Dual-Targeted Therapy and Molecular Imaging with Radiolabeled Nanoparticles

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Abstract Radiolabeled targeted nanoparticles have been extensively studied for medical applications. Their multifunctionality and multivalency (among other properties) make them suitable candidates to target different diseases by means of pharmacophore groups for molecular, cellular, and/or tissue targeting. They have been used for molecular imaging and as drug delivery systems to improve drug efficacy and decrease side effects by passive accumulation of drugs in healthy tissues. Metallic nanoparticles can be radiolabeled or be radioactive themselves in order to deposit a large amount of energy into malignant cells, which produces irreversible damage. Because of their high surface area, these can be functionalized with small molecules and biomacromolecules for targeted radiotherapy. Moreover, their quantum size effect and resulting properties recently proved to produce hyperthermia. Polymeric nanoparticles are also acquiring importance in molecular imaging as diagnostic and therapeutic agents, due to their biocompatibility, biodegradability, and pharmacokinetic advantages, including the ability for controlled drug release or targeted radiotherapy. Both metallic and polymeric nanoparticles have been proposed as new, smart, pharmaceutical devices to produce dual-targeted therapy and molecular imaging. In this chapter, we will discuss the development and potential medical applications of radiolabeled metallic and polymeric nanoparticles as intelligent targeted systems.

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1 Introduction

Nanoparticles (NPs) play an important role in life science research. Particularly, nanosystems that enable molecular imaging of biological processes and therapeutic applications have been successfully developed based on their capacity to produce multifunctional and multivalent effects.

In the medical field, these nanosensors can be designed to target pharmacophore groups in select cells in order to produce a desired in vitro or in vivo effect. NPs have been purposed as in vitro approaches for diagnosis, in vivo molecular imaging or targeted delivery, and in vivo tissue engineering [1].

For human applications, only a few nanosystems or nanoplatforms have been approved for use in patients. Several shortcomings, mainly safety issues, have challenged their translation to clinical applications. Among them, their inherent toxicity produced by the accumulation in the reticuloendothelial system (RES) originated by their relatively slow hepatic uptake and biliary excretion continues to hamper their widespread use in vivo [2].

Molecular imaging for clinical use refers to the implementation of imaging techniques with highly sensitive and specific recognition with an additional high degree of spatial resolution. Modalities based on nuclear techniques combined with nuclear resonance imaging (NMR) promise a high degree of efficiency, increasing the diagnostic accuracy. Additionally, radiolabeled techniques extend the possibility for their therapeutic application using proper surface architecture to guarantee selectivity by molecular targeting.

Nuclear imaging modalities include single-photon emission computed tomography (SPECT), positron emission tomography (PET), and more recently, Cerenkov luminescence (CL) has also gained prominence. By using these imaging modalities, several approaches based on nanoparticles are being currently studied.

In this chapter, we discuss the development and potential medical applications of radiolabeled metallic and polymeric nanoparticles as intelligent targeted systems for applications in molecular imaging and therapy.

2 Multitargeting Receptors

In several diseases, including cancer, the heterogeneity of overexpressed receptors is well known. This fact opens the possibilities to target concurrently multiple receptors in vivo, in order to improve the detection sensitivity. In general, there are three different strategies for multireceptor targeting [3]:

(a) Heteromultivalent ligands, which allow simultaneous binding to different receptors.
(b) The co-injection of multiple radiotracers.
(c) The sequential injection of different imaging agents.

NPs have emerged as heteromultivalent and multifunctional systems that enable targeting of more than one receptor site to enable both therapy and imaging [4]. In the medical field, multifunctional nanoparticles that combine therapeutic molecules, molecular targeting, and diagnostic imaging abilities and exhibit appropriate features for in vivo use can improve the efficacy of cancer therapy and disease diagnosis. Although most of the nanosystems studied have demonstrated a wide variety of properties, multifunctional and multivalent nanoapproaches that simultaneously exhibit all needed functionalities for human applications are currently limited. Essential functionalities for multifunctional nanocarriers comprise:

- In vivo stability before attainment the target sites.
- Long circulation time in the bloodstream.
- Sensitivity to local stimuli to produce controlled release (temperature and/or pH).
- High drug loading content.
- Ability to specifically accumulate in the target sites.
- Ability to effect the intracellular drug uptake behavior.
- Capability to monitor disease advancement.

Targeting molecules that are capable of attaching onto the surface of nanoparticles include peptides, aptamers, small molecules, and antibodies [5].

3 Nuclear Imaging Based on Nanoparticles

A wide number of nanoplatforms have the capability for chemical conjugation to a chelator or to be radiolabeled on a chelator-free way. The selection of radionuclide to be attached or adsorbed onto the nanoparticle surface depends on the usefulness of that nanoplatform. Some features to be considered include the emission mode, emitted energies, and physical half-life. Gamma-emitting radionuclides with a short half-life are preferred for imaging, and beta-particle emitters are chosen for therapeutic purposes. Radionuclides that enable both imaging and therapeutic capabilities are called "theranostic" (^{177}Lu, ^{90}Y or ^{198}Au). In nuclear imaging, gamma radiation emitted by different radionuclides in diverse decay modes allows the acquisition of images (Fig. 1).

Positron emission tomography (PET) allows measurement of physiologic processes. This imaging can be performed by the annihilation of a positron emitted from a radionuclide with an electron. In this phenomenon, two 511 keV photons are emitted at 180°, which pass through the body and are detected by a ring of detectors around the subject. Radiolabeled NPs can be imaged in a quantitative mode to define the tumor uptake provided by the radiolabeled NPs [5]. Among PET radionuclides,

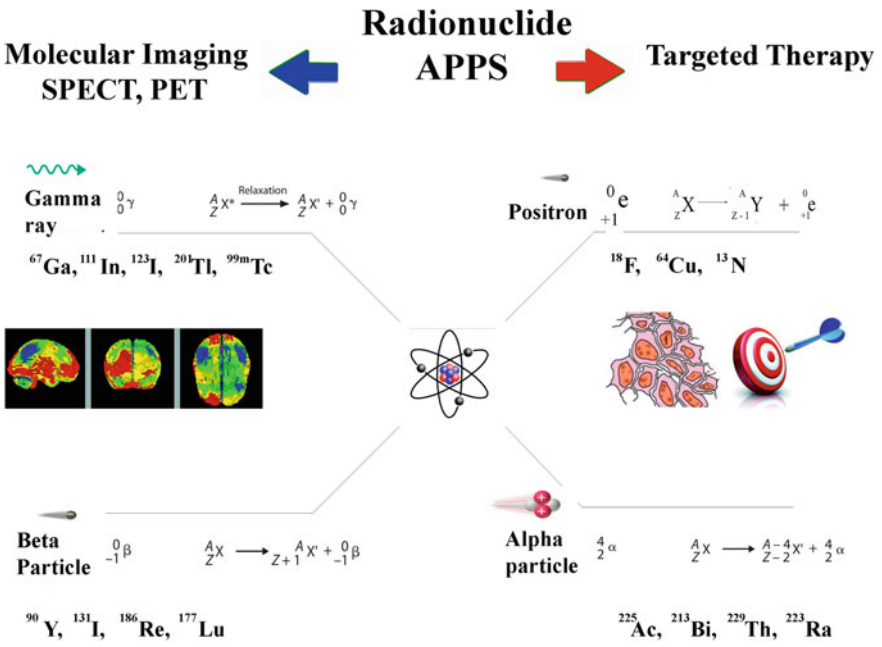

Fig. 1 Decay modes for nuclear imaging and therapy

^{68}Ga ($t_{1/2} = 68$ min) has a $t_{1/2}$ necessary to produce in vivo imaging of NPs and has been used for both PET and Cerenkov imaging. The ^{18}F ($t_{1/2} = 110$ m) radionuclide is also employed to label NP. For longer in vivo PET imaging, ^{64}Cu ($t_{1/2} = 12.7$ h), ^{89}Zr ($t_{1/2} = 78.4$ h), and ^{124}I ($t_{1/2} = 4.18$ d) are commonly used [6].

In single-photon emission computed tomography (SPECT), the emission of a gamma photon originated by the nucleus produces regional foci of the in vivo distribution. Collimators are used to detect a specific range of photon energies. Usually, two opposite detectors are used to obtain images through rotating from multiple angles around the field of view, which are then reconstructed to render three-dimensional images [7].

Cerenkov imaging is produced by the visible light wavelength produced by a charged particle traveling through a dielectric medium faster than the speed of light in that medium [8]. Radionuclides ^{177}Lu and ^{90}Y are used as imaging and therapeutic agents. Moreover, other radionuclides can be used in combination with NPs to obtain a theranostic agent [5].

4 Radiolabeling of Nanoparticles

In general, there are four main strategies to radiolabel nanoparticles:

- Bifunctional approach using chelators to coordinate radionuclides, chemically bound to the nanoparticle surface.
- A chelator-free radiolabeling method whereby radionuclides can be directly bound to the nanoparticle surface.
- Direct bombardment with neutrons or protons to produce some radioactive atoms in the nanoparticle.
- Radionuclides can be embedded into the nanoparticle.

In nuclear imaging, several chelators have been used to bind radionuclides onto the nanoparticle surface. NOTA (1,4,7-triazacyclononane-1,4,7-triyltriacetic acid), DOTA(1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetrayltetra-acetic acid), *p*-SCN-Bn-DOTA (S-2-(4-isothiocyanatobenzyl)-1,4,7,10-tetraazacyclododecane tetraacetic acid), and diethylenenetriaminepentaacetic acid (DTPA) are bifunctional complexing agents which bind radioactive atoms to a target biomolecule.

The conditions of radiolabeling include reaction temperature, incubation time, and biomolecule degradation control, making some modifications on affinity, binding properties, and consequent pharmacokinetic behavior, possible.

5 Radiolabeled Metallic Nanoparticles

Stable inorganic NPs have been prepared using different approaches. Mainly, NPs for biomedical applications are based on nanocolloids formed by heavy metal suspensions stabilized with a coating process using polymers, proteins, or polysaccharides. The coating provides NPs colloidal biocompatibility, stability, and increases their circulation time reducing their uptake by the RES. Nanoparticle biodistribution generally depends on their coating but also on their size. Small NPs with a mean diameter less than 10 nm undergo fast renal filtration; unlike NPs with a diameter greater than 200 nm are quickly removed by the RES system from the bloodstream. Therefore, NPs with diameters between 10 and 100 nm have achieved a higher accumulation at the target site, as a result of their longer circulation times. Furthermore to minimize the opsonization and clearance processes, generally NPs can be coated with some polymers as poly(ethylene glycol) (PEG) [9].

The most investigated inorganic NPs are gold NPs (AuNPs) and iron oxide NPs (IONPs), but there are also some reports of other noble metals such as silver and copper. Nanoparticles offer two key advantages as targeted agents: Firstly, nanoparticle geometry consists of a core, typically with thousands of detectable atoms such as iron and gold; secondly, they can be coated with targeting peptides, antibodies, or any molecules with biological activity. In addition, they have a large surface area, which is ideal not only for efficient modification but also can incorporate various functional moieties on the surface to produce systems with multiple receptor targeting at the same time. This produces multivalent effects caused by multiple simultaneous interactions between the surface of the nanoparticle and that of the cell [10–12].

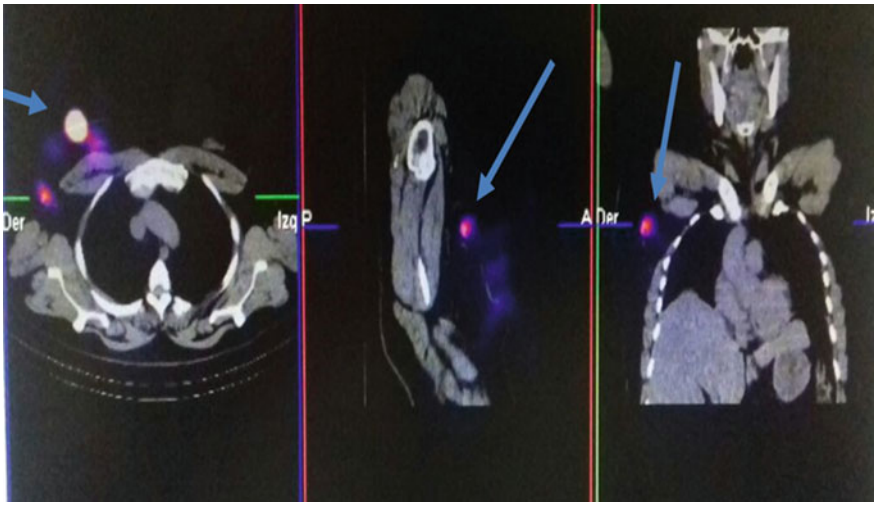

Fig. 2 Sentinel node localization by SPECT/CT in patient with breast cancer (24 h ^{99m}Tc-AuNP-mannose post-administration). Image courtesy of National Cancer Institute (Mexico)

5.1 Radiolabeled Gold Nanoparticles (AuNPs)

Gold nanoparticles continue to show great potential for clinical applications. In recent years, important breakthroughs have been made in the development of gold radiolabeled nanoparticles, which can be used as novel diagnostic tools in multimodality imaging systems. Some multimeric systems of AuNPs radiolabeled with ^{99m}Tc have been reported as suitable target-specific drugs for molecular imaging of tumors and sentinel lymph node detection [13, 14]. Moreover, ^{177}Lu-AuNPs conjugated to different targeting peptides have been proposed as theranostic radiopharmaceuticals [15–18]. Recently, Ferro-Flores et al. (2017) developed an antiangiogenic cancer-specific dual-targeting ^{177}Lu-Au-nanoradiopharmaceutical based on AuNPs. The nuclear localization sequence (NLS)-Arg-Gly-Asp peptide and an aptamer (HS-pentyl-pegaptanib) to target both the α(v)β(3) integrin and the vascular endothelial growth factor (VEGF) overexpressed in the tumor neovasculature has been demonstrated. The nanosystem showed properties of angiogenesis inhibition [19].

Only few examples of AuNPs have demonstrated successful clinical applications, but several approaches are still in clinical trials [20]. To localize sentinel lymph node in breast cancer patients (Fig. 2), ^{99m}Tc-AuNP-mannose radiopharmaceutical showed a suitable response by using 1-day or 2-day conventional protocols [21].

Plasmonic Gold Nanoparticles for Photothermal Therapy

NPs of noble metals have a broad absorption band in the visible spectrum, due to plasmon resonance. Metallic nanomaterials display strong absorption in the near-infrared (NIR) region (700–1100 nm); mostly, it converts optical energy into thermal energy. This effect is called photothermal ablation and can be used to destroy tumor cells by local heating. Photothermal ablation therapy has gained increasing attention because of its minimally invasive approach for cancer treatment. Several specific targeting approaches for photothermal heating with gold nanoparticles have been widely reported [22–26]. The plasmon resonance for common gold 20-nm nanosphere is 520 nm and redshift in NIR region from 800–1200 nm. Further, these materials can be conjugated with specific targeting molecules for better efficacy [27, 28].

In order to elucidate the temperature increase necessary to produce cell death by photothermal therapy when AuNPs in different tissues are irradiated with a Nd-YAG laser (532 nm), the optical properties (coefficient of extinction, absorption, and scattering) were calculated [29].

Recently, a new generation of nanosystems, which enables more than one pathway of producing therapy and imaging, has emerged. As expected, these systems have demonstrated clear advantages to those of individual therapy approaches. The photothermal and radiotherapeutic potential of the ^{177}Lu-dendrimer conjugated toward folate and bombesin conjugated with gold nanoparticles in the dendritic cavity (^{177}Lu-DenAuNP-folate-bombesin) was demonstrated. The intense NIR fluorescence emitted at 825 nm from the conjugate inside breast cancer cells corroborated the effectiveness of ^{177}Lu-DenAuNP-folate-bombesin for optical imaging [30]. Moreover, the synergistic interaction in a breast cancer model between heat produced by photoconversion and cytotoxicity with doxorubicin was demonstrated by small AuNPs (less than 20 nm) when irradiated by laser [31].

Intrinsically Radiolabeled Gold Nanoparticles

Au-198 can be used for tumor therapy because of its half-life of 2.7 days and higher energy β-emission ($\beta_{max} = 0.96$ meV) which enables it to penetrate up to 11 mm in tissue to produce therapeutic cross-fire effect on the tumor cells with a minimal radiation dose to the normal tissue surrounded. In vitro/in vivo biocompatible of Au-198 compounds was produced and evaluated the first time by Katti et al. [32, 33]. They prepared trigonal and tetrahedral gold compounds functionalized with biocompatible water-soluble hydroxymethyl phosphine that showed suitable in vivo clearance by renal and hepatobiliary pathways. The present article also demonstrates antitumor properties of these complexes against some types of human cancer established in mice and dogs as lung, breast, non-Hodgkin's lymphoma, prostate, and pancreatic tumors [34]. The promising radiochemical and biodistribution properties of these Au-198 nanoparticles encouraged their stabilization with other polymers as epigallocatechin gallate (EGCG) and gum arabic glycoprotein (GAP) [35]. The utility of amino acid-based phosphines for reducing gold salt into gold nanoparticles has

allowed to prepare biocompatible ^{198}AuNPs for theranostic applications [36, 37]. Recently, Axiak-Bechtel et al. used dogs to develop a human-mimicking prostate cancer model. They found that dogs with spontaneous prostatic tumors treated with a single dose of GAP-^{198}AnNP (105 Gy) did not show short-term toxicity.

In addition, the combination of imaging modalities (CT/SPECT) revealed that, following the injection of GAP-^{198}AuNP, the therapeutic agent was mainly localized in the prostate, with some loss in the bladder and urethra [38]. Advantageous Au-198 radiochemical properties also encouraged Chanda et al. to conjugate ^{198}AuNPs with BBN peptides in order to develop a tumor-targeted therapeutic agent. ^{198}AuNP-BBN in vitro and in vivo studies in mice evidenced a high binding affinity (IC_{50}) in microgram ranges and a selective uptake in GRP-receptor-rich organs such as the pancreatic acne in normal mice and the tumors in prostate tumor-bearing mice. The difference in prostate tumor sites between the mice treated with ^{198}AuNP-BBN and the pretreated group demonstrated the realistic clinical potential of these targeted nanoparticles [39]. Radioactive AuNP has been also functionalized with mangiferin, a promising xanthonoid for tumor targeting. The therapeutic efficacy studies of MGF-^{198}AuNPs provided conclusive evidence that the nanosystem has the ability to reduce tumors volume and did not cause any adverse radiotoxicity [40].

5.2 Radiolabeled Iron Oxide Nanoparticles

Iron oxide nanoparticles (IONPs) are one of the most widely studied NPs for imaging applications over the past two decades, because they can enable contrast in MRI through the production of localized magnetic field inhomogeneities. IONP size can range from several nanometers to microns and can be classified according to their hydrodynamic diameter into: ultra-small paramagnetic iron oxide (USPIO) NPs below 50 nm; superparamagnetic iron oxide (SPIO) from 60 to 250 nm; and micron-sized iron oxide particles (MPIO) from 1 to 8 μm [41].

Iron oxide NPs are produced by physical, chemical, and biological methods. However, chemical synthesis methods based on the co-precipitation of Fe^{2+} and Fe^{3+} aqueous salt solutions by addition of a base are the most commonly used due to their low production cost and the high yield. In addition, using these methods is easy to control the size, composition, and the shape of the NPs produced, changing some factors as the Fe^{2+} and Fe^{3+} ratio, the type of salts used (e.g., chlorides, sulfates, nitrates, or perchlorates), pH, and the ionic strength. Other chemical methods such as precipitation (solgel and gas/aerosol gel preparation) have been developed [42].

Functionalized IONPs provide the opportunity to develop tumor-specific thermal therapy for metastatic cancer when inductively heated by an externally applied, alternating magnetic field. To be used as targeted agents, however, IONP cores have to be first stabilized with an adsorbed layer of a biocompatible polymer (such as dextran, chitosan, or polymethacrylate) and then conjugate the target-specific molecules such as antibodies, proteins, peptides [9].

IONPs have been radiolabeled with SPECT and PET imaging isotopes using direct, indirect labeling, and doping approaches, in order to develop multimodality imaging agents for dual PET/MR or SPECT/MRI, as well as trimodality imaging (MR/NIR/PET or SPECT) when conjugated to fluorescent near-infrared optical agents [41].

Several dual-mode imaging probes for PET/MRI using ^{64}Cu have been reported. Jarrett et al. designed iron oxide nanoparticles coupled with ^{64}Cu for the diagnosis of vascular inflammation. Glaus et al. reported ^{64}Cu-DOTA-PEG-IONPs showed strong MR and PET signals and stability in mouse serum. ^{64}Cu-bis (dithiocarbamate-bisphosphonate) conjugated to IONPs has also been reported for in vivo lymphatic imaging. To image $\alpha_v\beta_3$ expression, multifunctional ^{64}Cu-labeled IONPs conjugated to the RGD (Arg-Gly-Asp) peptide have been developed and demonstrated a specific glioblastoma tumor-targeting capability by PET/MRI dual imaging [43]. Xie et al. dual-labeled IONPs encapsulated into human serum albumin matrices with ^{64}Cu-DOTA and Cy5.5, and using in vivo PET/NIR fluorescence/MRI trimodality imaging in a subcutaneous U87MG xenograft mouse model, demonstrated a huge accumulation in lesions, a high extravasation rate, and low uptake by macrophages in tumor microenvironment [44].

Both Ga-67 and Ga-68 have been used for multimodal imaging. Jalilian et al. reported a ^{67}Ga-labeled IONP-folate system with adequate cell membrane permeability and paramagnetic properties for thermotherapy. This system showed excellent stability at room temperature, low liver uptake, and high blood circulation after 24 h. Stelter et al. covalently bonded the transfection agent HIV-1 Tat, the fluorescent dye fluorescein isothiocyanate, and ^{68}Ga to IONPs, and demonstrated that the radionanoconjugate can be applied to efficient cell labeling, subsequent multimodal molecular imaging, and possible thermoablative therapy [44].

Madru et al. prepared ^{99m}Tc-labeled IONPs for the SPECT/MRI imaging multimodality of sentinel lymph nodes. The labeling was carried out through polyethylene glycol coated over the solid iron oxide core. SPECT/MRI imaging confirmed its potential applications in the diagnosis of breast cancer and malignant melanoma, due to the accumulation of ^{99m}Tc-IONPs in animal lymph nodes. Shanehsazzadeh et al. evaluated the biodistribution in mice of dextran-coated IONPs labeled with ^{99m}Tc and found high uptake in the reticuloendothelial system.

In order to study the concomitant efficacy of heating injected magnetic nanoparticles, ^{111}In-labeled ChL6 was conjugated to carboxylated polyethylene glycol (PEG) in different-sized, dextran-coated IONPs, with one to two ChL6 antibodies per nanoparticle. Using athymic mice bearing the human breast cancer model, it was observed that heating the nanoparticles with an externally applied AMF caused tumor necrosis in all cases. SPECT imaging showed a tumor uptake of 14% of the injected dose per gram at 48 h. However, although the heating capacity of the large nanoparticles (30 and 100 nm) was several times greater, the tumor-targeting efficacy was significantly less than that of their 20-nm-sized counterparts [43].

Also, beta-particle emitters such as I-131 have been conjugated to NPs for radiotherapy purposes. For example, Liang et al. radiolabeled IONPs with Re-188 using a direct method with a labeling efficiency of 90% and good in vitro stability and

Table 1 Radiolabeled iron oxide nanoparticles for SPECT/PET MR imaging

Nanoparticle	Application	References
^{99m}Tc-IONPs/diethylene triamine pentaacetic acid (DTPA) and 1,4,7-triazacyclononane-triacetic acid (NOTA)	Multimodality contrast agents for sentinel lymph node mapping	[45]
^{99m}Tc-PEG-BP-USPIO/Poly etilenglycol-bisphosphonates (BP)	Visualization of blood vessels and vascular organs with high spatial definition	[46]
^{99m}Tc-USPIO-bevacizumab	Targeted imaging of hepatocellular carcinoma	[47]
^{99m}Tc-PEG-SPIONs	Molecular imaging for sentinel lymph node (SLN)	[48]
^{111}In-antimesothelin antibody (mAbMB)-SPION	Early diagnosis and treatment planning of mesothelin-expressing cancers using SPECT-MR imaging	[49]
^{64}Cu-DTPA-SPION-Fluorochrome	Trimodality reporter for macrophage and inflammatory plaque components	[50]
^{68}Ga/^{111}In-TAT-FITC-aminosilated-SPIONs	Cell labeling for trimodal imaging	[51]
^{64}Cu-PEG-fosfolipid-SPIONs	Dual PET-MRI imaging agent	[52]
^{64}Cu-bifosfonate-dextran-SPIONs	PET-MR dual modality for draining lymph nodes image	[6]
^{64}Cu-DOTA-polyaspartic acid (PASP)-IONPs-RGD	Dual PET and MRI of tumor integrin expression	[53]
Intrinsically radiolabeled [^{59}Fe]-SPIONs	Dual SPECT-MR detection	[54]
$^{67}Ga^{3+}$ and Cu^{2+}-labeled SPIONs	Multimodal PET/SPECT-MRI agent	[55]

demonstrated the ability of ^{188}Re-IONPs to kill liver cancer cells. Cao et al. prepared silica-coated magnetite nanoparticles immobilized with histidine and linked the Re-188 onto their surface, obtaining a labeling yield of 91%. Chen et al. reported the development of ^{131}I-anti-VEGF cross-linked to dextran-coated IONPs and investigated their therapeutic effects in nude mice with induced liver tumors. Tumor growth delay and tumor inhibition were observed. Therefore, their results suggested that the radioimmunotherapy of an intratumoral injection of ^{131}I-anti-VEGF-IONP is effective for the treatment of liver cancer [44] (Table 1).

5.3 Radiolabeled Silver Nanoparticles

Silver NPs (AgNPs) have been used as antimicrobial agents because they can be incorporated into plastics, textiles, and other materials. However, little is known about in vivo trafficking and deposition of AgNPs. Therefore, a few studies have been reported recently to study the accumulation of AgNPs in organs and their toxicological implications. Ichedef et al. [56] reported a synthesis method for radiolabeled silver nanoparticles from proton activation of silver metal powder, enriched in Ag-107, with a 30.7 meV proton beam to produce the γ-emitter Ag-105 g (half-life of 41.29 days). Following the activation, the powder was dissolved in concentrated nitric acid in order to form silver nitrate ($AgNO_3$), which was used to synthesize the ^{105}AgNP. Chrastina and Schnitzer [57] developed a rapid method for the radiolabeling of AgNPs with I-125 in order to track in vivo tissue uptake of silver nanoparticles after systemic administration by SPECT imaging. Biodistribution analysis revealed uptake of the nanoparticles in the liver (24.5% ID/g) and spleen (41.5% ID/g) at 24 h. Similar results were obtained by Ashraf et al. [58] using water-based suspension of bare silver nanoparticles and dextran-coated AgNPs (dextran AgNPs) radiolabeled with Tc-99m. Both ^{99m}Tc-AgNPs and Tc-99m-dextran-AgNPs were mainly accumulated in the liver/spleen region although dextran delayed liver uptake, enhancing the blood retention time. Farrag et al. reported a simple and rapid method for radiolabeling of three types of Ag NPs using I-125, with high labeling yields (>90%), without disturbing the optical properties. After intravenous injection of the radiocompound in normal and solid tumor-bearing mice, they found that ^{125}I-AgNPs was localized in the tumor site for a long period of time [59].

5.4 Radiolabeled Copper Nanoparticles

Synthesis of intrinsically radiolabeled nanoparticles is an emerging concept in cancer theranostics and is expected to play an imperative role in translating nanotechnology research. Therefore, recently Zhou et al. [60] synthesized radioactive ^{64}CuS NPs, in which ^{64}Cu is an integral building block of CuS rather than a chelate to the NPs. These simple to make ^{64}CuS NPs demonstrated to possess excellent stability and to be suitable both for PET imaging and as photothermal coupling agents for photothermal ablation. Furthermore, the ^{64}CuS NPs showed a passive targeting preference over the tumor site and a strong NIR absorption that mediated ablation of U87 tumor cells after either intratumoral or intravenous injection. Based on these results, a viable strategy for a large-scale production (GBq level) of Cu-64 using medium flux research reactors was explored. Biological studies of ^{64}CuS NPs produced with this method on mice-bearing melanoma tumors revealed a significant tumor uptake (4.64 ± 1.71% ID/g) within 4 h post-injection, with good tumor-to-background contrast [61].

A smart nanosystem was developed for tumor-targeting drug delivery and PET/MR imaging. The nanocarrier is based on superparamagnetic iron oxide

nanoparticles radiolabeled with ^{64}Cu and demonstrated favorable properties for combined targeted anticancer drug delivery and PET/MRI dual-modality imaging of tumors overexpressing integrin $\alpha_v\beta_3$. The size (hydrodynamic diameter) was 68 ± 2 nm and was pH-sensitive in order to deliver Doxorubicin. The in vivo ^{64}Cu-labeled cRGD-conjugated SPIO nanocarrier uptake was mainly in the tumor and liver, but not in most normal tissues. The system demonstrated good tumor-targeting capability and successful tumor contrast [4].

6 Radiolabeled Polymeric Nanoparticles

Polymeric nanoparticles have been extensively reported as effective carriers to therapeutic pharmaceuticals and are recently emerging as a new class of molecular imaging (MI) agents for detection and treatment of human diseases [62]. An optimal polymeric nanosystem for MI applications possesses the following components: (a) controlled- and sustained-release properties; (b) smaller size (5–250 nm) to facilitate internalization and probing of cells and they do not have rapid renal clearance; (c) their surface is easily modified with molecular signaling and receptor-targeting molecules; (d) payload-carrying capacity delivers high concentrations of imaging agents to desired region; (e) multimodal potential offers visualization in more than one imaging modality; and (f) theranostic capability enables detection and treatment of disease using a single platform [63].

A wide variety of natural or synthetic polymers (chitosan, PLA, PGA, PLGA, PEG, HPMA, and other acrylate derivatives) with outstanding biocompatibility and biodegradability and nanoparticle preparation techniques (nanoparticles obtained by polymerization of a monomer or obtained directly from a preformed polymer) have been described for polymeric nanoparticle production [64]. There is no exclusive polymer for the encapsulation of any therapeutic or imaging agent, and not all molecules can be incorporated in all polymers. Both the physicochemical properties of the polymer and candidate molecule to be incorporated must be considered.

There are two general methods for the generation of polymeric nanosystems for imaging applications. The first is **covalent conjugation** of contrast agents to a polymeric matrix, followed by the formation of nanoparticles by conventional techniques or the conjugation can be in the surface of preformed nanoparticles. The second is the **physical encapsulation** of the contrast agent within polymeric nanoparticles.

The major advantage of grafted polymers is that the contrast agent is covalently bound to the polymer; thus, the burst release does not occur. However, disadvantages include poor loading efficiency and nonhomogeneous distribution of contrast agents within the polymeric matrix. The physical encapsulated systems may have superior advantages over the covalently bound polymer because of high loading efficiency within the polymeric matrix. However, controlling the burst release contrast agents from nanoconjugates within a biological system remains a significant challenge [65].

For nuclear imaging, radionuclides such as ^{11}C, ^{18}F, ^{64}Cu, ^{76}Br, ^{99m}Tc, ^{111}In, and ^{90}Y have been used with a wide range of copolymers to formulate robust nanosized

Table 2 Examples of polymeric nanoparticles used in nuclear imaging

Polymeric system	Agent	Modality	References
^{99m}Tc-PLGA	^{99m}Tc	SPECT	[66]
HPMA-LMA	^{18}F	PET	[67, 68]
Poly(*t*-butyl acrylate), PEG, methyl acrylate, styrene	^{64}Cu	PET	[69]
Poly-glycidyl-methacrylate(poly-2,3-epoxy-propylmethacrylate)	^{68}Ga	PET	[70]
Polyethylene glycol-coated micelles dually labeled	Cy^7, ^{111}In	SPECT, NIR, FL	[71]
PVPh	^{124}I	PET	[72]
PAMAM dendrimer-entrapped gold NPs	^{99m}Tc	SPECT/CT	[73]
PEG-b-PPA/DNA micellar nanoparticles	^{111}In	SPECT/CT	[74]
PEGylated dendrimer poly(amidoamine) (PAMAM)-folic acid conjugates	^{99m}Tc	SPECT	[75]
Poly(*N*-vinylimidazole-co-*N*-vinylpyrrolidone)g-poly(D,L-lactide)	^{123}I	SPECT/CT	[76]
Dextran nanoparticles	^{89}Zr	PET/MR	[77]

CT, Computed tomography; *FL*, Fluorescence

delivery systems. Additionally, the fluorescence imaging technique is integrated with polymeric NPs to develop the image-guide drug delivery system to monitor drug pharmacokinetics, intratumoral drug distribution, and drug tumor accumulation in real time.

The versatility of these nanomaterials makes them an attractive platform for developing highly sensitive molecular imaging agents. Table 2 covers the recent use of polymeric nanoparticles as carriers of molecular MI agents.

7 Discussion

Many different types of nanoparticles have been designed and evaluated over the years. Initially, nanosystems were primarily used for therapeutic purposes, that is, for a more efficient delivery of therapeutic drugs to pathologic sites, while reducing their accumulation in potentially endangered healthy tissues. Currently, some therapeutic nanoparticles are used clinically, and more of these so-called nanomedicine formulations are being evaluated in preclinical and clinical trials. However, in recent years, interest for nanoparticles as diagnostic agents has increased.

Radiolabeled nanoparticles developed as a smart multifunctional platform, designed for in vivo imaging and/or therapy have demonstrated high potential to be used in medical applications. The use of noninvasive nuclear imaging modalities such as PET, SPECT, or CL allows for the study of NP biodistribution in animal models, which can provide essential information for clinical translation of radiolabeled nanosystems to human trials. Medical applications of multifunctional nanoparticles could be reached if therapeutic agents could be incorporated in the same platform as molecular targeting agents with diagnostic imaging capabilities.

The potential of using nanoparticles for molecular imaging is compromised because their pharmacokinetic properties are difficult to control. Among the challenges to translate, these nanoapproaches to human application for imaging and/or therapy are the lack of ability to administer them intravenously and their low specific activities are the main shortcomings to deal with. Nanoparticles would either have to be administered by an intratumoral injection or directly deposited on an artery that feeds a target organ to avoid RES in order to achieve therapeutic applications in humans. It is important to note that in order to facilitate the clinical translation of radiolabeled nanoparticles, appropriate dosimetry and toxicological studies should be included.

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Conflicts of Interest The authors declare no conflict of interest.

References

1. Choi, H., Lee, Y.-S., Hwang, D.W., Lee, D.S.: Translational radionanomedicine: a clinical perspective. Eur. J. Nanomed. **8**(2), 71–84 (2016)
2. Ma, Y., Mou, Q., Zhu, X., Yan, D.: Small molecule nanodrugs for cancer therapy. Mater. Today Chem. **4**, 26–39 (2017)
3. Reubi, J.C., Maecke, H.R.: Approaches to multireceptor targeting: hybrid radioligands, radioligand cocktails, and sequential radioligand applications. J. Nucl. Med. **58**(Supplement 2), 10S–16S (2017)

4. Yang, X., Hong, H., Grailer, J.J., Rowland, I.J., Javadi, A., Hurley, S.A., et al.: cRGD-functionalized, DOX-conjugated, and 64 Cu-labeled superparamagnetic iron oxide nanoparticles for targeted anticancer drug delivery and PET/MR imaging. Biomaterials **32**(17), 4151–4160 (2011)
5. Pratt, E.C., Shaffer, T.M., Grimm, J.: Nanoparticles and radiotracers: advances toward radionanomedicine. Wiley Interdisc. Rev.: Nanomed. Nanobiotechnol. **8**(6), 872–890 (2016)
6. Torres Martin de Rosales, R., Tavaré, R., Glaria, A., Varma, G., Protti, A., Blower, P.J.: ^{99m}Tc-bisphosphonate-iron oxide nanoparticle conjugates for dual-modality biomedical imaging. Bioconjug. Chem. **22**(3), 455–465 (2011)
7. Goel, S., Chen, F., Ehlerding, E.B., Cai, W.: Intrinsically radiolabeled nanoparticles: an emerging paradigm. Small **10**(19), 3825–3830 (2014)
8. Thorek, D.L., Robertson, R., Bacchus, W.A., Hahn, J., Rothberg, J., Beattie, B.J., et al.: Cerenkov imaging-a new modality for molecular imaging. Am. J. Nucl. Med. Mol. Imaging **2**(2), 163 (2012)
9. Abou, D.S., Pickett, J.E., Thorek, D.L.J.: Nuclear molecular imaging with nanoparticles: radiochemistry, applications and translation. Br. J. Radiol. **88**, 2015 (1054). https://doi.org/10.1259/bjr.20150185. PubMed PMID: WOS:000363315800012
10. Montet, X., Funovics, M., Montet-Abou, K., Weissleder, R., Josephson, L.: Multivalent effects of RGD peptides obtained by nanoparticle display. J. Med. Chem. **49**(20), 6087–6093 (2006). https://doi.org/10.1021/jm060515m. PubMed PMID: ISI:000240826200023
11. Montet, X., Montet-Abou, K., Reynolds, F., Weissleder, R., Josephson, L.: Nanoparticle imaging of integrins on tumor cells. Neoplasia **8**(3), 214–222 (2006). https://doi.org/10.1593/neo.05769. PubMed PMID: ISI:000239282800007
12. Khoobchandani, M., Katti, K., Maxwell, A., Fay, W.P., Katti, K.V.: Laminin receptor-avid nanotherapeutic EGCg–AuNPs as a potential alternative therapeutic approach to prevent restenosis. Int. J. Mol. Sci. **17**(3), 316 (2016)
13. Ocampo-García, B., Ferro-Flores, G., Morales-Avila, E., de María, Ramírez F.: Kit for preparation of multimeric receptor-specific ^{99m}Tc-radiopharmaceuticals based on gold nanoparticles. Nucl. Med. Commun. **32**(11), 1095–1104 (2011)
14. Orocio-Rodríguez, E., Ferro-Flores, G., Santos-Cuevas, C.L., Ramírez, FdM, Ocampo-García, B.E., Azorín-Vega, E., et al.: Two novel nanosized radiolabeled analogues of somatostatin for neuroendocrine tumor imaging. J. Nanosci. Nanotechnol. **15**(6), 4159–4169 (2015)
15. Ferro-Flores, G., E Ocampo-García, B., L Santos-Cuevas, C., de Maria Ramirez, F., Azorin-Vega, E., Meléndez-Alafort, L.: Theranostic radiopharmaceuticals based on gold nanoparticles labeled with ^{177}Lu and conjugated to peptides. Curr. Radiopharm. **8**(2), 150–159 (2015)
16. Vilchis-Juárez, A., Ferro-Flores, G., Santos-Cuevas, C., Morales-Avila, E., Ocampo-García, B., Díaz-Nieto, L., et al.: Molecular targeting radiotherapy with cyclo-RGDFK (C) peptides conjugated to ^{177}Lu-labeled gold nanoparticles in tumor-bearing mice. J. Biomed. Nanotechnol. **10**(3), 393–404 (2014)
17. Luna-Gutiérrez, M., Ferro-Flores, G., Ocampo-García, B.E., Santos-Cuevas, C.L., Jiménez-Mancilla, N., León-Rodríguez, D., et al.: A therapeutic system of ^{177}Lu-labeled gold nanoparticles-RGD internalized in breast cancer cells. J. Mex. Chem. Soc. **57**(3), 212–219 (2013)
18. Jiménez-Mancilla, N., Ferro-Flores, G., Santos-Cuevas, C., Ocampo-García, B., Luna-Gutiérrez, M., Azorín-Vega, E., et al.: Multifunctional targeted therapy system based on ^{99m}Tc/^{177}Lu-labeled gold nanoparticles-Tat(49-57)-Lys3-bombesin internalized in nuclei of prostate cancer cells. J. Labelled Compd. Radiopharm. **56**(13), 663–671 (2013)
19. González-Ruíz, A., Ferro-Flores, G., Azorín-Vega, E., Ocampo-García, B., de Maria, Ramírez F., Santos-Cuevas, C., et al.: Synthesis and in vitro evaluation of an antiangiogenic cancer-specific dual-targeting ^{177}Lu-Au-nanoradiopharmaceutical. J. Radioanal. Nucl. Chem. **314**(2), 1337–1345 (2017)
20. Anselmo, A.C., Mitragotri, S.: A review of clinical translation of inorganic nanoparticles. AAPS J. **17**(5), 1041–1054 (2015)

21. Ocampo-García, B.E., Ramírez, FdM, Ferro-Flores, G., De León-Rodríguez, L.M., Santos-Cuevas, C.L., Morales-Avila, E., et al.: ^{99m}Tc-labelled gold nanoparticles capped with HYNIC-peptide/mannose for sentinel lymph node detection. Nucl. Med. Biol. **38**(1), 1–11 (2011)
22. Alberti, C.: From molecular imaging in preclinical/clinical oncology to theranostic applications in targeted tumor therapy. Eur. Rev. Med. Pharmacol. Sci. **16**(14), 1925–33 (2012). PubMed PMID: WOS:000313936400006
23. Pissuwan, D., Valenzuela, S.M., Cortie, M.B.: Therapeutic possibilities of plasmonically heated gold nanoparticles. Trends Biotechnol. **24**(2), 62–67 (2006). https://doi.org/10.1016/j.tibtech.2005.12.004. PubMed PMID: ISI:000235574900004
24. Abadeer, N.S., Murphy, C.J.: Recent progress in cancer thermal therapy using gold nanoparticles. J. Phys. Chem. C **120**(9), 4691–4716 (2016)
25. Fekrazad, R., Naghdi, N., Nokhbatolfoghahaei, H., Bagheri, H.: The combination of laser therapy and metal nanoparticles in cancer treatment originated from epithelial tissues: a literature review. J. Lasers Med. Sci. **7**(2), 62 (2016)
26. Mendoza-Nava, H., Ferro-Flores, G., Ocampo-García, B., Serment-Guerrero, J., Santos-Cuevas, C., Jiménez-Mancilla, N., et al.: Laser heating of gold nanospheres functionalized with octreotide: in vitro effect on HeLa cell viability. Photomed. Laser Surg. **31**(1), 17–22 (2013)
27. Ocampo-Garcia, B.E., Ramirez, F.D., Ferro-Flores, G., De Leon-Rodriguez, L.M., Santos-Cuevas, C.L., Morales-Avila, E., et al.: Tc-99m-labelled gold nanoparticles capped with HYNIC-peptide/mannose for sentinel lymph node detection. Nucl. Med. Biol. **38**(1), 1–11 (2011). https://doi.org/10.1016/j.nucmedbio.2010.07.007. PubMed PMID: ISI:000286574800001
28. Patra, C.R., Bhattacharya, R., Mukhopadhyay, D., Mukherjee, P.: Application of gold nanoparticles for targeted therapy in cancer. J. Biomed. Nanotechnol. **4**(2), 99–132 (2008). https://doi.org/10.1166/jbn.2008.016. PubMed PMID: ISI:000257794200001
29. Carrillo-Cazares, A., Jiménez-Mancilla, N., Luna-Gutiérrez, M., Isaac-Olivé, K., Camacho-López, M.: Study of the optical properties of functionalized gold nanoparticles in different tissues and their correlation with the temperature increase. J. Nanomater. (2017)
30. Mendoza-Nava, H., Ferro-Flores, G., Ramírez, FdM, Ocampo-García, B., Santos-Cuevas, C., Azorín-Vega, E., et al.: Fluorescent, plasmonic, and radiotherapeutic properties of the ^{177}Lu–Dendrimer–AuNP–Folate–Bombesin nanoprobe located inside cancer cells. Mol. Imaging **16**, 1536012117704768 (2017)
31. Mendes, R., Pedrosa, P., Lima, J.C., Fernandes, A.R., Baptista, P.V.: Photothermal enhancement of chemotherapy in breast cancer by visible irradiation of gold nanoparticles. Sci. Rep. **7**(1), 10872 (2017)
32. Berning, D.E., Katti, K.V., Barnes, C.L., Volkert, W.A., Ketring, A.R.: Chemistry in environmentally benign media. 7. Chelating hydroxymethyl-functionalized bisphosphines as building blocks to water-soluble and in-vitro-stable gold(I) complexes. Synthesis, characterization, and x-ray crystal structures of Au{(HOH2C)(2)PC6H4P(CH2OH)(2)}(2) Cl and AU(2){(HOH2C)(2)PCH2CH2P(CH2OH)(2)}(2) Cl-2. Inorg. Chem. **36**(13), 2765–2769 (1997). https://doi.org/10.1021/ic961396b. PubMed PMID: WOS:A1997XF30900013
33. Berning, D.E., Katti, K.V., Volkert, W.A., Higginbotham, C.J., Ketring, A.R.: Au-198-labeled hydroxymethyl phosphines as models for potential therapeutic pharmaceuticals. Nucl. Med. Biol. **25**(6), 577–583 (1998). https://doi.org/10.1016/s0969-8051(98)00023-7. PubMed PMID: WOS:000075024800010
34. Higginbotham, M.L., Henry, C.J., Katti, K.V., Casteel, S.W., Dowling, P.M., Pillarsetty, N.: Preclinical tolerance and pharmacokinetic assessment of MU-Gold, a novel chemotherapeutic agent, in laboratory dogs. Vet. Ther. **4**(1), 76–82 (2003). PubMed PMID: WOS:000220158900008
35. Katti, K.V., Kannan, R., Katti, K., Kattumori, V., Pandrapraganda, R., Rahing, V., et al.: Hybrid gold nanoparticles in molecular imaging and radiotherapy. Czechoslovak J. Phys. **56**, D23–D34 (2006). PubMed PMID: WOS:000206057500003

36. Berning, D.E., Katti, K.V., Barnes, C.L., Volkert, W.A.: Chemical and biomedical motifs of the reactions of hydroxymethylphosphines with amines, amino acids, and model peptides. J. Am. Chem. Soc. **121**(8), 1658–1664 (1999)
37. Kannan, R., Rahing, V., Cutler, C., Pandrapragada, R., Katti, K.K., Kattumuri, V., et al.: Nanocompatible chemistry toward fabrication of target-specific gold nanoparticles. J. Am. Chem. Soc. **128**(35), 11342–11343 (2006)
38. Axiak-Bechtel, A.M., Upendran, A., Lattimer, J.C., Kelsey, J., Cutler, C.S., Selting, K.A., et al.: Gum arabic-coated radioactive gold nanoparticles cause no short-term local or systemic toxicity in the clinically relevant canine model of prostate cancer. Int. J. Nanomed. **9**, 5001–5011 (2014). https://doi.org/10.2147/ijn.s67333. PubMed PMID: WOS:000343863800001
39. Chanda, N., Kattumuri, V., Shukla, R., Zambre, A., Katti, K., Upendran, A., et al.: Bombesin functionalized gold nanoparticles show in vitro and in vivo cancer receptor specificity. Proc. Natl. Acad. Sci. U. S. A **107**(19), 8760–8765 (2010). https://doi.org/10.1073/pnas.1002143107. PubMed PMID: WOS:000277591200049
40. Al-Yasiri, A., Khoobchandani, M., Cutler, C., Watkinson, L., Carmack, T., Smith, C., et al.: Mangiferin functionalized radioactive gold nanoparticles (MGF-198 AuNPs) in prostate tumor therapy: green nanotechnology for production, in vivo tumor retention and evaluation of therapeutic efficacy. Dalton Trans. **46**(42), 14561–14571 (2017)
41. de Barros, A.L.B., Tsourkas, A., Saboury, B., Cardoso, V.N., Alavi, A.: Emerging role of radiolabeled nanoparticles as an effective diagnostic technique. EJNMMI Res. **2** (2012). https://doi.org/10.1186/2191-219x-2-39. PubMed PMID: WOS:000209435700039
42. Kogan, M.J., Olmedo, I., Hosta, L., Guerrero, A.R., Cruz, L.J., Albericio, F.: Peptides and metallic nanoparticles for biomedical applications. Nanomedicine **2**(3), 287–306 (2007). https://doi.org/10.2217/17435889.2.3.287. PubMed PMID: WOS:000248250400008
43. Assadi, M., Afrasiabi, K., Nabipour, I., Seyedabadi, M.: Nanotechnology and nuclear medicine; research and preclinical applications. Hellenic J. Nucl. Med. **14**(2), 149–59 (2011). PubMed PMID: WOS:000292952700009
44. Ferro-Flores, G., Ocampo-Garcia, B.E., Santos-Cuevas, C.L., Morales-Avila, E., Azorin-Vega, E.: Multifunctional radiolabeled nanoparticles for targeted therapy. Curr. Med. Chem. **21**(1), 124–38 (2014). PubMed PMID: WOS:000327778900009
45. Barrefelt, Å.A., Brismar, T.B., Egri, G., Aspelin, P., Olsson, A., Oddo, L., et al.: Multimodality imaging using SPECT/CT and MRI and ligand functionalized ^{99m}Tc-labeled magnetic microbubbles. EJNMMI Res. **3**(1), 12 (2013)
46. Sandiford, L., Phinikaridou, A., Protti, A., Meszaros, L.K., Cui, X., Yan, Y., et al.: Bisphosphonate-anchored PEGylation and radiolabeling of superparamagnetic iron oxide: long-circulating nanoparticles for in vivo multimodal (T1 MRI-SPECT) imaging. ACS Nano. **7**(1), 500–512 (2012)
47. Zhao, Y., Yao, Q., Tan, H., Wu, B., Hu, P., Wu, P., et al.: Design and preliminary assessment of ^{99m}Tc-labeled ultrasmall superparamagnetic iron oxide-conjugated bevacizumab for single photon emission computed tomography/magnetic resonance imaging of hepatocellular carcinoma. J. Radioanal. Nucl. Chem. **299**(3), 1273–1280 (2014)
48. Madru, R., Kjellman, P., Olsson, F., Wingårdh, K., Ingvar, C., Ståhlberg, F., et al.: ^{99m}Tc-labeled superparamagnetic iron oxide nanoparticles for multimodality SPECT/MRI of sentinel lymph nodes. J. Nucl. Med. **53**(3), 459–463 (2012)
49. Misri, R., Meier, D., Yung, A.C., Kozlowski, P., Häfeli, U.O.: Development and evaluation of a dual-modality (MRI/SPECT) molecular imaging bioprobe. Nanomed. Nanotechnol. Biol. Med. **8**(6), 1007–1016 (2012). https://doi.org/10.1016/j.nano.2011.10.013
50. Nahrendorf, M., Zhang, H., Hembrador, S., Panizzi, P., Sosnovik, D.E., Aikawa, E., et al.: Nanoparticle PET-CT imaging of macrophages in inflammatory atherosclerosis. Circulation **117**(3), 379–387 (2008)
51. Stelter, L., Pinkernelle, J.G., Michel, R., Schwartländer, R., Raschzok, N., Morgul, M.H., et al.: Modification of aminosilanized superparamagnetic nanoparticles: feasibility of multimodal detection using 3T MRI, small animal PET, and fluorescence imaging. Mol. Imag. Biol. **12**(1), 25–34 (2010)

52. Glaus, C., Rossin, R., Welch, M.J., Bao, G.: In vivo evaluation of ^{64}Cu-labeled magnetic nanoparticles as a dual-modality PET/MR imaging agent. Bioconjug. Chem. **21**(4), 715–722 (2010)
53. Lee, H.-Y., Li, Z., Chen, K., Hsu, A.R., Xu, C., Xie, J., et al.: PET/MRI dual-modality tumor imaging using arginine-glycine-aspartic (RGD)—Conjugated radiolabeled iron oxide nanoparticles. J. Nucl. Med. **49**(8), 1371–1379 (2008)
54. Hoffman, D., Sun, M., Yang, L., McDonagh, P.R., Corwin, F., Sundaresan, G., et al.: Intrinsically radiolabelled [^{59}Fe]-SPIONs for dual MRI/radionuclide detection. Am. J. Nucl. Med. Mol. Imaging **4**(6), 548 (2014)
55. Pham, T.N., Lengkeek, N.A., Greguric, I., Kim, B.J., Pellegrini, P.A., Bickley, S.A., et al.: Tunable and noncytotoxic PeT/sPecT–MrI multimodality imaging probes using colloidally stable ligand-free superparamagnetic iron oxide nanoparticles. Int. J. Nanomed. **12**, 899 (2017)
56. Ichedef, C., Simonelli, F., Holzwarth, U., Bagaria, J.P., Puntes, V.F., Cotogno, G., et al.: Radiochemical synthesis of Ag-105 g-labelled silver nanoparticles. J. Nanopart. Res. **15**(11) (2013). https://doi.org/10.1007/s11051-013-2073-8. PubMed PMID: WOS:000326322200001
57. Chrastina, A., Schnitzer, J.E.: Iodine-125 radiolabeling of silver nanoparticles for in vivo SPECT imaging. Int. J. Nanomed. **5**, 653–9 (2010). PubMed PMID: WOS:000283715300068
58. Ashraf, A., Sharif, R., Ahmad, M., Masood, M., Shahid, A., Anjum, D.H., et al.: In vivo evaluation of the biodistribution of intravenously administered naked and functionalised silver nanoparticles in rabbit. IET Nanobiotechnol. **9**(6), 368–374 (2015). https://doi.org/10.1049/iet-nbt.2014.0075. PubMed PMID: WOS:000366254300007
59. Farrag, N.S., El-Sabagh, H.A., Al-Mahallawi, A.M., Amin, A.M., AbdEl-Bary, A., Mamdouh, W.: Comparative study on radiolabeling and biodistribution of core-shell silver/polymeric nanoparticles-based theranostics for tumor targeting. Int. J. Pharm. **529**(1–2), 123–133 (2017). https://doi.org/10.1016/j.ijpharm.2017.06.044. PubMed PMID: WOS:000408009200012
60. Zhou, M., Zhang, R., Huang, M.A., Lu, W., Song, S.L., Melancon, M.P., et al.: A chelator-free multifunctional Cu–^{64}CuS nanoparticle platform for simultaneous micro-PET/CT imaging and photothermal ablation therapy. J. Am. Chem. Soc. **132**(43), 15351–15358 (2010). https://doi.org/10.1021/ja106855m. PubMed PMID: WOS:000283621700049
61. Chakravarty, R., Chakraborty, S., Ningthoujam, R.S., Nair, K.V.V., Sharma, K.S., Ballal, A., et al.: Industrial-scale synthesis of intrinsically radiolabeled (CuS)–Cu–64 nanoparticles for use in positron emission tomography (PET) imaging of cancer. Ind. Eng. Chem. Res. **55**(48), 12407–12419 (2016). https://doi.org/10.1021/acs.iecr.6b03405. PubMed PMID: WOS:000389623500012
62. Peng, H., Liu, X., Wang, G., Li, M., Bratlie, K.M., Cochran, E., et al.: Polymeric multifunctional nanomaterials for theranostics. J. Mater. Chem. B **3**(34), 6856–6870 (2015)
63. Choi, K.Y., Liu, G., Lee, S., Chen, X.: Theranostic nanoplatforms for simultaneous cancer imaging and therapy: current approaches and future perspectives. Nanoscale. **4**(2), 330–342 (2012)
64. Reis, C.P., Neufeld, R.J., Ribeiro, A.J., Veiga, F.: Nanoencapsulation I. Methods for preparation of drug-loaded polymeric nanoparticles. Nanomed. Nanotechnol. Biol. Med. **2**(1), 8–21 (2006)
65. Srikar, R., Upendran, A., Kannan, R.: Polymeric nanoparticles for molecular imaging. Wiley Interdisc. Rev.: Nanomed. Nanobiotechnol. **6**(3), 245–267 (2014)
66. Subramanian, S., Dandekar, P., Jain, R., Pandey, U., Samuel, G., Hassan, P.A., et al.: Technetium-99m–labeled poly (dl-lactide-co-glycolide) nanoparticles as an alternative for sentinel lymph node imaging. Cancer Biotherapy Radiopharm. **25**(6), 637–644 (2010)
67. Allmeroth, M., Moderegger, D., Gündel, D., Koynov, K., Buchholz, H.-G., Mohr, K., et al.: HPMA-LMA copolymer drug carriers in oncology: an in vivo PET study to assess the tumor line-specific polymer uptake and body distribution. Biomacromol **14**(9), 3091–3101 (2013)
68. Allmeroth, M., Moderegger, D., Gündel, D., Buchholz, H.-G., Mohr, N., Koynov, K., et al.: PEGylation of HPMA-based block copolymers enhances tumor accumulation in vivo: a quantitative study using radiolabeling and positron emission tomography. J. Controlled Release **172**(1), 77–85 (2013)

69. Sun, X., Rossin, R., Turner, J.L., Becker, M.L., Joralemon, M.J., Welch, M.J., et al.: An assessment of the effects of shell cross-linked nanoparticle size, core composition, and surface PEGylation on in vivo biodistribution. Biomacromol **6**(5), 2541–2554 (2005)
70. Cartier, R., Kaufner, L., Paulke, B., Wüstneck, R., Pietschmann, S., Michel, R., et al.: Latex nanoparticles for multimodal imaging and detection in vivo. Nanotechnology **18**(19), 195102 (2007)
71. Zhang, R., Xiong, C., Huang, M., Zhou, M., Huang, Q., Wen, X., et al.: Peptide-conjugated polymeric micellar nanoparticles for dual SPECT and optical imaging of EphB4 receptors in prostate cancer xenografts. Biomaterials **32**(25), 5872–5879 (2011)
72. Simone, E.A., Zern, B.J., Chacko, A.-M., Mikitsh, J.L., Blankemeyer, E.R., Muro, S., et al.: Endothelial targeting of polymeric nanoparticles stably labeled with the PET imaging radioisotope iodine-124. Biomaterials **33**(21), 5406–5413 (2012)
73. Li, X., Xiong, Z., Xu, X., Luo, Y., Peng, C., Shen, M., et al.: ^{99m}Tc-labeled multifunctional low-generation dendrimer-entrapped gold nanoparticles for targeted SPECT/CT dual-mode imaging of tumors. ACS Appl. Mater. Interfaces **8**(31), 19883–19891 (2016)
74. Patil, R.R., Yu, J., Banerjee, S.R., Ren, Y., Leong, D., Jiang, X., et al.: Probing in vivo trafficking of polymer/DNA micellar nanoparticles using SPECT/CT imaging. Mol. Ther. **19**(9), 1626–1635 (2011)
75. Zhang, Y., Sun, Y., Xu, X., Zhang, X., Zhu, H., Huang, L., et al.: Synthesis, biodistribution, and microsingle photon emission computed tomography (SPECT) imaging study of technetium-99m labeled PEGylated dendrimer poly (amidoamine)(PAMAM)—Folic acid conjugates. J. Med. Chem. **53**(8), 3262–3272 (2010)
76. Lu, P.-L., Chen, Y.-C., Ou, T.-W., Chen, H.-H., Tsai, H.-C., Wen, C.-J., et al.: Multifunctional hollow nanoparticles based on graft-diblock copolymers for doxorubicin delivery. Biomaterials **32**(8), 2213–2221 (2011)
77. Majmudar, M.D., Yoo, J., Keliher, E.J., Truelove, J.J., Iwamoto, Y., Sena, B., et al.: Polymeric nanoparticle pet/mr imaging allows macrophage detection in atherosclerotic plaques novelty and significance. Circ. Res. **112**(5), 755–761 (2013)