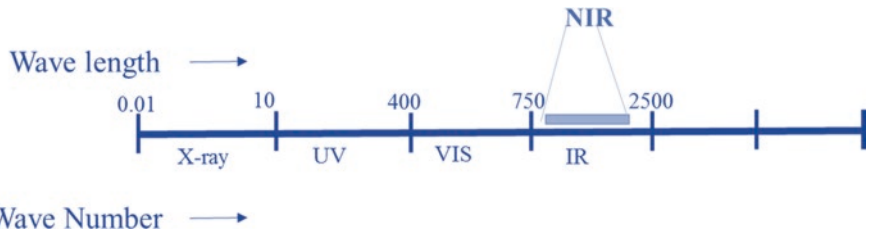

Fig. 1.6 Electromagnetic spectrum

- **NIR II-emission imaging**. Probes used for this type of imaging emit NIR II radiation upon excitation. Four types of probes are used for this purpose, namely,
  - ***Small molecule dyes*** like indocyanine green (ICG) which usually emits luminescence in the NIR I region; however, its liposomal formulation emit radiations in the second near-infrared window (NIR II) (Bhavane et al. 2018).
  - ***Single-walled carbon nanotubes (SWNTs)***
  - ***Quantum dots (QDs)***
  - ***Rare earth-doped nanoprobes***, for example, ytterbium (Yb^{3+}), neodymium (Nd^{3+}), praseodymium (Pr^{3+}), holmium (Ho^{3+}), erbium (Er^{3+}), and thulium ions (Tm^{3+})-doped nanoprobes can emit strong NIR II emission under suitable external excitation sources.
- **NIR II-excitation imaging.** In this type NIR II radiations as excitation source is used. Upon light excitation, the NIR II-excited probes release the luminescence signals in combination with acoustic signal (sound) or thermal heat. Consequently, three types of probes are used in this type of imaging to get luminescence, photoacoustic and thermal image (Liu et al. 2018).

Magnetic Resonance Imaging (MRI)

In MRI contrast agents are widely used to increase the contrast difference between normal and abnormal tissues. The majority of MRI contrast agents are either paramagnetic (having unpaired electron and are attracted toward an applied magnetic field. It includes aluminum, oxygen, titanium, and iron oxide. These are also temporarily magnetized upon application of external magnetic field) or superparamagnetic (iron oxide) magnetite particles (Xiao et al. 2016). However, MRI contrast agents may be divided into lanthanides and transition elements. Lanthanides include gadolinium (Gd), iron, nickel, and cobalt (Faulkner and Blackburn 2014). However, Gd is the only one that can be magnetized at room temperature. Transition element includes manganese and iron (Cortezon-Tamarit et al. 2017). Manganese is used to detect liver lesion and functional brain imaging. Iron is used either as superparamagnetic iron oxide (SPIO) or as ultrasmall superparamagnetic iron oxide (USPIO) and both are used for detection of liver cancer. Superparamagnetic iron platinum particles (SIPPs) after encapsulated in phospholipids are used to detect prostate cancer.

Although MRI contrast agents are routinely used in the clinics, they are associated with numerous side effects and short half-life. Nonetheless, nanoparticles can render them safer. Against this back drop AuNPs, Gd-loaded acetylated dendrimer-entrapped gold nanoparticles (AuDENPs), silica layer-coated gold nanorods have been developed and have displayed better results (Ghosh et al. 2008; Vinhas et al. 2015).

Nuclear Imaging Agents (PET/SPECT Agents)

Nuclear imaging agents are done via gamma and positron emitters. It includes positron emission tomography (PET) and single photon emission computed tomography (SPECT) (Velikyan 2012). Technetium-99m or iodine-123 are gamma emitters and SPECT uses gamma cameras to detect them. Whereas, gallium-68 is positron emitter and SPECT uses it (Yordanova et al. 2017).

1.4 Targeted Therapy or Image-Guided Therapy

Targeted therapy is the foundation of precision therapy and a wide variety of molecules have been utilized for this purpose that may range from hormones to cytokines, antibodies, and peptides. In image-guided therapy digital imaging is utilized to guide therapy or surgery.

1.4.1 Antibody Theranostics

For a successful theranostic agent, targeted therapy is essential that could be achieved through monoclonal antibodies (mAbs). It makes treatment more specific. To date, several mAbs have been approved by the Food and Drug Administration (FDA) for the treatment of cancer. However, for antibodies to be used determination of target expression is necessary and also to understand whether target antigen is associated with disease progression or not.

Target expression can be determined by various techniques, such as:

- Immunohistochemistry (IHC).
- Hematological analysis by ELISA or flow cytometry.
- Immuno-positron emission tomography (PET)/immuno-single photon emission computed tomography (SPECT) (Fleuren et al. 2014).

1.4.2 Photothermal Ablation Agents

Thermal ablation of cancerous cells is a well-known therapy in which nanoparticles absorb energy of the illuminating laser and generate heat. The heat ultimately destroys the surrounding cells that might be diseased or healthy cells as well (Grosges and Barchiesi 2018). Scientists, therefore, are trying to develop target-specific photothermal ablation agents. Gold nanorods and colloidal gold nanospheres have more frequently been used as theranostic agents (Vinhas et al. 2015).

1.4.3 Aptamers Theranostics

Aptamers are peptide molecules or oligonucleotides that bind to specific target only and are selected from pools of oligonucleotides by a process known as systematic evolution of ligands by exponential enrichment (SELEX). They have the ability to recognize a wide variety of targets with high affinity and specificity just like antibodies. However, they are more preferred over antibodies as they are more stable, less immunogenic, and easy to prepare (Xing et al. 2014).

1.5 Limitations

Herceptin® is the first of the humanized antibody capable of simultaneously detecting and treating HER2-positive metastatic breast cancer. Unfortunately, many other scientists tried to follow Herceptin® model but failed to develop successful therapeutic agent. However, the emerging field of nanotechnology has paved the way for the development of theranostics agents for a sustained, controlled, and targeted delivery of therapeutics coupled with the capability to follow in real-time distribution to tissues and organs, thus allowing therapy evaluation. These nanotheranostics have been designed keeping in mind the selectivity for the most appropriate and effective therapy with fewer side effects. Albeit, many nanomedicines like Doxil® Myocet®, DaunoXome®, DepoCyt®, Abraxane®, Resovis®, Genexol-PM®, and Oncaspar® have already been to the market. Thus, smartly designed NPs have already made their way to the clinics, but the development of an equivalent able to combine both strategies is still underway. Indeed, several platforms have already been proposed integrating therapeutic strategies (i.e., chemo-, genetic-, immunotherapy, photothermal ablation) and imaging agents to monitor NP fate, e.g., MRI, CT, and photoacoustic tomography (PAT) (Vinhas et al. 2015).

Potential obstacles to successful nanotheranostics include the discovery and targeting of new biomarkers, the innate toxicity of the nanoparticle components, formulation stability, production costs, and control of intellectual property (Janib et al. 2010; Vinhas et al. 2015).

There is no single therapeutic agent, which has the same effect on all patients, suffering with the same type and stage of cancer while treating cancer. This is the point where precision medicine or personalized medicine are considered as a treatment of choice, as they can personalize a treatment that is best suited for individual patient. The molecular mechanism of action of these medicines is designed on the basis of patient genetic makeup, expressed proteins, and metabolites. Therefore, with the help of genetic sequencing of patient, personalized medicines help in discerning individual patient susceptibility (Kim et al. 2016) toward the developed disease and in turn designing the disease prevention regimes. Understanding and further research in this field specifically will help the pharmaceutical industry in improving the efficacy of these drugs for individual patient to

benefit at maximum. The therapy design based on identified molecular information of individual patient may promise patient treatment with lesser side effects (Kim et al. 2016).

1.6 Conclusions

Converging diagnosis and therapeutics based on nanotechnology is opening a new way toward accurate and personalized medicine. Developing smart nanotheranostics that act on the bioresponsive systems have recently evolved and offering promising result with high accuracy and efficiency at targeted point via on-demand drug release. Intelligent nanotheranostics has both therapeutic and diagnostic capabilities. It can be said that nanotheranostics is a promising and emerging field that can offer rapid detection and targeted delivery system that is rapid and cost-effective with reduced risks. However, there is a need to address some of the limitations related to this field before properly introducing this application in the clinics.

Considering the limitation of external stimuli, numerous internal stimuli such as glucose concentrations, pH differences, redox reactions, and other ions/small biomolecules are more efficient for the designing of smart drug delivery systems.

The emergence of nanotechnology has provided an opportunity to promote the development and design of novel nanotheranostics. From this perception, the performance of nanotheranostics should be observed not only before or after but also throughout the therapy and after gaining extensive information about their genotoxicity, cytotoxicity, immunotoxicity, and cost-effectiveness, the nanotheranostics can be introduced into routine healthcare as an important element of personalized and predictive medicine.

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