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Title page

Current update on nanoplatforms as therapeutic and diagnostic tools: a review for the materials used as nanotheranostics and imaging modalities

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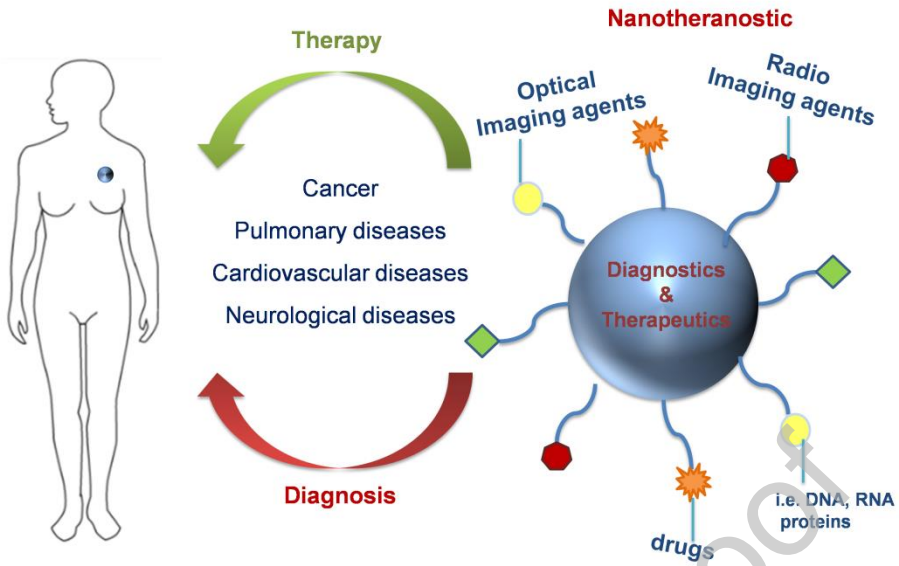

Graphical Abstract

Abstract:

In the last decade, the use of nanotheranostics as emerging diagnostic and therapeutic tools for various diseases, especially cancer, is held of great attention. Up to date, several approaches have been employed in order to develop smart nanotheranostics, which combine bioactive targeting on specific tissues as well as diagnostic properties. The nanotheranostics can deliver therapeutic agents by concomitantly monitor the therapy response in real-time. Consequently, the possibility of over- or under-dosing patients is decreased. Various non-invasive imaging techniques as positron emission tomography, single photon emission computed tomography, computed tomography, magnetic resonance imaging, optical imaging and ultrasound, have been used to quantitatively monitor the drug delivery processes. Radiolabeling of nanomaterials is widely used as powerful diagnostic approach on nuclear medicine imaging. In fact, various radiolabeled nanomaterials have been designed and developed for imaging tumors and other lesions due to their efficient characteristics. Inorganic nanoparticles as gold, silver, silica based nanomaterials or organic nanoparticles as polymers, carbon based nanomaterials, liposomes have been reported as multifunctional nanotheranostics. In this review, the imaging modalities according to their use in various diseases are summarized, providing special details for radiolabeling. In further, the most current nanotheranostics categorized via the used nanomaterials are also summed up. To conclude, this review can be beneficial for medical and pharmaceutical society as well as material scientists who work in the field of nanotheranostics since they can use this research as guide for producing newer and more efficient nanotheranostics.

Keywords: Theranostics; Nanomedicine; Nanotechnology; Nanoparticles; Radiopharmaceuticals

1. Introduction

Nanomedicine is an emerging field combining nanoscience, nanoengineering, and nanotechnology with life sciences, revealing interesting results for the medical community and society[1,2]. There are several nanomedicine platforms; however nanotechnology-based drug delivery systems as well as imaging nano-agents are of the greatest interest[3].

Theranostic nanomedicine involves the use of theranostics with nanosizes and multiple capabilities such as targeted delivery, sustained/controlled release, greater transport efficiency via endocytosis, stimuli responsive systems and the combination of therapeutic approaches such as multimodality diagnosis and therapy [4]. The "theranostics" word is referred to systems that can be both applied as therapeutics and imaging agents [5]. Nanotheranostics (Fig. 1) are strategies based on carriers of submicron or nano sizes [1,6]. Such nanotheranostics can be obtained from polymeric nanoparticles [7], dendrimers[8], liposomes [9], carbon based nanomaterials [10], metal or inorganic nanocarriers [11] and systems which integrate both of such categories i.e. polymeric coated nanocarriers [12,13]. Carbon based nanomaterials, as carbon nanotubes either alone or decorated with other materials[14,15], graphene oxide[16–18], fullerenes, carbon quantum dots[19], have been employed for the detection of drugs in biological samples or their imaging ability. Prussian blue cubes are octahedral metal hexacyanoferrates which have been developed as detection tools due to their conductive and magnetic properties [20,21]. An ideal nanotheranostic should circulate for a long time in the body, present sufficient release behavior, great tissue target specificity and penetration, imaging probability and high target to background ratio[22]. Various nanotheranostics have the ability to localize diagnostic and therapeutic agents in specific sites of diseases and reduce undesired side effects. Their extended circulation time in blood is related with their nanometric size. In case of nanotheranostics applying for tumor diagnosis and therapy, the nanosized particles can easily extravagate from the blood into tumor tissues and be retained as a result of poor lymphatic drainage when compared to multifunctional small molecules or functionalized macromolecules [23–25].

At present, nanomedicine has provoked novel and promising applications in diagnostics and invasive therapy of various diseases. However, the development of novel tools with improved imaging characteristics, which can lead to early detection of diseases, is still of high importance. In addition, imaging agents, which can efficiently detect cancer in early stages,

are beneficial for medical society. Aside from this, the nanotherapeutics are also key components for treatment of serious diseases [26]. Nonetheless, currently, most of the reported nanoparticles (NPs) are evaluated according to the results of animal models, and clinical studies are rarely performed. In the past, most of the applications based on nanotheranostics involved their use in cancer [27] but in the present, nanotheranostics for diseases such as neurological disorders [28], cardiovascular diseases (CVD) [29] have been also arised. Preclinically, theranostics have been gradually applied to CVD with encouraging findings[30].

Nuclear medicine imaging has been widely examined as advanced diagnostic tool and includes the introduction of radionuclides into the body, detection of the emitted gamma rays and generation of images which provide detailed radionuclides distribution as well as physiological characterization of organs and tissues [31]. Various nanoimaging agents have been produced presenting dual behavior as both diagnostic and therapeutic tools. However, some of these nanomaterials present low distribution, low cell penetration and thus their undesired pharmacokinetics should be improved. Many novel strategies have been employed in order to improve their pharmacokinetics and biodistribution [32].

The past years, the applications of nanotheranostics or NP based theranostics have shown an enormous advancement. By summing up the current developments on nanotheranostics could assist medical professionals on providing further progress in this field. All the more, analyzing the current application of imaging modalities and nanotheranostics could also provoke an evolution on nanomedicine field.

2. The application of imaging modalities in nanomedicine field

The last years, the integration of nanotools with life sciences led to the design of various diagnostic devices, contrast agents, and drug delivery nanosystems. The multifunctional nanoscaled materials (Fig. 2) in most cases present promising biological activities, stability and improved biodistribution compared to larger monofunctional particles [1,2]. Besides, it has been reported that there is a correlation between the sizes and the chemical composition of nanoparticles and their internalization on cellular or intracellular surfaces. In general, nanoparticles with sizes under 200 nm can be attached into the cells [33]. Although these nanosystems could provide complementary information arisen from different imaging agents, they don’t present equivalent properties. Thus, when a new nanotheranostic system is

designed, the imaging part should be chosen according to the intended administration route. For example, the targeted delivery of imaging agents should be carefully examined in order to evaluate the possible effects of the specificity of targeting and potential toxic side effects caused by off-target accumulation of NPs[1,2].

There are many imaging systems used in radiopharmacy, nuclear medicine and radiology areas. The radiographs, ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are common imaging techniques in radiology. These methods allow the diagnosis of many diseases, mostly in cancer. Nonetheless, when the cancer cell becomes visible, it will contain about 1 billion cancer cells at about 1 cm^3. Thus, the diagnosis of tumor area would be too late since the phenotypic changes begin. The detection of cancer earlier at the molecular level is very important for therapy. Because of this, the research has been focused on from radiological imaging to nuclear medicine imaging. Nuclear medicine imaging is described as the *in vivo* measurement of biological processes at the cellular and molecular levels, and the genetic alterations in the tissues. It also images the pathophysiologic situation noninvasively, and provides information regarding specific molecular changes, to perform early diagnosis, identify the stage of disease, fundamental information on pathological processes, and prognosis of disease and personalized medicine administration [34,35]. Nanotheranostics offer multiple and desirable advantages over conventional drug products. They can be easily prepared using standard nanotechnology procedures to provide designed functionalities and to achieve specific targeting; their surface can be conveniently modified with numerous ligands or moieties by linking, conjugation or coating[11,36,37].

Generally, NPs for imaging are classified in four major groups: magnetic NPs[38], magnetofluorescent NPs [39], Fluorescent NPs [6] and radiolabeled NPs [40]. They are being applied into various imaging modalities including optical, molecular, radiologic and nuclear medicine imaging [41–43]. Magnetic NPs are consisted of metals which have magnetic features. They can be prepared directly or by integrating into polymeric matrix. Recently, magnetic micro/nanoparticles have been widely used to facilitate location of cancer cells [44,45] either with the help of hyperthermia or non. Due to their magnetic features, they are handful in the diagnosis of various diseases such as treatment of cancer and neurologic disorders. In various cases, drugs are attached to magnetic NPs creating a driving force for delivery. Additionally, magnetic NPs are used as contrast agents for cancer diagnosis, molecular imaging, hyperfusion region visualization, T cell-based radiotherapy, detection of

angiogenesis, apoptosis and gene expressions [46,47]. Fluorescent-magnetic NPs are multifunctional nanomedicals, composed of magnetic and fluorescent parts. The combination of these properties in single system plays a crucial role in theranostics field. They are beneficial for *in vitro* studies and *in vivo* imaging such as magnetic resonance imaging and fluorescence microscopy [48–50]

Radiopharmacy is a multidisciplinary science area and responsible for the development, formulation, preparation, quality control and administration of radiopharmaceuticals[35]. Radiopharmaceuticals are drugs containing radionuclides and pharmaceutical parts, used for the diagnosis or treatment of many diseases [51]. The pharmaceutical part is chosen on its on the basis of its preferential localization in the organ which is desired to be imaged or participation its in the physiological function of the organ. After its selection, the pharmaceutical part is labeled with a suitable radionuclide and after its localization in the organ it can be detected with various imaging methods [52]. Various nanotheranostics based on polymeric NPs have been developed and radiolabeled with available radionuclides using various methods [53,54] aiming the diagnosis and treatment of diseases [55]. Linking molecules such as chelator agents are binding to radionuclides and NPs (Fig. 3) in order to improve their stability [56]. The properties of short, medium, and long half-lives of radionuclides, its radioactive decay and chemical structure could affect their potential application in clinical trials (Fig. 3). Hence, the radiopharmaceutical should be carefully chosen. For example, radiopharmaceuticals which emit gamma rays and beta particles have theranostic features. They serve both of diagnostic and therapeutic facilities to determine the physiological or anatomic situation in tissues. The selection of radionuclide has important role for targeting of nanotheranostic to desired area. If gamma, beta and alpha emitters are used to radiolabel NPs, then the NPs obtain the theranostic property [57]. These emitters can also induce the visualization of the cellular function and the monitoring of the molecular process in the cells. Technetium-99m is frequently applied as radionuclide to radiolabel nanosytems, presumably because of its wide availability, low cost, favorable imaging properties, and a half-life (6 h) that allows imaging for up to 24 h [58]. Indium-111 is the second most-used radionuclide, followed by radioisotopes of iodine [59]. More recently, positron-emitting radionuclides such as Flour-18, Manganez-52, Zirconium-89[60] have been increasingly used, reflecting the growing interest in positron emission tomography (PET) imaging and the increasing availability of preclinical and clinical PET scanners in radiopharmacy and nuclear

medicine applications [54]. Another important parameter for the selection of radiation types are the energy levels of the emitters. The β- and γ- emitters are widely used, due to their long ranges and manageable energy levels. The α particle, or helium nucleus, is of very high mass and high energy, with very short range and thus it considered as unsuitable for radiation therapy due the extensive damage it causes to tissues[61].

Another significant factor for choosing the suitable radionuclide is the effective half-life, which is the net half-life considering both physical half-life and biological half-life within the patient's body or organs. It has been reported that an acceptable half-life is within 6 h and 7 d. This is because a very limited physical half-life restricts the delivery . In further, a physical long-life reserves the radiation dose and patients should be isolated for longer time while surrounding people are being exposed in radiation doses for more time. If the biological half-life is too short, the radionuclide will be discharged with a significantly high activity, leading to extensive radioactive waste management. Another feature which should be considered is decay product. More specifically, an ideal radiopharmaceutical should be able to decay into a stable daughter product [62]. While the radionuclides with short half-lives are preferred due to their diagnostic properties (e.g., technetium-99m, gallium-68 and iodine-123) and used as imaging agents, radionuclides with medium half-lives present therapeutic properties (e.g., gallium-67, lutesium-177, yttrium-90 and iodine-131) and used in radiation therapy. The use of radionuclides containing very long half-lives in clinical research are common for the determination of absorption, distribution, metabolism, and elimination parameters of new drug delivery systems [63,64].

2.1. Nanoimaging applications for cancer

Cancer is the second leading cause of death worldwide [65]; hence, early diagnosis and timely treatment of cancer are of great importance. The most common type of cancer is lung cancer followed by hepatic, colorectal, gastric and breast. In the last decade, various diagnostics and therapeutic tools for cancer have been emerged [66,67]. Laboratory diagnosis of cancer is limited to later stages of the disease and specific malignancies [68]. Consequently, early diagnostics markers should be encouraged. The classic approaches on cancer management involve the combination of surgery, radiotherapy, chemotherapy and hormonal therapy [69]. The available chemotherapy pathways as intravenous, oral [70] and topical [71].

The current cancer theranostics include the detection of novel biomarkers as advanced molecular diagnostics, new molecular imaging probes and techniques for early identification

of cancer, molecular imaging guided cancer therapy and nanoplatforms incorporating both cancer imaging and therapeutic substances. The imaging techniques such as PET and single-photon emission computed tomography (SPECT) and fluorescence reflectance imaging (FRI) are widely used. Especially, PET and SPECT systems are nuclear medine imaging techniques and various radiolabeled nano systems have been administered through these methods. For these methodologies , the important fact is all the targeted molecules or the cells to become visible. Genetic agents such as photoproteins, PET [72] and Magnetic Resonance detectable reporter genes or radiolabeled particles[73], fluorochrome [74], magnetic molecules as labeled antibodies, small molecules or biorthogonal agents [75] are widely used.

The nanotheranostics for cancer can be categorized as conventional and biomimetics[76]. Conventional nanocarriers, such as liposomes, micelles, nanogels, and nanoparticles present great potentional as anticancer strategies. However, their use as imaging or diagnostics is limited since they should be efficiently conjugated with fluorescent dyes or other active molecules before their application [76]. In addition, such systems should be also functionalized with agents such as poly(ethylene glycol) (PEG) which can increase the circulation time [2,77]. Biomimetics nanosystems as nanotheranostics have gained researchers' attention since they can combine biological activities of biomimetic compounds such as proteins, phospholipids, cholesterol, cell and cell membranes, pathogens as bacteria and viruses and other pathogens, apatite and exosomes [76]. The current cancer nanotherapeutics rely on the improved permeability and retention (EPR) effect according to which NPs tend to accumulate in tumor tissue much more than they do in normal tissues. However, such a phenomenon is dependent on the tumor microenvironment and is not consistently observed in all tumor types, thereby limiting drug transport to the tumor site. In addition, it has been shown that EPR effect is not translated in the majority of humans cancers. Thus, cancer nanotheranostics should be studied in more clinically relevant cancer models should be used or in tumors which present a strong EPR effect in the clinic, such as Kaposi sarcoma and head and neck tumors [78,79].

Furthermore, cancer nanotheranostics are associated with stimuli such as light, temperature, magnetism, and sound. Photodynamic, photothermal, or phototriggered therapeutic systems are related with light or photo stimuli. The photodynamic therapy (PDT) [80] involves the administration of a tumor localizing photosensitizing agent, which may require metabolic synthesis (i.e., a prodrug), followed by activation of the agent by light of a specific

wavelength. This therapy results in a sequence of photochemical and photobiologic processes that cause irreversible damage to tumor tissues. However, conventional PDT is not yet widely used for clinical cancer treatment [81]. Photothermal therapy (PTT) includes cancerous tissue irradiation with electromagnetic radiation, which induces thermal tissue damage. Finally, in phototriggered drug release, the active molecule modified with light responsive agent and the drug release in proper amount and time [82]. For example, recently a light triggered system for tumor diagnosis, combined photodynamic and hypoxia-activated prodrug therapy based on liposomes gene probe, hypoxia-activated prodrug Tirapazamine and photosensitizer Chlorin e6 was r prepared[83]. Optical imaging theranostics involve phosphorescence, bioluminescence, fluorescence, Raman, and photoacoustic imaging[72]. Fluorescence imaging [84] is a form of luminescence that results from the emittion of light of a certain wavelength after absorbing electromagnetic radiation[74]. Through fluorescence, images of fluorescent dyes and fluorescent proteins to mark molecular mechanisms and structures can be obtained [85]. A nanoplatform, comprised from silicon naphthalocyanine encapsulated in PEG-b-poly(ε-caprolactone) nanoparticles, was developed for Fluorescence image-guided surgery. The animal studies exhibited that the activatable NPs can accumulate at the tumor site following systemic administration, releasing the silicon naphthalocyanine. It was revealed that the combinatorial phototherapy mediated by the nanoparticles could efficiently eradicate chemoresistant ovarian cancer tumors [86].

Magnetic nanotheranostics composed of magnetic substances (magnetite, iron oxide etc) which after providing an external magnetic field can concentrate and retain the nanocarriers in specific cancerous area [87]. They are used for imaging (serving as contrast agents for MRI), therapy (combined hyperthermia-chemotherapy) as well as cell separation (cell labeling/tracking and isolation using magnetic force). Another example of magnetic nanotheranostics is their ability to be heated under a high frequency magnetic field which can induce cancer cell death [24,88]. The most common used magnetic diagnostic tool is MRI. MRI is a non-invasive tool, which produces images with high spatial and temporal resolution and used in radiology to form pictures of the anatomy and the physiological processes of the body. MRI scanners use strong magnetic fields, magnetic field gradients, and radio waves to generate images of the organs in the body. The majority of MRI scans don't need contrast agents, however over than 35% of clinical MR scans use contrast agents to improve their sensitivity and diagnostic accuracy. For instance, Prussian blue nanoprobes were designed as

nanoplatforms for tumor imaging via PTT and MRI, due to their low toxicity and excellent *in vivo* performance [89]. Another example is the development of hollow manganese/cobalt oxide nanoparticles as cancer nanotheranostics. The developed nanoplatforms can act as glutathione-responsive contrast agents for dual T_1/T_2-weighted MRI [90].

Ultrasound nanotheranostics are another significant category used for cancer diagnosis. Ultrasound contrast agents are mostly gas-filled microbubbles with echogenicity high degree [91]. Ultrasound as tumor diagnostic tools is present various advantages as real-time, portable, non-ionizing, and deep tissue-penetrating capability [92]. Besides, it can be also be applied in cancer therapy as high intensity-focused ultrasound [93] and sonodynamic therapy [94]. Contrast-enhanced ultrasound could improve ultrasound backscatter, or reflection of the ultrasound waves which can produce unique sonogram with increased contrast due to the high echogenicity difference. More specifically, ultrasound can be used for imaging blood perfusion, blood flow as well as receptor density in tumors [95]. In summary, ultrasound molecular imaging includes photoacoustic imaging, phase-changeable imaging, multi-modality ultrasound imaging, TME-responsive ultrasound imaging, acoustic reporter genes imaging whereas ultrasound targeting therapy: Sonodynamic therapy, high intensity-focused US ablation [92]. Inorganic nanoparticles as contrast agents for ultrasound theranostics, include perfluorocarbon nanoparticles, Noble metal materials, such as Au, Ag, Pd, and Pt, Carbon-based nanomaterials, such as carbon nanotubes, carbon dots, graphenes, and graphene oxides, silica-based nanomaterials [92,96]. Small molecule organic dyes with high photothermal conversion efficiency, such as indocyanine green (ICG), IR780, IR825, can absorb near infra-red (NIR) light and convert into heat energy. Most of the above diagnostic modalities can be applied for the diagnosis and treatment of other diseases.

2.2 Nanoimaging applications for Pulmonary diseases

Respiratory diseases include a wide spectrum of illnesses associated with upper and down respiratory system. Nanomedicine has shown to benefit various chronic obstructive pulmonary diseases such as asthma [97] or genetic diseases as cystic fibrosis. In addition, pulmonary tuberculosis and lung cancer can be detected and treated by using nanoplatforms. It has been reported that lung can be easily targeted especially by using inhaled aerosols given that these nanosystems can be easily transferred to the airways [98]. Imaging nanoplatforms for pulmonary diseases detection are difficult to be found. However, various systems have been developed [99]. For example, Aillon et al. revealed that the iodined nanoclusters could

also be an alternative option as contrast agents for lung visualization [100]. It can be said that PET and MRI [101,102] are the most frequently used techniques for nanoparticles lung imaging[103]. Various are the nanodelivery systems used for treatment of pulmonary diseases. Nonetheless, combined imaging and therapeutic nanosystems are quite limited [104]. Lanza et al. prepared lipase labile phospholipid prodrug forms of fumagillin or docetaxel loading to lipid-based micelles for asthma management. The anti-angiogenic efficacy in asthma of αvβ3-targeted micelles -αvβ3 are expressed on lung endothelial cells- was studied via MR simultaneous dual 19F/1H neovascular molecular imaging [105]. Superparamagnetic iron oxide NPs were conjugated with a biocompatible antibody in order to examine their *in vivo* effect after pulmonary administration. The developed system enable specific targeting and imaging of a particular macrophage subpopulation in lipopolysaccharide-induced Chronic obstructive pulmonary disease mice model [106].

2.3 Nanoimaging applications for neurological disorders

Neurodegenerative diseases as Alzheimer's (AD) [107], Parkinson's (PD) [108] or Huntigton's (HD) [109] or in general neurological disorders affects millions of people worldwide. Their therapy has not been achieved yet due to the insufficient active molecules which have limited therapeutic activity, their low penetration on the targeted tissue due to blood brain barrier (BBB) and the fact that their pathophysiological mechanisms are poorly understand [110]. Thus, more and more researchers are focused on designing promising drug delivery systems or novel drug substances able to cross BBB and reach brain [111,112]. In addition, detection of these disorders mainly focused on PET, SPECT, MRI and X-ray CT [28]. PET owing to its great sensitivity and better resolution provides enhanced imaging ability in comparison with SPECT. MRI and CT as non-invasive imaging techniques can depict morphological alterations in brain diseased tissues. It can be said that in order to achieve better penetration of drugs in brain, the nanocarriers surface can be modified with various biologically active substances which can exclusively couple expressed receptors on the brain endothelial cell [113,114]. For example, an innovative nanosystem aiming to be used as AD nanotheranostic was prepared from ceria and iron oxide nanocrystals surface coated onto the mesoporous silica nanoparticles (MSNs) which were functionalized with amino-T807 (PET tau tracer), and methylene blue [115]. Birgitte et. al also developed manganese oxide NPs functionalized with L-DOPA able to release Mn^{2+} ions and L-DOPA

concurrently in water due to NPs degradation. The specific nanosystem was served as MRI agent for imaging, diagnosis and therapy tool in PD [116].

2.4 Nanoimaging applications for cardiovascular disorders

CVD such heart failure, coronary cardiac disease, myocardial infarction and inflammatory heart disease, hypertension, dyslipidemia, diabetes are the most frequent disorders.The most common problem for medications prescribed in these disorders is their low lipophilicity and thus their bioavailability [117,118]. Nanotechnology based systems are among the most useful for CVD since they present control drug delivery ability for a variety of active molecules which can be directed for the management of lipid disorders, inflammation [119] and angiogenesis within atherosclerotic plaques, and prevention of thrombosis. Herein, various imaging modalities can be applied for detection of disorder. For example, ^{89}Zr-based PET imaging was employed to detect macrophages in atherosclerotic plaques. Macrophages in atherosclerotic lesions actively participate in lipoprotein ingestion and accumulation rising to foam cells filled with lipid droplets. Accumulation of foam cells contributes to lipid storage and atherosclerotic plaque growth. In this study, dextran nanoparticles were functionalized with desferoxamine to enable hybrid PET-MR imaging and it was shown prominent localization in macrophages in plaques in the aortic root of atherogenic ApoE−/− mice. Dextran is a biocompatible and biodegradable molecule, and thus it can be applied in bioimaging applications [120]. Another group, developed dextran-coated iron oxide based magneto-fluorescent nanoagent for near-infrared fluorescent imaging and generation of singlet oxygen. The application of nanotheranostics in an ApoE−/− mouse animal model showed desirable accumulation inside the atherosclerotic lesions and caused photo-induced apoptosis of phagocytic macrophages[121]. Gonçalves et al. developed PEGylated gold nanoparticles with 5-Aminolevulinic acid which were found to be accumulated into atheromatous plaques in atherosclerotic rabbits. It was further revealed that the acid was transformed to the active photosensitizer porphyrin IX. Thus, the nanoplatforms might be helpful in early diagnosis of atherosclerosis [122].

To summarize, nanotechnology is already playing and will play major role in developing novel and promising imaging probes and therapeutic strategies for various diseases.

3. Nanotheranostics categories according to their chemical nature

At present, an urgent need for early detection and diagnosis of diseases is needed. The main challenges for the development of efficient nanotheranostics are the use of non toxic contrast

agents which can be circulate in body for more time in order to provide fast and detailed imaging of the lesions[123]. In this review, the nanobased theranostics are categorized according to their chemical nature as organic and inorganic. The most frequently found organic nanotheranostics are lipid, polymers, micelles or carbon materials whereas the most common inorganic materials are calcium phosphate, iron oxide, and metal- and silica-based NPs.

The nanotheranostics could be carefully modified in order to present small sizes which will prevent their rapid clearance from blood stream mononuclear by phagocyte system (MPS) and reticuloendothelial system (RES) [2,23,70]. Except their tiny sizes, the particles surface could be also modified with aptamers, antibodies etc to avoid innate immunosystem recognition and to secure sufficiently long circulation to reach their targets [2,23,70]. Thus, inorganic and organic molecules could be modified or entrapped in polymer nanoparticles cores, liposomes or dendrimers in order to be used sufficiently [1].

The clearance and toxicity of the used nanomaterials are issues, which should be carefully examined. According to numerous studies, it is believed that the toxicity and the clearance of nanomaterials are correlated with their physicochemical characteristics. For instance, injected nanoparticles are vigorously cleared from bloodstream as a result of their sequestration by cells of the mononuclear phagocyte system preventing them reaching their target sites. Macrophages in particular are believed to be among the first and primary cell types that process nanoparticles, mediating host inflammatory and immunological biological responses [124]. Several studies reported that the clearance of NPs is size and dose dependent [125]. A study reports that iron oxide NPs presenting large sizes (over 100nm) are rapidly trapped in the liver and spleen through macrophage phagocytosis. On the other hand, iron oxide NPs with sizes under than 10 nm are possibly eliminated through renal clearance[126]. Tsoi et al. showed that hard nanoparticles as quantum dots, gold and silica NPs cleared primarily in liver by Kupffer cells, endothelial cells, B cells and other cells [127]. Other studies associated the shape of NPs [128,129] and surface charge with their *in vivo* fate [130]. On the other hand, soft NPs resist macrophage uptake indicating higher blood circulation [131,132]. PEG-like and other hydrophilic polymers could reduce opsonin adsorption on nanoparticles inducing them as unrecognized by the elimination mechanisms from the human body [133].

Toxicity is also a concern of NPs intended to be used in biomedical applications [134]. Similarly to clearance, the toxicity of NPs is correlated with the size [135], shape [136], the

dose [137] and the surface coated [138,139]. In example, Feng et al. demonstrated that PEGylated iron oxide NPs (IONs) in BALB/c mice did not show any toxicity signs whereas poly(ethylene imine) (PEI) coated IONs exhibited dose-dependent lethal toxicity [137]. A research group showed that gold NPs with sizes lower than 6 nm effectively enter the cell nucleus, whereas larger NPs (10 or 16 nm) only penetrate through the cell membrane and are found only in the cytoplasm. This fact relates that small NPs, which enter the nucleus can present higher toxicity [135]. Similarly, the cytotoxicity of metallic is strictly reliant on the pathway of cellular internalization [140]. Furthermore, the toxicity of NPs can be associated with their chemical composition. Since many NPs can be degraded, a leakage of metal ions from the NP core can occur. Some metal ions, such as Ag and Cd, are in fact toxic causing cell damage. Others as Fe and Zn, are biologically useful which however in high concentrations could damage cellular pathways causing high toxicity [141]. In addition, it has been claimed that the toxicity of hard NPs can be decreased [141] via their incorporation on biodegradable polymeric capsules-particles[23,70], coating with biocompatible polymers [108,142] and materials or other strategies.

3.1 Inorganic-metal and carbon based nanoparticles

Until now, the use of inorganic nanoparticles as drug carriers or diagnostic tools offered great results (Fig. 4). It thought that inorganic NPs were more stable than organic NPs; nonetheless, some evidences show that inorganic NPs may degrade individually *in vivo*, contributting in toxicity effects [143]. Hence, in many cases such inorganic NPs are coated with other biocompatible molecules [1,23,108,134]. MSN present solid framework of 50-300 nm particle diameter, interior porosity (pore size 2-6 nm), large pore volume, high surface area and ordered pore networks. They are relatively nontoxic with large loading capacity, great cytocompatibility and they can be easily modified [70,144]. Chen et al. prepared supramolecular photosensitizers based on MSNs as part of PDT. Tirapazamine-MSNs were further chelated with paramagnetic Gd^{3+} (Gadolinium). It was revealed that the nanosystem was able to be uptaken by CD44 receptor overexpressed in tumor cells whereas tumor growth was inhibited due to the combination of PDT and bioreductive chemotherapy under NIR fluorescence/MR imaging guidance. Bioreductive chemotherapy relies on the reductive activation of drugs by enzymes such as quinone oxidoreductase and P450 reductase as well as the identification of tumors abundant in such enzymes and differentiation in oxygen and pH levels within normal and tumor tissues. Subsequently, the developed system provides a new

approach on nanotheranostics [145]. Another example using MSNs and quantum dots was published from Muhammad et al. Camptothecin, was loaded in quantum dots conjugated with MSNs. In further, fluorescent doxorubicin was coupled to quantum dots surface which also led to fluorescent quantum dots. The novel nanosystem showed great *in vitro* anticancer activity while confocal microscopy revealed the efficient imaging and release of both active molecules [146]. A very interesting study which involved functional nanocarriers of gold cluster bovine serum albumin nanogates which were engineered on MSNs, was prepared by Croissant et al. Authors loaded two anticancer agents; gemcitabine which was entrapped on positively-charged ammonium-functionalized MSN and doxorubicin which was conjugated in the negatively-charged of gold cluster bovine serum albumin nanogates which were further electrostatically-attached onto ammonium-functionalized MSN. The dual delivery system was applied for targeted red nuclear staining and in-vivo tumor imaging revealing its capability to act as multifunctional cancer nanotheranostic [147].

Calcium phosphate NPs are based on nanocrystalline hydroxyapatite [108], but there is a growing interest in amorphous calcium phosphate. Indeed, calcium phosphate has been investigated for its optical ability [148]. Last years, metal nanoparticles have been reported of the most promising candidates on biomedical field. Metal NPs can both serve as diagnostic and drug delivery tools because of their intriguing abilities such as small size, high reactive surface area, targetability to cells, functionalization capability etc. Metal or metaloid nanoparticles as gold [149,150], silica [151] and silicon oxide [152,153], silver [154], titanium oxide [155] and iron oxide [156] are commonly used in nanotheranostics.

Magnetic nanoparticles are based on metals (Iron-Fe, Cobalt-Co, Nickel-Ni), metal oxides (FeO, Fe_2O_3, Fe_3O_4 [157]), alloys (FePt, FePd) and ferrites ($CoFe_2O_4$, $CuFe_2O_4$). Superparamagnetic iron oxide nanoparticles (SPIONs) are used as contrast imaging agent in magnetic particle imaging (MPI), due to their small size, good biocompatibility and the ability of surface engineering. MPI is a novel imaging modality that accomplishes a direct measurement of the magnetization of ferromagnetic NPs to calculate their local concentration. Also, they can act as therapeutic agents in hyperthermia. There are many types of MNPs products that have been developed for biomedical applications: Resovist® (Fujifilm RI Pharma), EndoremTM (Guerbet S. A.), Feraheme®(AMAG Pharmaceuticals), Nanotherm®(MagForce Nanotechnologies) etc. Although some of are already commercially available on the market for clinical use. Unfortunately, the majority of them is still under development [158].

Spherical gold NPs are of the most frequent gold nanoplatforms in drug delivery. Gold nanorods are used in photothermal and NIR application. Gold nanoantennas loaded with Cetuximab were characterized as an efficacious nanoprobe for *in vivo* tumor identification via Raman spectroscopy. Raman spectroscopy relies on the modification of frequency of light when it is inelastically scattered by molecules or atoms resulting in fingerprint information on molecular structure or environment. The nanosystem showed capability of targeting specified cancer biomarkers such as epidermal growth factor receptors. The developed nanosystem exhibits great raman signal in cancerous cells or mice tumors. According to the authors, the nanoantennas easily bind to epidermal growth factor receptors, blocking the epidermal growth factor protein from reaching the cancer cells and inhibit the signaling cascade, consequently stop proliferation and survival of targeted cells [159].

Carbon based nanomaterials (Fig. 5) such as fullerenes, carbon nanoparticles, carbon nanotubes, graphene, and nano-diamonds have shown a tremendous development as biomedical applications especially in nanotheranostics [160]. Carbon nanotubes can be either single-walled (SWCNTs) or multi-walled (MWCNTs), and they are highly ordered, pseudo one-dimensional carbon allotropes. SWCNTs composed of rolled-up single layer of graphite tube of 0.3–2 nm diameter, while MWCNTs are multiple concentric cylindrical shells of graphite sheets. Furthermore, CNTs can penetrate into various cells and deliver drugs or other compounds to specific target tissue [161,162]. Fullerenes have been explored as tumor theranostics since they exhibit potential in cancer therapeutic approaches such as PDT, PTT, radiotherapy and chemotherapy, but they have also been used as novel contrast agents in MRI [163]. Huang et al. prepared fluorescent fullerene (C60) grafted with carboxyl groups. The developed NPs showed great water dispersibility, biocompatibility as well as fluorescence activity. Furthermore, researchers loaded cisplatin drug which released in controlled manner. The novel nanoplatform due to its properties of bioimaging and controlled drug delivery can act as promising nanotheranostic. However, *in vivo* studies should be further carried out in order to confirm the results [164]. Nanodiamonds are carbon NPs with a truncated octahedral architecture with 2 to 8 nm diameter. They demonstrate chemical stability, and extremely high hardness, stiffness and strength as well as small size, large surface area, and high adsorption capacity [165]. Su et al. developed fluorescent nanodiamonds in order to quantitatively track the human placenta choriodecidual membrane-derived mesenchymal stem cells in miniature pigs through magnetic modulation[166]. Graphene and graphene oxide

(GO) are nanosheets of two-dimensional single monoatomic layers of sp^2 hybridized carbon atoms. They are an improtant category of theranostics due to their easy synthesis and their interesting structure which can be easily conjugated with active molecules or polymers [167]. Nonetheless, their *in vivo* tracking is quite a challenge. Recently, a dual-element labelling method using lanthanum and cerium tagged on poly(vinylpyrrolidone) (PVP) modified graphene oxide, developed from Liang et al. The authors used the laser ablation inductively coupled plasma mass spectrometry combined with Trasmission Electron Microscope observation. It was revealed that the modified GO nanosheets, after intravenous injection, entered into lung, liver, and spleen and the kidney, whereas they were slowly eliminated from the accumulated organs and some of excreted via urine[125]. A previous study also exhibited that ^{125}I-labeled nanographene sheets after intravenous administration mainly accumulate in the reticuloendothelial system including liver and spleen and can be gradually cleared, by both renal and fecal excretion [168].

3.2 Polymer, Liposomes and dendrimers as nanotheranostics

Various polymeric, liposomal and dendritic formulations have been applied as nanotheranostics (Fig. 6). As it was mentioned previously, they can coat the inorganic particles for improving their properties, avoiding their clearance and reducing their toxicity. Nonetheless, they can be also used as primary materials decorating with fluorescent molecules and drugs[1,2].

3.2.1 Polymeric Nanoparticles

Polymers are among the most easy-handled and economical carriers due to their important characteristics such as biocompatibility, biodegradability and stability against degradation [1]. Both synthetic and natural macromolecules have been utilized as nanotheranostics. However, in most cases they should be firstly modified in order to possess imaging ability and therapeutic activity [32]. Chitosan is a fundamental linear polysaccharide with numerous properties as low toxicity, cost-effectiveness, antimicrobial activity, antioxidant properties, etc [108,169–172]. In nanotheranostics, chitosan can be used as coating agent or polymeric core matrix. A novel multifunctional theranostic nanoplatform was fabricated via in situ growth of ultrasmall silver(I) selenide (Ag_2Se) nanodots on the surface of chitosan coated-sodium yttrium tetrafluoride: ytterbium/erbium@sodium lutetium tetrafluoride: neodymium/ytterbium@ sodium lutetium tetrafluoride ($NaYF_4$:Yb/Er@$NaLuF_4$:Nd/Yb@$NaLuF_4$) upconversion NPs. The theranostic agents were

able of tetra-modal imaging-guided photothermal therapy of cancer for rapid and accurate delineation and elimination of tumors. The prepared nanosystems showed excellent luminescent properties, high X-ray attenuation coefficient and strong NIR absorbance [173]. Sachdev et al. developed chitosan-based hydrogel loaded with highly fluorescent carbon dots and anticancer drug, 5-fluorouracil. It was found out that the system was able to show cellular uptake as well as therapeutic effects. In addition, *in vitro* studies exhibited apoptosis in A549 cells. To sum up, green fluorescence of carbon dots could be used to detect apoptosis instigated by 5-fluorouracil, eliminating the need for multiplex dyes [174].

Chitosan due to its carboxyl and amino groups can be easily modified with various molecules showing remarkable properties. PEG and palmitoylated PEG-grafted chitosan were applied as polymeric shell for magnetic nanoparticles ($Fe_{1-x}Mn_xFe_2O_4$). Methotrexate was encapsulated into chitosan coated NPs as anticancer drug. The prepared pH sensitive system was able to target *in vitro* tumor tissues, but still *in vivo* studies should also be performed [175]. Another derivative of chitosan, thiol chitosan was used as coating agent of gold nanoshells loaded with paclitaxel and the anti-epidermal growth factor receptor antibody. The multifunctional agents were acted as fluorescence/photoacoustic dual-modal imaging-guided chemophotothermal synergistic therapy. The nanoplatforms exhibited great biocompatibility, biosafety, broad NIR absorbance, photostability, fast and laser irradiation-controlled release as well as high targetability. It can be concluded that the prepared nanosystem can be used for tumor visualization and sufficient chemophotothermal combination cancer therapy under the guidance of photoacoustic imaging. [176]. A plasma membrane-activatable polymeric core-shell nanosystem was prepared by conjugating the photosensitizer protoporphyrin IX and PEG with glycol chitosan. The prepared nanoagents showed accumulation in tumor cells and improved *in vivo* fluorescence at the tumor site [177]. Chitosan and folic acid-conjugated chitosan NPs loaded with SPIONs were prepared as nanomagnetic onco-diagnostic and targeted nanomagnetic onco-diagnostic systems. In addition, uptake studies and competitive inhibition study verified the folate receptor mediated endocytosis of targeted system by MCF-7 as a folate receptor-positive cell line. The prepared novel tumor-targeting nanotheranostic agent can be applied for simultaneous MRI imaging and treatment of folate receptor-positive cancers. Nonetheless, the nanosystem lacks of *in vivo* studies[178]. Folate-conjugated N-palmitoyl-chitosan was formulated to novel nanobubbles combined with therapeutic ultrasound (US) to act as a safe and effective physical targeted cancer therapy. The modified

nanobubbles were capable of killing cancer cells and inhibiting tumor growth. Considering their US irradiation, the innovative folate nanobubbles can be associated with promising outcomes on oncology diagnosis and therapy [179]. A nanoplatform for therapy and imaging of non-small cell lung cancer was fabricated by Zhang et al. The nanotheranostic agent composed of ICG entrapped into MSNs coupled with ZnO quantum dots. The nanosystem further coated with erlotinib-modified chitosan. The nanosystem exhibited a pH/redox dual-responsive release of ICG for precise fluorescent imaging. *In vivo* studies demonstrated that the nanotheranostic can provoke anticancer effect and can be an alternative option for imaging and therapy of non-small cell lung cancer [180]. Theranostic polyfunctional gold-iron oxide nanoparticles (polyGIONs) surface coated β-cyclodextrin-chitosan and loaded with therapeutic miRNAs and the chemotherapy drug temozolomide were able to be accumulated and released in mice glioblastoma. The prepared nanosystem was administrated via intranasal route. The stable nanosystem exhibited *in vivo* optical fluorescence and MRI capability and thus can be applied as nanotheranostics[181].

Hyaluronic acid (HA) or hyaluronan is an anionic, nonsulfated glycosaminoglycan distributed widely throughout connective, epithelial and neural tissues. It possesses low toxicity and has been widely utilized in pharmaceutical technology. In the literature, pure HA based nanotheranostics are limited found. Nonetheless, derivatives of HA or its salts are being fabricated into nanoplatforms. A current research of Zhang et al. involved the use of gadolinium modified mesoporous silica (GD-MS) as MRI agent. Authors in order to further improve system targeting ability they further grafted HA on GD-MS. The grafted system was further modified with iopamidol or doxorubicin so as to prepare both diagnostic and therapeutic nanomolecules against lymph cancer [182]. Zhu et al. produced bioresponsive and fluorescent HA-iodixanol nanogels aiming to be applied as targeted X-ray computed tomography imaging and chemotherapeutic agent. The anticancer drug paclitaxel was loaded into the nanogels so as to target MCF-7 human breast tumors. A high cell uptake of the nanogel and tumor inhibition was demonstrated. Moreover, an improved CT imaging was observed for MCF-7 breast tumors in nude mice while fluorescence showed that nanogels were distributed thoughout the whole tumor indicating deep tumor penetration [183]. A very recent study of Yu et al. included the use of deoxycholic acid-HA-methotrexate as carriers of ICG and doxorubicin. The developed NPs demonstrated intracellular doxorubicin uptake on CD44/folate receptors. Authors believe that the nanotheranostic present superior abilities as

imaging-guided chemo-photothermal combination therapy [184]. In another study, nanoprobes from copolymers based on oxidized sodium hyaluronate and aggregation-induced emission-active dye were formulated in fluorescent NPs. It was revealed that the polymeric nanoparticles are well dispersed in water with good biocompatibility as well as confocal imaging capability. Thus, they can be applied as alternative nanotheranostic system[185].

Cellulose is natural linear polysaccharide which is widely applied in pharmaceutical applications. Cellulose can be easily modified with active group providing derivatives with various functionalities. Carboxymethylcellulose is among the most utilized cellulose derivatives. Leonel et al. produced core-shell nanofluids comprised from magnetic iron oxide and cobalt-doped magnetic IONs which further functionalized with carboxymethyl cellulose. The nanoconjugates showed hyperthermia ability due to iron oxide and thus can be used as anticancer nanotheranostics generated heat by magnetic hyperthermia of MION nanoconjugates[186]. In a different study, ZnS fluorescent quantum dots were modified with carboxymethylcellulose and formulated nanocolloidal system which was further conjugated with doxorubicin. Nanocolloids with average size of 3.6 nm revealed photoluminescence emission property and biocompatibility. Thus the developed system can act as fluorescent nanoprobes and drug nanocarriers with ability to inhibit [187]. SPIONs were coated with sodium carboxymethyl cellulose and cross-linked with epichlorohydrin to improve the stability of coating. Rhodamine B was loaded as model molecule. Although the study was in preliminary stages, the characterization revealed that the nanosystem can be applied in drug magnetic targeting applications [188].

Other natural polymers were also acted as coating agents. Alginate is natural polymer which also used in drug delivery application due to to its low toxicity[169]. Doxorubicin loaded modified alginate with folate-terminated PEG and rhodamine B nanogels were produced by Pei et al. Folate conjugation led to improved targeted on cancer cells while pH-responsive release behavior was also achieved. Cytotoxicity and cellular uptake studies revealed that the anticancer drug was vastly distributed in cancer cells provoking their death. Rhodamine provides fluorescent properties to the nanogels and consequently the nanosystem can be applied as real-time and noninvasive theranostic [189]. Nanogels with magnetic and dual responsive properties were developed by coupling SPIONs with a disulfide-modified alginate. The nanogels were simultaneously loaded with the anticancer drug doxorubicin. It was revealed that the dual nanosystem demonstrated magnetic-targeted ability, high drug loading

content, co-triggered release behavior, high toxicity to tumor cells, low side effects to normal cells and MRI function [190]. Mohapatra et al. modified SPIONs with Carboxymethyl Assam bora rice starch-in order to evaluate its potential as magnetic drug targeting moiety. Scientists further loaded the system with the anticancer doxorubicin. It was demonstrated that the magnetic nanosystem exhibited high uptake and inhibition against HER-2 and folate receptor-α receptors over expressed in cancer cells[191]. An interesting study involved the fabrication of H_2O_2-activatable CO_2 bubble generating ICG-loaded boronated maltodextrin NPs for imaging and therapy of peripheral arterial disease. The developed nanobubbles demonstrated improved fluorescence, US and photoacoustic signals as well as significant anti-inflammatory and proangiogenic effects in H_2O_2-stimulated vascular endothelial cells. Researchers revealed that the nanosystem can provide a novel insight for imaging and treatment of peripheral arterial disease [192].

Cyclodextrins are cyclic oligosaccharides which comprised from glucopyranoside units linked with (1–4) bonds and present a conical shape with an empty cavity which can host small molecules like drugs in proportion with molecules size[193]. Multifunctional nanoconjugates of magnetic Fe_3O_4 NPs, β-cyclodextrin and poly(N-isopropylacrylamide) were applied as drug carriers. Doxurobicin or curcumin was encapsulated and released under acidic pH conditions and elevated temperature whereas folic acid was further coupled in to the nanoconjugates to induce folate receptor targeting. Fluorophores were conjugated onto NPs to provide to system fluorescence imaging ability. Moreover, nanoconjugated were able to accumulate on cancer tissues with magnetic hyperthermia. *In vivo* studies exhibited that after administration of nanoconjugates tumor growth was inhibited [194]. Xu et al. fabricated fluorescent organic NPs coupling red fluorescence and aggregation-induced emission dye through interactions between β-cyclodextrin and adamantine terminating aggregation-induced emission dye. The developed nanofeatures revealed excellent cytocompatibility and bioimaging ability [195].

Polypyrrole is heterocyclic conductive polymer which is used in biomedical devices or general biomedical field. Yang et al prepared a novel nanotheranostic system based on polypyrrole which was coupled with Gd modified bovine serum albumin. The nanotheranostic presented high stability, great photothermal property and improved uptake on cancer cells. MRI revealed that the biocompatible nanoplatforms were distributed in cancer cells. *In vivo* studies with mice showed that polypyrrole system after exposed to 808 nm laser can hinder

the tumor growth due to photothermal ablation. From the above, all the results demonstrated the well-designed nanotheranostics can utilized as tumor diagnostic and photothermal therapy[196]. In another work, tantalum oxide NPs were impregnated into polypyrrole for dual imaging guided photothermal removal of tumor. Small sized NPs of an average diameter at 45 nm were capable of reaching tumor site after systemic administration. It was revealed that the nanoplatform could improve X-ray CT and photoacoustic imaging *in vivo*. It should be noted that after intratumoral injection tumor was completely inhibited showing that the system can be efficiently act as targeted diagnostic and therapeutic system[197]. Except cancer applications, polypyrrole-PEI nanocomplexes were studied by Bournouf et al. as fibrinolytic therapeutics for venous or arterial thrombotic syndromes. Authors provide novel nanocomplexes exposed to near-infrared radiation as an alternative option of recent thrombolytic agents. It was demonstrated that the nanocomplexes were able of generating local hyperthermia upon NIR treatment, which appeared to produce reactive oxygen species (ROS). *In vivo* studies involving rats demonstrated biocompatibility, photothermal behavior and biodistribution [198] .

PEG is the most frequent used hydrophilic moiety in biomedical application. PEG coating or PEGylation method onto various macromolecules is a common approach aiming to improve blood circulation of drug loaded NPs. Moreover, PEGylation can reduce toxicity of the nanosystem enhanced drug protection from degradation and numerous other properties[2]. Bovine serum albumin coated PEGylated magnetic NPs were loaded with vascular endothelial growth factor and doxorubicin as a novel cancer nanotheranostic system for improved targeting in murine breast adenocarcinoma 4T1 cell line. It was demonstrated that the NPs were capable of improving survival rate of mice bearing tumors a well as MRI imaging providing simultaneous cancer therapy and diagnostics[199]. An amphiphilic semiconducting polymer based on PEG- grafted poly(cyclopentadithiophene-alt-benzothiadiazole) (PEG-PCB) (PEG-PCB) was developed by Jiang et al. The nanoplatform can be a diagnostic component for NIR fluorescence and photoacoustic imaging as well as therapeutic agent for photothermal cancer therapy[200].

Another work included the preparation of a hierarchical tumor acidity-responsive magnetic nanobomb composed from chlorin e6 (Ce6)-functionalized polypeptide ligand, methoxy poly (ethyleneglycol)-block-poly (dopamine-ethylenediamine-2,3-dimethylmaleic anhydride)-L-glutamate-Ce6 and SPIONs. The nanobombs were able to circulated in blood system for

hours and provoked tumor inhibition due to their high cancer cell uptake. Both *in vitro* and *in vivo* methods demonstrated efficient tumor distribution and superior photodynamic therapy effect [201]. Nanomicelles based on PEG-b-poly(L-leucine) entrapped doxorubicin, chemosensitizing agent XMD8-92, and superparamagnetic iron oxide NPs exhibited targeting ability, MRI imaging, controlled release behavior, improved cytotoxicity on MDR cells and sufficient tumor inhibition [202]. PEGylated graphene oxide-manganese ferrite NPs loaded with doxorubicin were developed by Qian et al. as nanotheranostic system. PEG moiety was applied for enhanced biocompatibility. The nanosystem presented MRI imaging ability whereas the system was further conjugated with radioisotope. The nanocomposites were able to reach tumor revealing high accumulation. Under the guidance of MRI/SPECT imaging, *in vivo* combined radioisotope therapy and chemotherapy was carried out an ihnibition of tumor growth after intravenous injection [203]. Multi-functional core-shell Fe_3O_4-Au NPs, conjugated with doxorubicin , methoxy poly(ethylene glycol) (mPEG), and folic acid-linked poly(ethylene glycol) were synthesized for cancer theranostic applications. The system showed saturation magnetization, improved release property and enhanced cellular distribution on cancer cells. Moreover, the NPs demonstrated high cytotoxicity under laser irradiation which led to photothermal effect [204]. PEG was also coated magnetic gold nanoparticles loaded with doxorubicin as anticancer nanotheranostics. *In vitro* and *in vivo* methods confirmed that the nanoplatforms were biocompatible, can release drug in controlled type, induce PTT via heat by NIR laser absorption. In addition, the multifunctional NPs can also act as MRI contrast agents[205]. Tong et al. developed PEI-PEG-reduced graphene oxide as biocompatible alternative for photothermal and chemotherapy against hepatocarcinoma. Doxorubicin was chosen as the anticancer agent. It can be concluded that the nanomaterials could effectively deliver and release drug in SMMC-7721 cells provoking cells death[206]. PEGylated black phosphorus NPs with great biocompatibility and water-solubility were prepared aiming to reduce cancer cells growth. The NPs can convert NIR light into heat, and exhibit excellent photostability. *In vivo* studies demonstrated the NPs accumulation in mice tumors whereas irradiation can be used for photothermal ablation of tumors [207]. A photosensitizer-assembled graphene/gold nanostar hybrid was formulated for combined cancer synergistic PDT and PTT as well as effective photothermal imaging. As it was expected, the stable PEG composite showed anticancer efficacy, tumor accumulation and inhibition and improved optical imaging [208]. Magnetic graphene nanohybrids based on

graphene oxide-modified PEG and γ-Fe_2O_3 were prepared by Chen et al as an encouraging option for synergistic anticancer therapy and imaging. Doxorubicin was chosen as anticancer drug. It was exhibited that the nanosystem can be mapped by MRI, photothermal and fluorescence imaging. In addition, the anticancer efficacy was revealed by both *in vitro* and *in vivo* methods which showed tumor ablation after hyperthermia and NIR light exposure [209]. Multifunctional nanotheranostics incorporating IR-780 dye, a NIR imaging probe as well as the anticancer compound known as α-tocopheryl succinate were developed by Palao-Suay et al. The core shell NPs were fabricated using PEG and poly(methacrylic α-tocopheryl succinate. The system presented photo-inducing and fluorescence ability due to the presence of the dye. *In vitro* studies showed that the theranostic NPs can be effectively localized in cells revealing promising characteristics [210]. Finally, He et al. developed a peptide-based nanotheranostic based on p53-activating peptide termed PMI, functionalized PEG and fluorescent lanthanide oxyfluoride nanocrystals. It was revealed that the nanoplatform exhibit improved tumor targeting and imaging properties. *In vivo* studies involving a mouse model with human colon cancer showed that the nanosystem is efficacious. More specifically, the nanorods can inhibit tumor growth and be easily mapped [211]. You et al. prepared multifunctional nanosystems with sufficient cellular uptake, specific target and controlled release efficacy. The nanosystem was consisting of folate and cyclic arginine-glycine-aspartic-peptide modified NPs based on NIR light and glutathione dual stimuli-responsive release system loaded with cisplatin and ICG. The core polymer was a copolymer between poly(ε-captolactone) (PCL) and carboxylated PEG. The nanospheres were able of accumulation to tumor sites showing decreased cancer cells viability and thus it can be an alternative nanotheranostic in nanomedicine field [212].

PCL is hydrophobic polymer which is used in biomedical field especially in controlled release applications [213]. As nanotheranostics, PCL is used as coating or core material. For instance, PCL-AuNC/$Fe(OH)_3$-PAA Janus nanoparticles were fabricated by Zhang et al. and loaded with doxorubicin and docetaxel. The nanoplatform demonstrated greater therapeutic efficacy due to synchronous release of two drugs as well as the excellent computed X-ray tomography/magnetic resonance (CT/MR) imaging capabilities. *In vivo* studies using mice further depicted tumor inhibition revealing that the aforementioned system can be effective as combined cancer therapy[214].

Poly(lactic) acid (PLA) is an aliphatic polyester with high cytocompatibility which can be easily modified or formulated in various nanoforms [215]. In case of nanotheranostics, NPs of PLA were loaded with doxorubicin and further surface coated with Mn-porphyrin as potential MRI agent and pH-responsive drug delivery system. Firstly, the system exhibited that the drug was released at greater extent in acidic pH. Moreover, nanoformulations showed efficient tumor inhibition in HeLa cells and HT-29 cells. All the more, the system demonstrated that it can act as MRI contrast agent for sufficient cancer diagnosis and therapy [216].

Poly(lactic-co-glycolic acid)-PLGA is the copolymer between PLA and poly(glycolic acid) and presents high biocompatibility and extremely promising properties. It is widely used in pharmaceutical industry and technology as nanocarrier. As nanotheranostic, PLGA-based NPs impregnated with paclitaxel and superparamagnetic iron oxides to act as both therapeutic and imaging tool. The visualization of NPs accumulation was conducted using Electron Spin Resonance spectroscopy and MRI and it was depicted that the nanoplatforms exhibited improved NPs distribution, MRI contrast ability and most importantly anti-cancer activity [217]. A mPEG-PLGA-poly-l-lysine triblock copolymer was designed as photothermally triggered immunotherapeutic system loaded with SPIONs and cytosine-phosphate-guanine oligodeoxynucleotides. The under magnetic-responsive immunostimulatory nanoagents acted both as contrast agent for PA/MRI bimodal imaging and magnetic-targeting therapeutic agent. It was revealed that the NPs were accumulated in tumors and inhibit metastatic tumors simultaneously with high specificity, easy maneuverability and favorable biocompatibility [218]. Another system involved quantum dots as imaging molecule and EpCAM aptamer as target ligand which conjugated to nutlin-3a loaded PLGA NPs. The nanoplatform exhibited intriguing properties such as cell targeting and biomaging and it can be served as nanotheranostic approach on cancer therapy[219]. Castellani et al studied CdSe/ZnS QD-loaded PLGA NPs as targeted system for metastatic liver cancer as hyperthermia triggered system. Localized MW irradiation which led to mild hyperthermia played a significant role to NPs accumulation in tumor [220]. Zhang et al. design NPs of modified PEG-PLGA with iron-gallic acid as MRI guided chemo-photothermal synergistic therapy of tumors. The drug Gallic acid was able to be released in acidic pH as tumor environment inducing apoptosis. The study revealed that the nanonetwork due to its extraordinary photostability and photothermal therapy capacity is quite promising as nanotheranostic[221]. Furthermore, paclitaxel was

loaded into nanocapsules comprised from PLGA-PEG and perfluorooctyl bromide (PFOB) as nanotheranostic agents. The prepared nanocapsules showed anticancer efficacy when studied *in vitro* on CT-26 colon cancer cells whereas *in vivo* studies revealed passive accumulation of drug in CT-26 tumors in mice and tumor inhibition. Imaging capability was induced due to the presence of PFOB. Consequently, the system has great potential as cancer theranostic agents [222].

PEI is a branched cationic polymer which can be modified and act as polymer nanotheranostic. In a recent research, Shao et al. fabricated PEI-PLA NPs which simultaneously load hydrophobic antiangiogenesis agent combretastatin A4, NIR dye IR825 and heat shock protein 70 (HSP70) inhibitor (siRNA against HSP70). The nanosystems studied *in vivo* in a xenograft mouse tumor model, demonstrating improved photocytotoxicity and tumor inhibition and synergistic anticancer efficacy with NIR laser irradiation. The copolymer acted as drug carrier as well as self-monitor to real-time tracking of NPs biodistribution and tumor accumulation via fluorescence imaging. Finally, due to the above and fact that the nanoplatform can also be applied as photoacoustic agent for *in vivo* photoacoustic imaging, the nanosystem offer encouraging results as current multifunctional cancer nanotheranostic [7]. Deng et al. also used PEI as modifying agent of black phosphorus nanomaterials along with dextran. The nanoplatforms were further functionalized with folic acid and cyanine 7 depicting great stability and cell viability, near infrared optical properties for targeted imaging of tumors through photoacoustic imaging and NIR fluorescence imaging. In addition, the nanosystem is efficient as photothermal cancer therapeutic [223].

Poly(N-isopropyl acrylamide) (PNIPAM) is a pH- and temperature- responsive polymer used in variou medicine applications. Roy et al. fabricated stimuli-responsive PNIPAM-co-tyrosine modified gadolinium doped IONs as cancer theranostic agent. Methotrexate was loading in great extent and released with a stimuli dependent manner. In further, the NPs showed MRI activity as well as desirable *in vitro* hyperthermia response [224]. Poly(vanillin oxalate) (PVO) is antioxidant polymer which was formulated into nanoparticles generating CO_2 through H_2O_2-triggered oxidation of peroxalate esters and release vanillin, which exerts antioxidant and anti-inflammatory activities. PVO nanoparticles exhibited improved ultrasound signal in the site of hepatic I/R injury and also effectively suppressed the liver damages by inhibiting inflammation and apoptosis. Consequently, the system can act as ultrasound contrast agents and therapeutic tool in H_2O_2-associated diseases [225].

Other polymers have also been employed as nanotheranostics. More specifically, poly (N-(2-hydroxypropyl) methacrylamide) nanocarriers of paclitaxel were further coupled with self-quenched Cy5 (SQ-Cy5). Activatable fluorescent probes as SQ-Cy5 employ a fluorescent signal which is silenced/"OFF" under physiological conditions, and is Turned-ON at the designated site. Polymeric nanotheranostics could present an 'always ON' signal. Förster resonance energy transfer is the most common and efficient turn-on mechanism. The system was able to release the drug due to enzymic degradation in cathepsin B-overexpressing breast cancer cells. The drug releases took place simultaneously with the activation of the fluorophore to its Turn-ON state. The copolymer NPs showed better distribution and drug release in comparison with the pure drug and the probe. In addition, the marketed taxol administration system utilize the toxic chremophor EL substance for the solubilization of taxol. The developed system is water soluble and thus it can be administered in aqueous solution overcoming the use of chremophor [22]. Similarly, tumor-targeted photodynamic therapy using polymeric photosensitizers of poly (N-(2-hydroxypropyl) methacrylamide) conjugated pyropheophorbide-a was found to be a significant strategy for cancer treatment. As the majority of the nanotheranostics, the copolymeric NPs can act as encouraging therapeutic strategy in oncology field. In further, nanomicelles showed high tumor accumulation, antitumor effect under irradiation using normal xenon light source of endoscope, and clear tumor imaging profiles even in the metastatic lung cancer [226]. Shi et al. fabricated fluorescent organic nanoparticles based on dopamine (DA) containing copolymers (poly(AC-co-PEGMA)). PEI was also mixed and the NPs demonstrated great water dispersibility, strong green fluorescence and desirable biocompatibility [227]. Polyacrylamide hydrogel NPs were surface modified and conjugated with oxygen indicator and PEG groups as photoacoustic oxygen imaging nanosystem for tumor targeting and detection. The prepared nanosystem provides an *in vivo* non-invasive imaging and assesement method of hypoxic tumor microenvironments. This method is crucial for the evaluation of cancer progression, metastasis and treatment [228].

PVP has been also used as pharmaceutical excipient. Herein, authors present ternary copper-based chalcogenide nanotheranostics which combine high photothermal conversion efficiency and a simultaneous ROS generation effect. Except these facts, the nanoplatforms also revealed remarkable contrast enhancement and thus they can act as multifunctional nanotheranostic agents for photoacoustic imaging, photothermal/photodynamic cancer

therapy [36]. Pluronics are copolymers of polyethylene- and polypropylene oxide widely used in pharmaceutical industry. In this work, authors fabricated Pluronic coated gold NPs loaded with IR780 iodide dye as combined photodynamic and photothermal therapeutic activity with surface-enhanced resonance Raman scattering imaging facility. The nanosystem exhibited improved water-solubility, stability and NPs accumulation in Plu-IR780 by murine colon carcinoma cells (C-26). Finally, the NPs indicated that simultaneous photodynamic and photothermal activity can be achieved [229]. Another work involved the preparation of folic acid armed polymeric core–shell iron oxide nanoparticles as a new type of nanotheranostic agent. The NPs were further coated hyperbranched polyglycerol aiming to improve their biocompatibility. Folic acid was used to target folate receptors overexpressing on cancer cells. The results showed that NPs can be applied as cancer nanotheranstics[230].

3.2.2 Liposomes

Liposomes are structured biocompatible and biodegradable lipid carriers. Some liposomes have been approved from FDA as drug nanocarriers[231] . Liposomes comprised from one or more bilayers of natural or synthetic lipids and an aqueous core. They have been utilized as carriers for many active molecules either hydrophilic or lipophilic [232,233]. Radio-labeled liposomes with radionuclides such as ^{67}Ga,^{111}In and ^{99m}Tc present diagnostic, monitoring and therapeutic functions. Besides their imaging ability due to the radio-labeling, such liposomes are an excellent tool for choosing the best therapeutic action in individual patients [234,235]. A research group radio-labeled iminothiolane-Tc-tricarbonyl complex a model liposome system. The system mimics the Epaxal® and Inflexal V® which are FDA approved liposomal drugs[236].

In most cases, liposomes are funtionalized or coated with active molecules such as PEG, vitamins which can induce their biocompatibility. For example, vitamin E TPGS-coated liposomes are widely prepared [237]. In further, PEG-coated and folate-PEG-coated long-circulating and pH-sensitive liposomes loaded with ^{159}Gd and poly-L-lysine were studied as cancer nanotheranostics. The prepared liposomes provide increased animal survival and high tumor uptake [238]. Liposomes and PEGylated liposomes were functionalized with gadolinium (III) diethylenetriamine pentaacetic acid salt which acted as MRI contrast and zinc phthalocyanine as a model photosensitizer. The results showed that the liposomal formulations can serve as imagine agents[239]. A novel system comprised from liposomes containing NIR carbon dots and the anticancer drug, cinobufagin, was developed and

evaluated as potential anticancer nanotheranostics. Bioimaging of the prepared system was significantly high whereas liposomes could be uptaken by cells and delivered to the tumor site. Moreover, a prolonged release behavior and high anticancer activity was recorded[240]. The theranostic liposomes were functionalized with arginine-glycine-aspartic acid-Tocopheryl succinate and loaded with docetaxel and quantum dots by Sonali et al. A prolonged drug release and biocompatibility was achieved revealing that the nanosystem can serve as brain nanotheranostic [241]. Another promising study involves the application of ultrasmall iridium nanocrystals into stealth liposomal features. The developed system showed efficient photothermal conversion ability, since the iridium nanocrystals present effective NIR responsive catalytic activity towards H_2O_2 decomposition. In addition, the system exhibited improved blood circulation which enhances sufficient retention in mice tumors. Thus, it could be used in enhancing cancer radiotherapy[242]. Sheng et al. prepared anticancer nanotheranostics by using the cytocombatible NIR dye, ICG. They entrapped perfluorooctyl bromide (PFOB) in nanoliposomes which revealed *in vivo* CT contrast imaging. Moreover, the formulation after intravenous administration hindered completely the MDA-MB-231 tumor growth due to excellent oxygen carrying ability of PFOB, which effectively attenuated tumor hypoxia, improved the efficiency of collisional energy transfer between ICG and oxygen and reduced the expression of heat shock protein [243]. Stimuli-responsive liposomes were also produced featuring diagnosis and treatment features. In fact, ROS-responsive liposome were designed showing light scatter and fluorescence intensity. Authrs inserted lipid oxidation sensor, C11-BODIPY (581/591), to liposomal bilayer to provide ratiometric fluorescent nanoprobe for ROS detection. Afterwards, Mitoxantrone- chemotherapeutic substance, was loaded into C11-BODIPY (581/591) functionalized liposome. This novel system exhibited prolonged release, improved anticancer actibvity and imaging ability [244]. Finally, multifunctional RNA-loaded magnetic liposomes were prepared as an early biomarker of treatment response. The iron oxide loaded RNA-liposomes deliver RNA to dendritic cells, activate those dendritic cells, and enable prediction of tumor regression with MRI [245].

3.2.3 Dendrimers

Dendrimers are of the most significant nanostructured materials due to their external groups, which can be modified with antibodies, peptides or proteins. Dendrimers which own their

name to the Greek word "dendro-tree", show a structure of tree-like arms or branches [246,247].

An interesting study reports the use of multifunctional polymeric dedrimers comprised from a copolymer of Boltorn H40, PCL and P(oligo(ethylene glycol) monomethyl ether methacrylate -co-3-azidopropyl methacrylate AzPMA) as cancer targeted drug delivery and MRI contrast. In fact the H40-PCL-b-P(OEGMA-co-AzPMA) was further modified with alkynyl-functionalized cancer cell-targeting moieties, alkynyl-folate, and T1-type MRI contrast agents, alkynyl-DOTA–Gd (DOTA is 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrakisacetic acid). Moreover, the dendritic polymers were loaded with the anticancer paclitaxel. It was revealed that drug was released in controlled manner while *in vivo* MRI imaging in rats showed desirable distribution of unimolecular micelles within rat liver and kidney, prominent positive contrast enhancement, and relatively long duration of blood circulation. Thus, they can be used as alternative nanotheranostics[248]. In another study authors employed the use of dendrimers as *in vivo* anti-lymphoma efficient system which also can act as diagnostic tool due to the fluorescent dye conjugation in the polymer core. Doxorubicin was used as anticancer drug, and the dendrimers were studied in murine models of malignant lymphomas including one cell line-derived xenograft and two patient-derived lymphoma xenografts (VFN-D1 and VFN-M2) [249]. Polydopamine (PDA) coated magnetite nanoparticles were loaded in dendrimers and they were characterized as chemo- and photothermal therapeutics and imaging agents by MRI and CT-PTT of the liver cancer cells. *In vivo* studies exhibited that the dual therapeutics can provoke apoptosis and thus is a promising and smart system [250].

Similarly, doxorubicin and indodicarbocyanine fluorescent dye was attached to dendritic polyglycerol nanocarriers. The results exhibited that the dendritic carriers were monitored in real time in intact cancer cells revealing its potential [251]. Poly(amidoamine)-(PAMAM) are the most frequently used polymers as dendrimers. Carbon quantum dots from sweet lemon peel conjugated with PAMAM dendrimers to act as nanotheranostics to triple negative breast cancer. A peptide, known as arginine–glycine–aspartic acid (RGD) peptide was further conjugated to the system to target integrin which is over expressed in the specific cancer. It was found out that the system is an alternative theranostic option since it can be sufficiently bind into cancer cells [252]. Another study included Gd-doped ferrite NPs which were further encapsulated into PAMAM dendrimers whereas doxorubicin was also added to enhance their

anticancer activity. Almost 78% of doxorubicin released in the presence of a low-frequency alternating magnetic field and mildly acidic pH environment [253]. In a different study folate–poly(ethylene glycol) was attached in PAMAM dendrimers aimed to target folate receptors in cancer cells. This core was conjugated with Cadmium selenide/ Zinc sulfide (CdSe/ZnS) quantum dots which are widely used as diagnostic tool. It was demonstrated that the folate coated dendritic system show high cell uptake, binding in the cell surface and doxorubicin released into the tumor cells. The developed nanosystem can act as bioimaging and therapeutic tool[254].

Multifunctional PAMAM dendrimers loaded with gold NPS which were coupled with α-tocopheryl succinate were developed as cancer targeted nanotheranostic agent for CT imaging and therapy. In addition, PAMAM dendrimers were modified with fluorescein isothiocyanate, PEG-modified α-TOS, as well as PEGylated folic acid which served as templates to synthesize Au nanoplatforms. It was found out the nanoplatfomrs exhibited sufficient targetability to cancer cells overexpressing FA receptors as well as were able to target CT imaging of the cancer cells *in vitro* and the xenografted tumor model *in vivo* [255]. Same team studied multifunctional dendrimer-entrapped gold nanoparticles with alpha-tocopheryl succinate and arginine–glycine–aspartic acid peptide for targeted chemotherapy and CT imaging of cancer cells. Authors also used fluorescein isothiocyanate, RGD peptide coupled with PEG and PEG-linked α-TOS. The prepared nanotheranostics were stable in several conditions and can target to cancer cells overexpressing αvβ3 integrin. Moreover, they show improved growth inhibition of the cancer cells. Authors conclude that the system can be promisingly applied as nanoprobe[256].

4. Conclusions and authors' opinion

Nanotheranostic field is an emerging research field which however has not still meet the clinical standards. This fact is arising from the complexity and the synergistic mechanisms of the used nanotheranostics. For instance, some of the systems although show great diagnostic efficacy they lack of therapeutic ability. Other systems have shown important therapy index with low imaging ability. Nonetheless, the scientific community has conducted great efforts to translate these new nanotheranostics into clinical trials by examining various nanomaterials or modification techniques and evaluating their *in vivo* performance. As it is detailed in this work, most of the current studies evaluate the diagnostic and therapeutic application of nanotheranostics using *in vivo* animal models, showing promising results. Nonetheless, if the

nanotheranostics applied on human individuals, their application mostly fails. This is correlated with the fact that other mechanisms lead the diffusion of nanotheranostics in animals and others in human. In the past, EPR effect believed as one of the leading phenomena affecting the diffusion of nanoparticles in tumors. Hence, many researchers evaluate the passive targeting of nanoparticles in animals. However, EPR effect is not prominent in the majority of human tumors. Thus, efficient animal models should be utilized when studying the nanotheranostics.

Another issue of nanotheranostics is their possible toxicity and safety when used in humans. Among the applied nanotheranostics, carbon nanotubes and metallic nanoparticles have raised a concern of safety due to their slow degradation and *in vivo* fate. Consequently, various attempts have been performed as surface coating with biocompatible macromolecules as PEG, poly(lactic acid) and chitosan to enhance their suitability for future clinical use. Another idea is the use of nanotheranostics synthesized by biodegradable or biocompatible materials which have been clinically approved. Besides, several biocompatible polymers, liposomes or dendrimers have been clinically approved for other pharmaceutical applications. Hence, the modification or conjugation of already approved therapeutic formulations or materials with functional ligands which will improve their diagnostic index could be essential.

Compared to the past, more sophisticated nanotheranostics have been developed worldwide. However, a huge advancement should be done before their clinical application. As it is addressed, in this review the current nanotheranostics have been evaluated mostly for their *in vitro* performance. In other works, the *in vivo* imaging evaluation of nanotheranostics might be performed but their *in vivo* drug delivery was not attenuated. In further, the toxic profile of many of the developed nanotheranostics is absent. Therefore, the promising properties of nanotheranostics, which are discussed in this review, should be advanced more before their translational in clinical medicine. To conclude, although a great effort is still needed, the future of nanotheranostics utility in clinical practice is near.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Figure legends

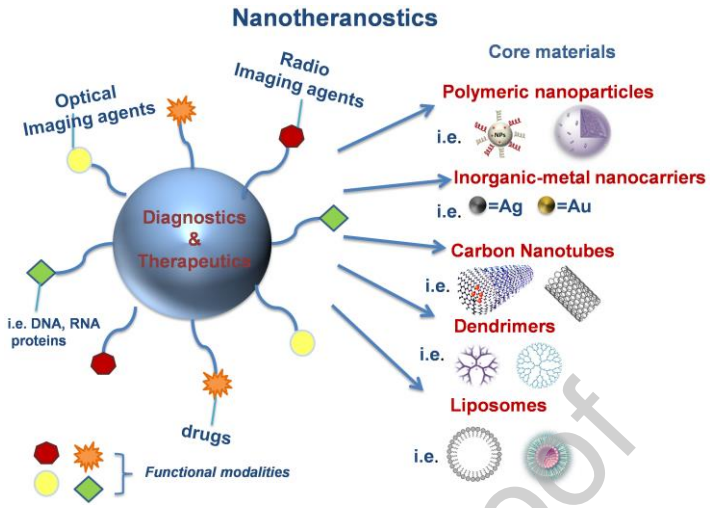


Fig. 1. A schematic representation of nanotheranostics used for simultaneous release and imaging. The functional groups of nanotheranostics can be drugs, DNA, RNA, imaging agents while their core material are polymers, inorganic and carbon based nanocarriers, dendrimers as well as liposomes.

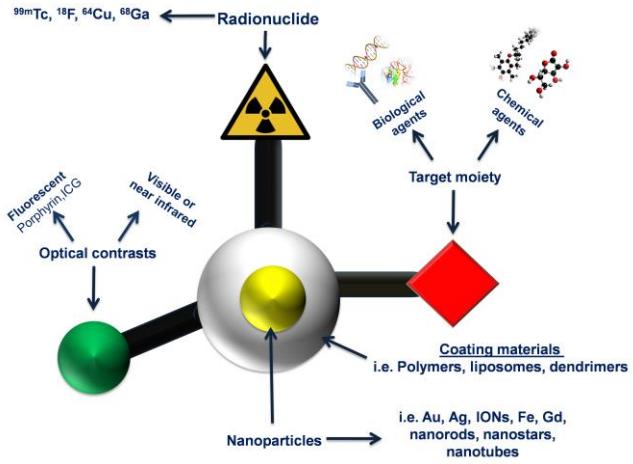
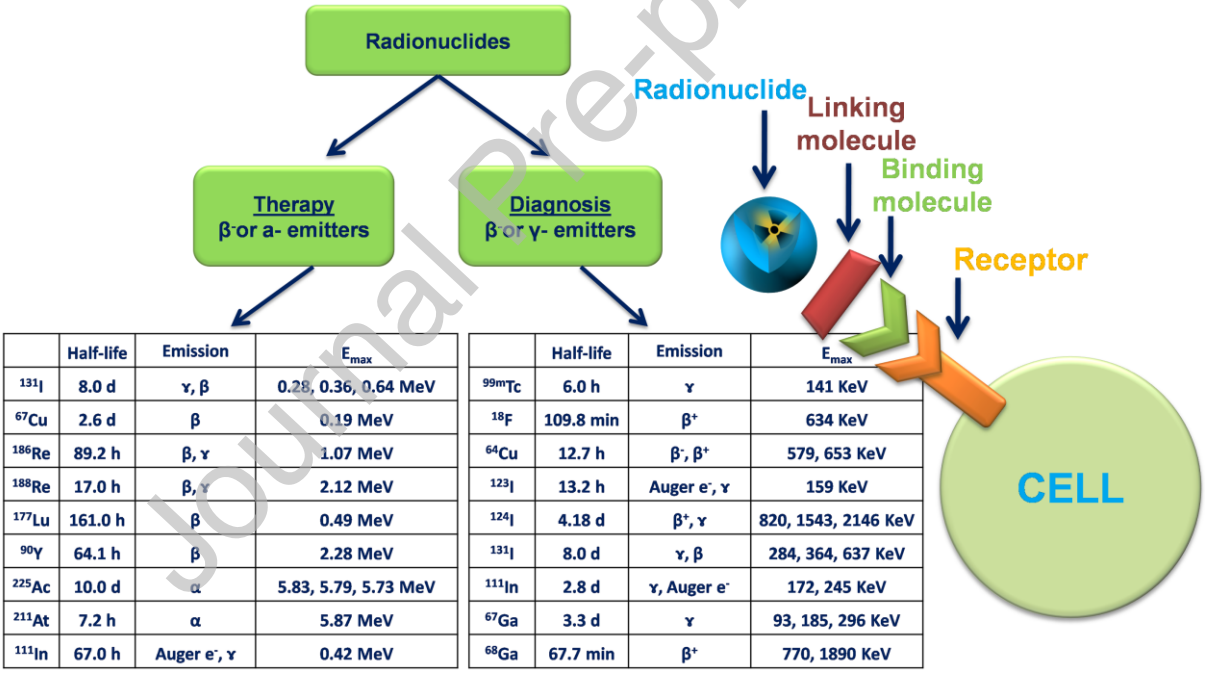


Fig.2. A detailed schematic illustration of multifunctional coated nanotheranostics. The imaging agents can be categorized on fluorescent or visible-infrared moieties, radionuclides whereas therapeutic target groups could be both chemical and biological agents.



	Half-life	Emission	E_{max}
^{131}I	8.0 d	γ, β	0.28, 0.36, 0.64 MeV
^{67}Cu	2.6 d	β	0.19 MeV
^{186}Re	89.2 h	β, γ	1.07 MeV
^{188}Re	17.0 h	β, γ	2.12 MeV
^{177}Lu	161.0 h	β	0.49 MeV
^{90}Y	64.1 h	β	2.28 MeV
^{225}Ac	10.0 d	α	5.83, 5.79, 5.73 MeV
^{211}At	7.2 h	α	5.87 MeV
^{111}In	67.0 h	Auger e$^-$, γ	0.42 MeV

	Half-life	Emission	E_{max}
^{99m}Tc	6.0 h	γ	141 KeV
^{18}F	109.8 min	β$^+$	634 KeV
^{64}Cu	12.7 h	β$^-$, β$^+$	579, 653 KeV
^{123}I	13.2 h	Auger e$^-$, γ	159 KeV
^{124}I	4.18 d	β$^+$, γ	820, 1543, 2146 KeV
^{131}I	8.0 d	γ, β	284, 364, 637 KeV
^{111}In	2.8 d	γ, Auger e$^-$	172, 245 KeV
^{67}Ga	3.3 d	γ	93, 185, 296 KeV
^{68}Ga	67.7 min	β$^+$	770, 1890 KeV

Fig. 3. The categories of radionuclides used as theranostics and diagnostic agents. According to their emmision type they can act as therapeutic or diagnostic agents.

*E_{max}= maximum energy, half-life= the time length it takes for half of the radioactive atoms of a specific radionuclide to decay.

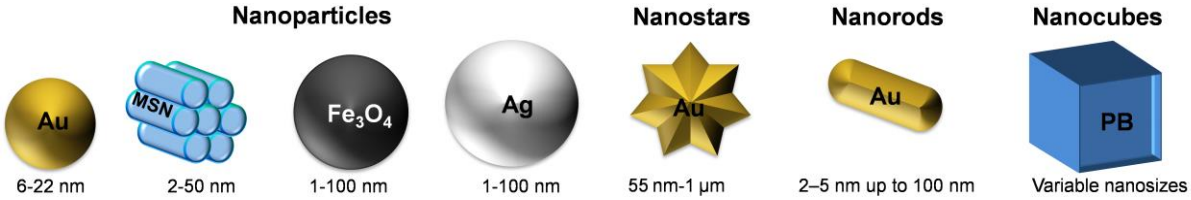


Fig. 4. Various examples of inorganic nanoparticles used as nanotheranostics. Description: Au=Gold, Ag=Silver, MSN= Mesoporous Silica Nanoparticles, Fe_3O_4= Iron oxide, PB=Prussian blue

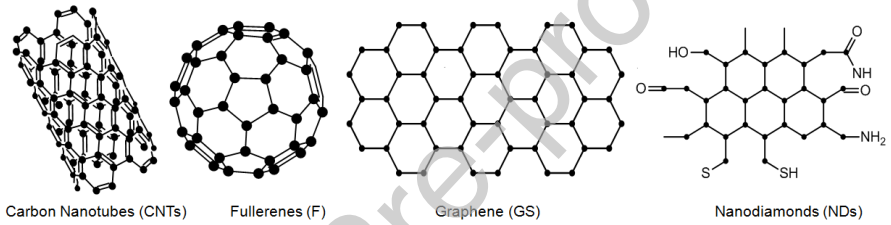


Fig. 5. Carbon based nanomaterials used as detection diagnostic nanotools

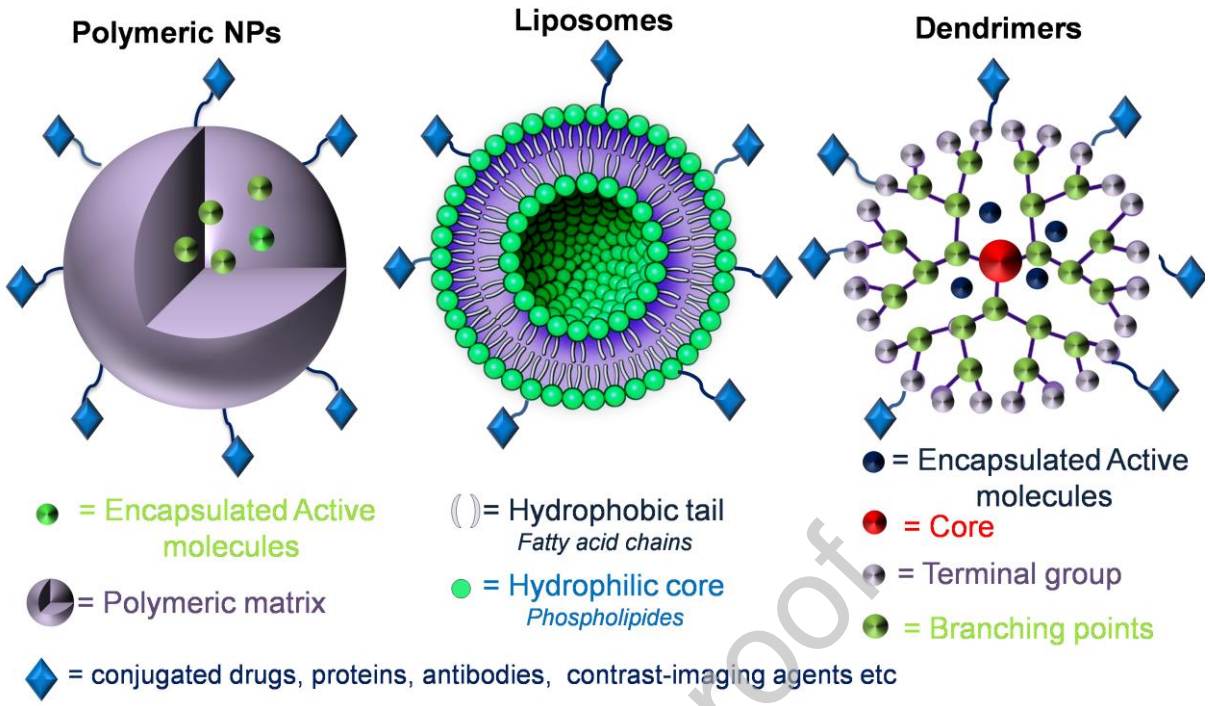


Fig. 6. Various structures of nanotheranostics based on polymeric NPs, liposomes and dendrimers