Invited Perspective

In a “nutshell”: intrinsically radio-labeled quantum dots

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Abstract: Quantum dots (QDs) have many intriguing properties suitable for biomedical imaging applications. The poor tissue penetration of optical imaging in general, including those using QDs, has motivated the development of various QD-based dual-modality imaging agents. In this issue of AJNMMI (http://www.ajnmmi.us), Sun et al. reported the synthesis and in vitro/in vivo characterization of intrinsically radio-labeled QDs (r-QDs), where $^{109}$Cd was incorporated into the core/shell of QDs of various compositions. These r-QDs emit in the near-infrared range, have long circulation half-life, are quite stable with low cytotoxicity, exhibit small size and low accumulation in the reticuloendothelial system, and can allow for accurate measurement of their biodistribution in mice. With these desirable features demonstrated in this study, future development and optimization will further enhance the biomedical potential of intrinsically radio-labeled QDs.

Keywords: Quantum-dots (QDs), nanoparticle, positron emission tomography (PET), single-photon emission computed tomography (SPECT), near-infrared (NIR), optical imaging

The first decade of the 21st century has witnessed an explosion of biomedical research based on various nanomaterials, which hold tremendous potential to revolutionize disease diagnosis and treatment [1-3]. In the second decade of this century, clinical translation is the key in this vibrant research area and it is expected that nanotechnology will advance into clinical trials and eventually the day-to-day clinical practice in the near future. In this blooming nanotechnology arena, one of the most extensively studied classes of nanomaterials is quantum dots (QDs) [4, 5]. Due to the many intriguing properties that are more advantageous than traditional organic dyes, QDs are desirable fluorophores for biomedical imaging applications. Since the first demonstration of the biomedical potential of QDs in 1998 [6, 7], QD-based research has increased exponentially and QDs have become powerful tools in an array of research disciplines such as molecular biology, cell biology, molecular imaging, and medical diagnostics. For imaging applications, QDs have been investigated in a wide variety of scenarios in both cells and live animals. Aside from applications based on non-specific distribution/accumulation of QDs such as vasculature imaging, lymph node mapping, etc. [4, 5, 8], active tumor targeting using QD-based probes has also been achieved by several research groups [9-13].

One of the major limitations for optical imaging in general is poor tissue penetration, even in the relatively optically clear near-infrared (NIR, 700-900 nm) window [14-16]. Since magnetic resonance imaging (MRI) has no limit in tissue penetration, a wide variety of QD-based dual-modality agents have been reported for both optical imaging and MRI [17, 18]. However, the very low sensitivity of MRI severely limits the potential applications of these QD-based dual-modality agents. Furthermore, whether combination of optical imaging and MRI is a desirable approach is questionable, since neither imaging technique is highly quantitative. On the other hand, radionuclide-based imaging techniques, such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET) [19, 20], are very sensitive and highly quantitative with virtually no limit in tissue penetration. Clinically, PET/SPECT imaging has been widely used in oncology for cancer staging and monitoring the therapeutic re-
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 spurred [20-26]. Clearly, combination of QD-based optical imaging and SPECT/PET can offer synergistic advantages over either modality alone.

In this issue of the American Journal of Nuclear Medicine and Molecular Imaging, Sun et al. reported a novel approach to synthesize intrinsically radio-labeled QDs (r-QDs), which can allow for accurate quantitation of their biodistribution in mice through measurement of the radioactivity signal (Figure 1) [27]. In this work, the radioactive nuclide of cadmium (i.e. $^{109}$Cd) was incorporated into the core/shell of QDs of various core compositions such as CdSe and CdTeSe. The significance of this intriguing study lies in several aspects. First, NIR r-QDs were synthesized which is suitable for in vivo imaging applications. The peak emission of the NIR r-QDs generated in this report was at about 780 nm and within the most optimal wavelength range for in vivo imaging, where the combined absorbance of all biomolecules in living tissues is at the minimum. In addition, these NIR r-QDs are very bright, with quantum yields of 40% and 11% in chloroform and aqueous solution (after ligand exchange to render water solubility) respectively.

Second, these r-QDs have very long circulation half-life in mice (~20 h) because of the surface functionalization with zwitterionic ligands (Figure 1). In most literature reports, polyethylene glycol (PEG) was used for the coating of QDs, which indeed was able to increase the circulation lifetime of the resulting QDs [28]. However, PEG chains of molecular weight above 5,000 Da are typically needed to observe prolonged circulation half-life in mice as QDs coated with 2,000 Da PEG chains only exhibited very short circulation lifetime on the order of minutes [29]. Similar phenomenon was also observed in this study: PEG-coated r-QDs had a circulation half-life of a few minutes, which is several orders of magnitude shorter than the r-QDs coated with small zwitterionic ligands [27]. Through future engineering and exploration of the zwitterionic ligands, it is expected that the circulation half-life of these r-QDs can be adjusted to match specific applications. For in vivo imaging applications, circulation half-life in the range of a few hours is perhaps most desirable. Another advantage resulted from the use of small zwitterionic ligands is that the hydrodynamic size of functionalized QDs is significantly smaller than the PEG-coated r-QDs, which may lead to better extravasation from the vasculature and improve the targeting efficacy in future studies.

Third, the biodistribution of these r-QDs can be accurately and quantitatively measured because of the radioactive signal, which would not have been possible with optical imaging. Since the radioisotope $^{109}$Cd is inside the r-QDs (i.e. within the shell) instead of on the surface, in vivo stability of the radio-label is quite good. The commonly used approach to generate QD-based dual-modality agents for optical and PET/SEPCT imaging applications is through direct/indirect labeling of QDs with radioisotopes [29-35]. However, the stability of the radio-label in living animals is not very high. For example, a few hours after intravenous injection of $^{64}$Cu-labeled NIR QDs into mice, the PET and NIR fluorescence imaging data were in good agreement with each other [30, 32]. However, distribution of $^{64}$Cu (measured by PET) and the QDs (detected by optical imaging) was substantially different at late time points. Incorporation of the radio-label inside the r-QDs eliminated the concerns regarding in vivo stability of the radio-label relative to the QDs, since it has been well documented that QDs do not undergo significant degradation unless they are subjected to very harsh condi-

Figure 1. $^{109}$Cd-containing quantum dots coated with zwitterionic ligands.
functionalized Cd125mTe/ZnS QDs with the re-

between vascular targeting and interaction of

reported) [41]. Subsequently, the competition

SPECT imaging (no optical imaging was re-

was evaluated with biodistribution studies and

lung endothelium, where the targeting efficacy

was demonstrated by the

Antigen-specific uptake of antibody-conjugated

ZnS QDs were used for targeting the mouse

Reticuloendothelial system was investigated [42].

Lower accumulation in these organs/tissues is undoubtedly

due to the presence of reticuloendothelial system, and can enable accurate meas-

urement of their biodistribution in mice, it is

expected that more interesting studies in this

area will continue to emerge in the near future. For SPECT imaging, different

isotopes that emit different energy gamma rays can be differentiated based on the energy [43].

Since QDs are ideal agents for multiplexed fluores-

cence imaging [44], combination of the mul-

tiplexing capabilities of both SPECT and QDs can enable the interrogation of a number of biological events simultaneously using molecu-

larly-targeted r-QDs, which should be explored in the future.

The recent trend for generating more biocom-

patible NIR QDs is in the use of other less toxic materials such as InAs and InP [45, 46], which can alleviate the concerns regarding the long term toxicity of Cd, Se, and Te. Incorporation of radionuclides of these more biocompatible elements should be investigated in future work. For example, 111In has been widely used for SPECT imaging and arsenic isotopes (e.g. 72As and 74As) have been reported for PET imaging [47]. It is likely that we will see reports on r-QDs that contain clinically relevant radionuclides in the near future, such as 111In-containing r-QDs.

Although the efficiency of incorporating 109Cd into the shell of these r-QDs is almost 100%, the total radioactivity injected into each mouse was only about 1 µCi in this study [27]. Thanks to the high sensitivity of gamma counting, such a low level of radioactivity was sufficient for accu-

rate quantification of the biodistribution of r-

QDs in mice. Much more radioactivity will need to be injected into each mouse for in vivo imaging. Since SPECT has significantly lower sensitiv-

ity than PET [48], it will be more desirable to incorporate PET isotopes into future generations of r-QDs if feasible. Lastly, the decay half-life of 109Cd is 464 days, which is too long for biomedi-

cal applications. Future incorporation of other radioisotopes with suitable half-lives on the or-

der of several hours to a few days is preferred. Given the proof-of-principle demonstrated in

this study for generating r-QDs that emit in the NIR range, have long circulation half-life, are quite stable with low cytotoxicity, exhibit small size and low accumulation in the reticuloendo-

thelial system, and can enable accurate measure-

ment of their biodistribution in mice, it is expected that more interesting studies in this

area will continue to emerge in the near future.

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References


