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Radiolabelled Nanoparticles for Diagnosis and Treatment of Cancer

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1. Introduction

Cancer is one of the leading cause of death worldwide.¹ In 2010, a total of 1,529,560 new cancer cases and 569,490 cancer deaths were estimated in the United States alone.¹

Despite advances in our understanding of tumor biology, cancer biomarkers, surgical procedures, radio- and chemotherapy, the overall survival rate from cancer has not improved significantly in the past two decades. Early detection, pathological characterization, and individualized treatments are recognized as important aspects for improving the survival of cancer patients. Many novel approaches, such as imaging for the early detection of molecular events in tumors, comprehensive and personalized treatments, and targeted delivery of therapeutic agents to tumor sites, have been developed by various research groups; and some of these are already in clinical trials or applications for cancer patients. Radiation therapy, in conjunction with chemotherapy and surgery, is an effective cancer treatment option, especially for radiation-sensitive tumors. Radiation therapy utilizes high dose ionizing radiation to kill cancer cells and prevent progression and recurrence of the tumor. Traditionally, radiation therapies fall into one of three categories: external radiation, internal radiation and systemic radiation therapy. External radiation therapy delivers high-energy x-rays or electron or proton beams to a tumor from outside the body, often under imaging guidance. Internal radiation therapy (also called brachytherapy) places radiation sources within or near the tumor using minimally invasive procedures. Systemic radiation therapy delivers soluble radioactive substances, either by ingestion, catheter infusion, or intravenous administration of tumor-targeting carriers, such as antibodies or biocompatible materials, which carry selected radioisotopes. Although systemic radiation offers desirable advantages of improved efficacy as well as potentially reducing radiation dosage and side effects, in vivo delivery of radioisotopes with tumor targeted specificity needs to address many challenges that include: (i) the selection of radioisotopes with a proper half life; (ii) a delivery vehicle that can carry an optimal amount of radioisotopes and has favorable pharmacokinetics; (iii) suitable tumor biomarkers that can be used to direct the delivery vehicle into cancer cells; and (iv) specific tumor targeting ligands that are inexpensive to produce and can be readily conjugated to the delivery vehicles. In addition, a multifunctional carrier that not only delivers radioisotopes but also provides imaging capability for tracking and quantifying radioisotopes that have accumulated in the tumor is highly desirable.²

Recent advances in nanotechnology have led to the development of novel nanomaterials and integrated nanodevices for cancer detection and screening, *in vivo* molecular and cellular imaging,³ and the delivery of therapeutics such as cancer cell killing radioisotopes.^{4,5} An increasing number of studies have shown that the selective delivery of therapeutic agents into a tumor mass using nanoparticle platforms may improve the bioavailability of cytotoxic agents and minimize toxicity to normal tissues.^{6–8} Radiolabelled nanoparticles represent a new class of agents which has enormous potential for clinical applications. This book chapter provides deep insight into designing radiolabeled nanocarriers or nanoparticles tagged with appropriate radionuclides for cancer diagnosis and therapy. The combination of newer nuclear imaging techniques providing high sensitivity and spatial resolution such as dual modality imaging with positron emission tomography/computed tomography (PET/CT) and use of nanoscale devices to carry diagnostic and therapeutic radionuclides with high target specificity can enable more accurate detection, staging and therapy planning of cancer.

2. Molecular imaging with radiolabeled nanoparticles

The visualization, characterization and measurement of biological processes at the molecular and cellular levels in humans and other living systems is termed as molecular imaging.⁹ Molecular imaging includes 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).¹⁰ The availability of scanners for small animals provide similar *vivo* imaging capability in mice, primates and humans. This facilitates correlation of molecular measurements between species.^{11,12} Molecular imaging gives whole body readout in an intact system which is more relevant and reliable than *in vitro*/ *ex vivo* assays.¹³ Non-invasive detection of various molecular markers of diseases lead to earlier diagnosis, earlier treatment and better prognosis. Radionuclide-based imaging includes SPECT and PET, where internal radiation is administered through a low mass amount of pharmaceutical labeled with a radioisotope. The major advantages of radionuclide-based molecular imaging techniques (SPECT and PET) over other modalities (optical and MRI) are that they are very sensitive, quantitative without any tissue penetration limit.^{10,15} But the resolution of SPECT or PET is same as that of MRI. Mostly, nanoparticles are labeled with a radionuclide for non-invasive evaluation of its biodistribution, pharmacokinetic properties and/or tumor targeting efficacy with SPECT or PET.¹⁶

Radioisotopes used for SPECT imaging include ^{99m}Tc ($t_{1/2}$: 6.0 h), ¹¹¹In ($t_{1/2}$: 2.8 days) and radioiodine (¹³¹I, $t_{1/2}$: 8.0 days). The source of SPECT images are gamma ray emissions. The radioisotope decays and emits gamma rays, which can be detected by a gamma camera to obtain 3-D images.^{17,18} The pharmacokinetics, tumor uptake and therapeutic efficacy of an ¹¹¹In-labeled, chimeric L6 (ChL6) monoclonal antibody linked iron oxide (IO) nanoparticle was studied in athymic mice bearing human breast cancer tumors.¹⁹ The ¹¹¹In-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. It was proposed that the nanoparticles remained in the circulation for long period of time which provides them the opportunity to 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. Pharmacokinetic and whole-body autoradiography studies demonstrated that only 5% of the injected dose was targeted to the tumor after 24 h.²²

As cancer cells undergo metastasis i.e. they invade and migrate to a new tissue. They penetrate and attach to the target tissue's basal matrix. This allows the cancer cell to pull itself forward into the tissue. The attachment is mediated by cell-surface receptors known as integrins, which bind to components of the extracellular matrix. Integrins are crucial for cell invasion and migration, not only for physically tethering cells to the matrix, but also for sending and receiving molecular signals that regulate these processes.²³ Till date 24 integrins have been discovered, integrin $\alpha_v\beta_3$ is the most intensively studied.^{24,25} It is expressed in many types of tumor and plays a critical role in tumor angiogenesis.²⁶ Integrin $\alpha_v\beta_3$ -targeted ¹¹¹In-labeled perfluorocarbon (PFC) nanoparticles were tested for the detection of tumor angiogenesis in New Zealand white rabbits. The PFC nanoparticles bearing approximately 10 ¹¹¹In per particle was found to have better tumor-to-muscle ratio than those containing approximately 1 ¹¹¹In 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. Biodistribution studies revealed that nanoparticles were principally cleared from spleen.²⁷ Carbon nanotubes are promising carriers for use in biomedical and pharmaceutical sciences. Wang *et al.* (2004) studied its biological properties in vivo.²⁸ They labeled water-soluble hydroxylated carbon single-wall nanotubes with radioactive ¹²⁵In atoms, and then the tracer was used to study the distribution of hydroxylated carbon single-wall nanotubes in mice. They moved easily among the compartments and tissues of the body, behaving as small active molecules though their apparent mean molecular weight is tremendously large. This study gave a quantitative analysis of carbon nanotubes accumulated in animal tissues. Singh *et al.* (2006) functionalized water-soluble SWNTs with the chelating molecule diethylenetriaminepentaacetic (DTPA) and labeled them with ¹¹¹In for imaging purposes.²⁹ Both the studies suggested that 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. Villa *et al.* (2008) synthesized and studied the biodistribution of oligonucleotide functionalized tumor targetable carbon nanotubes.³⁰ Recently Mehmet Toner have developed a microfluidic device composed of carbon nanotubes which can detect cancer cells in 1ml of patient's blood.³¹

SPECT and PET are extremely valuable technologies in nuclear medicine. SPECT has superior spatial resolution, it can potentially allow for simultaneous imaging of multiple radionuclides, since the gamma rays emitted from different radioisotopes can be differentiated based on energy.^{32,33} PET on the other hand has much higher detection efficiency.³⁴ The biodistribution of ⁶⁴Cu ($t_{1/2}$: 12.7 h)-labeled SWNTs in mice has been investigated by PET imaging and Raman spectroscopy. It was found that these SWNTs are highly stable in vivo. 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. 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.³⁵ Molecular imaging of living subjects continues to rapidly evolve with bioluminescence and fluorescence strategies, in particular being frequently used for small-animal models. Keren *et al.* (2008) demonstrated noninvasive molecular imaging of small living subjects using Raman spectroscopy. Surface-enhanced Raman scattering nanoparticles and single-wall carbon nanotubes were used to demonstrate whole-body Raman imaging, nanoparticle pharmacokinetics, multiplexing, and *in vivo* tumor targeting, using an imaging system adapted for small-animal Raman imaging. This imaging modality holds significant potential as a strategy for biomedical imaging of living subjects.³⁶ An optimized noninvasive Raman microscope was used to evaluate tumor targeting and localization of single walled carbon nanotubes (SWNTs) in mice. Raman images were acquired in two groups of tumor-bearing mice. The control group received plain-SWNTs, whereas the experimental group received tumor targeting RGD-SWNTs intravenously. Raman imaging commenced over the next 72 h and revealed increased accumulation of RGD-SWNTs in tumor ($p < 0.05$) as opposed to plain-SWNTs. These results support the development of a new preclinical Raman imager.³⁷ Photoacoustic imaging of living subjects offers higher spatial resolution and allows deeper tissues to be imaged compared with most optical imaging techniques. Many diseases do not exhibit a natural photoacoustic contrast, especially in their early stages, so it is necessary to administer a photoacoustic contrast agent. De la Zerda *et al.* (2008) showed that single-walled carbon nanotubes conjugated with cyclic Arg-Gly-Asp (RGD) peptides can be used as a contrast agent for photoacoustic imaging of tumours. Intravenous administration of these targeted nanotubes to mice bearing tumours showed eight times greater photoacoustic signal in the tumour than mice injected with non-targeted nanotubes. These results were verified ex vivo using Raman microscopy. Photoacoustic imaging of targeted single-walled carbon nanotubes may contribute to non-invasive cancer imaging and monitoring of nanotherapeutics in living subjects.³⁸

Carbon nanotubes are promising new materials for molecular delivery in biological systems. The long-term fate of nanotubes intravenously injected into animals in vivo is currently unknown, an issue critical to potential clinical applications of these materials. Liu *et al.* (2008) using the intrinsic Raman spectroscopic signatures of single-walled carbon nanotubes (SWNTs), measured the blood circulation of intravenously injected SWNTs and detected SWNTs in various organs and tissues of mice ex vivo over a period of three months. Functionalization of SWNTs by branched polyethylene-glycol (PEG) chains was developed, to prolong SWNT residence time in blood up to 1 day, relatively low uptake in the reticuloendothelial system (RES), and near-complete clearance from the main organs in approximately 2 months. Raman spectroscopy detected SWNT in the intestine, feces, kidney, and bladder of mice, suggesting excretion and clearance of SWNTs from mice via the biliary and renal pathways. No toxic side effect of SWNTs to mice was observed in necropsy, histology, and blood chemistry measurements. These findings pave the way to future biomedical applications of carbon nanotubes.³⁹ Liu *et al.* (2008) further conjugated paclitaxel to branched polyethylene glycol chains on SWNTs via a cleavable ester bond to obtain a water-soluble SWNT-PTX conjugate. SWNT-PTX affords higher efficacy in suppressing tumor growth than clinical Taxol in a murine 4T1 breast cancer model, owing to

prolonged blood circulation and 10-fold higher tumor PTX uptake by SWNT delivery likely through enhanced permeability and retention. Drug molecules carried into the reticuloendothelial system are released from SWNTs and excreted via biliary pathway without causing obvious toxic effects to normal organs. Thus, nanotube drug delivery is promising for high treatment efficacy and minimum side effects for future cancer therapy with low drug doses.⁴⁰ Selective tumor targeting with a soluble, nanoscale SWNT construct mediated by appended specific antibodies was also achieved. The soluble, reactive SWNT platform was used as the starting point to build multifunctional constructs with appended antibody, metal-ion chelate, and fluorescent chromophore moieties to effect specific targeting, to carry and deliver a radiometal-ion, and to report location, respectively.⁴¹ 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 ⁸⁶Y (t_{1/2}: 14.7 h)-labeled SWNTs in a mouse model. It was found that ⁸⁶Y 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.⁴² Most of the molecular imaging modalities detect nanoparticle only, whereas 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 (usually 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 should always be interpreted with caution.⁷

No single molecular imaging modality is perfect and sufficient to obtain all the necessary information for a particular study.² 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. So, combination of 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. For this nanoparticles can be investigated as they have large surface areas where multiple functional moieties can be incorporated for multimodality molecular imaging.⁷

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, 700–900nm) range, narrow emission spectra, and large effective Stokes shifts.^{41–43} 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.^{41–44} Radioactive cadmium telluride/zinc sulfide (Cd^{125m}Te/ZnS) nanoparticles were targeted to mouse lung with antibody to mouse lung endothelium and quantified using radiological histology in order to test the *in vivo* targeting efficacy of a nanoparticle–

antibody (NP-mAb) system. The nanoparticles were linked to either a monoclonal antibody to mouse lung thrombomodulin (mAb 201B) or a control antibody (mAb 33), and injected into groups of 6-week-old Balb/C female mice. Animals were sacrificed at 1, 4, 24, 72 and 144 h post-injection, and biodistribution in major organs was determined. Full body microSPECT/CT imaging was performed on a pair of mice (experimental and control) providing visual confirmation of the biodistribution. The Cd^{125m}Te/ZnS NPs conjugated to mAb 201B principally target the lungs while the nanoparticles coupled to mAb 33 accumulate in the liver and spleen. These data provide, for the first time, a quantitative measurement of the *in vivo* targeting efficacy of an inorganic nanoparticle-mAb system.⁴⁵ In a follow-up study it was found that CdTe NP, either targeted or untargeted, interact with the reticuloendothelial system very soon after intravenous injection. This interaction promotes uptake in the liver and spleen and limits even very rapid targeting efforts. For the first several hours after injection, the CdTe NP are subject to interaction with the reticuloendothelial system of the animal but then become refractory to removal. Temporary depletion of phagocytic cells can increase targeting efficiency and retention of the CdTe NP at the target site. The elimination of CdTe NP from the body is complex, and at least, some of the injected NP remain in body tissues for weeks after injection. Long whole-body retention times can lead to increased organ toxicity and radiotoxicity.⁴⁶ Quantum dots (QDs) can be used to perform multicolor images with high fluorescent intensity and are of a nanosize suitable for lymphatic imaging via direct interstitial injection. Kobayashi *et al.* (2007) showed simultaneous multicolor *in vivo* wavelength-resolved spectral fluorescence lymphangiography using five quantum dots with similar physical sizes but different emission spectra. This allows noninvasive and simultaneous visualization of five separate lymphatic flows draining and may have implications for predicting the route of cancer metastasis into the lymph nodes.⁴⁷ 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 ¹⁸F (t_{1/2}: 110 min) and ⁶⁴Cu.⁴⁸⁻⁵⁰ 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.⁵¹⁻⁵³ PET has been routinely used in the clinic for staging and evaluating many types of cancer.⁵⁴ 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.⁵⁵ Vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) signaling pathway plays a pivotal role in regulating tumor angiogenesis.⁵⁶ Many therapeutic agents targeting VEGF or VEGFR are currently in preclinical and clinical development.^{57,58} 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.⁵⁹ Tumor uptake of ⁶⁴Cu-labeled DOTA-QD was significantly lower than that of ⁶⁴Cu-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. In clinical settings, optical imaging is relevant for tissues close to the surface of the skin, tissues accessible by endoscopy, and during intraoperative visualization.⁴¹ 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.¹⁵

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.⁶⁰ 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.⁶¹ The presence of thousands of iron atoms in each particle can give very high T2 relaxivity.⁶²

Accurate localization of PET probe uptake is very difficult in cases where anatomical structures are not identifiable, particularly in the abdomen.^{63,64} 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.⁶⁵ The future of PET/MR scanners will greatly benefit from the use of dual-modality PET/MR probes. Recently, an ¹²⁴I ($t_{1/2}$: 4.2 days)-labeled IO nanoparticle was also reported as a dual-modality PET/MR probe for lymph node imaging in rats.⁶⁶ 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.⁶⁸

3. Radiation 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.^{76,77} 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 a sensitive cell-cycle phase, such as mitosis.^{78,79} The radiation dose is divided into a number of treatment fractions to allow DNA repair to take place within the normal cells and let proliferating tumor cells redistribute through the cell cycle and move into more radiosensitive phases. The main goal of radiotherapy is to kill tumor cells selectively, without damaging the normal cells.¹⁵ Radiation therapy utilizes radiation energy to induce cell death. By directly delivering external radiation beams to a tumor in the patient, external radiation therapy offers a relatively simple and practical approach to cause radiation damage in the tumor. Although the intensity, location and timing for external radiation can be well controlled and modulated, its main disadvantages include: 1) the destruction of normal tissue adjacent to tumors and in the path of the beam; 2) the need of high radiation doses for penetrating tissues with a large field or volume; 3) prolonged treatment with the requirement of daily hospital visits for 5–6 weeks; and 4) the

use of only selected radiation sources due to the technical requirements and limitations of radiation devices and radiation sources (e.g. high energy x-rays). Therefore, external radiation treatment may not be applicable to certain cancers and not effective in the improvement of clinical symptoms.⁶⁸ In contrast to external radiation treatment, systemic radiotherapy delivers radiation energy from the radioisotopes that are conjugated to a suitable delivery carrier, such as antibodies, liposome emulsions or nanoparticles with tumor targeting ligands, and transported to the tumor site as illustrated in Figure 1.

External radiation

Systemic radiation

Fig. 1. External radiation therapy and systemic radiation therapy (Reference 2).

Since tumor targeted and localized delivery of radiation enhances the treatment effect and reduces the toxicity to normal tissue, systemic radiotherapy is considered to be a promising approach for personalized oncology. Although systemic radiotherapy presents major challenges in the design and production of delivery vehicles, it offers great opportunities for the application of novel nanomaterials and nanotechnologies.

Although many radioisotopes can be used as radiation sources, only a few have been developed and applied in preclinical and in vivo studies. When selecting a candidate for experimental and clinical studies, the advantages and disadvantages of radioisotopes should be evaluated based on their physical and chemical properties, patient and environmental safety, specific requirements for in vivo applications and technical feasibility. Table 1 summarizes the physical and radiation properties of therapeutic radioisotopes that have been used in previous studies. These radioisotopes can be categorized into three types, ie, α , β and auger particles.

Radioisotopes	Particle(s) emitted	Half-life	Particle energy (keV)	Maximum particle range
α-particle				
²¹¹ At	α	7.2 hours	6,000	0.08
²²⁵ Ac	α , β	10 days	6-8,000	0.1 mm
²¹² Bi	α , β	60.6 minutes	6,000	0.09 mm
²¹³ Bi	α , β	46 minutes	6,000	<0.1 mm
²²³ Ra	α , β	11.4 days	6-7,000	<0.1 mm
²¹² Pb	α , β	10.6 hours	7,800	<0.1 mm
¹⁴⁹ Tb	α	4.2 hours	400	<0.1 mm
β-particle				
¹³¹ I	β , γ	193 hours	610	2.0 mm
⁹⁰ Y	β	64 hours	2,280	12.0 mm
⁶⁷ Cu	β , γ	62 hours	577	1.8 mm
¹⁸⁶ Re	β , γ	91 hours	1,080	5.0 mm
¹⁷⁷ Lu	β , γ	161 hours	496	1.5 mm
⁶⁴ Cu	β	12.7 hours	1,670	2.0 mm
Auger-particle				
⁶⁷ Ga	Auger, γ	78.3 hours	90	10 nm
¹²³ I	Auger, γ	13.3 hours	159	10 nm
¹²⁵ I	Auger, γ	60.5 days	27	10 nm

Abbreviation: keV, kilo electron volts.

Table 1. Characteristics of some therapeutic radioisotopes (Reference2)

3.1 α -emitters

Many radioisotopes emit α -particles but most of them decay too quickly to be considered for therapeutic use. Only a few α -emitters, including actinium-225 (²²⁵Ac), astatine-211 (²¹¹At), bismuth-213 (²¹³Bi) and bismuth-212 (²¹²Bi), have therapeutic potential and have been investigated in animal models or humans. 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 μ m). α -particles have linear energy transfer

(LET) of 100 keV/ μm . LET refers to the average radiation energy deposited in tissue per unit length of track (keV/ μm). Cell death occurs only when α -particles traverse the cell nucleus. By virtue of these properties, α -particles are highly efficient and specific in treatment of microscopic and small-volume tumors, or residual tumors in a variety of cancer types, including leukemia, lymphoma, glioma, melanoma, and peritoneal carcinomatosis.⁷⁶⁻⁸¹ However, poor radionuclide supply, complicated methodologies for calculating the radiation dosimetry and the need for relevant data relating to normal organ toxicity limit the applications of α -emitter radioisotopes and impede the development of targeted α -emitters.⁸²

3.2 β -emitters

β -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.¹⁵ Commonly used β -emitter radioisotopes are iodine-131 (^{131}I), yttrium-90 (^{90}Y), copper-67 (^{67}Cu), rhenium-186 (^{186}Re), lutetium-177 (^{177}Lu), and copper-64 (^{64}Cu). ^{131}I and ^{90}Y are the most popular candidates since these two isotopes are readily available and inexpensive. ^{131}I has a long half-life (8 days) and also provides γ -emissions that can be used in imaging for tracking and quantifying the radioisotope in vivo. It can be easily attached to tumor targeted antibodies.^{83,84} ^{131}I gets rapidly degraded and has a short retention time in the tumor.⁷⁹ Additionally, the high energy γ -emission presents some safety concerns to patients and the environment. ^{90}Y has fewer environmental radiation restrictions than ^{131}I because of its pure β -emitter nature, higher energy and low-range (12 mm), and a longer residence time in the tumor, making it more suitable for the irradiation of large tumors that require a higher radiation dose and a stable link between radioisotopes and the tumor targeting antibody.⁷⁹ β -particles have lower LET and longer radiation ranges than α -particles. Because of their long radiation range (several millimeters), β -particles can destroy tumor cells through the “crossfire effect,” even though the radioimmunoconjugate is not directly bound to the cells. Therefore, they are particularly useful in overcoming treatment resistance. β -particles are considered to be most suitable for the treatment of bulky or large volume tumors.⁸⁵

3.3 Auger-emitters

An auger is a low energy (≤ 1.6 keV), and short-range (≤ 150 nm) electron derived from inner-shell electron transition. During the decay of these radioisotopes, the vacancy formed in the K shell as a consequence of electron capture or internal conversion is rapidly filled by electrons dropping in from higher shells, resulting in a cascade of atomic electron transitions and emitting a characteristic X-ray photon or an auger. Auger emitters, such as gallium-67 (^{67}Ga), iodine-123 (^{123}I) and iodine-125 (^{125}I), have been used for cancer radiotherapy. Auger emitters deposit high linear energy transfer (LET) over extremely short distances and are therefore most effective when the decay occurs in the nucleus and less so when the decay occurs in the cytoplasm. The dimensions of many mammalian cell nucleus components, such as chromatin fiber (30-nm), fall in the range of the auger emitter (< 150 nm); therefore, auger emitters are more damaging to these cellular structures. As a result, the use of auger emitters has been relatively restricted because of the extreme toxicity of such radioisotopes.⁸⁶ 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.

The selection of radioisotopes for cancer therapy should take into account the specific cancer types, characteristics of the tumor, toxicity and safety of radioisotopes, availability and production of radioisotopes, and the chemistry that is involved in assembling the radioisotopes to the delivery carriers. It has been shown that a combination of radioisotopes with different energies can be more beneficial than using a single radioisotope. It was experimentally found that the combination of a high energy and long tissue range radioisotope with a medium energy and shorter tissue range radioisotope is able to destroy both large-volume tumors and micrometastases.⁷⁹ Tumor-targeted nanocarriers have been designed to deliver radionuclide payloads in a selective manner to improve the efficacy and safety of cancer imaging and therapy.^{1,73-75}

4. Antibodies conjugated radioisotopes for tumor targeted radiation therapy

Most of the anticancer drugs are unable to differentiate between cancerous and normal cells, leading to systemic toxicity and adverse effects. A simple tumor targeting strategy is the use of monoclonal antibodies (mAb) interacting with cancer cell surface markers.⁸⁷

Small, high affinity antibody fragments, such as single chain antibodies and affibodies, which are expressed as recombinant proteins in prokaryotic cells, are cost effective targeting ligand.⁸⁸ They have been extensively investigated for the delivery of radioisotopes, as internal radiation sources.⁸⁹⁻⁹¹ This method of using mAbs conjugated with radioisotopes for internal or systemic radiation treatment is known as radioimmunotherapy.

There are several limitations in using antibody conjugated radioisotopes for the delivery of radiation therapy. Firstly, mAbs may bind to cell surface markers on normal tissues, causing potential systemic toxicity. Secondly, mAbs have only a few sites available for conjugating radioisotopes. Therefore, delivery of a large dose of therapeutic radioisotopes may require a larger amount of antibodies. Thirdly, the use of mAbs presents potentially unwanted immune responses. Additionally, antibodies may be susceptible to protease degradation. Attempts are being made to overcome these limitations using nanoparticulate delivery systems.

5. Biocompatible nanoparticles

Nanoparticles are colloidal materials that can be fabricated with a variety of compositions and morphologies using special techniques and chemistries. Nanomaterials currently used in biomedical applications include fluorescent CdSe nanoparticles known as quantum dots (QDs), photosensitive gold nanoparticles, magnetic nanoparticles, as well as polymeric nanoparticles and nanoscale liposomes. Nanoparticles, especially metallic and metal oxide nanoparticles, in the “mesoscopic” size range of 5–100 nm in diameter often exhibit unique chemical and physical properties that are not possessed by their bulk or molecular counterparts.⁹² For example, QDs made from CdSe exhibit photoluminescence with a controllable wavelength ranging from the visible to near infrared depending on their size. Colloidal gold nanoparticles exhibit unique surface plasmon resonance (SPR) properties derived from the interaction of electromagnetic waves with the electrons in the conduction band.⁹³ Magnetic nanoparticles, such as iron III oxide (Fe₃O₄), are superparamagnetic and exhibit high magnetization and yet no residual magnetization in the absence of an externally

applied magnetic field.⁹⁴ Both the chemical properties and reactivity of the nanoparticles are controlled by the surface chemistries offered by functionalized polymer coatings or blocks, which are also important to the stability and biocompatibility of the nanoparticles, interactions between particles, biomolecules and cells, in addition to tissue distributions of the nanoparticles. Nanoparticles provide a large surface area and various types of functional groups that allow for chemical reactions taking place on the nanoparticle surface and to assemble or load bioactive ligands or small molecular agents.

6. Biocompatibilities and functionalization of nanoparticles

Metal oxide nanoparticles are coated with polymers to stabilize them from aggregating and precipitating in physiological conditions while maintaining the desired physical properties. These polymers improve biocompatibility of metallic nanoparticles by minimizing toxicity and modulating interactions between nanoparticles and biomolecules, cells and tissues. They alter secretion and biodistribution of nanoparticles. Coating polymers are functionalized with reactive functional groups, such as $-\text{COOH}$, NH_2 and $-\text{SH}$, for conjugation with tumor targeting ligands. For carrying and delivering therapeutic radioisotopes, coating polymers with reactive functional groups allows for covalent cross-linking or non-covalently incorporating chelates of radioisotopes. There are a variety of polymers and their derivatives, such as dextran, polyethylene glycol (PEG), and dendrimer, developed for ensuring the biocompatibility and functionalization of nanoparticles.^{95,96} For instance, Zhang and co-workers modified the surface of iron oxide nanoparticles with trifluoroethyl ester-terminal-PEG-silane, which was then converted to an amine-terminated PEG.⁹⁷ The terminal amine groups were used for the conjugation of Cy5.5, a near infrared (NIR) optical probe, and chlorotoxin, a targeting peptide for glioma tumors. In vitro MRI and confocal fluorescence microscopy showed a strong preferential uptake of the multimodal nanoparticles by glioma cells compared to the control nanoparticles and noncancerous cells. To reduce nonspecific uptake of nanoparticles by normal tissues and extend the blood circulation time of nanoparticles to allow particle accumulation at the target site, polymer coatings must be specifically designed to meet such applications. The physical characteristics of polymer coated nanoparticles affect their in vivo performance. Surface morphology, overall particle size and surface charge are all considered important factors that determine toxicity and biodistribution. The overall particle size must be small enough to evade uptake by reticuloendothelial system (RES) but large enough to avoid renal clearance, leaving a window of between 5.5 and 200 nm.⁹⁸ However, it has also been demonstrated that for particles smaller than 40 nm in diameter, both the biodistribution and the half-life of nanoparticles are determined by the coating material rather than the mean size.⁹⁹ The surface charge of nanoparticles depends on the nature of the coating material, which in turn plays an important role in determining blood half-life. Nanoparticles with strong positive or negative charge tend to bind to cells.^{100,101} Thus, nanoparticles with a neutral surface charge are recommended to extend circulation times. Nanoparticles with neutral surfaces resist protein binding and provide steric hindrance for preventing aggregation after in vivo administration.⁹⁸ New coating materials composed of zwitterionic polymers have been developed to provide a biocompatible surface with both positive and negative charges, which exhibit high resistance to nonspecific protein adsorption and uptake by macrophages in liver and spleen.¹⁰²⁻¹¹⁴ Chen and colleagues developed an antibiofouling copolymer PEO-*b*-P_γMPS for coating nanocrystals.¹¹⁵ This new copolymer

made hydrophobic iron oxide nanoparticles mono-disperse in physiological conditions with great stability. This amphiphilic blocked coating polymer can be functionalized with reactive amine groups on the particle surface, making it readily available for the conjugation of tumor targeting ligands and therapeutic agents such as radioisotope chelates. These composite nanoparticles showed a reduced nonspecific uptake.

7. Advantages of nanoparticulate drug delivery system

Radioisotopes undergo rapid elimination due to their widespread distributions into normal organs and tissues. One common solution to this problem is to administer large quantity of radioisotope, which is not cost effective and often results in undesirable toxicity. Nanoparticles with proper biocompatible polymer coatings provide better platforms for carrying radioisotopes and subsequently delivering the agents to the tumor. There are several advantages of using nanoparticles to deliver therapeutic radioisotopes:

- i. Nanoparticles have prolonged blood retention time, ranging from 30 minutes to 24 hours, depending on the morphology and size of the particle, coating materials and compositions of nanoparticle conjugates.
- ii. Nanoparticulate carriers used for targeting cancer cells exhibit high tumor retention time and thus enhance the concentration of therapeutic agents.
- iii. Nanoparticles have high loading capacity, they can even carry more than one type of radioisotope.
- iv. Internalization of receptor targeted nanoparticles leads to the uptake of large amounts of radioisotopes into the target cells, resulting in effective killing of tumor cells with a relatively low level of receptor-expression.
- v. The unique chemical and physical properties of nanoparticles, such as magnetization and photosensitizing provide additional capabilities and functions for improving delivery of the radioisotopes and monitoring the response to radiotherapy.

With the controlled formulation and optimized drug carrying strategies, nanoparticle platforms may offer appropriate pharmacokinetics for optimal delivery of radioisotopes for cancer treatment. Radioisotopes can be conjugated on to hydrophilic functional groups present on the surface of micelles for better transport.¹⁰⁶ Nanoparticulate drug delivery system often possess multi-functional capacity which enables it to load multiple moieties like targeting ligands and therapeutic agents. This is of immense importance to tumor targeted delivery of radioisotopes in vivo. It has been reported that nanoparticles consisting of streptavidin that linked three biotinylated components: the antiHer2 antibody trastuzumab, the tat peptide and the ¹¹¹In-labeled antiRla messenger RNA antisense morpholino (MORF) oligomer, produce significant radiation-induced antisense mediated cytotoxicity of tumor cells in vitro.¹⁰⁷

8. Strategies for targeting nanoparticles to cancer

Principally, two mechanisms are used for targeting nanoparticles to tumors, passive and active targeting. In passive targeting, nanoparticles reach the tumor through highly permeable tumor vasculature. They get accumulated in the tumor and subsequently remain there due to its lack of lymphatic drainage. In active targeting, nanoparticles are engineered to target specific biomarker molecules that are unique and over populated in a tumor or cancer cell surface. Differences in the expression of cellular receptors between normal and tumor cells provides an

opportunity for targeting nanoparticles to cancer cells. Active targeting nanoparticles carrying radioisotopes to tumors are the current research focus and the subject of intensive investigations. The surface coating polymer of nanoparticles is conjugated to ligands like antibodies, peptides and small molecules targeting the receptors highly expressed on tumor cells. Extensive reviews and discussions on the mechanisms of targeting nanoparticles to tumors have been published.^{3,108-109} In vivo tumor targeting have been achieved using folic acid modified dendrimers,¹¹¹ synthetic small-molecule modified iron oxide nanoparticles,¹¹² PEGylated arginine-glycine-aspartic acid peptide modified carbon nanotubes¹¹³ and PEGylated single chain variable fragment antibody modified gold nanoparticles.⁹³ Tumor targeted nanoparticles are believed to be a promising platform for nanobiotechnology.

Antibodies have been extensively studied as tumor targeting ligand for magnetic or photosensitive nanoparticles in the area of cancer imaging. Conjugates of nanoparticles and antibodies were found to retain the properties of both the antibody and the nanoparticle. Herceptin, a well-known antibody against HER2/neu receptors which are over-expressed in breast cancer cells when conjugated with magnetic iron oxide nanoparticles showed in vivo cancer targeting and imaging of HER2/neu with a high sensitivity. The smallest parts of the antibody, the so called ScFv, are among the frequently used ligands. Nanoparticles conjugated with mAb fragments have increased circulation times in the blood compared to nanoparticles conjugated with whole mAbs. Because mAb fragments lack the Fc domains which binds to Fc receptors on phagocytic cells.¹¹⁴

Besides mAbs and antibody fragments, small molecule ligands can be readily obtained from chemical synthesis in a large quantity. Small peptide ligands, such as Arg-Gly-Asp (RGD) has high affinity for tumor integrins $\alpha_v\beta_3$ or $\alpha_v\beta_5$ in its conformationally constrained cyclic form than its linear form, have been extensively investigated for their applications in delivering tumor targeted nanoparticles carrying imaging and therapeutic agents. This increases the probability of RGD-targeted nanoparticles to act on tumor endothelial cells and produce anti-angiogenesis effect.^{115,116} The folate receptor (FR) is an attractive molecular target for tumor targeting because it is over expressed by most of tumor cells like ovarian, colorectal, breast, nasopharyngeal carcinomas and has limited expression in normal tissues.^{117,118} FR-mediated tumor delivery of drugs, gene products, radionuclides and nanoparticles for imaging have been reported.¹¹⁹⁻¹²¹ Folic acid, attached to polyethyleneglycol-derivatized, distearyl-phosphatidylethanolamine, was used to target in vitro liposomes to folate receptor (FR)-overexpressing tumor cells. Confocal fluorescence microscopic observations demonstrated binding and subsequent internalization of rhodamine-labeled liposomes by a high FR-expressing, murine lung carcinoma line (M109-HiFR cells), with inhibition by free folic acid. Additional experiments tracking doxorubicin (DOX) fluorescence with DOX-loaded, folate-targeted liposomes (FTLs) indicate that liposomal DOX is rapidly internalized, released in the cytoplasmic compartment, and, shortly thereafter, detected in the nucleus, the entire process lasting 1-2 h. FR-mediated cell uptake of targeted liposomal DOX into a multidrug-resistant subline of M109-HiFR cells (M109R-HiFR) was unaffected by P-glycoprotein-mediated drug efflux.¹²²

9. Radioisotope loaded nanoparticles for tumor targeting

Radioisotopes are very powerful agents in diagnosis and treatment of solid tumors.¹³⁰⁻¹³¹ However they lack tumor selectivity, damage surrounding normal tissues and organs, which results severe toxicity that often outweighs their anti-tumor effects. Many researchers

have focused on the direct administration of radioisotopes into the tumor site. This method appears to be very effective, but failed due to rapid clearance from the injected tumor site. There is a strong indication that radioisotope carriers can improve the efficiency of intratumoral administration.^{126,127} Suzuki et al. described the biodistribution and kinetics of the Holmium 166–chitosan complex in rats and mice. They suggested that chitosan prolonged the retention time of Holmium 166 in the tumor site.¹²⁶ Nakajo et al. also designed a ¹³¹I-labeled lipiodol for the treatment of liver cancer patients. They determined that the radioactive concentration in blood after ¹³¹I-lipiodol administration could be maintained at levels as low as $10 \times 10^{-4}\%$ injected dose (ID)/mL for 8 days.¹²⁷ Stimuli-sensitive polymeric nano-carriers are another potential candidate for intratumoral radioisotope administration. They are readily administered due to their favorable biocompatibility, small size, and low viscosity. Alterations in their properties (hydrophilic to hydrophobic) help them accumulate in tumor sites, which results in prolongation of radioisotope retention time.¹²⁸ Very few studies have been conducted using polymeric nanoparticles labeled radioisotopes for anti-tumor treatment.¹²⁹ Conventional polymeric nanoparticles from amphiphilic block or random copolymers possess insufficient functional groups for radioisotope labeling, which results in lower labeling efficiency. Whereas, self assembled nanoparticles from polysaccharide derivatives facilitate the tagging process, as a consequence of their abundant functional groups, which enable the direct labeling of radioisotopes. Park *et al.* utilized ionic strength (IS)-sensitivity in the development of new radioisotope carriers for intratumoral administration. A polysaccharide derivative, pullulan acetate nanoparticle (PAN) was prepared via dialysis. The PAN had a spherical shape with size range of 50–130 nm and a low critical aggregation concentration (CAC) (<8 g/mL). With increases in the IS of the dialysis media, the CAC of PAN was reduced gradually and the rigidity of the hydrophobic core in PAN was increased. This suggests that the property of PAN was altered more hydrophobically at high IS values. PAN evidenced a high degree of ^{99m}Technetium (^{99m}Tc) labeling efficiency (approximately 98%). The percentage retention rate (%RR) of the ^{99m}Tc-labeled PAN was significantly longer than that of the free ^{99m}Tc ($p < 0.05$), due largely to PAN's IS-sensitivity. Thus, PAN may constitute a new approach to the achievement of maximal radioisotope efficiency with regard to intratumoral administration.¹²² Noninvasive, focused hyperthermia can be achieved by using an externally applied alternating magnetic field (AMF) if effective concentrations of nanoparticles can be delivered to the target cancer cells. Monoclonal antibodies or peptides, linked to magnetic iron oxide nanoparticles (NP), represent a promising strategy to target cancer cells. A new radioconjugate NP ((111)In-DOTA-di-scFv-NP), using recombinantly generated antibody fragments, di-scFv-c, for the imaging and therapy of anti-MUC-1-expressing cancers was developed by Natarajan *et al.*¹³⁰

10. Future implications

With the advent of nanotechnology, researchers world over are interested in designing a magic bullet which would detect the malignant tissue and destroy it. Radionuclides can be targeted to malignant tissue by coupling them to antibodies or their parts. These radioimmunoconjugates are being developed to meet the challenges facing cancer detection and therapy today and in the future. Several radiolabeled multifunctional and multimodality nanoparticles have been effectively demonstrated in detecting and treating cancer in animal models. However, further preclinical and clinical efficacy and toxicity

studies are required to translate these advanced technologies to the health care of cancer patients.

11. References

- [1] Ting G, Chang CH, Wang HE. Cancer nanotargeted radiopharmaceuticals for tumor imaging and therapy. *Anticancer Res.* 2009 ;29(10):4107-18.
- [2] American Cancer Society, Inc., Surveillance and Health Policy Research, 2010.
- [3] Zhang et al, Nanotechnology, Science and Applications 2010;3: 159-170.
- [4] Jarzyna PA, Skajaa T, Gianella A, et al. Iron oxide core oil-in-water emulsions as a multifunctional nanoparticle platform for tumor targeting and imaging. *Biomaterials.* 2009;30:6947-6954.
- [5] Peng X, Qian X, Mao H, et al. Targeted magnetic iron oxide nanoparticles for tumor imaging and therapy. *Int J Nanomed.* 2008;3:311-321.
- [6] Yang L, Peng X, Wang A, et al. Receptor-targeted nanoparticles for in vivo imaging of breast cancer. *Clin Cancer Res.* 2009;15:4722-4732.
- [7] Shenoy D, Little S, Langer R, Amiji M. Poly(ethylene oxide)-modified poly(beta-amino ester) nanoparticles as a pH-sensitive system for tumor-targeted delivery of hydrophobic drugs. 1. In vitro evaluations. *Mol Pharm.* 2005;2:357-366.
- [8] Bae Y, Diezi TA, Zhao A, Kwon GS. Mixed polymeric micelles for combination cancer chemotherapy through the concurrent delivery of multiple chemotherapeutic agents. *J Control Release.* 2007;122:324-330.
- [9] Lee H, Lee E, Kim K, Jang NK, Jeong YY, Jon S. Antibiofouling polymer-coated superparamagnetic iron oxide nanoparticles as potential magnetic resonance contrast agents for in vivo cancer imaging. *J Am Chem Soc.* 2006;128:7383- 7389.
- [10] Mankoff DA. A definition of molecular imaging. *J Nucl Med.* 2007;48:18N. 21N.
- [11] Massoud TF, Gambhir SS. "Molecular imaging in living subjects: Seeing fundamental biological processes in a new light" *Genes Dev* 2003;17:545-580.
- [12] Koo V, Hamilton PW, Williamson K. Non-invasive in vivo imaging in small animal research. *Cell. Oncol.* 2006;28:127-139.
- [13] Pomper MG, Lee JS. Small animal imaging in drug development. *Curr Pharm Des.* 2005;11:3247-3272.
- [14] Cai W, Rao J, Gambhir SS, Chen X. How molecular imaging is speeding up anti-angiogenic drug development. *Molecular Cancer Therapeutics*, 2006, 5, 2624-2633.
- [15] Gambhir SS. Molecular imaging of cancer with positron emission tomography. *Nat Rev Cancer* 2002;2:683-693.
- [16] Hong H, Zhang Y, Sun J, Cai W. Molecular imaging and therapy of cancer with radiolabeled nanoparticles. *Nano Today* 2009; 4: 399-413.
- [17] Peremans K, Cornelissen B, Van Den Bossche B, Audenaert K, Van de Wiele C. A review of small animal imaging planar and pinhole spect Gamma camera imaging. *Vet Radiol Ultrasound* 2005;46:162-170.
- [18] Kjaer A. Molecular imaging of cancer using PET and SPECT. *Adv Exp Med Biol* 2006;587:277-284.
- [19] DeNardo SJ, DeNardo GL, Miers LA, Natarajan A, Foreman AR, Gruettner C, Adamson GN, Ivkov R. *Clin Cancer Res* Development of tumor targeting bioprobes

- (¹¹¹In-chimeric L6 monoclonal antibody nanoparticles) for alternating magnetic field cancer therapy. 2005;11:7087s-7092s.
- [20] DeNardo SJ, DeNardo GL, Natarajan A, Miers LA, Foreman AR, Gruettner C, Adamson GN, Ivkov R. Thermal dosimetry predictive of efficacy of ¹¹¹In-ChL6 nanoparticle AMF--induced thermoablative therapy for human breast cancer in mice. *J Nucl Med*. 2007 48(3):437-444.
- [21] Natarajan A, Gruettner C, Ivkov R, DeNardo GL, Mirick G, Yuan A, Foreman A, DeNardo SJ. NanoFerrite particle based radioimmunonanoparticles: binding affinity and in vivo pharmacokinetics. *Bioconj Chem* 2008;19:1211-1218.
- [22] Natarajan A, Xiong CY, Gruettner C, DeNardo GL, DeNardo SJ. Development of multivalent radioimmunonanoparticles for cancer imaging and therapy. *Cancer Biother Radiopharm* 2008;23:82-91.
- [23] Hood JD, Cheres DA. Role of integrins in cell invasion and migration. *Nat Rev Cancer*. 2002;2:91-100.
- [24] Cai W, Chen X. Anti-angiogenic cancer therapy based on integrin $\alpha_v\beta_3$ antagonism. *Anti-cancer Agents Med Chem*, 2006; 6: 407-428.
- [25] Cai W, Niu G, Chen X. Imaging of integrins as biomarkers for tumor angiogenesis. *Curr Pharm Des* 2008;14:2943-2973.
- [26] Hu G, Lijowski M, Zhang H, Partlow KC, Caruthers SD, Kiefer G, Gulyas G, Athey P, Scott MJ, Wickline SA, Lanza GM. Imaging of Vx-2 rabbit tumors with alpha(nu)beta3-integrin-targeted ¹¹¹In nanoparticles. *Int J Cancer*. 2007; 1;120:1951-1957.
- [27] Wang H, Wang J, Deng X, Sun H, Shi Z, Gu Z, Liu Y, Zhao Y. Biodistribution of single-wall carbon nanotubes in mice. *J Nanosci Nanotechnol* 2004;4:1019-1024.
- [28] Singh R, Pantarotto D, Lacerda L, Pastorin G, Klumpp C, Prato M, Bianco A, Kostarelos K. *Proc Natl Acad Sci USA* 2006;103:3357-3362.
- [29] Villa CH, McDevitt MR, Escorcia FE, Rey DA, Bergkvist M, Batt CA, et al. Synthesis and Biodistribution of Oligonucleotide-Functionalized, Tumor-Targetable Carbon Nanotubes. *Nano Lett*. 2008; 8: 4221-4228.
- [30] Chen GD, Fachin F, Fernandez-Suarez M, Wardle BL, Toner M. Nanoporous Elements in Microfluidics for Multiscale Manipulation of Bioparticles. *Small*, 2011; DOI: 10.1002/smll.201002076.
- [31] Shokouhi S, Metzler SD, Wilson DW, Peterson TE. Multi-pinhole collimator design for small-object imaging with SiliSPECT: a high-resolution SPECT. *Phys Med Biol* 2009;54:207-225.
- [32] Berman DS, Kiat H, Van Train K, Friedman JD, Wang FP, Germano G. Dual-isotope myocardial perfusion SPECT with rest thallium-201 and stress Tc-99m sestamibi. *Cardiol Clin* 1994;12:261-270.
- [33] Visser EP, Disselhorst JA, Brom M, Laverman P, Gotthardt M, Oyen WJ, Boerman OC. Spatial resolution and sensitivity of the Inveon small-animal PET scanner. *J Nucl Med* 2009;50:139-147.
- [34] Liu Z, Cai W, He L, Nakayama N, Chen K, Sun X, Chen X, Dai H. In vivo biodistribution and highly efficient tumour targeting of carbon nanotubes in mice. *Nat Nanotechnol* 2007;2:47-52.

- [35] Keren S, Zavaleta C, Cheng Z, de la Zerda A, Gheysens O, Gambhir SS. Noninvasive molecular imaging of small living subjects using Raman spectroscopy. *Proc Natl Acad Sci USA* 2008;105:5844-5849.
- [36] Zavaleta C, de la Zerda A, Liu Z, Keren S, Cheng Z, Schipper M, Chen X, Dai H, Gambhir SS. Noninvasive Raman spectroscopy in living mice for evaluation of tumor targeting with carbon nanotubes. *Nano Lett* 2008;8:2800-2805.
- [37] De la Zerda A, Zavaleta C, Keren S, Vaithilingam S, Bodapati S, Liu Z, et al. Carbon nanotubes as photoacoustic molecular imaging agents in living mice. *Nat Nanotechnol* 2008;3:557-562.
- [38] Liu Z, Davis C, Cai W, He L, Chen X, Dai H. Circulation and long-term fate of functionalized, biocompatible single-walled carbon nanotubes in mice probed by Raman spectroscopy. *Proc Natl Acad Sci USA* 2008;105:1410-1415.
- [39] Liu Z, Chen K, Davis C, Sherlock S, Cao Q, Chen X, Dai H. Drug delivery with carbon nanotubes for in vivo cancer treatment. *Cancer Res* 2008;68:6652-6660.
- [40] McDevitt MR, Chattopadhyay D, Kappel BJ, Jaggi JS, Schiffman SR, Antczak C, Njardarson JT, Brentjens R, Scheinberg DA. Tumor targeting with carbon nanotubes. *J Nucl Med* 2007;48:1180-1189.
- [41] McDevitt MR, Chattopadhyay D, Jaggi JS, Finn RD, Zanzonico PB, Villa C, Rey D, Mendenhall J, Batt CA, Njardarson JT, Scheinberg DA. *PLOS ONE* 2007;2:e907.
- [42] Cai W, Hsu AR, Li ZB, Chen X. Are quantum dots ready for *in vivo* imaging in human subjects?. *Nanoscale Res Lett.* 2007;2:265-281.
- [43] Michalet X, Pinaud FF, Bentolila LA, Tsay JM, Doose S, Li JJ, Sundaresan G, Wu AM, Gambhir SS, Weiss S. Quantum dots for live cells, in vivo imaging, and diagnostics. *Science* 2005;307:538.
- [44] Medintz IL, Uyeda HT, Goldman ER, Mattoussi H. Quantum dot bioconjugates for imaging, labelling and sensing *Nat Mater* 2005;4:435-446.
- [45] Li ZB, Cai W, Chen X. Semiconductor quantum dots for in vivo imaging. *J Nanosci Nanotechnol* 2007;7:2567-2581.
- [46] Woodward JD, Kennel SJ, Mirzadeh S, Dai S, Wall JS, Richey T, Avenell J, Rondinone AJ. *In vivo* SPECT/CT imaging and biodistribution using radioactive Cd^{125m}Te/ZnS nanoparticles. *Nanotechnology* 2007;18:175103.
- [47] Kennel SJ, Woodward JD, Rondinone AJ, Wall J, Huang Y, Mirzadeh S. The fate of MAb-targeted Cd^{125m}Te/ZnS nanoparticles in vivo. *Nucl Med Biol* 2008;35:501-514.
- [48] Kobayashi H, Hama Y, Koyama Y, Barrett T, Regino CA, Urano Y, Choyke PL. Simultaneous multicolor imaging of five different lymphatic basins using quantum dots. *Nano Lett* 2007;7:1711-1716.
- [49] Schipper ML, Cheng Z, Lee SW, Bentolila LA, Iyer G, Rao J, Chen X, Wu AM, Weiss S, Gambhir SS. microPET-based biodistribution of quantum dots in living mice. *J Nucl Med.* 2007;48:1511-1518.
- [50] Schipper ML, Iyer G, Koh AL, Cheng Z, Ebenstein Y, Aharoni A, Keren S, Bentolila LA, Li J, Rao J, Chen X, Banin U, Wu AM, Sinclair R, Weiss S, Gambhir SS. Particle size, surface coating, and PEGylation influence the biodistribution of quantum dots in living mice. *Small* 2009;5:126-134.
- [51] Duconge F, Pons T, Pestourie C, Herin L, Theze B, Gombert K, Mahler B, Hinnen F, Kühnast B, Dollé F, Dubertret B, Tavitian B. Fluorine-18-labeled phospholipid

- quantum dot micelles for in vivo multimodal imaging from whole body to cellular scales. *Bioconjug Chem* 2008;19:1921-1926.
- [52] Cai W, Shin DW, Chen K, Gheysens O, Cao Q, Wang SX, Gambhir SS, Chen X. Peptide-labeled near-infrared quantum dots for imaging tumor vasculature in living subjects. *Nano Lett* 2006;6:669-676.
- [53] Gao X, Cui Y, Levenson RM, Chung LWK, Nie S. In vivo cancer targeting and imaging with semiconductor quantum dots. *Nat Biotechnol* 2004;22:969-976. 2007;67:1138.
- [54] Tada H, Higuchi H, Wanatabe TM, Ohuchi N. In vivo real-time tracking of single quantum dots conjugated with monoclonal anti-HER2 antibody in tumors of mice. *Cancer Res* 2007;67:1138-44.
- [55] Gambhir SS, Czernin J, Schwimmer J, Silverman DH, Coleman RE, Phelps ME. A tabulated summary of the FDG PET literature. *J Nucl Med* 2001;42:1S-93S.
- [56] Cai W, Chen K, Li ZB, Gambhir SS, Chen X. Dual-function probe for PET and near-infrared fluorescence imaging of tumor vasculature. *J Nucl Med* 2007;48:1862-1870.
- [57] Cai W, Chen X. Multimodality imaging of vascular endothelial growth factor and vascular endothelial growth factor receptor expression. *Front Biosci* 2007;12:4267-4279.
- [58] Ellis LM, Hicklin DJ. VEGF-targeted therapy: mechanisms of anti-tumour activity. *Nat Rev Cancer* 2008;8:579-591.
- [59] Ferrara N, Hillan KJ, Gerber HP, Novotny W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. *Nat Rev Drug Discov* 2004;3:391-400.
- [60] Chen K, Li ZB, Wang H, Cai W, Chen X. Dual-modality optical and positron emission tomography imaging of vascular endothelial growth factor receptor on tumor vasculature using quantum dots. *Eur J Nucl Med Mol Imaging* 2008;35:2235-2244.
- [61] Pathak AP, Gimi B, Glunde K, Ackerstaff E, Artemov D, Bhujwala ZM. Molecular and functional imaging of cancer: advances in MRI and MRS. *Methods Enzymol* 2004;386:3-60.
- [62] Thorek DL, Chen AK, Czupryna J, Tsourkas A. Superparamagnetic iron oxide nanoparticle probes for molecular imaging *Ann Biomed Eng* 2006;34:23-38.
- [63] Bertini I, Kowalewski J, Luchinat C, Parigi G. Cross correlation between the dipole-dipole interaction and the Curie spin relaxation: the effect of anisotropic magnetic susceptibility. *J Magn Reson* 2001;152:103-108.
- [64] Ruf J, Lopez Hanninen E, Oettle H, Plotkin M, Pelzer U, Stroszczyński C, Felix R, Amthauer H. Detection of recurrent pancreatic cancer: comparison of FDG-PET with CT/MRI. *Pancreatology* 2005;5:266-272.
- [65] Pannu HK, Cohade C, Bristow RE, Fishman EK, Wahl RL. PET-CT detection of abdominal recurrence of ovarian cancer: radiologic-surgical correlation. *Abdom Imaging* 2004;29:398-403.
- [66] Wehrl HF, Judenhofer MS, Wiehr S, Pichler BJ. Pre-clinical PET/MR: technological advances and new perspectives in biomedical research. *Eur J Nucl Med Mol Imaging* 2009;36:S56-S68.

- [67] Choi JS, Park JC, Nah H, Woo S, Oh J, Kim KM, Cheon GJ, Chang Y, Yoo J, Cheon J. A hybrid nanoparticle probe for dual-modality positron emission tomography and magnetic resonance imaging. *Angew Chem Int Ed Engl* 2008;47:6259-6262.
- [68] Bogenrieder T, Herlyn M. Axis of evil: molecular mechanisms of cancer metastasis. *Oncogene* 2003;22:6524-6536.
- [69] Korb L. Radiotherapy for the palliation of prostate cancer. *Semin Surg Oncol*. 2000;18:75-79.
- [70] Sharkey RM, Goldenberg DM. Novel radioimmunopharmaceuticals for cancer imaging and therapy. *Curr Opin Investig Drugs* 2008;9:1302.
- [71] Buchholz TA. Radiation therapy for early-stage breast cancer after breast-conserving surgery. *N Engl J Med* 2009;360:6370.
- [72] Sakata K, Someya M, Matsumoto Y, Hareyama M. Ability to repair DNA double-strand breaks related to cancer susceptibility and radiosensitivity. *Radiat Med* 2007;25:433-438.
- [73] Sankaranarayanan K, Chakraborty R. Cancer predisposition, radiosensitivity and the risk of radiation-induced cancers. I. Background. *Radiat Res* 1995;143:121-143.
- [74] Mitra A, Nan A, Line BR, Ghandehari H. Nanocarriers for Nuclear Imaging and Radiotherapy of Cancer. *Curr Pharm Res* 2006;12:4729-4749.
- [75] Elbayoumi TA, Torchilin VP. Current trends in liposome research. *Methods Mol Biol*. 2010;605:1-27.
- [76] Torchilin VP. Targeted Pharmaceutical Nanocarriers for Cancer Therapy and Imaging. *AAPS* 2007; 9; E128-E147.
- [77] Hartmann F, Horak EM, Garmestani K, et al. Radioimmunotherapy of nude mice bearing a human interleukin 2 receptor alpha-expressing lymphoma utilizing the alpha-emitting radionuclide-conjugated monoclonal antibody ²¹³Bi-anti-Tac. *Cancer Res*. 1994;54:4362-4370.
- [78] Kennel SJ, Stabin M, Roeske JC, et al. Radiotoxicity of bismuth-213 bound to membranes of monolayer and spheroid cultures of tumor cells. *Radiat Res*. 1999;151:244-256.
- [79] Ballangrud AM, Yang WH, Charlton DE, et al. Response of LNCaP spheroids after treatment with an alpha-particle emitter (²¹³Bi)-labeled anti-prostate-specific membrane antigen antibody (J591). *Cancer Res*. 2001;61:2008-2014.
- [80] Goldenberg DM. Targeted therapy of cancer with radiolabeled antibodies. *J Nucl Med*. 2002;43:693-713.
- [81] Salvatori M, Indovina L, Mansi L. Targeted α -particle therapy: a clinical overview. *Curr. Radiopharm*. 2008;1:251-253.
- [82] Zalutsky MR. Targeted α -particle therapy of microscopic disease: providing a further rationale for clinical investigation. *J Nucl Med*. 2006;47:1238-1240.
- [83] Mühlhausen U, Schirmacher R, Piel M, et al. Synthesis of ¹³¹I-labeled glucose-conjugated inhibitors of O6-methylguanine- DNA methyltransferase (MGMT) and comparison with nonconjugated inhibitors as potential tools for in vivo MGMT imaging. *J Med Chem*. 2006;49:263-272.
- [84] Schipper ML, Riese CG, Seitz S, et al. Efficacy of ^{99m}Tc pertechnetate and ¹³¹I radioisotope therapy in sodium/iodide Symporter (NIS)-expressing neuroendocrine tumors in vivo. *Eur J Nucl Med Mol Imaging*. 2007;34:63 :638-650.

- [85] Mulford DA, Scheinberg DA, Jurcic JG. The promise of targeted α -particle therapy. *J Nucl Med.* 2005;46:199S–204S.
- [86] Mitra A, Nan A, Line BR, et al. Nanocarriers for nuclear imaging and radiotherapy of cancer. *Curr Pharm Des.* 2006;12:4729–4749.
- [87] Saravanakumar G, Kim K, Park JH, et al. Current status of nanoparticle based imaging agents for early diagnosis of cancer and atherosclerosis. *J Biomed Nanotechnol.* 2009;5:20–35.
- [88] Marcucci F, Lefoulon F. Active targeting with particulate drug carriers in tumor therapy: fundamentals and recent progress. *Drug Discovery Today.* 2004;9:219–228.
- [89] Li L, Wartchow CA, Danthi SN, et al. A novel antiangiogenesis therapy using an integrin or anti-FLK-1 antibody cotated ^{90}Y -labeled nanoparticles. *Int J Radiation Oncology Biol Phys.* 2004;58:1215–1227.
- [90] DeNardo SJ, DeNardo GL, Miers LA, et al. Development of tumor targeting bioprobes (^{111}In -chimeric L6 monoclonal antibody nanoparticles) for alternating magnetic field cancer therapy. *Clin Cancer Res.* 2005;11:7087S–7092S.
- [91] Chen J, Wu H, Han D, et al. Using anti-VEGF McAb and magnetic nanoparticles as double-targeting vector for the radioimmunotherapy of liver cancer. *Cancer Letters.* 2006;231:169–175.
- [92] Nie S, Xing Y, Kim GJ, Simons JW. Nanotechnology applications in cancer. *Annu Rev Biomed Eng.* 2007;9:257–288.
- [93] Qian X, Peng XH, Ansari DO, et al. In vivo tumor targeting and spectroscopic detection with surface-enhanced Raman nanoparticle tags. *Nat Biotechnol.* 2008;26:83–90.
- [94] Gupta AK, Gupta M. Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications. *Biomaterials.* 2005;26:3995–4021.
- [95] Veisheh O, Sun C, Gunn J, et al. Optical and MRI multifunctional nanoprobe for targeting gliomas. *Nano Letters.* 2005;5:1003–1008.
- [96] Xie J, Xu C, Kohler Y, et al. Controlled PEGylation of monodisperse Fe_3O_4 nanoparticles for reduced non-specific uptake by macrophage cells. *Adv Mater.* 2007;19:3163–3166.
- [97] Veisheh O, Sun C, Fang C, et al. Specific targeting of brain tumors with an optical/magnetic resonance imaging nanoprobe across the blood brain barrier. *Cancer Res.* 2009;69:6200–6207.
- [98] Sun C, Lee JS, Zhang M. Magnetic nanoparticles in MR imaging and drug delivery. *Adv Drug Deliv Rev.* 2008; 60:1252–1265.
- [99] Briley-Saebo K, Bjørnerud A, Grant D, et al. Hepatic cellular distribution and degradation of iron oxide nanoparticles following single intravenous injection in rats: implications for magnetic resonance imaging. *Cell Tissue Res.* 2004;316:315–323.
- [100] Fujita T, Nishikawa M, Ohtsubo Y, et al. Control of in-vivo fate of albumin derivatives utilizing combined chemical modification. *J Drug Target.* 1994;2:157–165.

- [101] Kairdolf BA, Mancini MC, Smith AM, et al. Minimizing nonspecific cellular binding of quantum dots with hydroxyl derivatized surface coatings. *Anal Chem.* 2008;80:3029–3034.
- [102] Ladd J, Zhang Z, Chen S, et al. Zwitterionic polymers exhibiting high resistance to nonspecific protein adsorption from human serum and plasma. *Biomacromolecules.* 2008;9:1357–1361.
- [103] Breus VV, Heyes CD, Tron K, et al. Zwitterionic Biocompatible Quantum Dots for Wide pH Stability and Weak Nonspecific Binding to Cells. *ACS Nano.* 2009;3:2573–2580.
- [104] Yang W, Zhang L, Wang S, et al. Functionalizable and ultra stable nanoparticles coated with zwitterionic poly(carboxybetaine) in undiluted blood serum. *Biomaterials.* 2009;30:5617–5621.
- [105] Chen H, Wu X, Duan H, et al. Biocompatible polysiloxane-containing diblock copolymer PEO-b-P_γMPS for coating magnetic nanoparticles. *ACS Applied Materials and Interfaces.* 2009;1:2134–2140.
- [106] Nasongkla N, Bey E, Ren J, et al. Multifunctional polymeric micelles as cancer-targeted, MRI-ultrasensitive drug delivery systems. *Nano Letters.* 2006;6:2427–2430.
- [107] Liu X, Wang Y, Nakamura K, et al. Auger radiation – induced, antisense mediated cytotoxicity of tumor cells using a 3- component streptavidin delivery nanoparticle with ¹¹¹In. *J Nucl Med.* 2009;50:582–590.
- [108] Wang MD, Shin DM, Simon JW, et al. Nanotechnology for targeted cancer therapy. *Expert Rev Anticancer Ther.* 2007;7:833–837.
- [109] Brannon-Peppas L, Blanchette JO. Nanoparticle and targeted systems for cancer therapy. *Adv Drug Deliv Rev.* 2004;56:1649–1659.
- [110] van Vlerken LE, Vyas TK, Amiji MM. Poly (ethylene glycol)-modified nanocarriers for tumor-targeted and intracellular Delivery *Pharm. Res.* 2007;24:1405–1414.
- [111] Kukowska-Latallo JF, Candido KA, Cao Z, et al. Nanoparticle targeting of anticancer drug improves therapeutic response In animal model of human epithelial cancer. *Cancer Res.* 2005;65:5317–5324.
- [112] Weissleder R, Kelly K, Sun EY, et al. Cell-specific targeting of nanoparticles by multivalent attachment of small molecules. *Nat Biotechnol.* 2005;23:1418–1423.
- [113] Liu Z, Cai W, He L, et al. In vivo biodistribution and highly efficient tumour targeting of carbon nanotubes in mice. *Nat Nanotechnol.* 2007;2:47–52.
- [114] Yang L, Mao H, Wang YY, et al. Single chain epidermal growth factor receptor antibody conjugated nanoparticles for in vivo tumor targeting and imaging. *Small.* 2009;5:235–243.
- [115] Zhang CF, Jugold M, Woenne EC, et al. Specific targeting of tumor angiogenesis by RGD-conjugated ultrasmall superparamagnetic iron oxide particles using a clinical 1.5-T magnetic resonance scanner. *Cancer Res.* 2007;67:1555–1562.
- [116] Cai WB, Chen XY. Preparation of peptide-conjugated quantum dots for tumor vasculature-targeted imaging. *Nature Protocols.* 2008;3:89–96.

- [117] Antony AC. Folate receptors. *Annu Rev Nutr.* 1996;16:501–512. 117. Ke CY, Mathias CJ, Green MA. Folate-receptor-targeted radionuclide imaging agents. *Adv Drug Deliv Rev.* 2004;56:1143–1160.
- [118] Das M, Mishra D, Dhak P, et al. Biofunctionalized, phosphonategrafted, ultrasmall iron oxide nanoparticles for combined Targeted cancer therapy and multimodal imaging. *Small.* 2009;5:2883–2893.
- [119] Thomas M, Kularatne SA, Qi L, et al. Ligand-targeted delivery of small interfering RNAs to malignant cells and tissues. *Ann N Y Acad Sci.* 2009;1175:32–39.
- [120] Setua S, Menon D, Asok A, et al. Folate receptor targeted, rare-earth oxide nanocrystals for bi-modal fluorescence and magnetic imaging of cancer cells. *Biomaterials.* 2010;31:714–729.
- [121] Goren D, Horowitz AT, Tzemach D, Tarshish M, Zalipsky S, Gabizon A. Nuclear delivery of doxorubicin via folate- targeted liposomes with bypass of multidrug-resistance efflux pump. *Clin Cancer Res.* 2000;6:1949–1957.
- [122] Seong SK, Ryu JM, Shin DH, Bae EJ, Shigematsu A, Hatori Y, Nishigaki J, Kwak C, Lee SE, Park KB, Biodistribution and excretion of radioactivity after the administration of ^{166}Ho -chitosan complex (DW-166HC) into the prostate of rat *Eur. J. Nucl. Med. Mol. Imaging* 2005; 32: 910–917.
- [123] Hafeli UD, Dasillas S, Dietz DW, Pauer GJ, Rybicki LA, Conzone SD, Day DE, Hepatic tumor radioembolization in a rat model using radioactive rhenium ($^{186}\text{Re}/^{188}\text{Re}$) glass microspheres, *Int. J. Radiat. Oncol. Biol. Phys.* 1999; 44:189–199.
- [124] Lau WY, Ho S, Leung TW, Chan M, Ho R, Johnson PJ, Li AK, Selective internal radiation therapy for nonresectable hepatocellular carcinoma with intraarterial infusion of ^{90}Y microspheres, *Int. J. Radiat. Oncol. Biol. Phys.* 1998; 40:583–592.
- [125] Suzuki YS, Momose Y, Higashi N, Shigematsu A, Park KB, Kim YM, Kim JR, Ryu JM, Biodistribution and kinetics of holmium-166-chitosan complex (DW-166HC) in rats and mice, *J. Nucl. Med.* 1998; 39:2161–2166.
- [126] Nakajo M, Kobayashi H, Shimabukuro K, Shirono K, Sakata H, Taguchi M, Biodistribution and in vivo kinetics of iodine-131 lipiodol infused via the hepatic artery of patients with hepatic cancer, *J. Nucl. Med.* 1988; 29:1066–1077.
- [127] Na K, Park KH, Kim SW, Bae YH, Self-aggregated hydrogel nanoparticles from curdlan derivatives: characterization, anti-cancer drug release and interaction with a hepatoma cell line (HepG2), *J Control. Release* 2000; 69:225–236.
- [128] Park YJ, Lee JY, Chang YS, Jeong JM, Chung JK, Lee MC, Park KB, Lee SJ, Radioisotope carrying polyethylene oxide-polycaprolactone copolymer micelles for targetable bone imaging, *Biomaterials* 2002; 23:873–879.
- [129] Park KH, Song HC, Na K, Bom HS, Lee KH, Kim S, Lee DH, Ionic strength-sensitive pullulan acetate nanoparticles (PAN) for intratumoral administration of radioisotope: Ionic strength-dependent aggregation behavior and $^{99\text{m}}\text{Tc}$ retention property, *Colloids and Surfaces B: Biointerfaces* 2007; 59:16–23.
- [130] Natarajan A, Xiong CY, Gruettner C, DeNardo GL, DeNardo SJ, Development of multivalent radioimmunonanoparticles for cancer imaging and therapy. *Cancer Biother Radiopharm.* 2008; 23:82–91.

- [131] Sofou S. Surface-active liposomes for targeted cancer therapy. *Nanomedicine* 2007; 2, 711-724.
- [132] Ogihara I, Kojima S, Jay M. Differential uptake of gallium-67-labeled liposomes between tumors and inflammatory lesions in rats. *J Nucl Med* 1986, 27, 1300-1307.

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