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Citation Classic

Quantum Dots Shed Light on Diagnoses

Sungjee Kim[1*]

Featured article: Kim S, Lim YT, Soltesz EG, De Grand AM, Lee J, Nakayama A, Parker JA, Mihaljevic T, Laurence RG, Dor DM, Cohn LH, Bawendi MG, Frangioni JV. Near-infrared fluorescent type II quantum dots for sentinel lymph node mapping. Nat Biotechnol 2004;22:93–7.[2]

Near-infrared (NIR)[3] (700–2500 nm) in vivo imaging with semiconductor quantum dots (QDs) can offer nonradioactive extraction of medical information, thus providing new opportunities for clinical diagnostic imaging in deep (>1 cm) tissues for diagnosing cancer and other tissue abnormalities *(1)*. NIR light can propagate over several centimeters because of the low absorbance of tissue chromophores. However, fluorescent imaging performed with NIR contrast agents had not been fully explored because of the limited sources of these agents. The fluorophores for NIR imaging had been typically limited to the general class of cyanine dyes such as indocyanine green. Molecule-based fluorophores inherently suffered from limited brightness because of enhanced coupling with vibrational modes at longer wavelengths. As a result, fluorescent molecules could not be easily found for emission wavelengths over 800 nm. Transitions in atomic energy levels (i.e., transition metals) could be exploited only after the drawbacks of low extinction and limited tunability of the emission wavelength were addressed. QDs represented a potentially ideal nanoemitter that promised bright and multiplexed imaging in the NIR region.

In 2003, simulations and modeling studies were performed for optical imaging in turbid media such as tissue and blood, and the results suggested 2 optimal optical windows for QD NIR imaging—a first optical window (FOW, 700–900 nm) and a second optical window (SOW, 1000–1400 nm) *(2)*. Lymphatic mapping and sentinel lymph node (SLN) biopsy was chosen as a proof-of-concept experiment for in vivo QD NIR imaging. SLN mapping was a good example for intraoperative procedures routinely practiced clinically and had the potential to be used in all solid tumors for visually guided surgery and minimized dissection. A QD probe was devised to be an approximately 20-nm hydrodynamic (HD)-sized QD emitting at approximately 850 nm. The emission wavelength was chosen within the FOW. The HD size was small enough to guarantee the rapid flow and escape from the injection site yet large enough for the selective retention at the SLNs. Type-II QDs with an oligomeric phosphine coating were successfully used to meet the design criteria. An in-house–constructed operational NIR fluorescence imaging system, the predecessor of FLARE™, beautifully showcased the identification of SLNs approximately 1 cm below the skin surface by use of reflectance imaging *(3)*. It was possible to improve the signal-to-noise ratios by over 100-fold by using QDs that emit light at 1320 nm (instead of 850 nm) *(2)*. However, the lack of bright fluorescent probes and the absence of sensitive charge-coupled device (CCD) cameras in this SOW have impeded the use of this highly sensitive spectral range for in vivo imaging. Our group has recently made quantitative and comprehensive comparisons for the imaging depths of NIR QDs in the FOW and SOW *(4)*. QDs in the SOW can currently extend optical diagnosis to depths that are several-fold deeper than those attainable with the FOW counterpart *(4)* and are expected to reach deeper as the CCD technology advances in the future. Because SLN mapping is a rudimentary application, targeting is not required for the contrast agent. Targeted imaging at the cellular level is of paramount importance to solve many of the most important clinical problems, including early cancer detection. To achieve such imaging, the signal-to-background ratio (SBR) must be enhanced by many orders of magnitude, but such radical improvement in the SBR is unlikely with simple affinity-based targeting because it relies on the concentration gradient, which is heavily restricted by biodistribution, clearance, and low target concentrations *(5)*. The SBR challenge can be overcome with QDs by acquisition of a "turn-on" function for spectral (color) and/or fluorescence intensity modulations in response to local environmental changes or particular binding events. For example, SLN QDs with this turn-on function can be used for simultaneous mapping and diagnosis of the

[1] Department of Chemistry, Pohang University of Science and Technology (POSTECH), Pohang, South Korea.
* Address correspondence to the author at: Department of Chemistry, Pohang University of Science and Technology (POSTECH) San 31, Hyojadong, Namgu, Pohang 790-784, South Korea. Fax +82-54-279-1498; e-mail sungjee@postech.ac.kr.
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[3] Nonstandard abbreviations: NIR, near infrared; QD, quantum dot; FOW, first optical window; SOW, second optical window; SLN, sentinel lymph node; HD, hydrodynamic; CCD, charge-coupled device; SBR, signal-to-background ratio.

malignancy. Sophisticated control of the QD surface is a prerequisite for the development of such a turn-on function *(6)*. Innovations in tomographical optical imaging techniques that can exploit multiply scattered photons from deep tissues are also required to achieve deep and sensitive NIR QD imaging for clinical applications.

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