J Nanopart Res (2013) 15:2100
DOI 10.1007/s11051-013-2100-9

REVIEW

Surface modification: how nanoparticles assemble to molecular imaging probes

Huilong Tan · Lun Yu · Feng Gao · Weihua Liao · Wei Wang · Wenbin Zeng

Received: 8 August 2013 / Accepted: 25 October 2013 / Published online: 16 November 2013

Abstract Nanomaterials have attracted widespread attention due to their unique chemical and physical properties, such as size-dependent optical, magnetic, or catalytic properties, thus have the great potential application, especially in the fields of new materials and devices. The emergence of nanoparticle-based probe has led to important innovations in molecular imaging field. Several types of nanoparticles have been employed for molecular imaging application, including Au/Ag nanoparticles, upconversion nanoparticles (UCNPs), quantum dots, dye-doped nanoparticles, magnetic nanoparticles (MNPs), etc. The preparation of nanoparticle-based probe for molecular imaging routinely includes three steps: synthesis, surface modification, and bioconjugation, among which surface modification plays an important role for the whole procedure. Surface modification usually possesses the safety, biocompatibility, stability, hydrophilicity, and terminal functional groups for further conjugation. This review aims to outline the surface modification of how nanoparticles assemble to probes, focusing on the developments of two widely used nanoparticles, UCNPs and MNPs. Recent advances of different types of linkers, a core component for surface modification, are summarized. It shows the intimate relationship between chemistry and nanoscience. Finally, perspectives and challenges of nanoparticle-based probe in the field of molecular imaging are expected.

Keywords Molecular imaging · Nanoparticle-based probe · Surface modification · Linker · Instrumentation · Nanomedicine

H. Tan · L. Yu · W. Zeng (✉)
School of Pharmaceutical Sciences, Central South University, 172 Tongzipo Road, Changsha 410013, People's Republic of China
e-mail: wbzeng@hotmail.com

H. Tan · L. Yu · F. Gao · W. Liao · W. Wang · W. Zeng
Molecular Imaging Research Center, Central South University, 172 Tongzipo Road, Changsha 410013, People's Republic of China

F. Gao · W. Wang
The Third Xiang Ya Hospital, Central South University, 172 Tongzipo Road, Changsha 410013, People's Republic of China

Introduction

Molecular imaging emerges as an intriguing technology which plays increasingly significant roles in early diagnosis and therapeutics (Hellebust and Richards-Kortum 2012). With the help of this promising tool, clinicians worldwide are able to visualize disease progress at cellular, even molecular levels. Molecular imaging, in comparison with traditional diagnostic imaging methods, tries to spot the molecular abnormalities via probes rather than obtain the images of the end effects of molecular variation. Molecular probe is

an agent frequently used to unveil the biological processes that make them visible both in vitro and in vivo in the living subjects (Reynolds and Kelly 2011). Typically, a probe is composed of three parts: signal agent, target agent, and linker (Ye et al. 2011a). At present, nanotechnology has become an active approach in many fields, and the emergence of new-type nanoparticle leads to the transformation of molecular imaging (Minchin and Martin 2010; Bai 2013) due to its unique optical and magnetic properties (He et al. 2008; Rosenblum et al. 2010). Nanoparticle usually is an ultra-fine particle with diameter varying from 1 to 100 nm, and can be distinguished from other bulk material owing to its unique properties (Mohanpuria et al. 2008). Various types of nanoparticle, including upconversion nanoparticles (UCNPs), quantum dots (QDs), dye-doped nanoparticles, and magnetic nanoparticles, hold promise as biomedical imaging, diagnostic, and theragnostic agents (Alivisatos 1996; Choi and Frangioni 2010; Kalayci et al. 2010, 2013; Hazer et al. 2011, 2012; Hazer and Hazer 2011; Liu et al. 2012; Zeng and Miao 2009). The typical near-infrared (NIR) fluorescent properties of UCNPs, QDs, and dye-doped nanoparticle make them a potential NIR probe. In contrast with visible light excitation, NIR light excitation for in vivo imaging has several desirable advantages, namely weak autofluorescence, deep penetration, minimal photo-bleaching, etc. In magnetic resonance imaging (MRI), superparamagnetic iron oxide nanoparticle (SPIO) is one of most commonly used signal agent. MRI is a powerful diagnostic imaging modality with high space resolution. It can visualize the tissue structures by employing the magnetic resonance of protons. SPIO, which becomes magnetic in an external magnetic field but nonmagnetic when the magnetic field is removed, has been the most T_2 probe for MRI (Lodhia et al. 2010; Jeon et al. 2013; Xie et al. 2011).

Even though nanoparticle has its unique advantages, some undesirable drawbacks still prohibit it being an ideal probe design platform (Ye et al. 2011b; Dutta et al. 2010). Nanoparticle can easily aggregate because of its high surface area, and for this regard, surface modification becomes necessary for keeping its stability. Practically speaking, the synthesized nanoparticle should be directly used in molecular imaging. But as synthesized, most nanoparticles are hydrophobic which is not suitable for clinical use. For example, nanoparticles modified with hydrophobic organic ligands (such as oleic acid) cannot be directly applied because of their poor hydrophilicity and lack of functional groups. With this regard, it is crucial to chemically modify the surface of nanoparticles as to make them hydrophilic and biocompatible (Sapsford et al. 2013). Anyway, surface modification is one of the most critical steps in the development of functionalized nanomaterials for bioimaging applications (Wang et al. 2010). Past decades have seen the rise of great interest in nanoparticles not only owing to their unique application in optical or MRI, but also their capability as ideal building blocks for multimodal bioimaging and therapy (Fig. 1) (Cai and Chen 2007, 2008; Gu et al. 2011; Licha and Resch-Genger 2011; Swierczewska et al. 2011; Zhou et al. 2012; Ladj et al. 2013). In this review, different methods for the preparation of different kinds of nanoparticles are summarized. We detailed on the synthesis and surface modification of nanoparticles in molecular imaging probe design, with a focus on two widely used nanoparticles (UCNPs and MNPs). Additionally, the perspectives and challenges of nanoparticle-based probe in molecular imaging are discussed.

Structure of nanoparticle-based probe

To be usual, three parts compose the molecular imaging probes: signal agent, target agent, and linker (Fig. 2) (Ye et al. 2011; Reynolds and Kelly 2011). Generally, the spectrum of target agent can range from small molecules to macro molecules, such as peptides, proteins, antibodies, etc. The signal agent encompass radionuclides (for PET, SPECT), bioluminescence or fluorescent molecules (for optical imaging), magnetic molecules (for MRI) (Lee et al. 2012; Misri et al. 2012). And a linker is employed to bridge two agents mentioned above. Different types of linker are very important in molecular imaging (Cheng et al. 2005).

Signal agent

The best representative examples in molecular imaging are MNPs and UCNPs. MNPs are the most commonly used contrast agent in MRI on account of their positive/negative enhancement effect on T1/T2 sequences. UCNPs are a kind of nanoparticle which has quite distinctive upconversion properties. Upconversion refers to the processes in which two or more

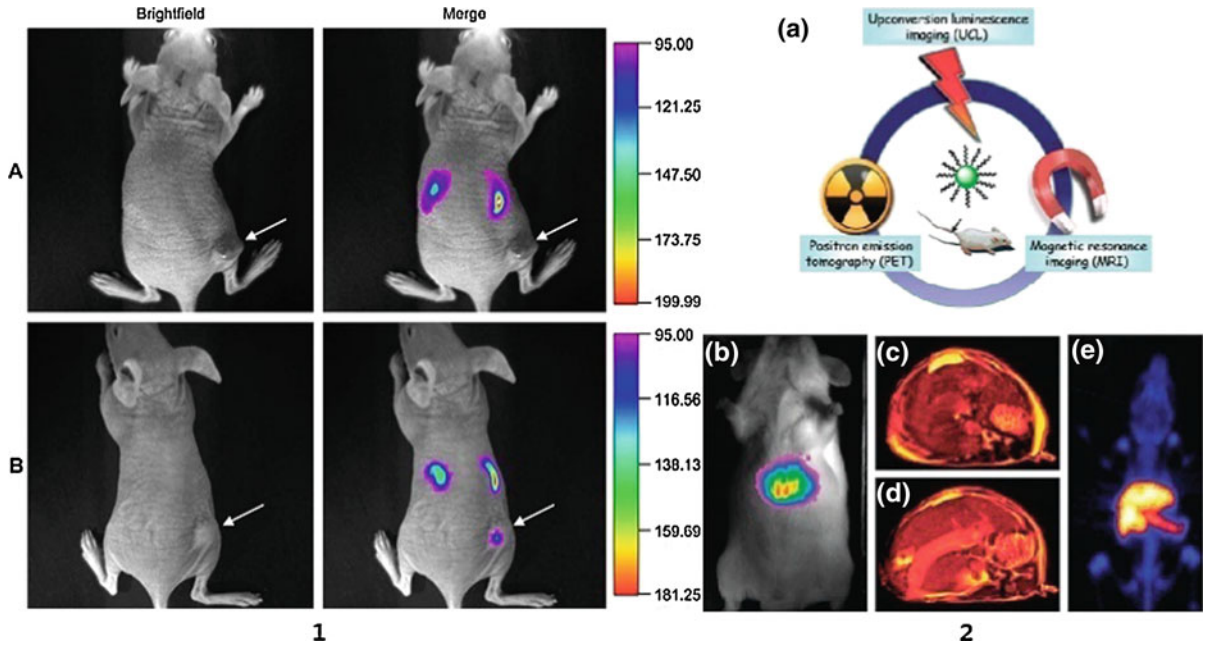

Fig. 1 *1* In vivo upconversion luminescence imaging of subcutaneous HeLa tumor-bearing athymic nude mice (*right* hind leg, pointed by *white arrows*) after intravenous injection of $UCNP\text{-}NH_2$ (**A**) and UCNPs-FA (**B**) (Xiong et al. 2009a). *2* (**a**) Scheme of a multimodal imaging probe. (**b**) UCL, (**c**, **d**) MRI and (**e**) PET (Liu et al. 2011a)

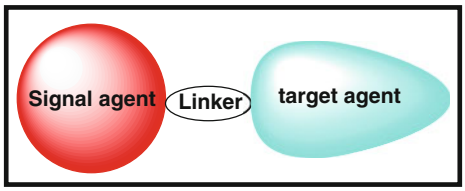

Fig. 2 Schematic illustration of general molecular probe

low-energy input photons converted to a higher-energy output photon. When excited continuously at 980 nm under laser, UCNPs presents unique UCL (upconversion luminescence) properties, such as sharp emission lines, long lifetimes, a large anti-stokes shift, etc.

Target agent

An ideal target agent should have specific high binding affinity and selectivity with a target receptor. Importantly, the binding affinity and selectivity should be retained or not be dramatically changed after conjugation with signal agent. And even more importantly, the binding affinity or selectivity can be improved by some different ways such as dimerization, multimerization etc.

Linker

As an essential part connecting signal agent and target agent, the structural type, length, hydrophilicity of a linker can frequently influence the receptor target conjugation. What's more, the multivalent effect of a linker in further conjugation should also be considered. In recent years, nanoparticle has been a hot signal platform due to its unique properties in probe design. Under such circumstances, linker has gotten great importance.

Synthesis of nanoparticle-based probe

Preparation of nanoparticle

Generally speaking, suitable size and good imaging performance of the nanoparticles are the primary precondition for molecular imaging (Fig. 3). To date, there are mainly three synthesis methods reported for the preparation of nanoparticles with proper size and high-quality imaging performance: the co-precipitation, hydro (solvo) thermal, and thermal decomposition.

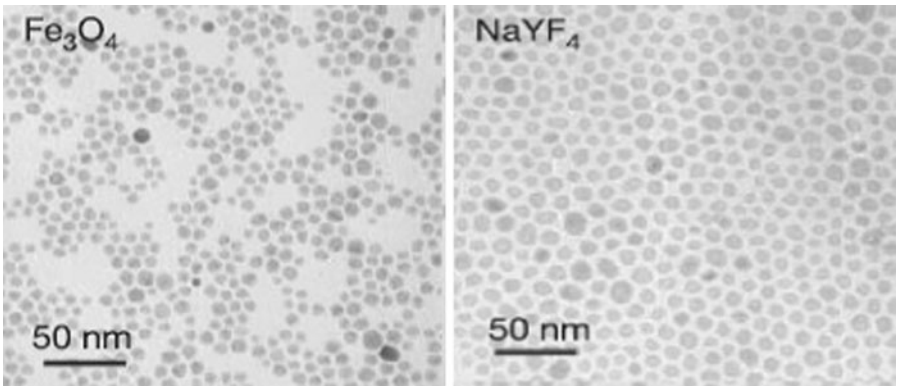

Fig. 3 Schematic illustration of nanoparticle (TEM)

Coprecipitation is a relatively easy and convenient method, which is based on the chemical reactions carried out in an aqueous medium. Taking the synthesis of MNPs as example, magnetic nanoparticles can be coprecipitated by adding a base into a solution of Fe(III) and Fe(II) salts. Furthermore, the stable MNPs can be synthesized in the presence of a proper coating agent. It doesn't need costly equipments, complex procedures, and harsh reactions (Mai et al. 2006). But it still has its own disadvantages, for example, it is difficult to obtain nanoparticles with uniform size using this method.

Hydro (solvo) thermal method is a typical solution-based nanoparticle synthesis method, which exploits a high temperature and pressure situation to increase the solubility and reactivity of inorganic particles. The advantages of this method include easy control of the reaction conditions, the relatively low cost, and high yield. By using this method, nanoparticles with uniform size can be prepared at mild temperatures. The shapes and sizes of nanopaticles can be well controlled by selecting different surfactants. In 2005, Wang introduced a general strategy for nanocrystal synthesis (Wang et al. 2005a, b). In a typical synthesis, the cocktail of noble metal salts solution, solvent, and surfactants were added to an autoclave tube under agitation. Then the reactions underwent for several hours at different temperature. When the autoclave was cooled down to room temperature, the products were collected at the bottom of the vessel. Based on the same synthesis process, the size of nanoparticle can be controlled between 10 and 100 nm.

Thermal decomposition is another common method to synthesize nanoparticles (Yi and Chow 2006; Boyer et al. 2007). For example, Fe^{3+} acetylacetonate or Ln^{3+} trifluoroacetates are decomposed in the presence of surfactants to prevent particles from aggregation (Boyer et al. 2007). Usually, the size of nanoparticle can also be well controlled using this method. However, the relatively harsh reaction conditions may be a major limit for its applications.

Surface modification of nanoparticle

Nanoparticle is typically prepared in the protection of coating materials to avoid aggregation. The surface coating of the nanoparticle can be achieved by using appropriate polymer or surfactants, e.g., poly (ethylene glycol) (PEG), dextran, carboxydextran, poly (vinyl alcohol) (PVA), polyethylenimine (PEI), oleic acid (OA), lauric acid etc.; or silane, precious metal, carbon, etc. (Butterworth et al. 2001; Sahoo et al. 2001; Berry et al. 2003; Chastellain et al. 2004; Sun et al. 2004; Lu et al. 2005; Briley-Saebo et al. 2006; Jeong et al. 2010; Liu et al. 2008, 2012; Chen et al. 2008; Cormode et al. 2009;). Surface coating materials such as polymers or surfactants are usually added during the formation of new surfaces to prevent nanoparticle from aggregation (Durán et al. 2008). Notably, the type of the surface coating materials not only determines the size of nanoparticle but also plays an important role in further biological imaging applications (Lu et al. 2007; Reddy et al. 2012).

Among different kinds of polymer coating materials (Fig. 4), PEG is the most widely used polymer for nanoparticle coating (Zhang and Ferrari 1998; Gref et al. 2000; Shang et al. 2006.) due to its impressive properties. In order to attach PEG to nanoparticle,

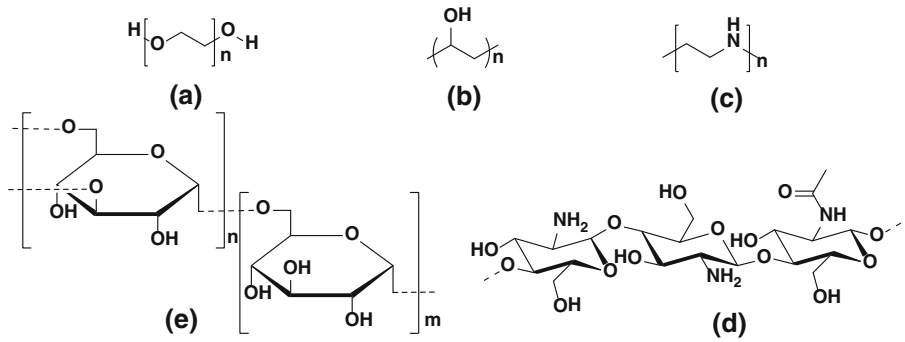

Fig. 4 Schematic illustration of polymer coating materials: PEG (**a**), PVA (**b**), PEI (**c**), chitosan (**d**), dextran (**e**)

various methods have been established, represented by nanoparticle polymerization (Lutz et al. 2006; Flesch et al. 2005), and the surface silane grafting (Butterworth et al. 2001; Zhang et al. 2002, 2004; Kohler et al. 2004; Veiseh et al. 2005; Larsen et al. 2009; Pilloni et al. 2010). Apart from PEG, the dextran was also been extensively exploited in nanoparticle surface coating for molecular imaging (Weissleder et al. 1995; Josephson et al. 1999; Corot et al. 2006). In order to lubricate further surface conjugation between target agent and nanoparticle, the dextran coat can be cross-amino-linker with the help of epichlohydrin and ammonia (Josephson et al. 1999; Schellenberger et al. 2002; Wunderbaldinger et al. 2002).

When taking into account of nanoparticle safety, biocompatibility, stability, and hydrophilicity, silane such as tetraethoxysilane is a good choice in nanoparticle coating (Lu et al. 2002; Tan et al. 2004; Tada et al. 2007; Bi et al. 2008; Sun et al. 2008). Precious metal (such as gold) could be used as surface coating material owing to its low reactivity. Moreover, gold surface can be modified with thiol groups for further conjugation (Colvin et al. 1992). However, disappointedly, such nanoparticle used in bioimaging should be hydrophilic, and some surface coating materials are instinctively hydrophobic (oleic acid). Therefore, much work still needs to be done in further modification on account of subsequent biological application.

A common approach to modify surface-coated nanoparticle is ligand engineering. It involves a ligand exchange reaction with hydrophilic materials or a direct oxidation of the terminal group. As an example, hydrophobic ligand-coated nanoparticle can be transformed into hydrophilic through ligand exchange reactions by a wide variety of hydrophilic agents such as 6-aminohexanoic acid (Meiser et al. 2004), hexanedioic acid (Zhang et al. 2007, 2009), citrate (Liu et al. 2010), polyacrylic acid (Naccache et al. 2009), and phosphate-derived molecules (Traina and Schwartz 2007). Apart from ligand engineering, ligand attraction, electrostatic layer-by-layer assembly, and surface polymerization can also fulfill the surface modification. Ligand attraction means attaching an amphiphilic ligand onto nanoparticle surface through the hydrophobic–hydrophobic interaction (Pedroni et al. 2011). Layer-by-layer assembly involves electrostatic attraction of oppositely charged ligand on the surface of nanoparticle (Wang et al. 2005a). Surface polymerization means growing a dense shell on the surface of nanoparticle with the help of auto-polymerize ligand (Sivakumar et al. 2006). A proper active functional group can provide easy access to nanoparticle for subsequent biological conjugation. Nevertheless, most nanoparticles lack functional groups after the hydrophilic modification. Therefore, an additional surface modification step to increase active functional group is required. The feasible solution here is connecting with a linker. Till now, many linkers have been designed and applied in the nanoparticle-based probe, and various linkers will be introduced as follows. Here, we divided linkers into several categories on the basis of their terminal functional group, such as carboxylic acid, amine, maleimide groups etc. (Zhou et al. 2012; Sapsford et al. 2013).

Carboxylic acid (–COOH) groups linker used in nanoparticle-based probe

Carboxylic acid group (–COOH) is especially useful for coupling with target agent like antibodies, folic acid, and DNA which contains $–NH_2$ groups (Fig. 5).

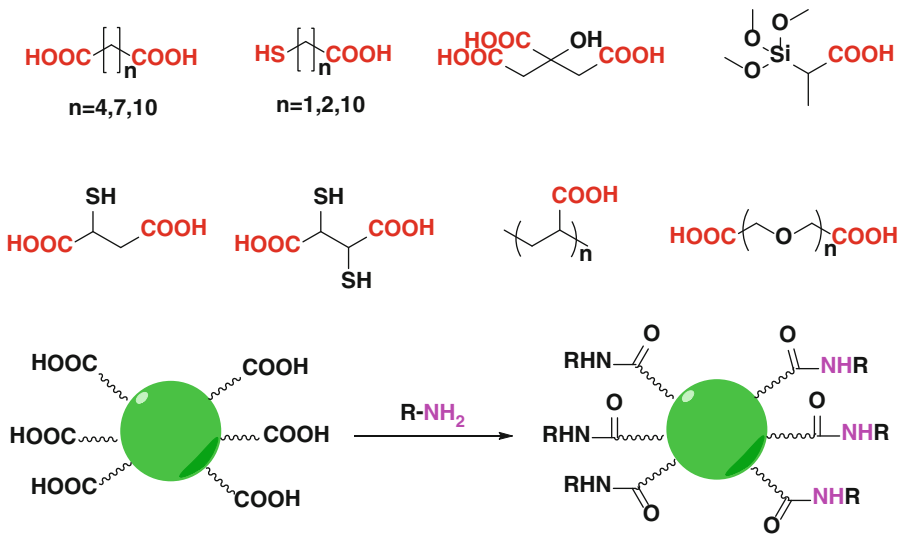

Fig. 5 Schematic illustration of carboxylic acid (–COOH) groups linker

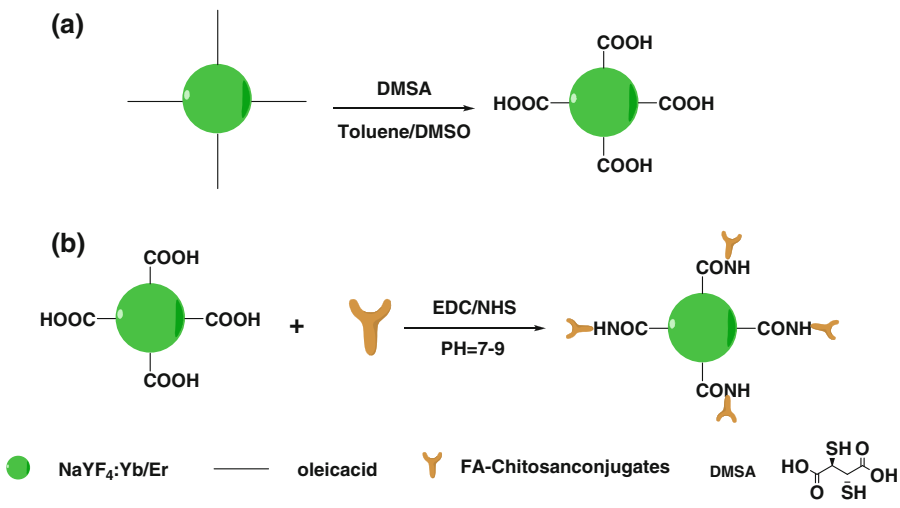

Fig. 6 Schematic illustration of modified nanoparticle

For example, Chen et al. (2011) reported the conjugation of dimercaptosuccinic acid (DMSA)-modified UCNP with folic acid-chitosan for targeted lung cancer imaging. The oleate-coated UCNPs were prepared according to solvothermal method just mentioned above. Surface modification of the as-synthesized $NaYF_4$: Yb/Er nanoparticle was carried out through ligand exchange with DMSA to afford the carboxyl group. The obtained DMSA-modified UCNP was separated by centrifugation and was finally redispersed in deionized water. The DMSA-modified UCNPs with folic acid-chitosan were demonstrated to be low cytotoxicity. Further biological evaluation showed a good targeted performance in H460 lung cancer imaging (Fig. 6).

Another research group developed a multifunctional nanoparticle-probe for imaging. The PEGylated PLGA-modified magnetic nanoparticles, conjugated with therapeutic drugs such as herceptin or Dox, have demonstrated ultrasensitive targeted performance and excellent synergistic effects in vitro and in vivo (Yang et al. 2007) (Fig. 7). Kumar and Zhang (2009) reported a new design of DNA biosensor by using upconversion nanoparticle ($NaYF_4$: Yb^{3+}, Tm^{3+}) as donor and dye (SYBR Green I) as acceptor. The test principle of detection was considered to be luminescence resonance energy transfer. The DTPA-modified UCNP exhibited good hydrophilic property and can attach to single-stranded DNA (ssDNA) probe perfectly with the help of EDC. Then DTPA-UCNP-

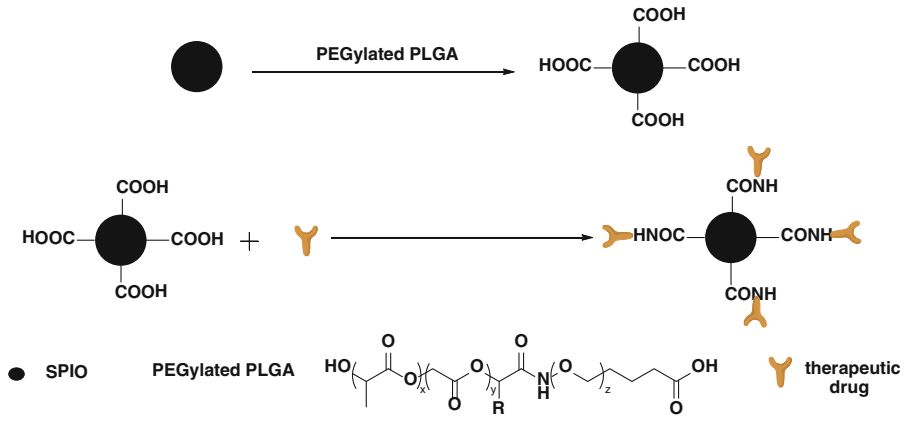

Fig. 7 Scheme illustration of modified nanoparticles

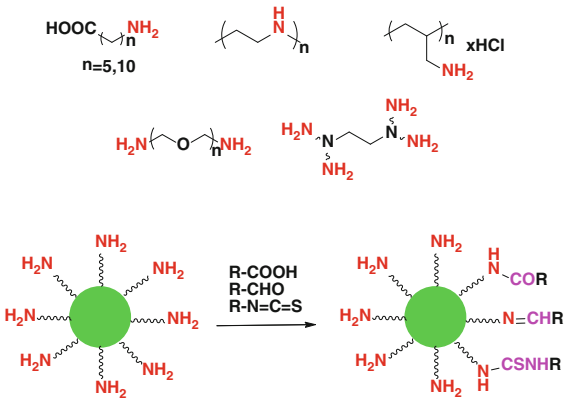

Fig. 8 Schematic illustration of Amine ($-NH_2$) groups linker

ssDNA probe and SYBR Green I were both present in the same solution. The quantum yield of SYBR Green I was rather low unless DTPA-UCNP-ssDNA probe met target DNA. Later, Liu et al. (2011a) modified UCNP with carboxylic acid groups by using poly (acrylic acid) (PAA) for further conjugation with ssDNA. Such amino groups on ssDNA were attached to the UCNP surface successfully with EDC/NHS-assisted standard procedures.

Amino ($-NH_2$) groups linker used in nanoparticle-based probe

As an important functional group in bioconjugation, $-NH_2$ group is present in many ligands coated on the surface of nanoparticle, such as PEI, diamino PEG, PAMAM, etc. Inspiringly, the $-NH_2$ group is particularly suitable for conjugation with target agent containing –COOH groups such as antibodies, folic acid, peptides, DNA, etc., (Fig. 8).

Generally, nanoparticles (NP) with silane shell can be easily amino-modified on the surface, which is facilitated by silane coupling agent, like 3-aminopropyltrimethoxysilane (APTES). Lu et al. (2004) reported a method of preparing streptavidin-nanoparticle probe with optical and magnetic properties. The nanoparticle composites were firstly synthesized and modified with silane like TEOS. Subsequently, the nanoparticle composites were covalently coupled with streptavidin via an APS-glutaraldehyde linker. A series of experiments have confirmed that streptavidin was conjugated successfully with the nanoparticle composites. In 2005, Veiseh et al. (2005) introduced a dual-modality nanoparticle-probe for targeting gliomas. APTES–PEG–NH_2 was used to provide amine group. The nanoparticle-probe was synthesized by covalently binding SPIO with APTES–PEG–NH_2, which was subsequently conjugated with chlorotoxin (CTX) and the NIR dye Cy5.5. The dual-modality nanoparticle-probe showed preferential targeting abilities and high stability in gliomas imaging (Fig. 9).

Wang and Li (2006) adopted a novel green upconversion nanoparticle for DNA detection. As is shown in Fig. 10, both magnetic particle and upconversion nanoparticle were amino-modified by polyelectrolyte using layer-by-layer technology (Hong et al. 2004). The conjugation of the modified nanoparticle with nucleic acids was achieved according to the reported method (Abe et al. 2003). The modified UCNP showed many excellent properties such as low background, photostability, and chemical stability.

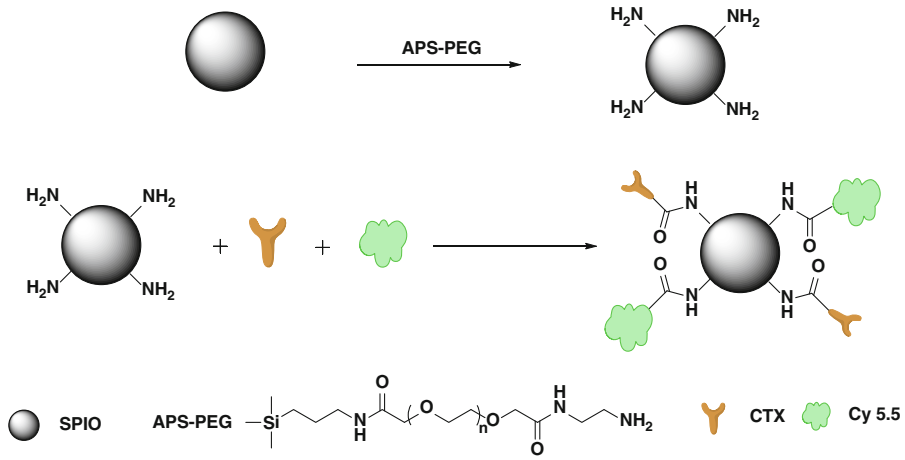

Fig. 9 Schematic illustration of modified SPIO

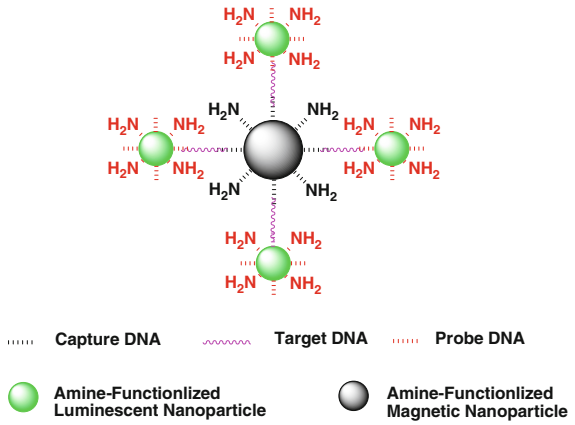

Fig. 10 Scheme illustration of the preparation of the DNA detector

These excellent properties of probe together hold the promise of observing molecular interactions and transportation in living cells.

Chatterjee et al. (2008) reported the polyethylene-amine(PEI)-modified UCNP ($NaYF_4$: Yb^{3+}, Er^{3+}) in vitro imaging of cancer cells and in vivo imaging in tissues. In order to equip nanoparticle with targeted performance, folic acid was conjugated to the PEI-modified UCNP ($NaYF_4$: Yb^{3+}, Er^{3+}). The imaging experiment in vitro and in vivo clearly showed that modified UCNP was stable, nontoxic, and resistant to photobleaching and of good targeting property. This is the first time that UCNP was applied as a signal agent in small animal imaging. Yu et al. (2010) reported a preparation of CTX: UCNP probe using a PEI linker. As is shown in Fig. 11, the PEI-modified UCNP with amino groups on the surface and CTX peptide with carboxyl groups were cross-linked using a standard protocol. After the conjugation between UCNP and CTX, the fluorescence properties of UCNP does not change too much, and the resulting CTX: UCNP nanoparticle probe was stable for several days when dispersed in aqueous solution.

The amino-modified nanoparticle can also react with agents containing –CHO or S=C=N groups for further conjugation. Bogdan et al. (2010) used PAMAM-modified UCNP for lectin recognition. PAMAM served as an amino linker in nanoparticle conjugation. PAMAM-UCNP was synthesized by a ligand-exchange reaction between UCNP ($NaGdF_4$:Er^{3+}, Yb^{3+}) and PAMAM. And at the last of their article, they introduced that the UCNP was successfully modified with both hydrophilic PAMAM and mannose to get hydrophilic nanoparticle with high biocompatibility and excellent optical properties (Fig. 12).

Maleimide (MA) groups linker used in nanoparticle-based probe

It is well known that thiol is a common group in many biomolecules such as peptides. So linker with MA groups, which can react quantitatively with thiol during the conjugation, is quite influential (Fig. 13).

Amine-modified nanoparticle usually can be transformed into maleimide-modified ones by reacting with a bifunctional linker. Xiong et al. (2009a) reported a bifunctional linker to convert amine-modified UCNP

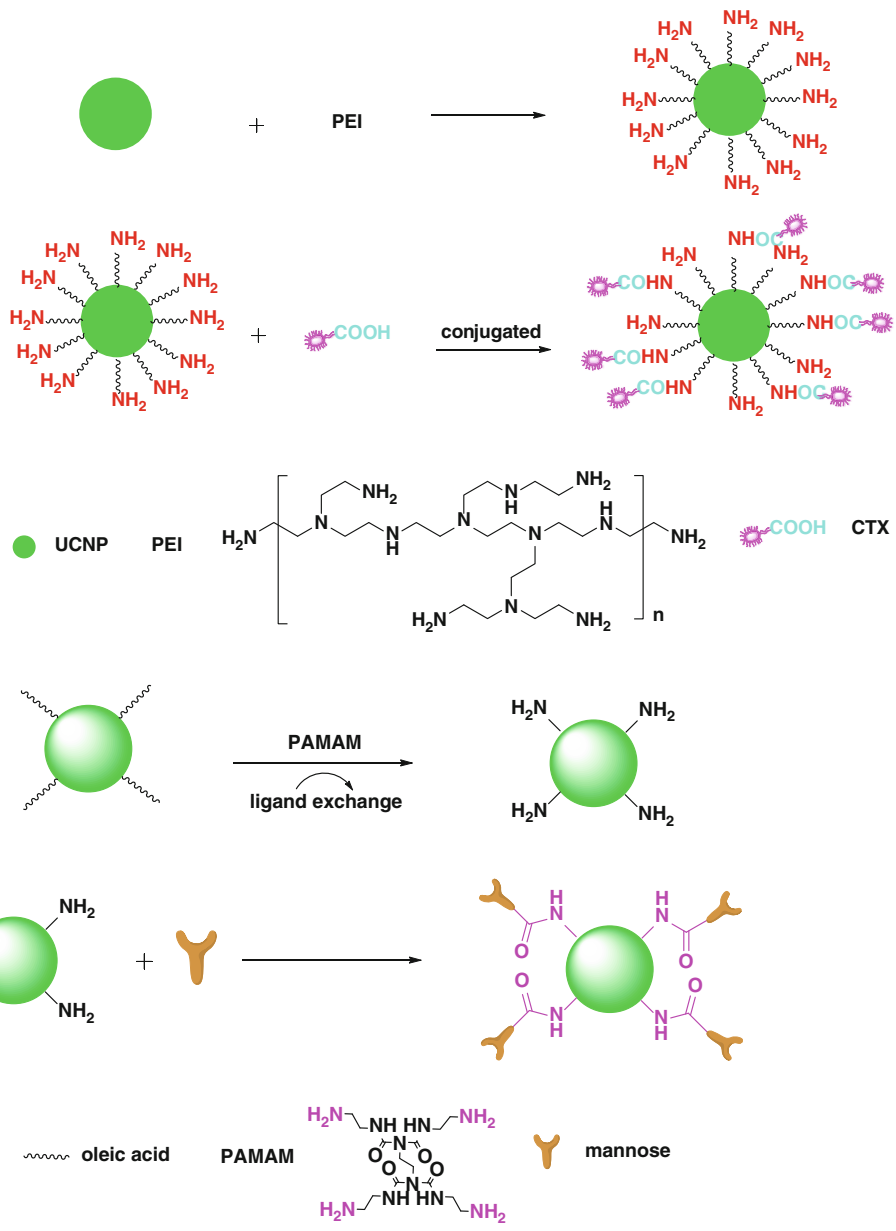

Fig. 11 Schematic illustration of the preparation of CTX: UCNP nanoparticle-probe

Fig. 12 Schematic illustration of preparation of PAMAM–UCNP

to maleimide-modified equivalents. Subsequently, the c(RGDFK) with thiol was conjugated with UCNP for targeted imaging through maleimide groups' linker. By the use of the EDC/NHS-assisted standard procedure, PEG was attached to the surface of UCNP. UCNP–PEG–NH_2 was further conjugated to a bifunctional linker, 6-maleimidohexanoic acid *N*-hydroxysuccinimide ester. Thiolated c (RGDFK) was attached to maleimide-modified nanoparticle to afford RGD-conjugated UCNP. The RGD-conjugated UCNP could be well dispersed in both hydrophilic solvents and hydrophobic solvent due to the presence of linker. The imaging experiments in vitro and in vivo showed that maleimide-modified nanoparticle had a nice coupling activity with the target agent (Fig. 14).

Ryu et al. (2010) reported that the conjugation of Ni-nitrilotriacetate (NiNTA) and UCNP ($NaGdF_4$: Yb^{3+}, Er^{3+}, Tm^{3+}) was achieved by a bifunctional linker,

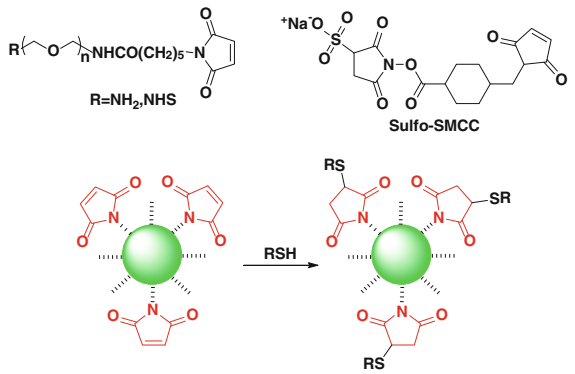

Fig. 13 Schematic illustration of maleimide (MA) groups linker

sulfosuccinimidyl 4-(*N*-maleimidomethyl) cyclohexane-1-carboxylate (sulfo-SMCC). It was found that both the hydrophobic and hydrophilic UCNP showed excellent upconverting and magnetic properties in the optical and MRI. These results indicated that the surface modification of UCNP was successful. Additionally, sulfo-SMCC has also showed its potential as a surface modification linker for the design of nanoparticle-based probe (Fig. 15).

Other groups linker used in nanoparticle-based probe

In 2009, Huang et al. (2009) reported a one-step method to conjugate a lung cancer-targeting peptide with SPIO. In order to connect the SPIO surface with the targeting-peptide, a PEG linker with thiol was attached to the peptide. In this way, a cysteine residue was disposed at the C-terminus of the peptide. And then, the modified peptide was able to attach to the as-synthesized SPIO through direct ligand exchange. The Prussian blue staining and MRI both confirmed that nanoparticle-probe targeted the $\alpha v\beta_3$ over expressed in human H2009 cancer cells nicely (Fig. 16).

In addition to the linkers noted above, there are also some other groups linkers used in nanoparticle-based probe (Veiseh et al. 2010; Erathodiyil and Ying 2011) (Fig. 15). Hayashi et al. (2009) innovatively introduced "click-chemistry" as a universal method into nanoparticle surface modification. With this method applied, azides can be developed as another type of linker for the conjugation of nanoparticle with target agents. A case in point, Fe_3O_4 nanoparticle was converted to azide-modified Fe_3O_4 nanoparticle through a series of surface modifications (Hayashi et al. 2010; Liu et al. 2011a, b). Finally, alkyne-bound folic acid was clicked onto the Fe_3O_4 nanoparticle surface with a high yield.

Biological characteristics of nanoparticle-based probe

As potential imaging agents, the toxicity of modified nanoparticles has been investigated with reference to in vitro cytotoxic activity and long-term living toxicity. Numerous studies have already suggested that modified nanoparticles have a low immediate toxicity when used within a certain range of concentrations and within a limited incubation period (Gupta and Curtis

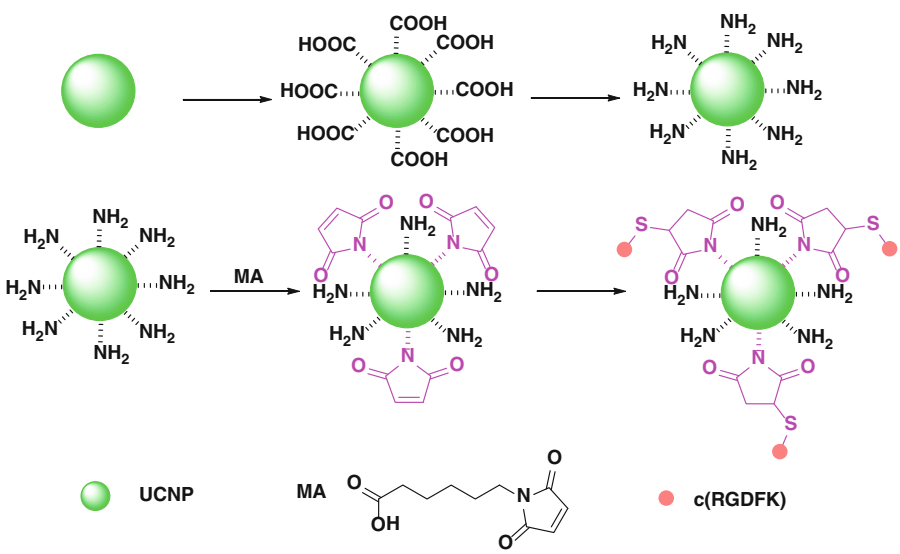

Fig. 14 Schematic illustration of the preparation of RGD–UCNP

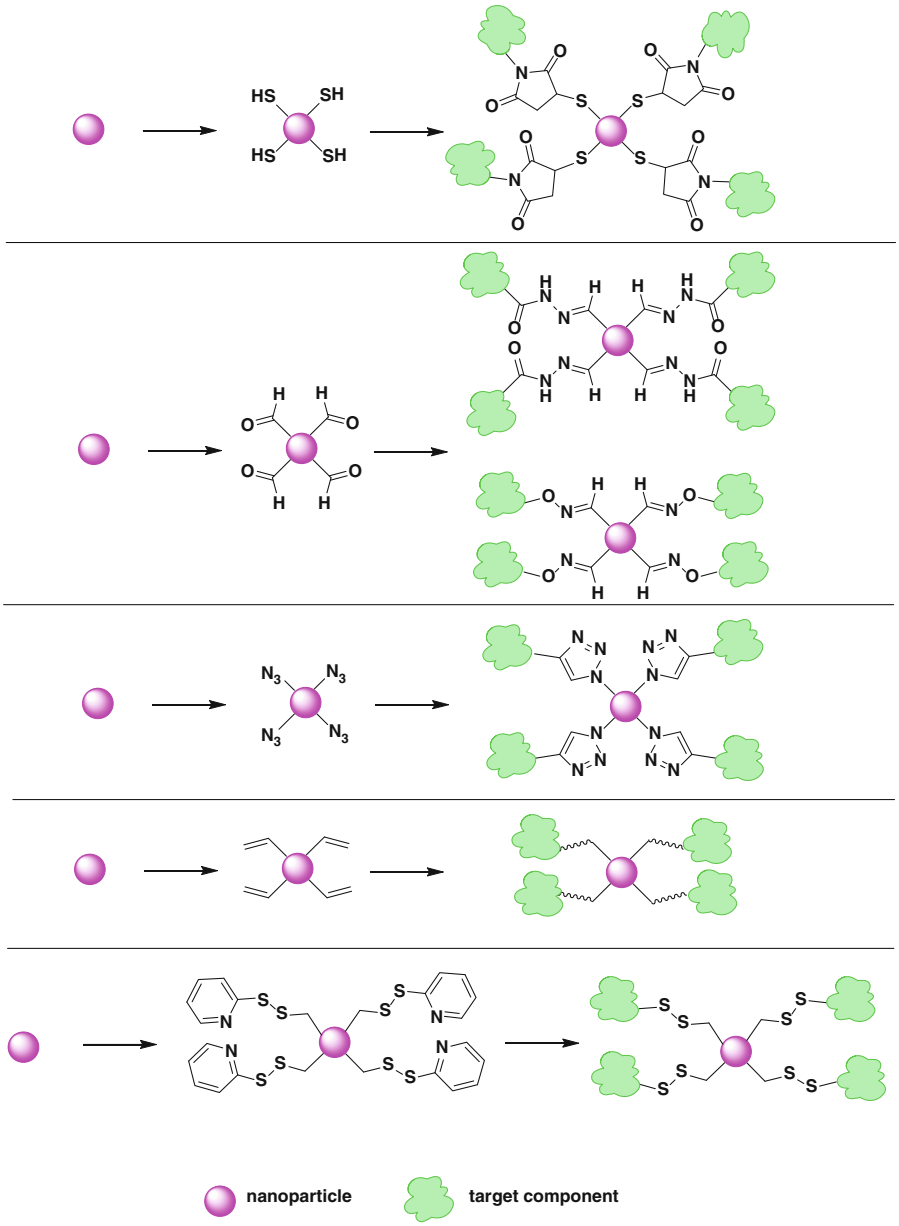

Fig. 15 Schematic illustration of other groups linker

2004; Nam et al. 2011; Chen et al. 2011; Zhou et al. 2012). The solubility and biocompatibility of modified nanoparticles in biological media also affect the efficiency of nanoparticles in the applications of molecular imaging. Numerous studies have been done to evaluate the changes of solubility and biocompatibility before and after the surface modification. To be sure, with the help of proper modifications, the solubility and biocompatibility have been markedly improved (Gupta and Curtis 2004; Xiong et al. 2009a; Reddy et al. 2012). However, few evaluations have been discussed about the details of solubility and biocompatibility in biologically environment by different modifications. Therefore, further understanding of the surface modification is needed.

To be sure, with the help of proper modifications, the solubility and biocompatibility have been markedly improved. Numerous studies have been done to

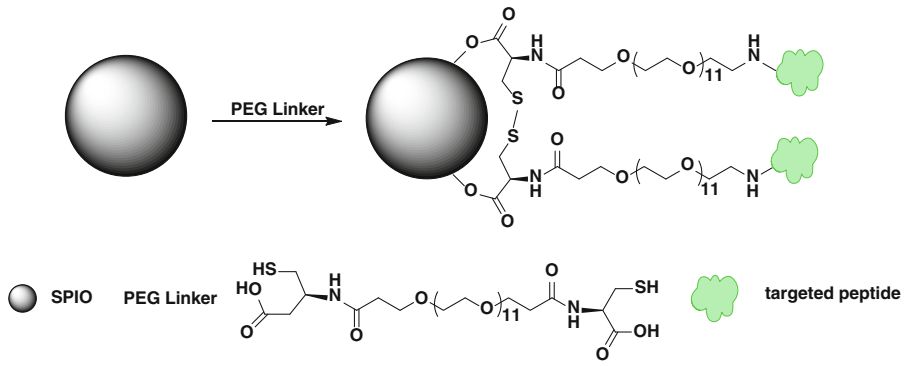

Fig. 16 Schematic illustration of modified SPIO

evaluate the changes of solubility and biocompatibility before and after the surface modification. The details can be found in the following references (Gupta and Curtis 2004; Nyk et al. 2008; Kobayashi et al. 2009; Xiong et al. 2009a; Wang et al. 2010; Reddy et al. 2012; Zhou et al. 2012).

Conclusion and perspective

Over the past decades, nanoparticle-based probes have attracted a great deal of interest. As signal agent, many kinds of nanoparticles like ferric oxide particles have been extensively studied in vitro and in vivo for several years. And the surface modifications of nanoparticle have completely changed molecular imaging field. It makes that carrying-out nanoparticles with unique properties in bioimaging become possible. In this review, the surface modification of how nanoparticle assembles to molecular imaging probe has been discussed. Particularly and intensively, two kinds of nanoparticle used in wide range within molecular imaging field were discussed in this paper. On the other hand, chemistry has demonstrated its power in preparing nanoparticle-based probes with controlled size, shape, morphology, and surface modifications. However, surface modifications sometimes could compromise some advantages of nanoparticle. For example, after the surface modification transfer nanoparticle from hydrophobic to hydrophilic, the magnetic/optical signal would probably decrease, or the potential long-term toxicity may change. That means much more time is needed devoting to further research.

Taken together, the design of molecular imaging probe has always been an exciting field filled with both challenges and opportunities. Medical research from bench to bed has been tremendously influenced by the efforts and achievements made in this scope. Moreover, with the development of nanotechnology, continuous discoveries of new types of nanoparticle or new technology, coupled with their application in surface modification, will undoubtedly help to improve the clinical treatment. As for the nanoparticle-based probe design, though lots of accomplishments have been made over the past decades, it is clear that there are still many problems remained to be solved. The safety, biocompatibility, stability, and targeting performance in vitro and in vivo all need to be addressed by a suitable surface modification approach. We expect that such challenges could help us a better understanding of nanoparticle application in molecular imaging.

Acknowledgments We are grateful to the National Natural Science Foundation of China (30900377, 81271634, 81371690, 81000596), New Century Excellent Talents Project (NCET-10-0800), the Fundamental Research Funds for the Central Universities, and Hunan Provincial Natural Science Foundation of China (12JJ1012).

References

Abe M, Lai J, Kortylewicz ZP, Nagata H, Fox IJ, Enke CA, Baranowska-Kortylewicz J (2003) Radiolabeled constructs for evaluation of the asialoglycoprotein receptor status and hepatic functional reserves. Bioconjug Chem 14(5):997–1006

Alivisatos AP (1996) Semiconductor clusters, nanocrystals, and quantum dots. Science 271(5251):933

Bai C, Liu M (2013) From chemistry to nanoscience: not just a matter of size. Angew Chem Int Ed Engl 52(10):2678–2683

Berry CC, Wells S, Charles S, Curtis AS (2003) Dextran and albumin derivatised iron oxide nanoparticles: influence on fibroblasts in vitro. Biomaterials 24(25):4551–4557

Bi S, Wei X, Li N, Lei Z (2008) In-situ formation of Fe_3O_4 nanoparticles within the thermosensitive hairy hybrid particles. Mater Lett 62(17–18):2963–2966

Bogdan N, Vetrone F, Roy R, Capobianco JA (2010) Carbohydrate-coated lanthanide-doped upconverting nanoparticles for lectin recognition. J Mater Chem 20(35):7543–7550

Boyer JC, Cuccia LA, Capobianco JA (2007) Synthesis of colloidal upconverting NaYF4: Er3 +/Yb3 + and Tm3 +/Yb3 + monodisperse nanocrystals. Nano Lett 7(3):847–852

Briley-Saebo KC, Johansson LO, Hustvedt SO, Haaldorsen AG, Bjørnerud A, Fayad ZA, Ahlstrom HK (2006) Clearance of iron oxide particles in rat liver: effect of hydrated particle size and coating material on liver metabolism. Invest Radiol 41(7):560–571

Butterworth MD, Illum L, Davis SS (2001) Preparation of ultrafine silica- and PEG-coated magnetite particles. Colloids Surf 179(1):93–102

Cai W, Chen X (2007) Nanoplatfoms for targeted molecular imaging in living subjects. Small 3(11):1840–1854

Cai W, Chen X (2008) Multimodality molecular imaging of tumor angiogenesis. J Nucl Med 49(6):113S–128S

Chastellain M, Petri A, Gupta A, Rao KV, Hofmann H (2004) Superparamagnetic silica-iron oxide nanocomposites for application in hyperthermia. Adv Eng Mater 6(4):235–241

Chatterjee DK, Rufaihah AJ, Zhang Y (2008) Upconversion fluorescence imaging of cells and small animals using lanthanide doped nanocrystals. Biomaterials 29(7):937–943

Chen Z, Chen H, Hu H, Yu M, Li F, Zhang Q, Zhou Z, Yi T, Huang C (2008) Versatile synthesis strategy for carboxylic acid-functionalized upconverting nanophosphors as biological labels. J Am Chem Soc 130(10):3023–3029

Chen Q, Wang X, Chen F, Zhang Q, Dong B, Yang H, Liu G, Zhu Y (2011) Functionalization of upconverted luminescent $NaYF_4$: Yb/Er nanocrystals by folic acid-chitosan conjugates for targeted lung cancer cell imaging. J Mater Chem 21(21):7661–7667

Cheng Z, Wu Y, Xiong Z, Gambhir SS, Chen X (2005) Near-infrared fluorescent RGD peptides for optical imaging of integrin alphavbeta3 expression in living mice. Bioconjug Chem 16(6):1433–1441

Choi HS, Frangioni JV (2010) Nanoparticles for biomedical imaging: fundamentals of clinical translation. Mol Imaging 9(6):291–310

Colvin VL, Goldstein AN, Alivisatos AP (1992) Semiconductor nanocrystals covalently bound to metal surface with self-assembled monolayers. J Am Chem Soc 114(13):5221–5230

Cormode DP, Skajaa T, Fayad ZA, Mulder WJ (2009) Nanotechnology in medical imaging: probe design and applications. Arterioscler Thromb Vasc Biol 29(7):992–1000

Corot C, Robert P, Idée JM, Port M (2006) Recent advances in iron oxide nanocrystal technology for medical imaging. Adv Drug Deliv Rev 58(14):1471–1504

Durán JD, Arias JL, Gallardo V, Delgado AV (2008) Magnetic colloids as drug vehicles. J Pharm Sci 97(8):2948–2983

Dutta RK, Sharma PK, Pandey AC (2010) Design and surface modification of potential luminomagnetic nanocarriers for biomedical application. J Nanopart Res 12(4):1211–1219

Erathodiyil N, Ying JY (2011) Functionalization of inorganic nanoparticles for bioimaging applications. Acc Chem Res 44(10):925–935

Flesch C, Unterfinger Y, Bourgeat-Lami E, Duguet E, Delaite C, Dumas P (2005) Poly(ethylene glycol) surface coated magnetic particles. Macromol Rapid Commun 26(18):1494–1498

Gref R, Lück M, Quellec P, Marchand M, Dellacherie E, Harnisch S, Blunk T, Müller RH (2000) 'Stealth' corona-core nanoparticles surface modified by polyethylene glycol (PEG): influences of the corona (PEG chain length and surface density) and of the core composition on phagocytic uptake and plasma protein adsorption. Colloids Surf B 18(3–4):301–313

Gu Y, Huang D, Liu Z, Huang J, Zeng W (2011) Labeling strategies with F-18 for positron emission tomography imaging. Med Chem 7(5):334–344

Gupta AK, Curtis AS (2004) Surface modified superparamagnetic nanoparticles for drug delivery: interaction studies with human fibroblasts in culture. J Mater Sci Mater Med 15(4):493–496

Hayashi K, Moriya M, Sakamoto W, Yogo T (2009) Chemoselective synthesis of folic acid-functionalized magnetite nanoparticles via click chemistry for magnetic hyperthermia. Chem Mater 21(7):1318–1325

Hayashi K, Ono K, Suzuki H, Sawada M, Moriya M, Sakamoto W, Yogo T (2010) One-pot biofunctionalization of magnetic nanoparticles via thiol-ene click reaction for magnetic hyperthermia and magnetic resonance imaging. Chem Mater 22(12):3768–3772

Hazer DB, Hazer B (2011) The effect of gold clusters on the autoxidation of poly (3-hydroxy 10-undecenoate-co-3-hydroxy octanoate) and tissue response evaluation. J Polym Res 18(2):251–262

Hazer DB, Hazer B, Dincer N (2011) Soft tissue response to the presence of polypropylene-G-poly(ethylene glycol) comb-type graft copolymers containing gold nanoparticles. J Biomed Biotechnol. doi:10.1155/2011/956169.2011:956169

Hazer DB, Mut M, Dincer N, Saribas Z, Hazer B, Ozgen T (2012) The efficacy of silver-embedded polypropylene-grafted polyethylene glycol-coated ventricular catheters on prevention of shunt catheter infection in rats. Childs Nerv Syst 28(6):839–846

He J, Van Brocklin HF, Franc BL, Seo Y, Jones EF (2008) Nanoprobes for medical diagnosis: current status of nanotechnology in molecular imaging. Curr Nanosci 4(1):17–29

Hellebust A, Richards-Kortum R (2012) Advances in molecular imaging: targeted optical contrast agents for cancer diagnostics. Nanomedicine 7(3):429–445

Hong X, Li J, Wang M, Xu J, Guo W, Li J, Bai Y, Li T (2004) Fabrication of magnetic luminescent nanocomposites by a layer-by-layer self-assembly approach. Chem Mater 16(21):4022–4027

Huang G, Zhang C, Li S, Khemtong C, Yang SG, Tian R, Minna JD, Brown KC, Gao J (2009) A novel strategy for surface modification of superparamagnetic iron oxide nanoparticles for lung cancer imaging. J Mater Chem 19(35):6367–6372

Jeon SL, Chae MK, Jang EJ, Lee C (2013) Cleaved iron oxide nanoparticles as T2 contrast agents for magnetic resonance imaging. Chemistry 19(13):4217–4222

Jeong J, Lee CS, Chung SJ, Chung BH (2010) Enhanced immobilization of hexa-arginine-tagged esterase on gold

nanoparticles using mixed self-assembled monolayers. Bioprocess Biosyst Eng 1(33):165–169
Josephson L, Tung CH, Moore A, Weissleder R (1999) High-efficiency intracellular magnetic labeling with novel superparamagnetic-tat peptide conjugates. Bioconjug Chem 10(2):186–191
Kalayci ÖA, Cömert FB, Hazer B, Atalay T, Cavicchi KA, Cakmak M (2010) Synthesis, characterization, and antibacterial activity of metal nanoparticles embedded into amphiphilic combe-type graft copolymers. Polym Bull 65(3):215–226
Kalayci ÖA, Duygulu O, Hazer B (2013) Optical characterization of CdS nanoparticles embedded into the comb-type amphiphilic graft copolymer. J Nanopart Res. doi:10.1007/s11051-012-1355-x
Kobayashi H, Kosaka N, Ogawa M, Morgan NY, Smith PD, Murray CB, Ye X, Collins J, Kumar GA, Bell H, Choyke PL (2009) In vivo multiple color lymphatic imaging using upconverting nanocrystal. J Mater Chem 19(36):6481–6484
Kohler N, Fryxell GE, Zhang M (2004) A bifunctional poly(ethylene glycol) silane immobilized on metallic oxide-based nanoparticles for conjugation with cell targeting agents. J Am Chem Soc 126(23):7206–7211
Kumar M, Zhang P (2009) Highly sensitive and selective label-free optical detection of DNA hybridization based on photon upconverting nanoparticles. Langmuir 25(11): 6024–6027
Ladj R, Bitar A, Eissa M, Mugnier Y, Le Dantec R, Fessi H, Elaissari A (2013) Individual inorganic nanoparticles: preparation, functionalization and in vitro biomedical diagnostic applications. J Mater Chem B 1(10):1381–1396
Larsen EK, Nielsen T, Wittenborn T, Birkedal H, Vorup-Jensen T, Jakobsen MH, Ostergaard L, Horsman MR, Besenbacher F, Howard KA, Kjems J (2009) Size-dependent accumulation of PEGylated silane-coated magnetic iron oxide nanoparticles in murine tumors. ACS Nano 3(7):1947–1951
Lee DE, Koo H, Sun IC, Ryu JH, Kim K, Kwon IC (2012) Multifunctional nanoparticles for multimodal imaging and theragnosis. Chem Soc Rev 41(7):2656–2672
Li N, Binder BH (2011) Click-chemistry for nanoparticle-modification. J Mater Chem 21(42):16717–16734
Li F, Li C, Liu X, Chen Y, Bai T, Wang L, Shi Z, Feng S (2012) Hydrophilic, upconverting, multicolor, lanthanide-doped NaGdF4 nanocrystals as potential multifunctional bioprobes. Chemistry 18(37):11641–11646
Licha K, Resch-Genger U (2011) Probes for optical imaging: new developments. Drug Discov Today 8(2–4):e87–e94
Liu D, Gu N (2012) Nanoparticle probes and molecular imaging in cancer. In: Srirajaskanthan R (ed) Nanomedicine and cancer. Science Publishers, New York, pp 105–122
Liu TY, Hu SH, Liu KH, Liu DM, Chen SY (2008) Study on controlled drug permeation of magnetic-sensitive ferrogels: effects of Fe_3O_4 and PVA. J Control Release 126(3):228–236
Liu Q, Li C, Yang T, Yi T, Li F (2010) "Drawing" upconversion nanophosphors into water through host-guest interaction. Chem Commun 46(30):5551–5553
Liu C, Wang Z, Jia H, Li Z (2011a) Efficient fluorescence resonance energy transfer between upconversion nanophosphors and grapheme oxide: a highly sensitive biosensing platform. Chem Commun 47(16):4661–4663
Liu Q, Sun Y, Li C, Zhou J, Li C, Yang T, Zhang X, Yi T, Wu D, Li F (2011b) 18F-Labeled magnetic-upconversion nanophosphors via rare-Earth cation-assisted ligand assembly. ACS Nano 5(4):3146–3157
Lodhia J, Mandarano G, Ferris Nj, Eu P, Cowell S (2010) Development and use of iron oxide nanoparticles (part 1): synthesis of iron oxide nanoparticles for MRI. Biomed Imaging Interv J 6(2):e12
Lu Y, Yin Y, Mayers BT, Xia Y (2002) Modifying the surface properties of superparamagnetic iron oxide nanoparticles through a sol–gel approach. Nano Lett 2(3):183–186
Lu H, Yi G, Zhao S, Chen D, Guo LH, Cheng J (2004) Synthesis and characterization of multi-functional nanoparticles possessing magnetic, up-conversion fluorescence and bio-affinity properties. J Mater Chem 14(8):1336–1341
Lu AH, Li WC, Matoussevitch N, Spliethoff B, Bönnemann H, Schüth F (2005) Highly stable carbon-protected cobalt nanoparticles and graphite shell. Chem Commun 1:98–100
Lu AH, Salabas EL, Schüth F (2007) Magnetic nanoparticles: synthesis, protection, functionalization, and application. Angew Chem Int Ed Engl 46(8):1222–1244
Lutz JF, Stiller S, Hoth A, Kaufner L, Pison U, Cartier R (2006) One-pot synthesis of pegylated ultrasmall iron-oxide nanoparticles and their in vivo evaluation as magnetic resonance imaging contrast agents. Biomacromolecules 7(11):3132–3138
Mai HX, Zhang YW, Si R, Yan ZG, Sun LD, You LP, Yan CH (2006) High-quality sodium rare-earth fluoride nanocrystals: controlled synthesis and optical properties. J Am Chem Soc 128(19):6426–6436
Meiser F, Cortez C, Caruso F (2004) Biofunctionalization of fluorescent rare-earth-doped lanthanum phosphate colloidal nanoparticles. Angew Chem Int Ed Engl 43(44):5954–5957
Minchin RF, Martin DJ (2010) Minireview: nanoparticles for molecular imaging—an overview. Endocrinology 151(2): 474–481
Misri R, Saatchi K, Häfeli UO (2012) Nanoprobes for hybrid SPECT/MR molecular imaging. Nanomed 7(5):719–733
Mohanpuria P, Rana NK, Yadav SK (2008) Biosynthesis of nanoparticles: technological concepts. J Nanopart Res 10(3):507–517
Naccache R, Vetrone F, Mahalingam V (2009) Controlled synthesis and water dispersibility of hexagonal phase $NaGdF_3$: Ho^{3+}/Yb^{3+} nanoparticles. Chem Mater 21(4):717–723
Nam SH, Bae YM, Park YI, Kim JH, Choi JS, Lee KT, Hyeon T, Suh YD (2011) Long-term real-time tracking of lanthanide ion doped upconverting nanoparticles in living cells. Angew Chem Int Ed Engl 50(27):6093–6097
Nyk M, Kumar R, Ohulchanskyy TY, Bergey EJ, Prasad PN (2008) High contrast in vitro and in vivo photoluminescence bioimaging using near infrared to near infrared upconversion in Tm3+ and Yb3+ doped fluoride nanophosphors. Nano Lett 8(11):3834–3838
Pedroni M, Piccinelli F, Passuello T, Giarola M, Mariotto G, Polizzi S, Bettinelli M, Speghini A (2011) Lanthanide doped upconverting colloidal CaF_2 nanoparticles preparation by a single-step hydrothermal method: toward efficient materials with near infrared-to-near infrared upconversion emission. Nanoscale 3(4):1456–1460
Pilloni M, Nicolas J, Marsaud V, Bouchemal K, Frongia F, Scano A, Ennas G, Dubernet C (2010) PEGylation and

preliminary biocompatibility evaluation of magnetite-silica nanocomposites obtained by high energy milling. Int J Pharm 401(1–2):103–112

Reddy LH, Arias JL, Nicolas J, Couvreur P (2012) Magnetic nanoparticles: design and characterization, toxicity and biocompatibility, pharmaceutical and biomedical applications. Chem Rev 112(11):5818–5878

Reynolds F, Kelly KA (2011) Techniques for molecular imaging probe design. Mol Imaging 10(6):407–419

Rosenblum LT, Kosaka N, Mitsunaga M, Choyke PL, Kobayashi H (2010) In vivo molecular imaging using nanomaterials: general in vivo characteristics of nano-sized reagents and application for cancer diagnosis. Mole Membr Biol 27(7):274–285

Ryu J, Park HY, Kim K, Kim H, Yoo JH, Kang M, Im K, Grailhe R, Song R (2010) Facile synthesis of ultrasmall and hexagonal NaGdF4: Yb3+, Er3+ nanoparticles with magnetic and upconversion imaging properties. J Phys Chem C 114(49):21077–21082

Sahoo Y, Pizem H, Fried T, Golodnitsky BL, Sukenik CN, Markovich G (2001) Alkyl phosphonate/phosphate coating on magnetite nanoparticles: a comparison with fatty acids. Langmuir 17(25):7907–7911

Sapsford KE, Algar WR, Berti L, Gemmill KB, Casey BJ, Oh E, Stewart MH, Medintz IL (2013) Functionalizing nanoparticles with biological molecules: developing chemistries that facilitate nanotechnology. Chem Rev 113(3):1904–2074

Schellenberger EA, Bogdanov A Jr, Högemann D, Tait J, Weissleder R, Josephson L (2002) Annexin V-CLIO: a nanoparticle for detecting apoptosis by MRI. Mol Imaging 1(2):102–107

Shang H, Chang WS, Kan S, Majetich SA, Lee GU (2006) Synthesis and characterization of paramagnetic microparticles through emulsion-templated free radical polymerization. Langmuir 22(6):2516–2522

Sivakumar S, Diamente PR, van Veggel FC (2006) Silica-coated Ln^{3+}-doped LaF_3 nanoparticles as robust down- and upconverting biolabels. Chemistry 12(22):5878–5884

Sun S, Zeng H, Robinson DB, Raoux S, Rice PM, Wang SX, Li G (2004) Monodisperse MFe2O4 (M=Fe, Co, Mn) nanoparticles. J Am Chem Soc 126(1):273–279

Sun C, Lee JS, Zhang M (2008) Magnetic nanoparticles in MR imaging and drug delivery. Adv Drug Deliv Rev 60(11): 1252–1265

Swierczewska M, Lee S, Chen X (2011) Inorganic nanoparticles for multimodal molecular imaging. Mol Imaging 10(1): 3–16

Tada DB, Vono LL, Duarte EL, Itri R, Kiyohara PK, Baptista MS, Rossi LM (2007) Methylene blue-containing silica-coated magnetic particles: a potential magnetic carrier for photodynamic therapy. Langmuir 23(15):8194–8199

Tan W, Wang K, He X, Zhao XJ, Drake T, Wang L, Bagwe RP (2004) Bionanotechnology based on silica nanoparticles. Med Res Rev 24(5):621–638

Traina CA, Schwartz J (2007) Surface modification of Y_2O_3 nanoparticles. Langmuir 23(18):9158–9161

Veiseh O, Gunn JW, Zhang M (2010) Design and fabrication of magnetic nanoparticles for targeted drug delivery and imaging. Adv Drug Deliv Rev 62(3):284–304

Veiseh O, Sun C, Gunn J, Kohler N, Gabikian P, Lee D, Bhattarai N, Ellenbogen R, Sze R, Hallahan A, Olson J, Zhang M (2005) Optical and MRI multifunctional nanoprobe for targeting gliomas. Nano Lett 5(6):1003–1008

Wang L, Li Y (2006) Green upconversion nanocrystals for DNA detection. Chem Commun 24:2557–2559

Wang X, Zhuang J, Peng Q, Li Y (2005a) A general strategy for nanocrystal synthesis. Nature 437:121–124

Wang L, Yan R, Huo Z, Wang L, Zeng J, Bao J, Wang X, Peng Q, Li Y (2005b) Fluorescence resonant energy transfer biosensor based on upconversion-luminescent nanoparticles. Angew Chem Int Ed Engl 44(37):6054–6057

Wang F, Banerjee D, Liu Y, Chen X, Liu X (2010) Upconversion nanoparticles in biological labeling, imaging, and therapy. Analyst 135(8):1839–1854

Weissleder R, Bogdanov A, Neuwelt EA, Papisov M (1995) Long-circulating iron oxides for MR imaging. Adv Drug Deliv Rev 16(2–3):321–334

Wunderbaldinger P, Josephson L, Weissleder R (2002) Tat peptide directs enhanced clearance and hepatic permeability of magnetic nanoparticles. Bioconjug Chem 13(2): 264–268

Xie J, Liu G, Eden HS, Ai H, Chen X (2011) Surface-engineered magnetic nanoparticle platforms for cancer imaging and therapy. Acc Chem Res 44(10):883–892

Xiong L, Chen Z, Tian Q, Cao T, Xu C, Li F (2009a) High contrast upconversion luminescence targeted imaging in vivo using peptide-labeled nanophosphors. Anal Chem 81(21):8687–8694

Xiong LQ, Chen ZG, Yu MX, Li FY, Liu C, Huang CH (2009b) Synthesis, characterization, and in vivo targeted imaging of amine-functionalized rare-earth up-converting nanophosphors. Biomaterials 30(29):5592–5600

Yang J, Lee CH, Ko HJ, Suh JS, Yoon HG, Lee K, Huh YM, Haam S (2007) Multifunctional magneto-polymeric nanohybrids for targeted detection and synergistic therapeutic effects on breast cancer. Angew Chem Int Ed Engl 46(46):8836–8839

Ye Y, Chen X (2011) Integrin targeting for tumor optical imaging. Theranostics 1:102–126

Ye F, Qin J, Toprak MS, Muhammed M (2011) Multifunctional core-shell nanoparticles: superparamagnetic, mesoporous, and thermosensitive. J Nanopart Res 13(11):6157–6167

Yi GS, Chow GM (2006) Synthesis of hexagonal-phase $NaYF_4$: Yb, Er and NaYF4: Yb, Tm nanocrystals with efficient upconversion fluorescence. Adv Funct Mater 16(18):2324–2329

Yu XF, Sun Z, Li M, Xiang Y, Wang QQ, Tang F, Wu Y, Cao Z, Li W (2010) Neurotoxin-conjugated upconversion nanoprobes for direct visualization of tumor under near-infrared irradiation. Biomaterials 31(33):8724–8731

Zeng W, Miao W (2009) Development of small molecular probes for the molecular imaging of apoptosis. Anticancer Agents Med Chem 9(9):986–995

Zhang M, Ferrari M (1998) Hemocompatible polyethylene glycol films on silicon. Biomed Microdevices 1(1):81–89

Zhang Y, Kohler N, Zhang M (2002) Surface modification of superparamagnetic magnetic nanoparticles and their intracellular uptake. Biomaterials 23(7):1553–1561

Zhang Y, Sun C, Kohler N, Zhang M (2004) Self-assembled coating on individual monodisperse magnetite nanoparticle for efficient intracellular uptake. Biomed Microdevices 6(1):33–40

Zhang T, Ge J, Hu Y, Yin Y (2007) A general approach for transferring hydrophobic nanocrystals into water. Nano Lett 7(10):3203–3207

Zhang Q, Song K, Zhao J, Kong X, Sun Y, Liu X, Zhang Y, Zeng Q, Zhang H (2009) Hexanedioic acid mediated surface-ligand-exchange process for transferring $NaYF_4$: Yb/Er (or Yb/Tm) upconverting nanoparticles from hydrophobic to hydrophilic. J Colloid Interface 336(1):171–175

Zhou J, Liu Z, Li F (2012) Upconversion nanophosphors for small-animal imaging. Chem Soc Rev 41(3):1323–1349