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Molecular imaging and therapy of cancer with radiolabeled nanoparticles

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Summary

This review summarizes the current state-of-the-art of radiolabeled nanoparticles for molecular imaging and internal radiotherapy applications targeting cancer. With the capacity to provide enormous flexibility, radiolabeled nanoparticles have the potential to profoundly impact disease diagnosis and patient management in the near future. Currently, the major challenges facing the research on radiolabeled nanoparticles are desirable (tumor) targeting efficacy, robust chemistry for both radionuclide encapsulation/incorporation and targeting ligand conjugation, favorable safety profile, as well as certain commercial and regulatory hurdles.

Keywords

Molecular imaging; nanoparticle; internal radiotherapy; cancer; positron emission tomography (PET); single-photon emission computed tomography (SPECT)

Introduction

Nanotechnology, an interdisciplinary research field involving physics, chemistry, engineering, biology, and medicine, has great potential for early detection, accurate diagnosis, and personalized treatment of various diseases, in particular cancer [1,2]. Generally, the diameter of a nanoparticle is within the range of 1 nanometer (nm) to a few hundred nm. With the size comparable to biological molecules such as antibodies, about one hundred to ten thousand times smaller than human cells, nanoparticles can offer unprecedented interactions with biomolecules both on the surface of and inside the cells which may revolutionize disease diagnosis and treatment. Research on nanoparticles has flourished over the last decade. A literature search of “nanoparticles” in PubMed returned more than 23,000 publications. More importantly, greater than 97% of these publications appeared within the last 10 years.

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One of the major applications of nanotechnology is in biomedicine. For in vitro and ex vivo applications, the advantages of state-of-the-art nanodevices (nano-chips, nano-sensors, etc.) over traditional assay methods are obvious [3,4]. Several barriers exist for in vivo applications in preclinical animal models and eventually clinical translation of nanotechnology, among which are the biocompatibility, in vivo kinetics, ability to escape the reticuloendothelial system (RES), targeting efficacy, acute and chronic toxicity, and cost-effectiveness. The most promising clinical applications of nanoparticles will be in cardiovascular medicine, where there is much less biological barrier for efficient delivery of nanoparticles, and in oncology, where the leaky tumor vasculature can allow for better tissue penetration than in normal organs/tissues.

Over the last decade, there have been numerous nanotechnology centers established world-wide [5,6]. Perhaps the biggest event in the history of nanotechnology research is the establishment of the National Cancer Institute (NCI) Alliance for Nanotechnology in Cancer (http://nano.cancer.gov/) in October 2005. This Alliance is a comprehensive, systematized initiative encompassing the public and private sectors, designed to accelerate the application of the best capabilities of nanotechnology to cancer. With the goals of developing novel research tools, agents, multi-functional targeted devices and systems, this $144.3 million five-year initiative funded eight Centers of Cancer Nanotechnology Excellence (CCNEs, multi-institutional hubs focusing on integrating nanotechnology into basic and applied cancer research) and twelve Cancer Nanotechnology Platform Partnerships (focused programs designed to develop the technologies to underpin new products in many key research areas). After establishing such an interdisciplinary nanotechnology workforce, it is expected that nanotechnology will mature into a clinically useful field in the near future.

In this review, we will first summarize the state-of-the-art of molecular imaging with radiolabeled nanoparticles, which incorporate certain targeting moieties and can interrogate specific molecular and cellular events in living systems (animals and potentially humans). Next, we will focus on the use of radiolabeled nanoparticles for internal radiotherapy applications. Lastly, we will discuss the challenges facing the research on radiolabeled nanoparticles as well as promising future directions in this area.

Molecular imaging

The field of molecular imaging, “the visualization, characterization and measurement of biological processes at the molecular and cellular levels in humans and other living systems” [7], has expanded tremendously over the last decade. In general, molecular imaging modalities include molecular magnetic resonance imaging (mMRI), magnetic resonance spectroscopy (MRS), optical bioluminescence, optical fluorescence, targeted ultrasound, single photon emission computed tomography (SPECT), and positron emission tomography (PET) [8]. Continued development and wider availability of scanners dedicated to small animal imaging studies, which can provide a similar in vivo imaging capability in mice, primates, and humans, can enable smooth transfer of knowledge and molecular measurements between species thereby facilitating clinical translation [9,10].

Molecular imaging takes advantage of the traditional diagnostic imaging techniques and introduces molecular imaging probes to measure the expression of indicative molecular markers at different stages of diseases. It can give whole-body readout in an intact system which is much more relevant and reliable than in vitro/ex vivo assays; reduce the workload and speed up the drug development process; provide more statistically accurate results since longitudinal studies can be performed in the same animal which serves as its own control; aid in lesion detection in patients and patient stratification; and help in individualized treatment monitoring and dose optimization [11,12]. Non-invasive detection of various molecular

markers of diseases can allow for much earlier diagnosis, earlier treatment, and better prognosis that will eventually lead to personalized medicine.

Radionuclide-based imaging includes SPECT and PET, where internal radiation is administered through a low mass amount of pharmaceutical labeled with a radioisotope. Radiolabeling of antibodies (~ 10 nm in size) dated back several decades, which has been widely used for both imaging and therapeutic applications [13–15]. Although the sizes of these antibodies are within the nanometer range, in this review, we will only focus on the nanoparticles that do not naturally exist in living subjects (i.e. the "synthetic" nanoparticles). The major advantages of radionuclide-based molecular imaging techniques (i.e. SPECT and PET) over other modalities (e.g. optical and MRI) are that they are very sensitive (down to the picomolar level), quantitative, and there is no tissue penetration limit [8,16]. However, one disadvantage is that the resolution (typically > 1 mm) of either SPECT or PET is not as high as the other imaging modalities such as MRI. In most cases, the purpose of labeling the nanoparticle with a radionuclide was for the non-invasive evaluation of its biodistribution, pharmacokinetic properties, and/or tumor targeting efficacy with SPECT or PET.

SPECT imaging with radiolabeled nanoparticles

The source of SPECT images are gamma ray emissions [17,18]. The radioisotope decays and emits gamma rays, which can be detected by a gamma camera to obtain 3-D images. The first object that an emitted gamma photon encounters after exiting the body is the collimator, which allows it to travel only along certain directions to reach the detector, to ensure that the signal position on the detector accurately represents the source of the gamma ray. The most common radioisotopes used for SPECT imaging include ^{99m}Tc ($t_{1/2}$: 6.0 h), ^{111}In ($t_{1/2}$: 2.8 days), and radioiodine (e.g. ^{131}I, $t_{1/2}$: 8.0 days).

The pharmacokinetics, tumor uptake, and therapeutic efficacy of an ^{111}In-labeled, chimeric L6 (ChL6) monoclonal antibody linked iron oxide (IO) nanoparticle was studied in athymic mice bearing human breast cancer tumors [19]. The ^{111}In-labeled ChL6 was conjugated to the carboxylated polyethylene glycol (PEG) on dextran-coated IO nanoparticles (~ 20 nm in diameter), with one to two ChL6 antibodies per nanoparticle (Fig. 1). It was proposed that the time this nanoparticle remained in the circulation was long enough to provide ample opportunity for it to exit the blood vessels and access the cancer cells. Inductively heating the nanoparticle by externally applied alternating magnetic field (AMF) caused tumor necrosis at 24 h after AMF therapy. In a follow-up study, different doses of AMF was delivered at 72 h after nanoparticle injection [20]. SPECT imaging was carried out to quantify the nanoparticle uptake in the tumor, which was about 14 percentage injected dose per gram (%ID/g) at 48 h post-injection. A delay in tumor growth occurred after the AMF treatment, which was statistically significant when compared with the untreated group. Subsequently, similar nanoparticles with diameters of 30 and 100 nm were also studied [21]. Although the heating capacity of these large nanoparticles is several times greater, the tumor targeting efficacy was significantly less than that of the 20 nm-sized counterparts. In another report, recombinant antibody fragments were tested for tumor targeting of these nanoparticles [22]. Pharmacokinetic and whole-body autoradiography studies demonstrated that only 5% of the injected dose was targeted to the tumor after 24 h.

Integrins, a family of cell adhesion molecules, are involved in a wide range of cell-extracellular matrix and cell-cell interactions [23]. The $\alpha_v\beta_3$ integrin, which binds to Arginine-Glycine-Aspartic acid (RGD)-containing components of the interstitial matrix such as vitronectin [24], is expressed in a number of tumor types and plays a critical role in tumor angiogenesis [25]. Among all 24 integrins discovered to date, integrin $\alpha_v\beta_3$ is the most intensively studied [26,27]. In one report, integrin $\alpha_v\beta_3$-targeted ^{111}In-labeled perfluorocarbon (PFC)

nanoparticles were tested for the detection of tumor angiogenesis in New Zealand white rabbits implanted with tumors [28]. The PFC nanoparticles bearing approximately 10 ^{111}In per particle was found to have better tumor-to-muscle ratio than those containing approximately 1 ^{111}In per particle. At 18 h post-injection, the mean tumor radioactivity in rabbits receiving integrin $\alpha_v\beta_3$-targeted PFC nanoparticle was about 4-fold higher than the non-targeted control. Based on biodistribution studies, spleen was the primary clearance organ.

Single-walled carbon nanotubes (SWNTs) exhibit unique size, shape and physical properties that make them promising candidates for biological/biomedical applications [29–31]. In one early report, water-soluble hydroxylated SWNTs were labeled with ^{125}I ($t_{1/2}$: 60.2 days) to study the distribution in mice [32]. Subsequently, another group functionalized water-soluble SWNTs with the chelating molecule diethylentriaminepentaacetic (DTPA) and labeled them with ^{111}In for imaging purposes [33]. Strikingly, both reports suggested that these SWNTs were not retained in any of the RES organs (e.g. liver or spleen) and were cleared rapidly from the circulation through the renal route. Neither of these studies investigated in vivo tumor targeting of SWNTs upon attachment of targeting ligands. Recently, biodistribution of radiolabeled SWNT-oligonucleotide conjugates was also evaluated in mice [34].

Because of the use of lead collimators to define the angle of incidence, SPECT imaging has a very low detection efficiency ($< 10^{-4}$ times the emitted number of gamma rays) [35]. However, SPECT technologies have been evolving toward greater sensitivity (which can be enhanced by multi-pinhole acquisition methods) and spatial resolution (SPECT has no theoretical limitation in terms of spatial resolution) [36,37]. Both SPECT and PET are extremely valuable technologies in nuclear medicine, and each has its own strength and disadvantages. The major advantage of SPECT imaging over PET, besides the superior spatial resolution, is that it can potentially allow for simultaneous imaging of multiple radionuclides, since the gamma rays emitted from different radioisotopes can be differentiated based on the energy [38]. However, no dual-isotope imaging of radiolabeled nanoparticles has been reported and whether it can provide significant advantages over single-isotope SPECT imaging remains to be tested. PET, on the other hand, has much higher detection efficiency (up to ~10%) [39]. It was first developed in the mid 1970s [40] and dedicated microPET scanners for small animal studies were first reported in the late 1990s [41]. Over the last decade, PET imaging has become increasingly more popular in both preclinical and clinical settings.

PET imaging with radiolabeled nanoparticles

The biodistribution of ^{64}Cu ($t_{1/2}$: 12.7 h)-labeled SWNTs in mice has been investigated by PET imaging, ex vivo biodistribution, and Raman spectroscopy [42]. It was found that these SWNTs are highly stable in vivo and the surface PEG chain length can significantly affect its blood concentration and biodistribution. Effectively PEGylated SWNTs exhibit relatively long circulation half-life (about 2 h) and low uptake by the RES. Most importantly, efficient targeting of integrin $\alpha_v\beta_3$-positive tumor in mice was achieved with SWNTs coated with PEG chains linked to cyclic RGD peptides [42]. The intrinsic Raman signatures of SWNTs were also used to directly probe the presence of SWNTs in mice tissues and confirm the PET imaging results (Fig. 2). All in vivo and ex vivo experiments confirmed that there was minimal renal uptake of the SWNT-RGD conjugate, and the majority of the conjugate was taken up by the tumor and the RES. Recently, tumor accumulation of the SWNT-RGD conjugate in living mice has also been non-invasively imaged using both Raman spectroscopy [43,44] and photoacoustic tomography [45]. It is worth noting that both Raman spectroscopy and photoacoustic tomography detect the SWNT itself, which unambiguously validated that the data obtained from PET imaging of this SWNT-RGD conjugate (based on ^{64}Cu detection) is a true representation of the SWNT distribution. After evaluating the pharmacokinetics and tumor-targeting efficacy, as well as confirming the lack of toxicity [46,47], the use of SWNT

as a nanoplatform for integrated multimodality imaging and molecular therapy is currently been explored [48].

Subsequently, tumor-targeting SWNT constructs with covalently attached tumor-specific monoclonal antibodies, radiometal chelates, and fluorescent probes were investigated [49]. These constructs were found to be specifically reactive with the human cancer cells they were designed to target, both in vitro and in vivo. In a follow-up study, PET imaging was carried out to determine the tissue biodistribution and pharmacokinetics of ^{86}Y ($t_{1/2}$: 14.7 h)-labeled SWNTs in a mouse model [50]. It was found that ^{86}Y cleared from the blood within 3 hours and distributed predominantly to the kidneys, liver, spleen, and bone. Although the activity that accumulated in the kidney cleared with time, the whole-body clearance was quite slow.

Radiolabeled nanoparticles represent a new class of agents which has enormous potential for clinical applications. Different from other molecular imaging modalities where typically the nanoparticle itself is detected, radionuclide-based imaging detects the radiolabel rather than the nanoparticle. The nanoparticle distribution is measured indirectly by assessing the localization of the radionuclide, which can provide quantitative measurement of the tumor targeting efficacy and pharmacokinetics only if the radiolabel on the nanoparticle is stable enough under physiological conditions. However, dissociation of the radionuclide (typically metal) from the chelator, and/or the radionuclide-containing polymer coating from the nanoparticle, may occur which can cause significant difference between the nanoparticle distribution and the radionuclide distribution. Thus, the biodistribution data of radiolabeled nanoparticles based on PET/SPECT imaging only should always be interpreted with caution. Rigorous validation of the stability of the radiolabel on the nanoparticle should always be carried out to obtain more reliable experimental results (e.g. direct measurement of SWNTs in various tissues using the intrinsic Raman signal in addition to the radionuclide-based imaging studies).

Dual-modality imaging with radiolabeled nanoparticles

Among all molecular imaging modalities, no single modality is perfect and sufficient to obtain all the necessary information for a particular question [8]. For example, it is difficult to accurately quantify fluorescence signal in living subjects, particularly in deep tissues; MRI has high resolution yet it suffers from low sensitivity; Radionuclide-based imaging techniques have very high sensitivity but they have relatively poor resolution. Combination of multiple molecular imaging modalities can offer synergistic advantages over any modality alone. Multimodality imaging using a small molecule-based probe is very challenging due to the limited number of attachment points and the potential interference with its receptor binding affinity. On the other hand, nanoparticles have large surface areas where multiple functional moieties can be incorporated for multimodality molecular imaging.

Radiolabeled quantum dots

Quantum dots (QDs) are inorganic fluorescent semiconductor nanoparticles with many desirable optical properties for imaging applications, such as high quantum yields, high molar extinction coefficients, strong resistance to photobleaching and chemical degradation, continuous absorption spectra spanning the ultraviolet (UV) to near-infrared (NIR, 700–900 nm) range, narrow emission spectra, and large effective Stokes shifts [51–53]. However, in vivo targeting and imaging of QDs is very challenging due to the relatively large overall size (typically > 20 nm in hydrodynamic diameter) and short circulation half-lives of most QD conjugates [51,54].

Radioactive $Cd^{125m}Te/ZnS$ ($t_{1/2}$: 57.4 days) QDs were targeted to the mouse lung with an antibody [55]. Animals were sacrificed at different time points post-injection and

biodistribution in major organs was determined. MicroSPECT/CT imaging was also performed to provide visual confirmation of the biodistribution. It was found that the target-specific antibody conjugated $Cd^{125m}Te/ZnS$ QDs principally targeted the lungs while the QDs linked to a control antibody mainly accumulated in the liver and spleen. This report, for the first time, provided a quantitative measurement of the in vivo targeting efficacy of a QD-antibody system. In a follow-up study, these $Cd^{125m}Te/ZnS$ QDs were used to document the competition between vascular targeting and the interaction of QDs with the RES [56]. It was suggested that targeting of QDs is a competition between the effectiveness of the targeting agent and the natural tendency for RES uptake of QDs. Temporary inhibition of the RES may enhance the usefulness of QDs, perhaps also other nanoparticles, for drug or radioisotope delivery.

Neither of these two studies performed optical imaging with the radiolabeled QDs, which did not take full advantage of such dual-modality molecular imaging agents, where typically data obtained from one imaging modality are used for validating the data obtained from the other imaging modality. For optical fluorescence imaging, QDs are ideal agents for multiplexing studies [57]. Combination of the multiplexing capabilities of both SPECT (with different isotopes) and QDs may be worth exploring in the future for multiple-event imaging. A few other reports have focused on radiolabeling QDs with PET isotopes such as ^{18}F ($t_{1/2}$: 110 min) and ^{64}Cu [58–60]. However, neither incorporation of a targeting moiety nor optical imaging was carried out in these studies.

Due to the difficulties in quantifying the fluorescence signal in vivo and many other technical challenges which remain to be solved, in vivo imaging of QDs is so far mostly qualitative or semi-quantitative [61–63]. PET has been routinely used in the clinic for staging and evaluating many types of cancer [64]. Development of a dual-modality agent containing both a NIR QD and a PET isotope will allow for sensitive, accurate assessment of the pharmacokinetics and tumor targeting efficacy of NIR QDs by PET, which may greatly facilitate future translation of QDs into clinical applications.

We reported a QD-based probe for both NIR fluorescence (NIRF) and PET imaging (Fig. 3) [65]. In this study, cyclic RGD peptides and DOTA chelators (DOTA denotes 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) were conjugated to a QD (maximum emission 705 nm) for targeted dual-modality PET/NIRF imaging after ^{64}Cu-labeling. Using this dual-modality PET/NIRF probe, we quantitatively evaluated the tumor targeting efficacy and found that the majority of the dual-modality agent in the tumor was within the tumor vasculature. Further, this PET/NIRF probe can confer sufficient tumor contrast detectable by PET at much lower concentration than that required for in vivo NIRF imaging [61], thus significantly reducing the potential toxicity of cadmium-based QDs which may greatly facilitate their future biomedical applications [66,67]. Ex vivo histological examination confirmed that DOTA-QD-RGD targets primarily the tumor vasculature via specific RGD-integrin $\alpha_v\beta_3$ interaction with little extravasation (Fig. 3).

Vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) signaling pathway plays a pivotal role in regulating tumor angiogenesis [25,68]. Many therapeutic agents targeting VEGF or VEGFR are currently in preclinical and clinical development [69,70]. Since the radiolabeled QDs primarily targeted the tumor vasculature rather than the tumor cells, we investigated VEGFR targeting of QDs in a follow-up study [71]. Similar as in the previous report, DOTA-QD-VEGF exhibited VEGFR-specific binding in both cell-binding assay and cell staining experiment. Both NIRF and PET imaging showed VEGFR-specific delivery of DOTA-QD-VEGF to the tumor vasculature. Tumor uptake of ^{64}Cu-labeled DOTA-QD was significantly lower than that of ^{64}Cu-labeled DOTA-QD-VEGF. Most importantly, good correlation was also observed between the results measured by ex vivo PET and NIRF imaging of excised major organs.

The major roadblocks for clinical translation of QDs are the inefficient delivery, potential toxicity, and lack of quantification [51]. However, with the development of smaller [72,73], less toxic [74,75], multifunctional [76,77] QDs and further improvement of the conjugation strategy, it is expected that QD-based probes may achieve optimal tumor targeting efficacy with acceptable toxicity profile for clinical translation in the near future. In clinical settings, optical imaging is relevant for tissues close to the surface of the skin, tissues accessible by endoscopy, and during intraoperative visualization [51]. Combination of PET and optical imaging overcomes the tissue penetration limitation of NIRF imaging and enables quantitative in vivo targeted imaging in deep tissue, which will be crucial for future image-guided surgery through sensitive, specific, and real-time intra-operative visualization of the molecular features of normal and diseased processes. One scenario where a QD-based dual-modality PET/NIRF agent will be particularly useful is that an initial whole body PET scan can be carried out to identify the location of tumor(s), and optical imaging can be subsequently used to guide tumor resection.

Radiolabeled iron oxide nanoparticles

MRI is a non-invasive diagnostic technique based on the interaction of protons (or other nuclei) with each other and with surrounding molecules in a tissue of interest [78]. Different tissues have different relaxation times which can result in endogenous MR contrast. The major advantages of MRI over radionuclide-based imaging are the absence of radiation, higher spatial resolution (usually sub-millimeter level), and exquisite soft tissue contrast. The major disadvantage of MRI is its inherent low sensitivity, which can be partially compensated for by working at higher magnetic fields (4.7 – 14 T in small animal models), acquiring data for a much longer time period, and using exogenous contrast agents. IO nanoparticles, consisting of a crystalline IO core surrounded by a polymer coating such as dextran or PEG, are the most-widely used nanoparticle-based MR contrast agents [79]. The presence of thousands of iron atoms in each particle can give very high T_2 relaxivity [80].

The recently developed PET/CT scanner, already being used on a routine basis in clinical oncology, greatly facilitated pinpointing the regions of increased activity on PET [81,82]. However, accurate localization of PET probe uptake, even with PET/CT, can be very difficult in some cases due to the absence of identifiable anatomical structures, particularly in the abdomen [83,84]. MRI has exquisite soft tissue contrast and combination of PET/MR can have many synergistic effects. PET/MR imaging, acquired in one measurement, has the potential to become the imaging modality of choice for various clinical applications such as neurological studies, certain types of cancer, stroke, and the emerging field of stem cell therapy [85]. The future of PET/MR scanners will greatly benefit from the use of dual-modality PET/MR probes.

An IO nanoparticle-based probe for PET/MR imaging of tumor integrin $\alpha_v\beta_3$ expression was reported (Fig. 4) [86]. Poly(aspartic acid)-coated IO nanoparticles (PASP-IO) were synthesized and the surface amino groups were coupled to cyclic RGD peptides for integrin $\alpha_v\beta_3$ targeting and DOTA chelators for PET imaging (after labeling with ^{64}Cu), respectively. The PASP-IO nanoparticle has a core size of 5 – 7 nm and a hydrodynamic diameter of ~ 40 nm. Both microPET imaging and T_2-weighted MRI showed integrin $\alpha_v\beta_3$-specific delivery of RGD-PASP-IO nanoparticles to the U87MG human glioblastoma tumor. Based on PET imaging, the tumor accumulation of ^{64}Cu-labeled RGD-PASP-IO peaked at about 4 h post-injection and the non-targeted particle (i.e. ^{64}Cu-DOTA-IO) had significantly lower tumor uptake. Blocking experiment with unconjugated RGD peptides was able to significantly reduce the tumor uptake of the dual-modality agent, thus demonstrating receptor specificity in vivo. T_2-weighted MRI, as well as Prussian blue staining of the tumor tissue, corroborated the PET findings and further confirmed integrin $\alpha_v\beta_3$ specific delivery of the RGD-PASP-IO nanoparticles. Similar to most other nanoparticle-based imaging agents, the RES uptake of this probe was also quite

prominent. Overall, good correlation between the in vitro, in vivo and ex vivo assays demonstrated that the imaging results accurately reflected the biodistribution of the dual-modality PET/MR probe. This study represents the first example of in vivo dual-modality PET/MR imaging using a single agent. Recently, an ^{124}I ($t_{1/2}$: 4.2 days)-labeled IO nanoparticle was also reported as a dual-modality PET/MR probe for lymph node imaging in rats [87]. This nanoparticle may be useful in the clinic for accurate localization and characterization of lymph nodes, which is critical for cancer staging since the lymphatic system is an important route for cancer metastasis [88].

Summary of imaging with radiolabeled nanoparticles

The use of molecularly targeted, radiolabeled nanoparticles affords many advantages over conventional molecular imaging probes. First, hundreds, thousands, or even more imaging labels or a combination of labels for different imaging modalities can be attached to a single nanoparticle which can lead to dramatic signal amplification. Second, multiple, potentially different, targeting ligands on the nanoparticle can provide enhanced receptor binding affinity/specificity. Third, the ability to integrate means to bypass biological barriers can enhance the targeting efficacy of nanoparticles. Comparing to nanoparticles labeled with other imaging tags, the two biggest advantages of radiolabeled nanoparticles are the extreme detection sensitivity and the capability for quantitative imaging, which is only true if the radioisotope remains attached to the nanoparticle.

Nanoparticles usually suffer from poorer extravasation when compared to small molecules or proteins. Thus, the majority of nanoparticle-based research is so far limited to vasculature-related diseases. In the context of cancer, non-targeted nanoparticles can accumulate in tumors through the enhanced permeability and retention (EPR) effect, since the tumor vasculature is usually quite leaky and there is no lymphatic drainage in the tumor [89,90]. However, the need for efficient in vivo tumor targeting of nanoparticles can not be over-emphasized. Imaging agents based on passive targeting only, taking advantage of the EPR effect, are not truly molecular imaging agents in a strict sense. The feasible targets reachable by targeted nanoparticles (the basis of most dual-modality imaging agents) will be mostly vasculature-related, as the overall hydrodynamic diameter of these nanoparticles with surface polymer coating and targeting ligands are quite large (usually > 20 nm in diameter) which prohibits extravasation. Newly developed nanoparticles with smaller sizes (preferably < 10 nm in diameter) and longer circulation half-lives (at least a few hours) may allow for extravasation from the leaky tumor vasculature to a certain extent. Since the major disadvantage of mMRI is its inherent low sensitivity, which is exacerbated by almost exclusively vasculature targeting, future development of novel contrast agents with the capability of targeting the tumor cells in addition to the vasculature may dramatically increase the MR signal and facilitate the biomedical applications of nanoparticle-based imaging agents.

The emergence of dual-modality molecular imaging agents took place only a few years ago and there is ample space for further development/improvement. Dual-modality imaging probes that combine radionuclide-based imaging (i.e. PET or SPECT), which is very sensitive and highly quantitative, and non-radionuclide-based approaches, for example optical imaging which can significantly facilitate ex vivo validation of the in vivo data or MRI which can provide high resolution anatomical information, should be of particular interest for future biomedical applications (e.g. PET/optical and PET/MR probes).

Molecularly targeted contrast agents that can be detected by more than two imaging modalities are also expected to emerge in the future. Although various combinations of different imaging modalities can serve different purposes depending on the study design, we envision that a PET/MR/optical probe will find the most future biomedical/clinical applications since such a combination provides extremely high sensitivity (PET), quantitation capability (PET),

excellent anatomical information and soft tissue contrast (MR), as well as a means for ex vivo validation (optical) which itself can also be useful for highly sensitive imaging in certain sites of the human body. Recently, one such multimodality probe was constructed based on a nanoparticle [91]. However, no targeting ligand was incorporated and in vivo imaging was only achieved with PET, but not with optical imaging or MRI.

Cancer therapy with radiolabeled nanoparticles

Radiation therapy (radiotherapy) has been quite effective in the treatment of different types of cancer and minimizing the risk of local recurrence after surgical removal of the primary tumor [92,93]. Radiation kills cells largely through the generation of free radicals, which deposits a large amount of energy that can cause single- and double-strand breaks in the DNA. Generally, tumor cells are less capable of repairing DNA damage than normal cells since the tumor cells are more frequently in radio-sensitive cell-cycle phases, such as mitosis [94,95]. Division of the radiation dose into a number of treatment fractions provides two important biological advantages: it not only allows DNA repair to take place within the normal cells/tissues but also let proliferating tumor cells redistribute through the cell-cycle and move into more radio-sensitive phases. The ultimate goal of radiotherapy is to kill tumor cells selectively, without damaging the normal cells.

The three major types of radiotherapy are external beam radiotherapy, brachytherapy or sealed source radiotherapy, and systemic radioisotope therapy or internal radiotherapy. Briefly, the common radioisotopes used for internal radiotherapy can be divided into three categories: α-particle emitters (e.g. ^{211}At and ^{225}Ac), β-particle emitters (e.g. ^{90}Y, ^{67}Cu, ^{131}I, ^{186}Re, and ^{188}Re), and Auger electron emitters (e.g. ^{111}In and ^{125}I) (Table 1) [96]. α-particle emitters can eject high energy (4 – 8 MeV) helium nuclei (i.e. α-particle) which can cause severe cytotoxicity, however their ejection range is quite short (typically 40 – 80 μm). β-particle emitters are the most widely used radioisotopes in cancer therapy. These radioisotopes can release electrons which have lower energy and cause lower cytotoxicity than the α-particle emitters do, but they can travel a much longer distance and kill cells by indirect damage to the DNA. Electrons from Auger electron emitters travel the shortest range (< 1 μm) and are cytotoxic only when they are very close to the nucleus, thus Auger electron emitters are generally not applicable to nanoparticle-based radiotherapy. Depending on the tumor location, tumor type, and a number of other factors such as availability, different radionuclides can be chosen for each specific application.

With the capacity for a large dose of radioactivity inside each particle, nanoparticles can be very useful for internal radiotherapy of cancer through passive targeting (i.e. based on the EPR effect) and/or active targeting (i.e. incorporating a targeting moiety on the nanoparticle) [97]. Liposomes, spherical vesicles of lipid bilayers which can range from 100 – 800 nm in diameter, are the most widely used nanoparticles for cancer therapy [98]. Several liposomal agents have been approved for human use or are currently in clinical trials [98].

Nanoparticles containing α-emitters

α-particle emitters were used mainly for liposome labeling. In 2000, ^{211}At-loaded liposomes were reported to be capable of delivering high doses of radiation to xenografted tumors in mice [99]. Subsequently, different α-emitter-loaded liposomes have been investigated for tumor-targeted radiotherapy [100]. The α-emitters used in this study included ^{223}Ra ($t_{1/2}$: 11.4 days), ^{224}Ra ($t_{1/2}$: 3.6 days), and ^{225}Ac ($t_{1/2}$: 10.0 days) and the sterically stabilized liposomes were conjugated to a folate-F(ab′)$_2$ construct for tumor targeting. Relatively good in vitro stability of the liposomes was observed yet in vivo testing was not performed. Another report investigated the effect of different sizes and charges of cholesterol-stabilized PEGylated liposomes on the retention of ^{225}Ac in liposomes [101]. High retention of radioactivity,

both ^{225}Ac (up to ~ 90% in 30 days) and its daughter nuclei ^{213}Bi, within the liposomes was observed, especially in those cationic and large ones (~ 650 nm in diameter). It was proposed that such observation was due to the fact that these radionuclides are relatively hydrophilic, thus the hydrophobic liposomal membranes could provide a barrier for preventing the loss by diffusion from the internal aqueous compartment in which ^{225}Ac was initially entrapped.

For cancer cells with low surface expression level of the target, direct tumor targeting of α-emitters using an antibody as the carrier may not be able to deliver enough α-emitters to cancer cells for effective cell killing, because these radiolabeled antibodies typically have relatively low specific activity (< 5 α-emitters per antibody). Recently, it was shown that passive ^{225}Ac entrapment in liposomes can stably retain the encapsulated ^{225}Ac for long time periods, and that antibody-conjugated liposomes with encapsulated ^{225}Ac can specifically target and become internalized by the cancer cells [102]. Although these ^{225}Ac-loaded liposomes with surface-conjugated antibodies partially overcame the limitations of low specific activity for molecular carriers, which are expected to be therapeutically useful against tumor cells with a low antigen density, stable encapsulation of a large dose of ^{225}Ac within each liposome remains a challenge.

The relatively short effective range of α-emitters within the tissue (typically < 100 μm), equivalent to a few cell layers, along with high linear energy transfer (LET, ~ 100 keV/μm), distinguishes the dosimetry of these radionuclides. High-LET radiation can induce more irreparable double-strand DNA breaks, more profound chromosomal damage at mitosis, as well as complex chromosomal rearrangements in a higher frequency than low-LET radiation (e.g. that caused by β-emitters) [103]. Further, high-LET α-irradiation provides more noticeable G2-phase delay than low-LET γ-irradiations [104]. Comparing with α-emitters, there are many more choices of different isotopes for β-particle-based internal radiotherapy. Therefore, nanoparticles containing β-emitters are used much more widely than α-emitter-loaded liposomes.

Nanoparticles containing β-emitters

β-emitters are the most widely used radionuclides in radiotherapy [105,106]. Passing through tissue, the ejected β-particles (i.e. electrons) interact with atoms, mainly in water molecules, and lose their energy, leading to the generation of excited and ionized atoms and free radicals which are responsible for the DNA damage in cells by inducing single-strand breaks in DNA [107]. The β-emitters that have been used for nanoparticle labeling in cancer therapy include ^{186}Re ($t_{1/2}$: 3.7 days), ^{188}Re ($t_{1/2}$: 17.0 h), ^{90}Y ($t_{1/2}$: 2.7 days), ^{131}I, ^{67}Cu ($t_{1/2}$: 2.6 days), ^{198}Au ($t_{1/2}$: 2.7 days), among others.

^{186}Re/^{188}Re-labeled nanoparticles—Rhenium nuclides were among the first radioisotopes tested for nanoparticle-based radiotherapy. In 1991, liposomes of 70 nm diameter were complexed with oxodichloroethoxy-bis-(triphenylphosphine) Re(V), with about 45% of the radioactive complex incorporated into the liposomal bilayer during liposome formation [108]. The stability of these radiolabeled liposomes was quite satisfactory, with only about 40% loss of radioactivity after 8 days. Addition of an anti-oxidant, ascorbic acid, reduced the loss of radioactivity to about 20%. Subsequently, glutathione-encapsulated liposomes were labeled with ^{186}Re/^{188}Re [109]. Biodistribution studies in Sprague-Dawley rats after intravenous injection of the ^{186}Re/^{188}Re-loaded liposomes showed slow blood clearance and high spleen accumulation, indicating good in vivo stability of the radiolabeled liposomes. Several dosimetry studies have highlighted the importance of liposome size, type (multilamellar, small unilamellar, or sterically stabilized), and steric barrier in the design of effective radionuclide-carrier systems [99,110]. These studies also demonstrated the feasibility of using liposomes for internal radiotherapy, because of the reduced absorbed dose in the bone

marrow (usually the dose-limiting organ for many anti-cancer therapies [111]) and other normal tissues.

In vivo applications of ^{188}Re-labeled liposomes have been investigated [112]. The dosimetry of micrometastases in the peritoneal cavity during intraperitoneal liposomal radioimmunotherapy was measured, in which the ^{188}Re-loaded liposomes were designed to target ovarian cancer cells that express the surface antigen CA-125. This study suggested that the relative importance of the surface-bound radioactivity increases with the tumor size for such microscopic tumors, as evidenced by the requirement for higher antigen densities on smaller tumors to reach a therapeutic effect. It was proposed that for small tumors, the unbound radioactivity is often capable of exerting a tumoricidal effect even before the targeted radiolabeled nanoparticles have enough time to accumulate significantly on the tumor surface. In anther report, the biodistribution and pharmacokinetics of ^{188}Re-labeled PEGylated liposomes (RePL) and analogous unencapsulated ^{188}Re-complex was studied in murine C26 colon tumor-bearing mice after intravenous administration [113]. Although the tumor-to-muscle ratio of RePL was about 7-fold higher than that of the free ^{188}Re-complex, the absolute tumor uptake was very low (< 4 %ID/g) since such tumor accumulation was based on passive targeting only.

Recently, a dosimetric analysis was performed to evaluate liposomes as carriers of radionuclides (^{188}Re-liposomes) or combination of radionuclides and chemotherapeutic drugs (^{188}Re-doxorubicin-liposomes, termed "^{188}Re-DXR-liposome") for treating colon carcinoma in two mouse models [114]. Pharmacokinetic data for the free ^{188}Re-complex, ^{188}Re-liposome, and ^{188}Re-DXR-liposome were obtained for the estimation of absorbed doses in tumors and other major organs. The mean absorbed doses derived from ^{188}Re-liposome and ^{188}Re-DXR-liposome in normal tissues were generally similar to those of the free ^{188}Re-complex after either intraperitoneal or intravenous administration. However, the mean absorbed doses in the tumor for both ^{188}Re-liposome and ^{188}Re-DXR-liposome were significantly higher (4 – 26 fold) than those of the free ^{188}Re-complex for both administration routes. This report suggested that loading liposomes with both therapeutic radionuclides and chemotherapeutic drugs, even with passively targeting only, may be feasible and efficacious for cancer therapy.

Rhenium nuclides have been used to label poly(L-lactic acid) nanoparticles for intratumoral radiotherapy [115]. Interestingly, ^{188}Re was also explored for magnetically targeted radiotherapy [116]. The surface of silica-coated magnetite nanoparticles was covalently modified and labeled with ^{188}Re, with > 90% labeling yield and good in vitro stability. Similar magnetite nanoparticles (~ 200 nm in diameter) have also been coated with human serum albumin [117] or polyacrylamide [118] and then labeled with ^{188}Re. These magnetically susceptible nanoparticles were designed for intravenous administration which, under simultaneous application of a magnetic field above the tumor area, could enhance the radioisotope uptake in the tumor [119]. In another report, amino-functionalized superparamagnetic IO nanoparticles (10 – 15 nm in diameter) were conjugated with a humanized monoclonal antibody directed against liver cancer cells, followed by ^{188}Re-labeling [120]. Since nanoparticles of such size range typically have very high uptake in the RES organs such as the liver, addition of a liver cancer-specific antibody was expected to give an extra boost for magnetically targeted radiotherapy in liver cancer treatment.

^{90}Y-labeled nanoparticles—^{90}Y and ^{131}I are the two most frequently used radionuclides for cancer radiotherapy. ^{90}Y has several advantages over ^{131}I such as pure β emission, an optimal decay half-life, higher energy of β emission hence longer range in tissue, and more stable retention in the tumor cells after endocytosis [121,122].

^{90}Y was used to label liposomes for potential radiotherapy applications more than a decade ago [123]. Investigation of ^{90}Y-labeled liposomes in a xenograft mouse model revealed that ^{90}Y was more suitable for labeling small unilamellar liposomes [99]. A dosimetry study of ^{90}Y-labeled liposomes in intramuscular tumors gave tumor-to-marrow and tumor-to-spleen absorbed dose ratios of 13.9 and 0.13 respectively, indicating that ^{90}Y-labeled liposomes possess quite favorable properties for internal radiotherapy [110].

Antibody-conjugated lipid nanoparticles, labeled with ^{90}Y, have been used for internal radiotherapy applications targeting tumor angiogenesis [124]. Integrin $\alpha_v\beta_3$ and VEGFR-2 are the most extensively studied and validated targets in tumor angiogenesis [25,27,68]. Therefore, ^{90}Y-labeled lipid nanoparticles were chemically linked to either an integrin antagonist (termed "IA-NP-^{90}Y") or a monoclonal antibody against murine VEGFR-2 (termed "anti-VEGFR-2-NP-^{90}Y") and intravenously injected into two different murine tumor models [124]. Significant growth delay in both tumors for both targeted nanoparticles was observed when compared with the control animals injected with non-targeted, ^{90}Y-labeled lipid nanoparticles. CD31 staining showed a considerable decrease in vessel density in the tumors treated with anti-VEGFR-2-NP-^{90}Y, which was associated with a high level of apoptosis.

A recent study compared the dosimetry of internal radiotherapy using nanoparticles labeled with different isotopes such as β-emitters (^{90}Y and ^{32}P, $t_{1/2}$: 14.3 days) and low-energy X-ray radionuclides (^{103}Pd, $t_{1/2}$: 17.0 days) [125]. It was found that for β-emitter-labeled nanoparticles, a set of data (e.g. covering fraction, biological half-life, and nanoparticle radius) were within acceptable ranges for conventional radioimmunotherapy. The sources with E_{max} of approximately a few MeV can be used for the treatment of tumors with a maximum diameter of about 1 cm. Low-energy X-rays (E < 25 keV) can be used to extend the range of treatable tumor diameter to 4 – 5 cm, however they have very strict requirement on the characteristics of the nanoparticle as a carrier.

^{131}I-labeled nanoparticles—The versatile chemistry of iodine makes the radioiodine isotopes very attractive for both imaging (e.g. ^{123}I and ^{124}I) and therapeutic (e.g. ^{131}I) applications. Surprisingly, there are only very few reports available for radiotherapy with ^{131}I-labeled nanoparticles. In one of the above-mentioned studies, ^{131}I was found to be quite efficient in labeling small unilamellar liposomes [99]. In another report, the diffusion capability and prostate cancer cell targeting efficacy (with an antibody against the prostate-specific membrane antigen) of the most clinically relevant liposome systems was investigated [126]. Dosimetric analyses were carried out for a variety of medium- and high-energy β-emitting radionuclides (^{32}P, ^{90}Y, ^{188}Re, ^{67}Cu, and ^{131}I). Surface characteristics of the liposomes appeared to have a noticeable influence on the profile of the absorbed doses. This study also suggested that it is possible to engineer liposome systems that are particularly effective in delivering an almost uniform absorbed dose profile at the central region of micrometastatic tumors, provided that the properties of the radionuclides are taken into account in the design of such systems.

In one report, ^{131}I was used to label nanoparticles for integrin $\alpha_v\beta_3$-targeted radiotherapy [127]. In another study, ^{131}I-labeled dextran-coated magnetic nanoparticles, conjugated with an anti-VEGF monoclonal antibody, were tested in nude mice bearing human liver cancer [128]. External magnetic field was applied to the tumor to enhance the therapeutic effect as well as safety. Both tumor growth delay and tumor inhibition were observed. Radioiodine labeled liposomes were also tested for pre-targeted immunotherapy [129]. Radiolabeling was achieved with high yield (typically > 60%) which was also quite stable (> 85% retention after 24 h in serum at 37 °C). It was concluded that as radioactivity carriers, liposomes possess strongly formulation-dependent, favorable pharmacokinetic parameters for pre-targeted radioimmunotherapy.

Nanoparticles labeled with other isotopes (^{67}Cu and ^{198}Au)—Other radionuclides such as ^{67}Cu and ^{198}Au have also been used to label liposomes for cancer therapy [99,110]. Given the favorable properties of ^{67}Cu, the availability is the major limiting factor for its widespread use in internal radiotherapy. Recently, poly(^{198}Au)-dendrimer composites of distinct sizes (diameter between 10 and 30 nm) were reported for cancer therapy in a melanoma mouse model [130]. A single intratumoral injection of the poly(^{198}Au)-dendrimer composite in phosphate-buffered saline, delivering a dose of 74 μCi, resulted in a 45% reduction in tumor volume after 8 days. The difference was statistically significant when compared with either the untreated mice or those injected with the “cold” composite. With no toxicity observed during the experiments, this study provides a proof-of-principle that radiolabeled dendrimers can deliver therapeutically efficacious radiation doses to tumors in vivo.

Summary and future perspectives

A wide variety of radiolabeled nanoparticles have been explored for molecular imaging and therapeutic applications (Fig. 5). For imaging purposes, nanotechnology has touched upon every single modality of the molecular imaging arena [1]. The most important feature of radionuclide-based imaging techniques (i.e. SPECT and PET) is that they are not only highly sensitive but also quantitative. Further, the emerging field of multimodality imaging with radiolabeled nanoparticles can allow researchers to detect the same radiolabeled nanoparticle with multiple imaging techniques. The capability of cross-modality validation can provide more accurate and reliable data of the radiolabeled nanoparticle than with SPECT or PET imaging alone. For therapeutic applications, radiolabeled nanoparticles have several advantages over drug-loading nanoparticles. First, the radiolabel can provide a direct and quantitative readout of the pharmacokinetics and tumor targeting efficacy through imaging studies, which can not only save the cost of both preclinical and clinical studies but also significantly reduce the work load. Second, tissue penetration in solid tumors is a major barrier for drug-loading nanoparticles, since in most cases the drugs have to enter the cells to be effective [131]. This is not the case for internal radiotherapy with radiolabeled nanoparticles as the radioisotopes can take effect as long as they are efficiently targeted to the tumor, which does not require extravasation. Third, controlled release of the drug over a long period of time is another major obstacle faced by drug-loading nanoparticles [132,133], which is not necessary for radiolabeled nanoparticles.

There are many challenges facing radiolabeled nanoparticles, and the most important of all is the (tumor) targeting efficacy. The majority of reports on radiolabeled nanoparticles utilized passive targeting only based on the EPR effect, which is relying on the long circulation half-life of the nanoparticles (liposomes in most cases). Although this can be therapeutically efficacious in some cases and many liposome-based drugs have been approved by the FDA for clinical use [132,134], this is by no means optimal. Long circulation half-life of the nanoparticle is a double-edged sword. Although it can lead to higher level of passive targeting to the tumor, it also causes prolonged exposure of the normal organs to the drug/radioisotope which can give rise to undesired toxicity. Based on the literature data, tumor vasculature targeting is the best bet for radiolabeled nanoparticles since many of these nanoparticles are too large to extravasate [25,61,65,135]. A circulation half-life of several hours, rather than a few days or weeks for liposomes, may be sufficient to allow for efficient tumor (vasculature) targeting.

Second, robust chemistry for both radionuclide encapsulation/incorporation and targeting ligand conjugation is of critical importance to the potential clinical applications of radiolabeled nanoparticles. For imaging applications, the stability of the radioisotope(s) on the nanoparticle should always be confirmed, otherwise the imaging results may be completely irrelevant to the actual nanoparticle distribution. Nanoparticles are usually large enough to enable multiple

targeting ligands on their surfaces to simultaneously bind to multiple targets, an aspect that has been virtually unexplored to date. Targeting multiple different but closely-related receptors by incorporating different targeting ligands on the same nanoparticle, with spacers of suitable length, require robust chemistry to minimize batch-to-batch difference and improve the reproducibility. Most of the radioisotopes used for nanoparticle labeling are radio-metal. Thus, the proper design and use of chelators for each isotope to ensure good in vivo stability can not be over-emphasized.

Third, like most new technologies, there are concerns about the possible side effects derived from the use of nanoparticles. The potential toxicity of nanoparticles mainly comes from two aspects. First, nanoparticles can enter the body through the skin, lungs, or intestinal tract, deposit in several organs and may cause adverse biological reactions. In addition, the toxicity of nanoparticles also depends on whether they get cleared from the body and whether the host can raise an effective response to sequester or dispose of the nanoparticles. Second, the toxicity can come from the material itself, such as CdSe/CdTe in QDs. Recently, nanotoxicology has emerged as a new branch of toxicology for studying the undesirable effects of nanoparticles [136,137]. Development of novel radiolabeled nanoparticles for biomedical applications must proceed in tandem with the assessment of any toxicological side effects. Taking SWNTs as an example, a wide variety of parameters can have considerable impact on the toxicity of SWNTs [29]. In rodent studies, pristine SWNTs were capable of producing inflammation, epithelioid granulomas, fibrosis, and biochemical/toxicological changes in the lungs. However, several recent reports clearly showed that stably functionalized SWNTs, when intravenously injected, displayed near-complete clearance from the main organs in a few months with no toxic side effect based on necropsy, histology, and blood chemistry measurements [46,47,138]. These reports further emphasized that robust chemistry for nanoparticle modification is the key to success in future biomedical and clinical applications.

Fourth, there are important commercial and regulatory challenges to be tackled with the emerging generation of more complex nanoparticles, in part owing to their multicomponent nature. Such nanoparticles are likely difficult and expensive to manufacture at large scale with appropriate quality. In particular, current good manufacturing practice (cGMP) compliance of manufacturing these complex nanoparticles for clinical trials is prohibitively expensive for academic institutions in most cases, while intellectual property-related issues may make pharmaceutical industry hesitant in taking part in this endeavor. Further, the use of radioisotopes adds an additional level of oversight, which is the radiation safety. However, on a positive note, some highly complex nanoparticles have reached clinical trials [139]. Although these and potentially other challenges exist for the translation of nanoparticles that are currently research tools into approved products for patients, their tremendous potential should drive their successful development and the continuing emergence of novel radiolabeled nanoparticles for cancer imaging and therapy.

The future of nanomedicine lies in multifunctional nanoplatforms which combine both therapeutic components and multimodality imaging (Fig. 6). This integration of diagnostic imaging capability with therapeutic interventions, sometimes termed “theranostics” [140, 141], is critical to addressing the challenges of cancer heterogeneity and adaptation. The ultimate goal of nanomedicine is that nanoparticle-based agents can allow for efficient, specific in vivo delivery of therapeutic agents (radioisotopes, drugs, genes, etc.) without systemic toxicity, and the dose delivered as well as the therapeutic efficacy can be accurately measured non-invasively over time. Much remains to be done before this can be a clinical reality and continuous multidisciplinary efforts on the use/optimization of such nanoplatforms will shed new light on molecular diagnostics and molecular therapy. With the capacity to provide enormous sensitivity and flexibility, nanoparticle-based agents have the potential to profoundly impact disease diagnosis and patient management in the near future.

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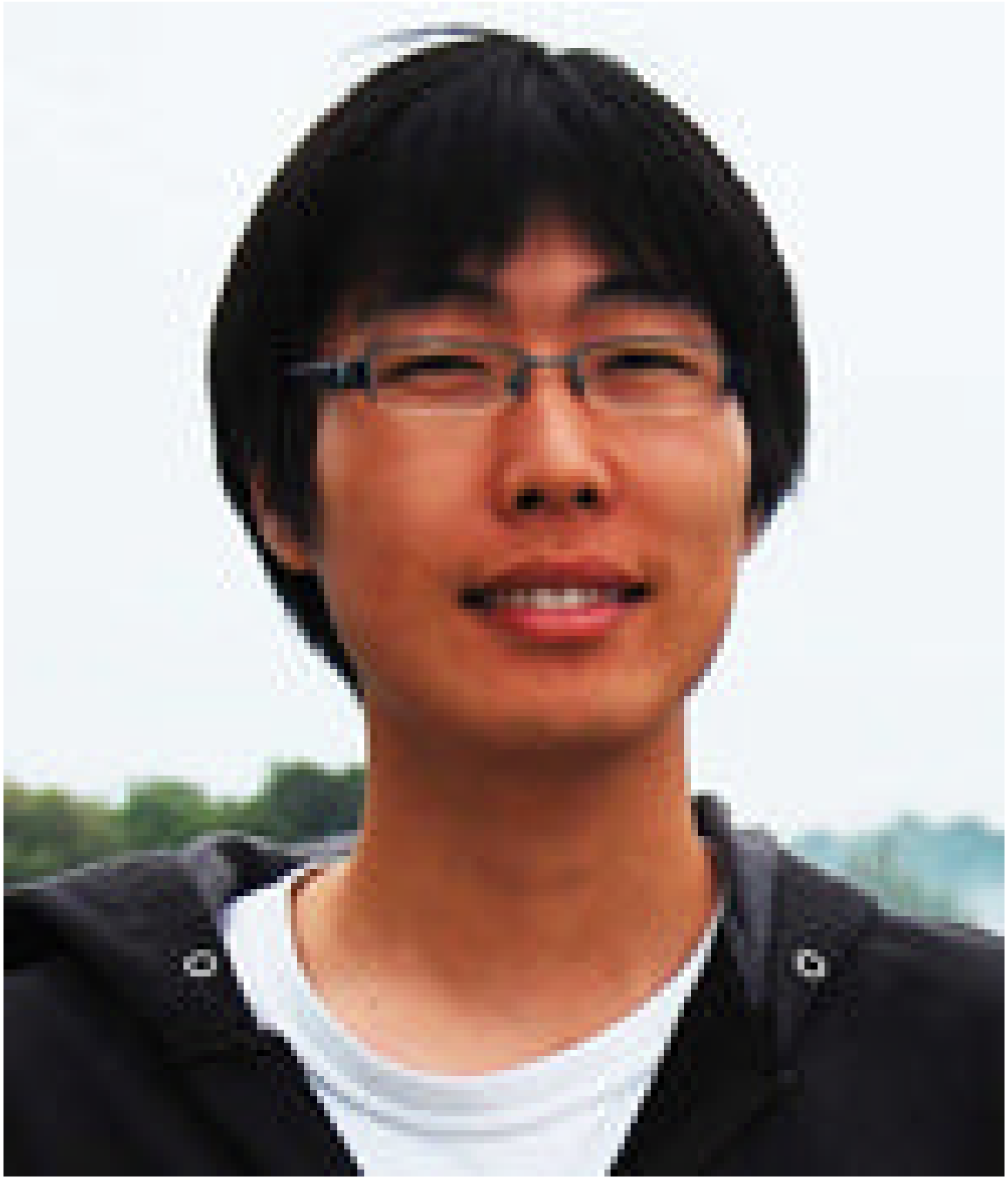
Biographies

Hao Hong received his PhD degree in Biochemistry and Molecular Biology from Nanjing University (P.R. China) in 2008. He is currently a Research Associate under the supervision of Prof. Weibo Cai in the Department of Radiology, University of Wisconsin - Madison. His research interest is in the design and optimization of new tracers for molecular imaging of cancer as well as modification/application of nanomaterials for molecular imaging (in particular positron emission tomography) of different diseases.



Yin Zhang is a second year graduate student in the Department of Medical Physics at the University of Wisconsin - Madison. He received a BS degree in Physics from University of Science and Technology of China (USTC) in 2006 and a MA degree in Physics from Johns Hopkins University in 2008. He is now pursuing a PhD degree in Medical Physics under the supervision of Professor Weibo Cai. Design and synthesis of novel PET tracers, as well as modeling and pharmacokinetic analysis of these tracers, is his major research interest.

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Weibo Cai is an Assistant Professor in Department of Radiology at the University of Wisconsin -Madison. He received a BS degree from Nanjing University in 1995 and a PhD degree in Chemistry from UCSD in 2004. After three years of post-doctoral research at the Molecular Imaging Program at Stanford University, he joined the University of Wisconsin - Madison as a biomedical engineering cluster hire in 2008. His current research focuses on the development of novel molecular imaging agents for early diagnosis of diseases and monitoring the efficacy of therapeutic intervention. Prof. Cai has authored more than 60 peer-reviewed publications and several book chapters. He has won many awards including the Society of Nuclear Medicine Young Professionals Committee Best Basic Science Award in 2007. He is currently on the Editorial Board of six scientific journals and serves as a reviewer for many peer-reviewed journals and funding agencies.

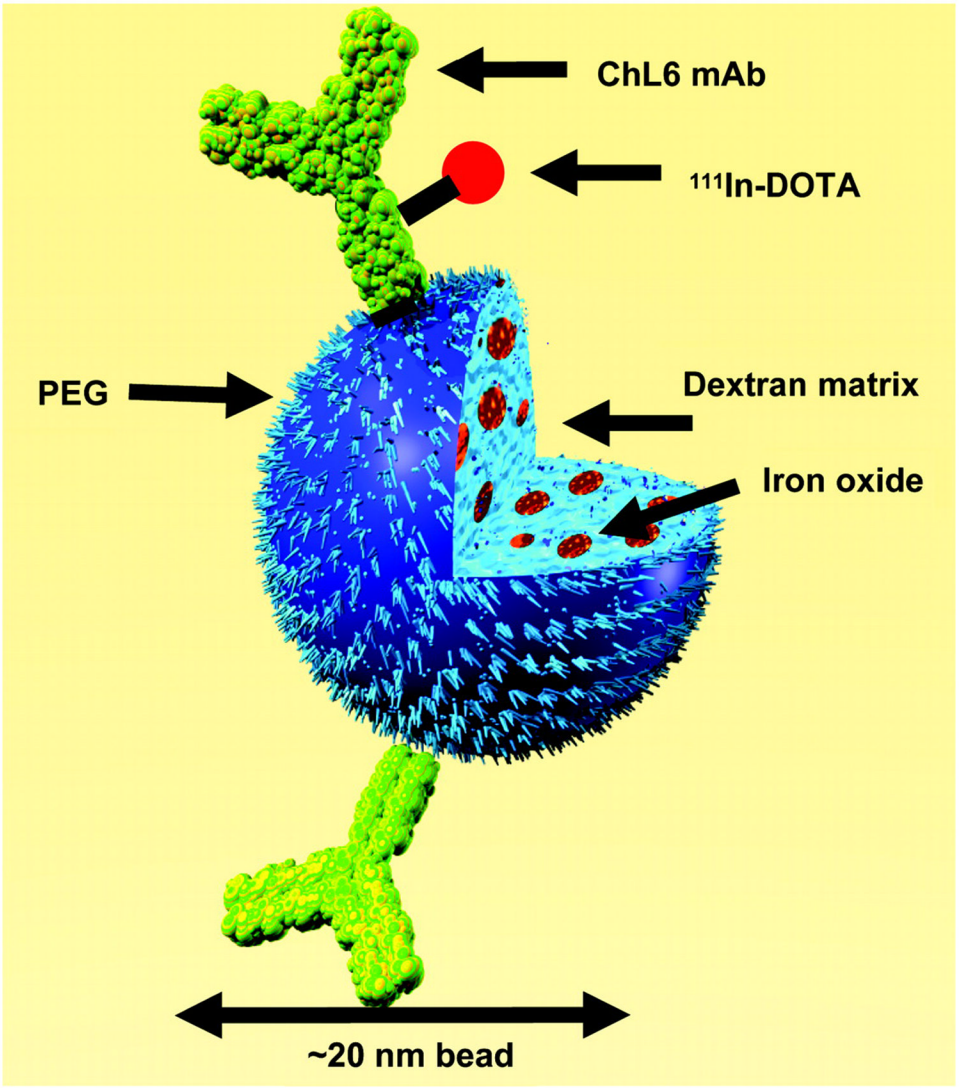

Figure 1.
^{111}In-labeled ChL6 antibody was conjugated to a 20 nm dextran bead coated with polyethylene glycol and impregnated with iron oxide nanoparticles. (Reprinted with permission from [20]. ©2007 Society of Nuclear Medicine.)

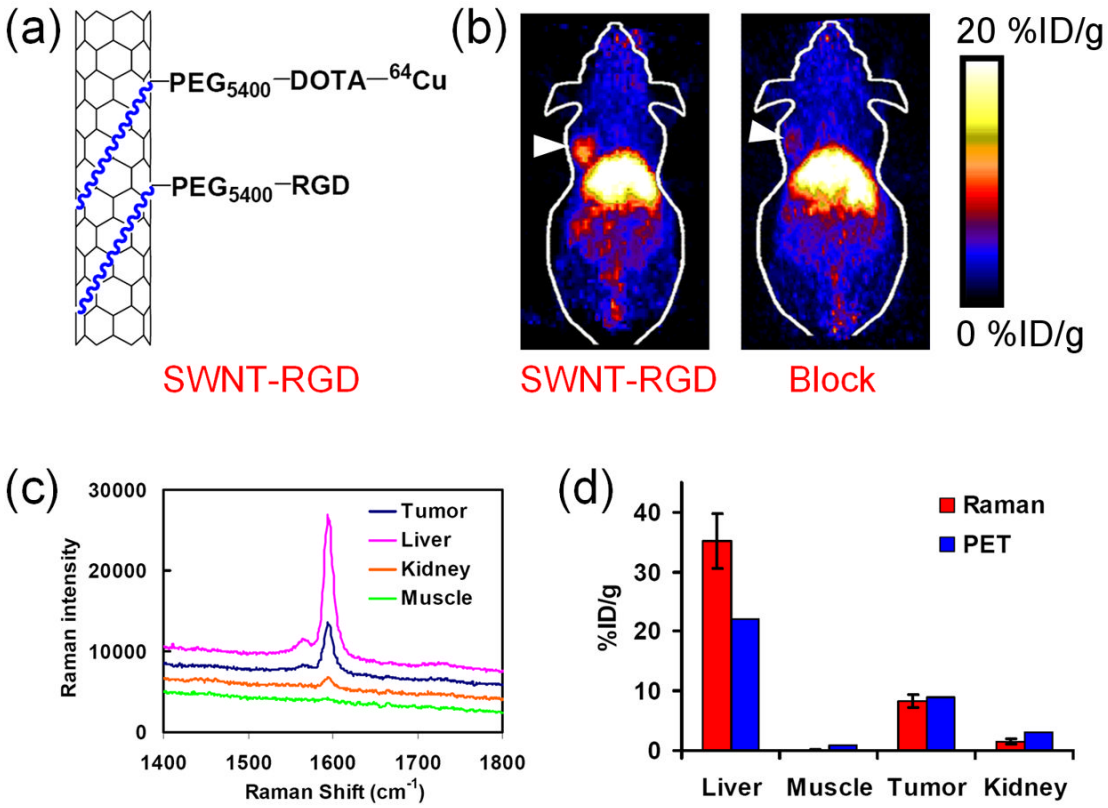

Figure 2.

^{64}Cu-labeled SWNTs for tumor integrin $\alpha_v\beta_3$ targeting. (a) A schematic drawing of the functionalized SWNTs. (b) Two-dimensional projection of PET images of U87MG tumor-bearing mice at 8 h after injection of ^{64}Cu-labeled, RGD-conjugated SWNTs with (Block) or without co-injection of RGD peptides. Arrowheads indicate tumors. (c) Raman spectra of tissue homogenate provided direct evidence of SWNT presence in the tumor. (d) Good agreement of biodistribution data obtained by PET and ex vivo Raman measurements confirmed the in vivo stability and tumor-targeting efficacy of SWNT-RGD. (Adapted with permission from [42]. ©2007 Nature Publishing Group.)

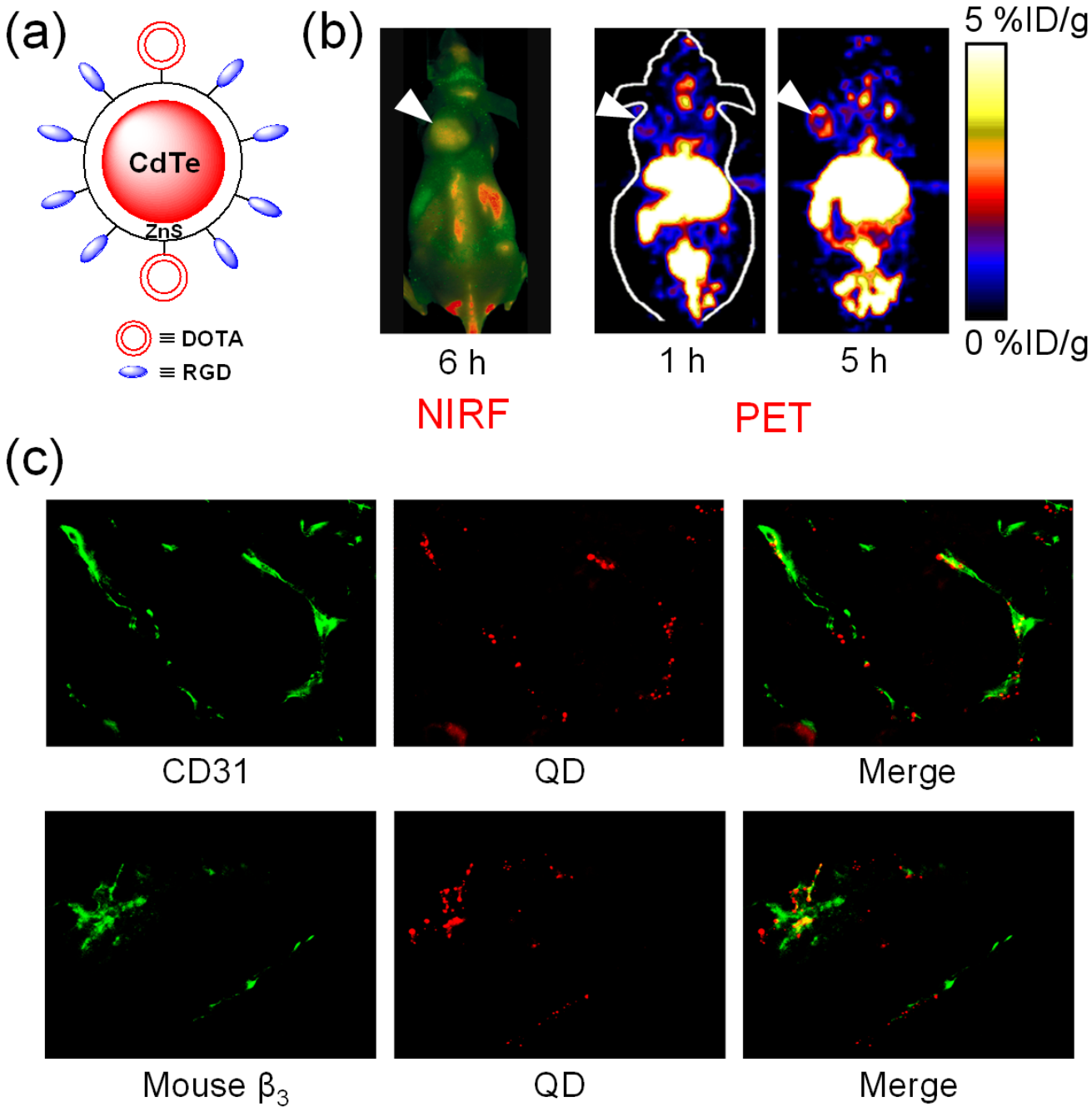

Figure 3.

Dual-modality PET/NIRF imaging of integrin $\alpha_v\beta_3$ in tumor vasculature. (a) A schematic structure of the dual-modality PET/NIRF probe. (b) NIRF (after injection of QD-RGD) and coronal microPET (after injection of ^{64}Cu-DOTA-QD-RGD) images of a U87MG tumor-bearing mice. Arrowheads indicate tumors. (c) Excellent overlay between CD31 and QD fluorescence, as well as between murine β_3 and QD fluorescence, confirmed that DOTA-QD-RGD mainly targeted integrin $\alpha_v\beta_3$ on the tumor vasculature. (Adapted with permission from [65]. ©2007 Society of Nuclear Medicine.)

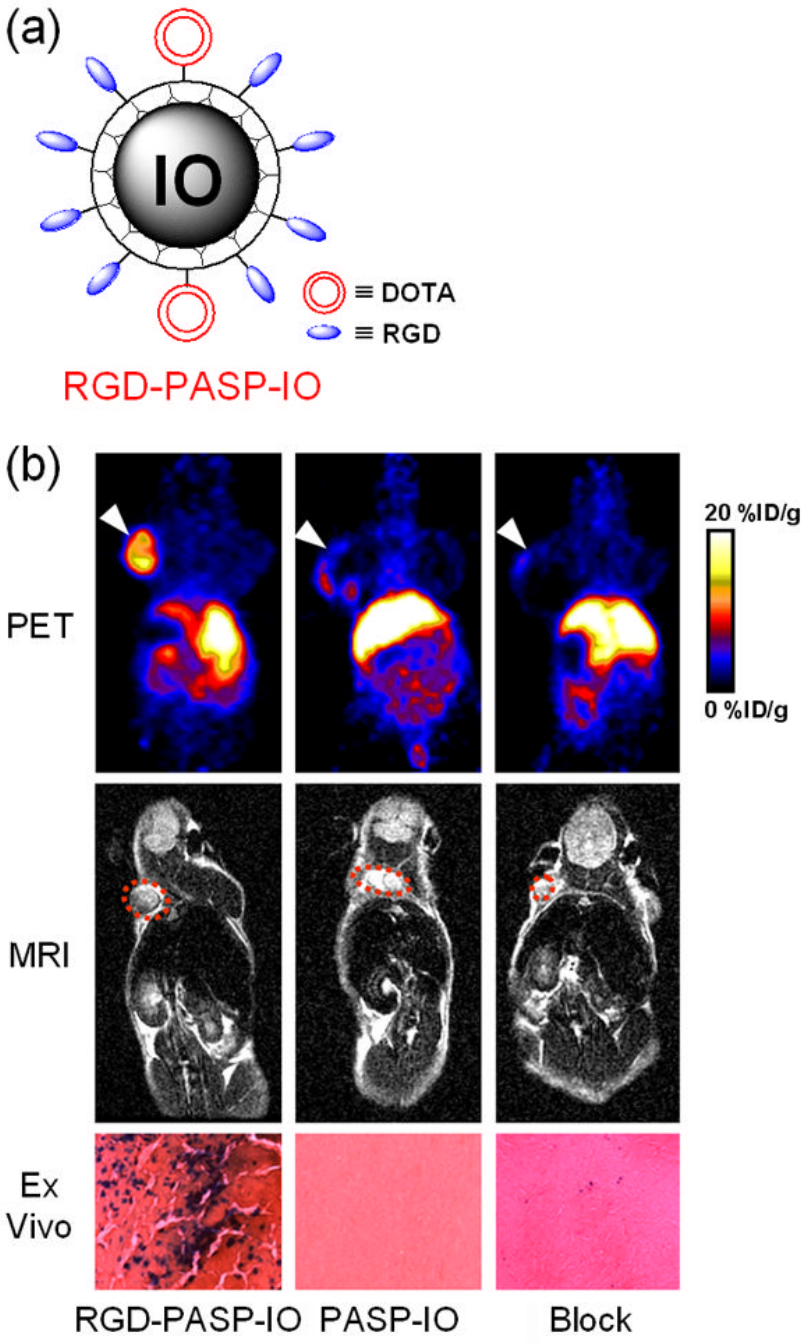

Figure 4.

Dual-modality PET/MR imaging of integrin $\alpha_v\beta_3$. (a) A schematic illustration of the dual-modality probe. The DOTA chelator enables PET imaging after ^{64}Cu-labeling. (b) Coronal PET and T_2-weighted MR images of tumor-bearing mice at 4 h after injection of ^{64}Cu-labeled RGD-PASP-IO, PASP-IO, and RGD-PASP-IO mixed with unconjugated RGD peptides (denoted as “Block”). Prussian blue staining of the U87MG tumor tissue slices after in vivo imaging is also shown, where blue spots indicate the presence of IO nanoparticles. (Adapted with permission from [86]. ©2008 Society of Nuclear Medicine.)

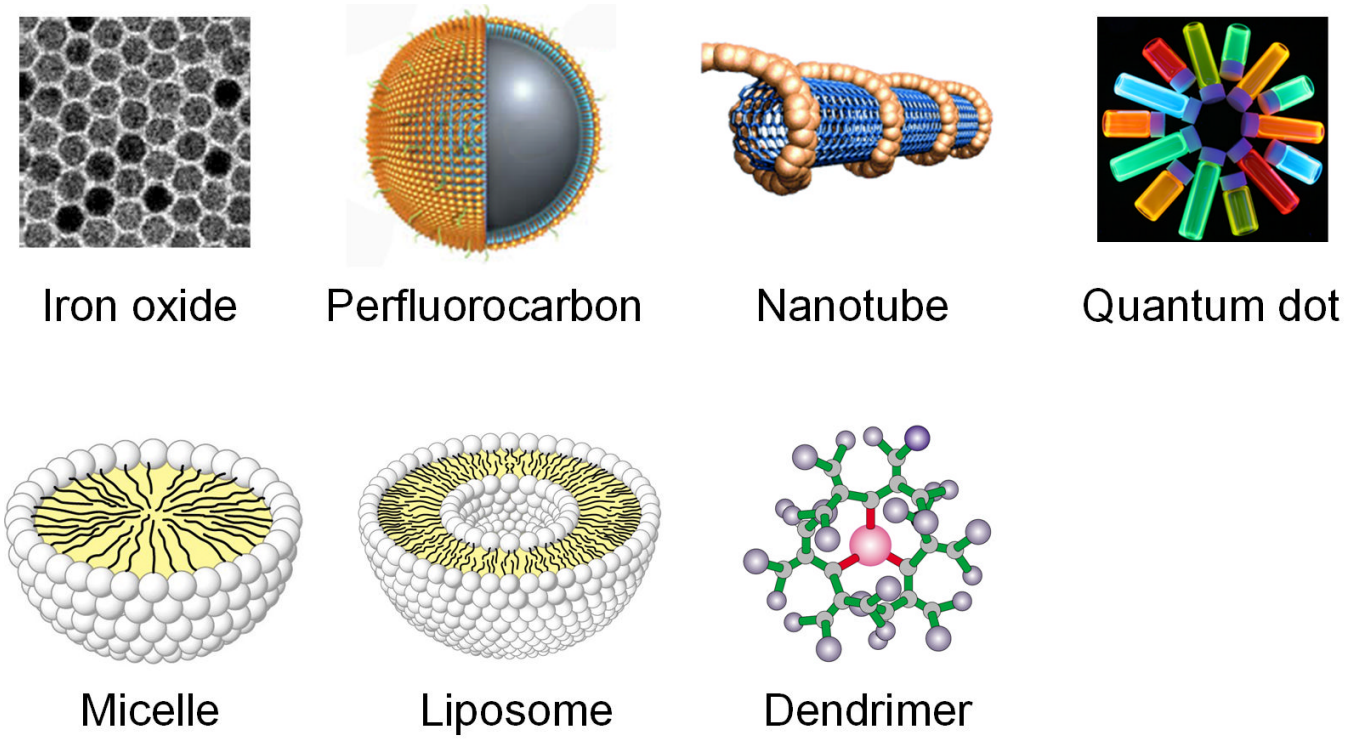

Figure 5.
Many types of nanoparticles have been radiolabeled for molecular imaging and therapy of cancer.

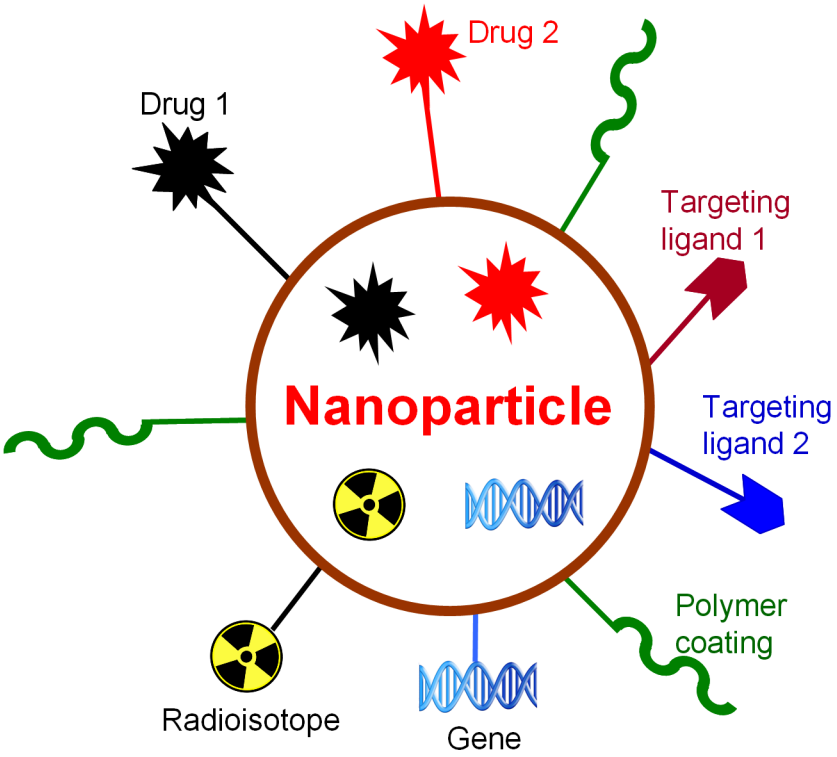

Figure 6.
A multifunctional nanoplatform incorporating multiple receptor targeting, multimodality imaging, and multiple therapeutic entities. Not all functional moieties will be necessary and only suitably selected components are needed for each individual application. The various functional moieties may be either on the surface of or encapsulated inside the nanoparticle.

Table 1

Nanoparticles have been labeled with a wide variety of radioisotopes for molecular imaging and therapy of cancer.

Isotope	Half-life	Major emission	E_{max} of α or β (keV)	Imaging/therapy
^{111}In	2.8 days	γ	--	SPECT imaging
^{125}I	60.1 days	γ	--	SPECT imaging
^{64}Cu	12.7 h	β^+, β	578	PET imaging
^{86}Y	14.7 h	β^+	--	PET imaging
^{125m}Te	57.4 days	γ	--	SPECT imaging
^{18}F	110 min	β^+	--	PET imaging
^{124}I	4.2 days	β^+	--	PET imaging
^{211}At	7.2 h	α	5870	therapy
^{223}Ra	11.4 days	α	not available	therapy
^{224}Ra	3.6 days	α	not available	therapy
^{225}Ac	10.0 days	α	5830	therapy
^{186}Re	3.7 days	β, γ	1069	both
^{188}Re	17.0 h	β, γ	2120	both
^{90}Y	2.7 days	β	2280	therapy
^{32}P	14.3 days	β	1710	therapy
^{103}Pd	17.0 days	X-ray	21	therapy
^{131}I	8.0 days	β, γ	606	both
^{67}Cu	2.6 days	β, γ	580	both
^{198}Au	2.7 days	β	960	therapy