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The potential clinical impact of quantum dots

“Transition of Qdot nanotechnology from bench to bedside would not happen in the near future until in vivo Qdot cytotoxicity is mitigated completely and Qdots are cleared from the body within an acceptable time period, similar to other clinically approved in vivo image contrast agents.”

KEYWORDS: bioimaging ■ drug delivery ■ fluorescence ■ nanomedicine ■ quantum dot

A decade-long story on quantum dot nanotech-enabled bioimaging

Luminescent quantum dots (Qdots), by virtue of their unique optical and electronic properties, have been extensively studied in biological systems as robust bioimaging and sensing probes [1–3]. Qdots represent a class of semiconductor nanocrystals with a size typically ranging between 1.5 nm and 12 nm [1–3]. Qdots are fluorescently bright and extremely photostable and, unlike traditional organic fluorescent dyes, they exhibit broad excitation and size-tunable luminescence properties. With increasing particle size, the band gap energy (i.e., the energy gap between the valence band and the conduction band) of Qdots decreases, resulting in the increase of emission wavelength. This unique optical property enables multiplexed imaging of biological specimens (e.g., cells and tissue samples) using Qdots of different sizes and by using a single excitation source. Furthermore, real-time live cell imaging with high resolution, once considered to be practically challenging and next to impossible using traditional fluorescent dyes, has been possible because of the photostability and high quantum efficiency of Qdots. Over the past decade, extensive studies have been conducted in the bioimaging area demonstrating successful applications of Qdot nanotechnology in cancer imaging and stem cell tracking both *in vitro* and *in vivo* [1–3].

In the past few years, extensive research has been carried out in Qdot engineering, including:

- Design of core/shell Qdots
- Development of synthesis techniques for growing high-quality Qdots

- Surface modification of Qdots for interfacing inorganic Qdots with organic ligands/biomolecules [1–3]

Appropriate selection of the semiconductor core and shell material is critical for achieving bright and photostable Qdots. Typically, an epitaxially matched wide band-gap shell material (including ZnS and ZnSe) is selected to passivate the Qdot core (including CdSe, CdS and InP). A high-temperature (usually above 200°C) synthesis technique is preferred for growing high-quality crystals. The synthesis technique typically involves the use of a high-boiling point coordinating solvent mixture to control Qdot nucleation and growth processes. For example, a combination of trioctylphosphine and trioctylphosphine oxide (TOPO) has been widely used, where the TOPO serves as a capping agent. Material scientists and chemists have immensely contributed to this area to produce high-quality Qdots covering a broad spectrum of emission (wavelengths ranging from UV/visible to near infrared [NIR]/infrared).

Qdots, as synthesized, are highly hydrophobic and, therefore, surface modification with suitable ligands is essential for the successful implementation of Qdot nanotechnology in bioimaging and biosensing applications. Over the years, a variety of surface-modifying agents such as thiolated small organic ligands (e.g., mercapto acetic acid, dihydrolipoic acid and *N*-acetyl cysteine), amphiphilic polymers, phospholipids and silica have been used for coating Qdots. These agents solubilize Qdots in water, minimize particle–particle interaction, improve Qdot biocompatibility and, in some cases, provide hydrophilic surface functional groups for further surface conjugation. Thiolated ligands bind to the Qdot surface via ligand exchange, whereas amphiphilic polymers interact with

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hydrophobically modified Qdots via hydrophobic–hydrophobic interaction. Studies have shown that amphiphilic polymer-coated Qdots are very stable, resistant to photobleaching and generally do not lose brightness. However, the overall Qdot size increases due to polymer coating. Over the past few years, much research has been done in developing different surface modification strategies for Qdots. However, batch-to-batch reproducibility of surface-modified Qdots is still not good enough due to inherent complexity in the entire chemical synthesis and surface fabrication processes involving a number of chemical components.

Current state of the art in Qdot nanotechnology: pushing the limits of *in vivo* imaging

To date, major research progress in Qdot nanotechnology has been made in the areas of live cell imaging, detection of tumor cells, biomarker detection and imaging of excised tumor tissues [1–3]. In recent years, a steady growth in research activities has been seen in developing Qdot-based theranostic nanoparticles [2,4–9]. A typical theranostic nanoparticle design includes adaptation of a multifunctional platform capable of performing disease diagnosis (via imaging) and therapy [10]. Similarly, a multifunctional theranostic Qdot design would involve Qdot surface modifications using more than one type of ligand, where each type of surface-bound ligand would have specific functionality (targetability or capability of carrying therapeutic payloads). *In vivo* cancer imaging, specifically imaging of solid tumors, and delivery of therapeutic payloads to tumor tissue in a targeted manner using theranostic Qdots is an active research area in nanomedicine. Studies have demonstrated that Qdot nanotechnology could facilitate image-guided tumor surgery as well as reliably imaging sentinel lymph nodes.

“The Qdot surface, when modified with a combination of polyethylene glycol and a cancer cell targeting agent, is shown to minimize nonselective binding to normal tissue as well as improve overall dispersibility of Qdots in physiological condition.”

Cytotoxicity of Qdots [1,2,9,11,12] is associated with the presence of constituent toxic heavy metal ions such as cadmium, lead and arsenic. Qdots are blamed for generating reactive oxygen species (ROS; e.g., hydroxyl radicals, super oxides and singlet oxygen species [1]) when exposed to an excitation source. These ROS are

responsible for causing cytotoxicity. It is desirable that Qdots are appropriately surface modified, which would allow selective binding of Qdots to tumor but not to normal tissue. The Qdot surface, when modified with a combination of polyethylene glycol and a cancer cell targeting agent, is shown to minimize nonselective binding to normal tissue, as well as improve overall dispersibility of Qdots in physiological condition [1]. Qdot surface modification technology is not robust enough to avoid nontargeted binding of Qdots, hence there is always a risk of damaging normal cells. Overall biocompatibility of Qdots will largely depend on the surface-coating material. Both Qdot size and surface coating are expected to influence Qdot pharmacokinetics as well as the *in vivo* clearance mechanism. Due to the complexity of the surface chemistry, as well as the lack of long-term research data confirming successful clearance of Qdots, safety remains a major concern for *in vivo* applications of Qdot nanotechnology [1,2,9,11,12].

Future perspective: the potential clinical impact

Major challenges in cancer nanotechnology include early cancer diagnostics, tracking tumor metastasis, imaging tumor angiogenesis, tracking intracellular delivery of therapeutic drugs and monitoring tumor therapy [2]. Multifunctional theranostic Qdots could certainly have tremendous potential to address some of these pressing challenges in the near future [1,13]. Selection of biocompatible surface-coating agents, which are capable of preventing the release of toxic heavy metals from the inorganic core of Qdots, as well as capable of minimizing ROS generation *in vivo*, is highly desirable. Design and fabrication of noncadmium or non-heavy metal- (e.g., ZnSe/ZnS, ZnS:Mn/ZnS) based Qdots could serve as an attractive alternative. Unfortunately, these Qdots may suffer from inherent limitations as they do not have the desirable optical properties (e.g., excitation at a longer wavelength) for *in vivo* imaging. For deep-tissue imaging applications, it is highly desirable to use NIR absorbing and NIR-emitting Qdots [14]. Due to reduced light scattering in the NIR wavelength range and minimal absorption of NIR energy by the tissue constituents (e.g., water and hemoglobin), NIR-emitting Qdots are suitable for *in vivo* imaging and sensing applications [14]. Unfortunately, most of the NIR-emitting Qdots developed to date are relatively large in size, possessing moderate to low quantum efficiency, and containing toxic heavy metal ions (including CdTe and PbS).

Transition of Qdot nanotechnology from bench to bedside would not happen in the near future until *in vivo* Qdot cytotoxicity is mitigated completely and Qdots are cleared from the body within an acceptable time period, similar to other clinically approved *in vivo* image contrast agents.

Conclusion

Qdot nanotechnology has established a strong niche in bioimaging, labeling and sensing. Qdots, due to their unique optical and electronic properties, will continue to find new applications in the area of disease diagnostics. Sensitive detection of disease-specific biomarkers in clinical samples such as blood/serum samples and excised tissue samples, as well as detecting circulating tumor cells will remain an active area of research for some time [6–8,15]. Qdot-based biosensing is an active research area. In this direction, research involving the design and fabrication of novel activatable Qdots (e.g., ‘off/on’ Qdots or fluorescence resonance energy transfer-based Qdots) for sensitive detection of intracellular drug release, tracking functional activity of intracellular biomolecules (e.g., RNAs, proteins and enzymes, among others) and quantification of the amount of therapeutic drug uptake will continue to expand [10,16]. Development of multifunctional Qdots that are imageable, targetable and capable of carrying therapeutic payloads into cancer cells will also continue to expand in the near future [1,4,10].

Due to heavy metal-induced cytotoxicity issues, *in vivo* applications of Qdot nanotechnology will, for now, be restricted primarily to small animal imaging [12,17]. In cancer management, some of the most pressing challenges are:

- Efficient delivery of anticancer drugs to tumors

- Monitoring cancer therapy
- Tracking tumor metastasis
- Early detection of angiogenesis (formation of new blood vessels, indicative of tumor progression)

Qdot-based multifunctional theranostic probes [1,4,10] powered by multimodality imaging (i.e., imaging with more than one modality, such as MRI and fluorescence – dual imaging) could potentially revolutionize Qdot research in the field of nanomedicine.

The application of heavy metal-containing Qdots as imaging, sensing or theranostic probes in human subjects is highly unlikely at this time. It is extremely challenging to study the long-term fate of Qdots in model animal systems that could potentially mimic heavy metal-associated toxicity in human subjects. There is still hope that further research could lead to the design and fabrication of biocompatible, non-immunogenic, ultra-small size (<5.0 nm; comparable to the size of protein molecules) Qdots that would be excreted through a renal clearance mechanism [1].

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References

Papers of special note have been highlighted as:

■ of considerable interest

- 1 Wang YQ, Chen LX. Quantum dots, lighting up the research and development of nanomedicine. *Nanomedicine* 7(4), 385–402 (2011).
- 2 Cinteza LO. Quantum dots in biomedical applications: advances and challenges. *J. Nanophoton.* 4, 042503 (2010).
- 3 Medintz IL, Uyeda HT, Goldman ER, Mattoussi H. Quantum dot bioconjugates for imaging, labelling and sensing. *Nat. Mater.* 4(6), 435–446 (2005).
- 4 Jokerst JV, Gambhir SS. Molecular imaging with theranostic nanoparticles. *Acc. Chem. Res.* 44(10), 1050–1060 (2011).
- 5 Zhang H, Yee D, Wang C. Quantum dots for cancer diagnosis and therapy: biological and clinical perspectives. *Nanomedicine (Lond.)* 3(1), 83–91 (2008).
- 6 Medintz IL, Mattoussi H, Clapp AR. Potential clinical applications of quantum dots. *Int. J. Nanomedicine* 3(2), 151–167 (2008).
- 7 Sahoo SK, Parveen S, Panda JJ. The present and future of nanotechnology in human health care. *Nanomedicine* 3(1), 20–31 (2007).
- 8 Jain KK. Applications of nanobiotechnology in clinical diagnostics. *Clin. Chem.* 53(11), 2002–2009 (2007).
- 9 Azzazy HME, Mansour MMH, Kazinierczak SC. From diagnostics to therapy: prospects of quantum dots. *Clin. Biochem.* 40(13–14), 917–927 (2007).
- 10 Mitra RN, Doshi M, Zhang XL *et al.* An activatable multimodal/multifunctional nanoprobe for direct imaging of intracellular drug delivery. *Biomaterials* 33(5), 1500–1508 (2012).

- 11 Hauck TS, Anderson RE, Fischer HC, Newbigging S, Chan WCW. *In vivo* quantum-dot toxicity assessment. *Small* 6(1), 138–144 (2010).
- 12 Rzigalinski BA, Strobl JS. Cadmium-containing nanoparticles: perspectives on pharmacology and toxicology of quantum dots. *Toxicol. Appl. Pharmacol.* 238(3), 280–288 (2009).
- 13 Luo GP, Long J, Zhang B *et al.* Quantum dots in cancer therapy. *Expert Opin. Drug Deliv.* 9(1), 47–58 (2012).
- 14 Altinoglu EI, Adair JH. Near infrared imaging with nanoparticles. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* 2(5), 461–477 (2010).
- 15 Morrow KJ, Bawa R, Wei CM. Recent advances in basic and clinical nanomedicine. *Med. Clin. North Am.* 91(5), 805–843 (2007).
- 16 Ghaderi S, Ramesh B, Seifalian AM. Fluorescence nanoparticles ‘quantum dots’ as drug delivery system and their toxicity: a review. *J. Drug Target.* 19(7), 475–486 (2011).
- 17 Bentolila LA, Ebenstein Y, Weiss S. Quantum dots for *in vivo* small-animal imaging. *J. Nucl. Med.* 50(4), 493–496 (2009).