Molecular Imaging with Multifunctional Nanoparticles

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The development of high-sensitivity and high-specificity probes that transcend the intrinsic limitations of organic fluorophores has been highly sought after by scientists in fields ranging from basic biology to molecular imaging and medical diagnostics. Since the first demonstrations of their bioapplications in 1998 (1, 2), fluorescent semiconductor nanocrystals, commonly known as “quantum dots” (Qdots), have been a particularly attractive candidate for analytically sensitive, multiplexed, and quantitative optical imaging. Remarkably, after 15 years of research, the interest and efforts in engineering multifunctional Qdot probes are still growing, because of Qdots’ combination of superior optical properties, the unique size and surface effect of nanomaterials in biological systems, the advantages offered by optical imaging, and the challenges of understanding and solving the nanotoxicity problem.

Compared with organic dyes, Qdots exhibit size-tunable and spectrally narrow emission properties, efficient light absorption across a wide spectrum, outstanding photostability, and a large Stokes shift—attributes that can greatly expand the capability of fluorescence imaging. The similarity in the sizes of Qdots and biomolecules allows them to be linked together for targeted imaging while maintaining compact sizes. More importantly, with the key advantages of optical imaging (high resolution, high sensitivity, multiplexing, and, particularly, low costs), Qdots serve as an outstanding model or prototype material for in-depth investigations of the interactions of nanoparticles with biological systems, through real-time monitoring of biodistribution, cellular uptake, and clearance.

After the initial excitement generated by the 2 Science articles (1, 2), it was soon realized that Qdot solubilization methods (involving ligand exchange at the nanoparticle surface leading to low-fluorescence quantum yields and colloidal stability) had to be improved. To solubilize nanoparticles and simultaneously keep their original hydrophobic surface ligands, we thought it natural to consider surfactant-like compounds. We picked block copolymers because of their broad availability, tunable composition, and the rich literature regarding liposome and polymersome self-assembly. Later, it turned out that a number of groups were independently working along the same lines. In fact, as we were writing up a manuscript on our initial finding and its application in staining cell surface receptors, 2 reports appeared before ours (3, 4). The first report described a method for solubilizing Qdots with random amphiphilic polymers and a demonstration of their uses in immunocytochemistry. The second report described the use of lipid–polyethylene glycol to solubilize Qdots and showed their uses in tracking embryo development. Although we never published our report on cell staining, we were fortunately able to demonstrate, through close collaboration with prostate tumor biologists and imaging instrumentation specialists, the use of multifunctional Qdots for targeted noninvasive imaging of tumors in live animals. This approach, first described in our 2004 Nature Biotechnology article, opened up new opportunities in ultrasensitive tumor detection.

Today, the development of unconventional imaging contrast agents for the early detection of cancer remains a major direction in my research. For example, my lab recently made magnetically and plasmonically coupled nanoparticles that offer contrast capabilities for multimodal imaging, including electron microscopy, magnetic resonance imaging, optical imaging, and photoacoustic imaging (5). Beyond these conventional imaging modes, combining multiple nanocomponents has allowed the creation of a new imaging modality (magnetomotive photoacoustic imaging), which is unavailable with either of the individual components. Compared with photoacoustic imaging, magnetomotive photoacoustic imaging is capable of enhancing imaging contrast by 2 to 3 orders of magnitude, and this contrast-enhancement technique has the potential to be expanded to other imaging techniques to aid in the early diagnosis of cancer.

Where will Qdot technology take us in the near future? With the breakthroughs in polymer encapsulation and nanoparticle surface modification that have occurred in the past 10 years, high-quality Qdots have become broadly available and have already fulfilled...
some promises as a new class of imaging probes, and their largest impact on biology and clinical diagnosis is just beginning to be realized. Because the long-term nanotoxicities and in vivo clearance pathways of Qdots are still largely unknown, I believe that the most immediate impact of Qdot technology likely will happen in systems biology, systems oncology, and single-cell proteomics, where a truly comprehensive understanding of physiological and pathological processes in complex biological systems can be achieved. In addition, Qdots will continue to serve as an indispensable model for systematic evaluations at all stages in drug discovery and drug-delivery research, with a high analytical sensitivity, with high resolution, and at low costs (6). Subsequently, the design parameters could help improve the efficacy of existing drugs and enable the development of new therapies.

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References