

Nanotechnology in the Clinical Laboratory

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Introduction:

Nanotechnology is a multidisciplinary scientific field of study that encompasses a vast array of technologies derived from engineering, physics, biology and chemistry. The advances in nanotechnology over the years in the electronics industry, for instance, have allowed for progressively smaller devices with greater complexity and memory. We are now beginning to see a promising future of nanotechnology in medicine and the clinical laboratory using devices and reagents on the nanometer scale that will hopefully mirror its success in other industries.

Currently, there has been success using nanotechnology in the clinical laboratory. Most significantly, is the use of quantum dots (QDs) in flow cytometry. Quantum dots (QDs) have also shown great success in immunohistochemistry applications, as well. The future of nanotechnology in medicine and the clinical laboratory offers many possibilities and may completely change the current methods of laboratory diagnostics.

Background:

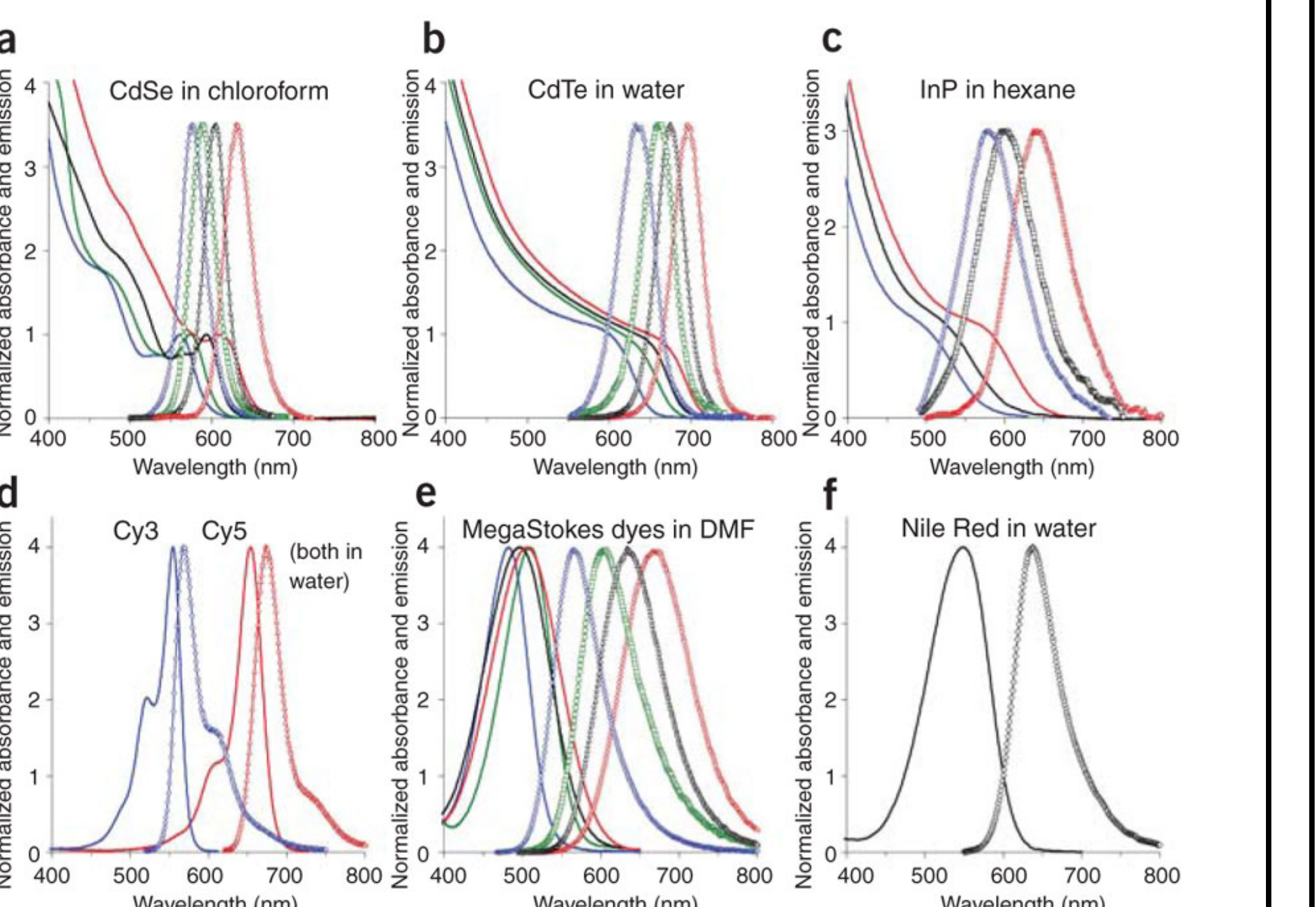
The concept of nanotechnology is not new. In fact, the concept of nanotechnology was first introduced in the 1950's by a physicist, Richard Feynman. Although the concept was first introduced 1950's, the actual term "nanotechnology" was not coined until the mid 1970's by a researcher, Norio Taniguchi. Initially, the electronics industry was the primary driving force in nanotechnology research, which endeavored to create smaller, faster and more complex devices.

Surprisingly, it's only been in the last 10 years or so, through public and private funding, that a real emphasis has been placed on nanotechnology in many different fields, including medicine. In addition to private and public funding, the U.S. government also funds billions of dollars to the National Nanotechnology Initiative to encourage research and development in nanotechnology in a variety of disciplines. The National Science Foundation has predicted the impact of advances emerging from nanotechnology developments over the next 20 years to be approximately \$1 trillion and in anticipation of this economic impact the number of nanotechnology research programs has increased substantially (Sahoo 2007). The rapid advances in science and technology have opened the door for nanotechnology and promises new opportunities on the horizon for disease treatment and diagnosis in health care.

Current Use of Nanotechnology in the Clinical Laboratory:

Currently, quantum dots are a type of nanotechnology being used in the flow cytometry laboratory. Quantum dots (QDs) are inorganic nanocrystals with unique properties that provide fluorescent labels. Flow cytometry analyzes complex antigen distributions on cell populations by applying fluorescent antibody conjugates to quantify antigen marker expression on cells, one color per marker (Buller, Zhang and Godfrey). Typically, organic dyes are used but are being outperformed by quantum dots in many ways. Compared to organic dyes, QDs have narrow emissions that require much less spectral compensation, more resistant to photobleaching, continuous absorption spectra from UV to near-infrared (NIR), longer fluorescence lifetime, and large Stokes shifts. Additionally, a single excitation source can be used to simultaneously visualize multiple QDs with different emission spectra (Cai, Hsu and Li). Over the last ten years, QDs have overcome many of the limitations of traditional organic dyes.

Figure 1 | Spectra of QDs and organic dyes (a-f) Absorption (lines) and emission (symbols) spectra of representative QDs (a-c) and organic dyes (d-f) color coded by size (blue < green < black < red). MegaStokes dyes were designed for spectral multiplexing in dimethylformamide (DMF). (Resch-Genger, Grabolle and Cavaliere-Jaricot)



Nanoparticles can also be used as scaffolds for enzyme labels. Traditionally in immunohistochemistry, one antibody is coupled with one to several dye labels. Quantum dots, given their larger size, can be couple with a number of antibodies. Fluorescent in situ hybridization (FISH) has adopted the use of oligonucleotide conjugated QDs which have proven to be significantly brighter and have more photostable signals than traditional organic dyes. This allows for more stable and quantitative uses of FISH (Cai, Hsu and Li).

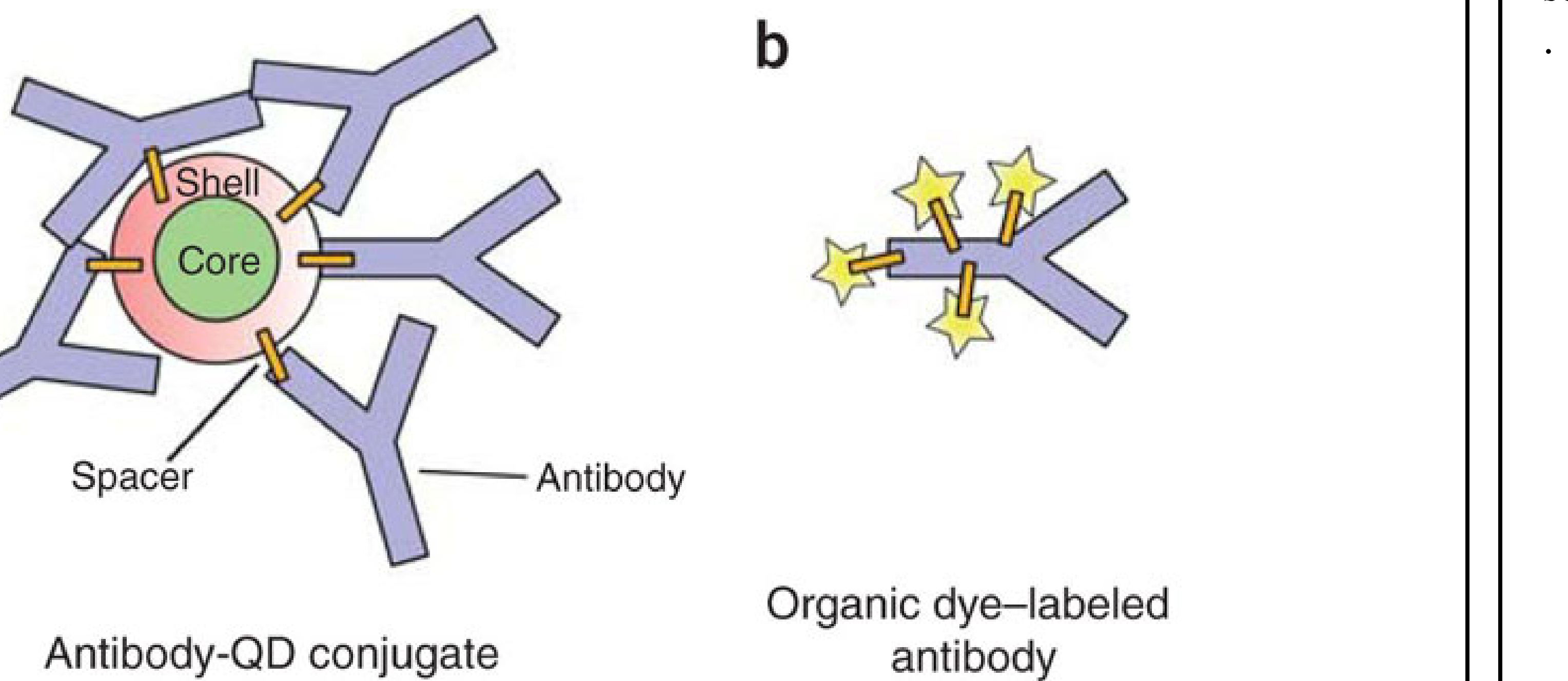


Figure 2 | Schematics of a QD-antibody conjugate and a dye-labeled antibody, reflecting the proportions of the components. (Resch-Genger, Grabolle and Cavaliere-Jaricot)

Future of Nanotechnology in the Clinical Laboratory:

Applications of nanotechnology in the future laboratory will be developed that completely replace current laboratory diagnostic methods. Hopes are high that in vivo imaging diagnostics methods are on the horizon which could potentially reduce or even replace current methods of biopsies and tissue processing. There are still many areas that still need to be resolved before nanoparticles (i.e. QDs) can become completely effective in vivo. The first issue is to be able to accurately direct nanoparticles to a specific organ or diseased tissue site without alteration. The size of the nanoparticle is another issue (QDs are approximately 20 nm). For example, being able to pass through pores and gain access to areas such as the nucleus. In vivo imaging has been successful in mice, but has not been accomplished in larger species, such as humans due to a short circulation time. Additionally, little is known about the toxicity of nanoparticles, especially since molecules on this scale behave differently. With continued research and demand for nanotechnology, the future of in vivo diagnostics in human health care is promising.

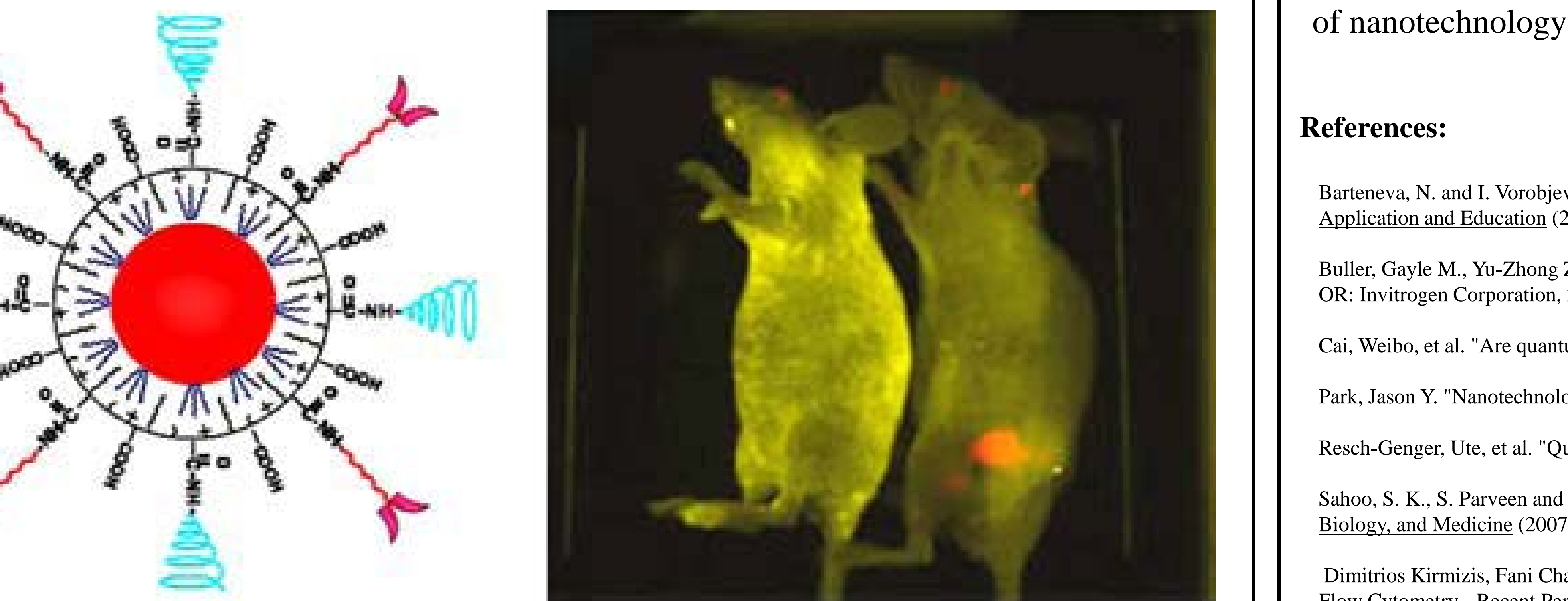


Figure 3 Antibody-conjugated QDs for in vivo cancer targeting and imaging. Mouse on the left was a control (Cai, Hsu and Li).

Since no single modality is perfect and sufficient to obtain all necessary information, one of the most promising uses of nanotechnology in the near future is the development of multifunctional QD-based probes for multimodality imaging both in vitro and in vivo (Cai, Hsu and Li). Imaging would include the use of positron emission tomography (PET), magnetic resonance imaging (MRI), and single photon emission computed tomography (SPECT). This would make it possible to image targeted QDs from the whole body down to the nanometer scale using a single probe.

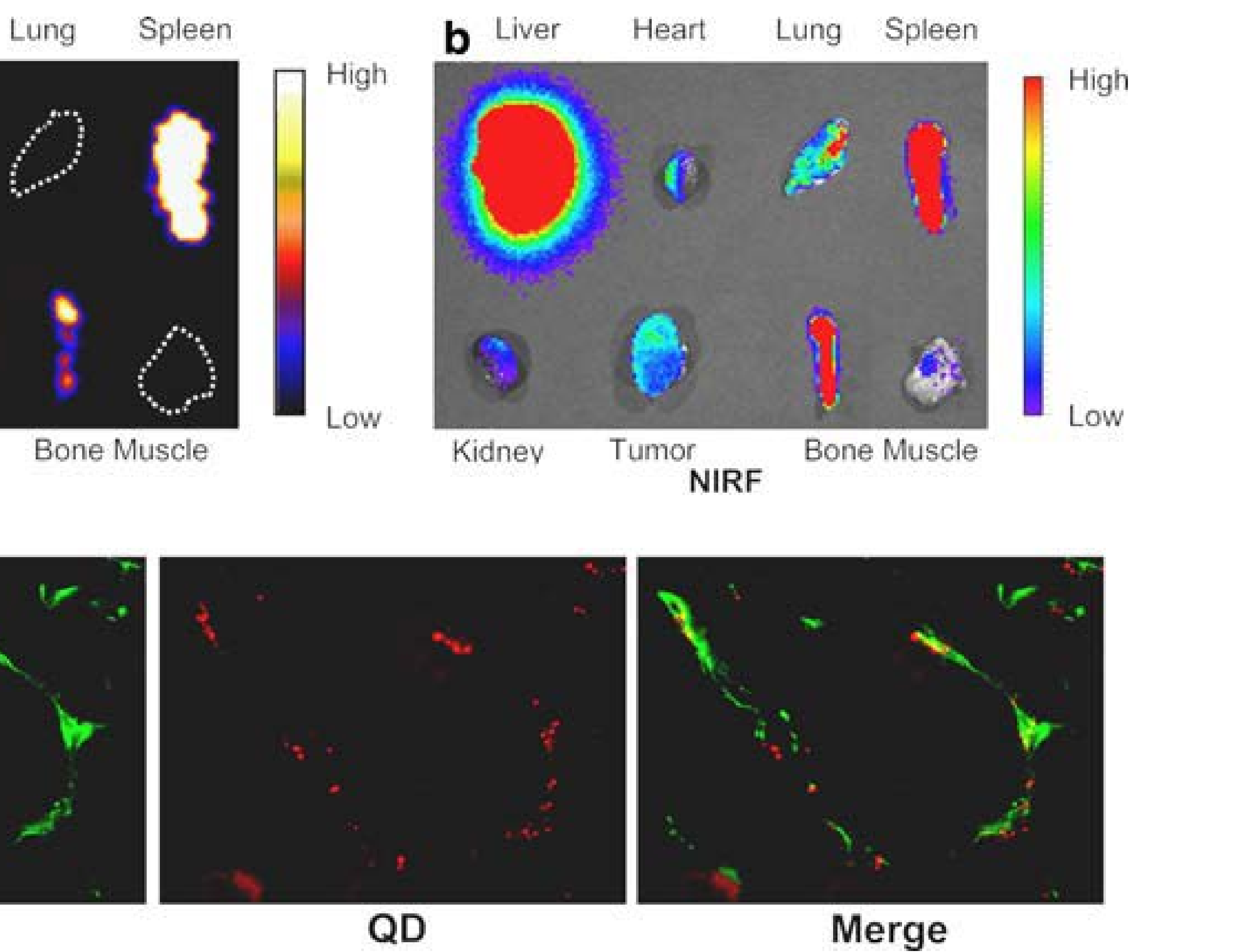


Figure 4. Dualfunctional QDbased probe for both PET and NIRF imaging. (a) PET image of harvested major organs/tissues at 5 h post-injection of the dualfunctional probe. (b) NIRF image of harvested major organs/tissues at 5 h post-injection of the probe. (c) Immunofluorescence staining of the tumor tissue revealed that QDs are targeting the tumor vasculature. (Cai, Hsu and Li)

Conclusion:

Nanotechnology has the potential to significantly impact disease diagnosis and patient disease management, as well as the methods used in the clinical laboratory. It is anticipated that nanotechnology will continue to evolve and be implemented in many areas of medical sciences and patient treatment as we have already seen with the use of quantum dots. Although there is still much to learn and many challenges overcome the future development and implementation of nanotechnology in medicine and the clinical laboratory are on the horizon.

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