Review

Quantum dots in biology and medicine

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Abstract

Semiconductor quantum dots (QDs) are nanometer-sized crystals with unique photochemical and photophysical properties that are not available from either isolated molecules or bulk solids. In comparison with organic dyes and fluorescent proteins, these quantum-confined nanoparticles are brighter, more stable against photobleaching, and can be excited for multicolor emission with a single light source. Recent advances have shown that nanometer-sized semiconductor particles can be covalently linked with biorecognition molecules such as peptides, antibodies, nucleic acids, or small-molecule ligands for use as biological labels. High-quality QDs are also well suited for optical encoding and multiplexing applications due to their broad excitation profiles and narrow/symmetric emission spectra. In this article, we discuss recent developments in QD synthesis and bioconjugation, their applications in molecular and cellular imaging, as well as promising directions for future research.

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1. Introduction

Research in semiconductor quantum dots (QDs) started with the realization that the optical and electronic properties of small semiconductor particles were strongly dependent on particle size, due to quantum confinement of the charge carriers in small spaces. A theoretical framework for these size-dependent properties was first described by Ekimov and Efros in 1982 [1,2]. During the following two decades, extensive research was carried out for potential applications in optoelectronic devices, quantum-dot lasers, and high-density memory [3–5]. In 1998 two groups, one led by Alivisatos at UC-Berkeley and another led by Nie (then at Indiana University—Bloomington), simultaneously demonstrated that semiconductor QDs could be made water soluble and could be conjugated with biological molecules [6,7].

QDs are somewhat spherical nanocrystals in the size range of 1–10 nm diameter [4,8]. Semiconductor nanocrystals can also be produced with other shapes such as rods and tetrapods [9], but spherical QDs are the most widely used for biological applications, and therefore will be the focus of this article. One of the most intriguing features of QDs is that the particle size determines many of the QD properties, most importantly the wavelength of fluorescence emission (Fig. 1). By altering the QD size and its chemical composition, fluorescence emission may be tuned from the near ultraviolet, throughout the visible, and into the near-infrared spectrum, spanning a broad wavelength range of 400–2000 nm [10–14].

Currently, scientists and engineers are utilizing these unique optical properties to create useful nanoscale devices. Given the fact that the QD photoluminescence emission maximum can be manipulated by changing the particle size, their use as fluorescent labels for biological macromolecules has attracted considerable attention. In particular, the potential for generating an entirely new series of probes with size-tunable emission...
wavelengths that span the visible electromagnetic spectrum is highly attractive for biological applications. These size-tunable properties allow one to choose an emission wavelength that is well suited to a particular experiment, and to synthesize the QD-based probe by using an appropriate semiconductor material and nanocrystal size. The current methods of producing QDs via chemical synthesis allow for excellent control over the mean particle size and particle size distribution, yielding milligram to gram quantities of QDs where the particles exhibit narrow and symmetric emission peaks (FWHM typically 25–35 nm). This is much better than the emission characteristics for typical organic dye species, which often have much broader and asymmetric emission profiles (Fig. 2). This particular property is useful when simultaneous labeling and detection of multiple analytes are desired [15].

In addition to their desirable photon emission properties, QDs have advantageous absorption properties. Unlike organic dyes, which show large absorption cross-sections only across a narrow band of resonant frequencies, the relatively large densities of states and overlapping band structures in semiconductor materials result in QDs with high molar absorptivities and broad absorption spectra [16]. This property allows efficient excitation of multiple QD-based fluorophores with a single light source. The combination of large molar absorptivities and high quantum yield provides the basis for a series of QD-based fluorescent labels. In fact, studies comparing the “brightness” of single CdSe/ZnS core/shell QDs to that of single rhodamine 6G molecules indicate that the fluorescent photon flux in QDs is 10–100 fold greater [7].

Several other QD properties have significant practical implications for their use as fluorescent labels. Their low photodegradation rates make continuous or long-term monitoring of slow biological processes possible, a task which is challenging with traditional organic fluorophores [7,17]. The long fluorescence lifetimes of QDs, on the order 10–50 ns, are advantageous for distinguishing QD signals from background fluorescence and for achieving high-sensitivity detection [6]. Although the case for using QD-based fluorescent labels is compelling, it should be noted that QDs are not likely to replace organic dyes in all biological applications. Some of the challenges that have yet to be overcome include economic factors: QDs are expensive in comparison to organic dyes, and there is an initial investment required for researchers and instrument suppliers to produce systems optimized for use with QDs. Also, probe size and steric hindrance must be examined when assessing the suitability of a QD-based approach to fluorescent labeling of molecules. Since QDs are an order of magnitude larger than organic dyes (Fig. 2), the extent to which their presence perturbs the biological process being observed must be determined. This is particularly

Fig. 2. Absorbance (dark grey, blue in the web version) and fluorescence (light grey, green in the web version) spectra of an organic dye (fluorescein isothiocyanate, FITC, left) and a CdSe QD (right) with identical emission wavelengths. The emission spectrum of the QD is more narrow and symmetric than that of the dye, and the absorption spectrum extends far into the ultraviolet region. The relative sizes of the dye and nanoparticle are also illustrated.
important when multicolor experiments are desired, since labeling several biomolecules with QDs of different sizes could result in varying degrees of perturbation due to the large differences in the QD sizes. In contrast, most organic dyes are of similar size in spite of their large differences in absorption/emission characteristics. Recently, however, it has been demonstrated that the size-differences of multicolor QDs could be addressed by using alloyed semiconductor QDs where tuning of the emission wavelength is achieved via nanocrystal composition rather than size (Fig. 1B) [12–14,18].

Of the semiconductor families investigated to date, II–VI materials have shown the most promise, and consequently their use in biological applications has predominated. Therefore, this review will focus on the advances and applications of II–VI semiconductor materials in the biological sciences.

2. Chemical synthesis and bioconjugation

Historically, the synthesis of colloidal nanocrystals from the II to VI semiconductor family was developed using techniques similar to those used to produce colloidal gold nanoparticles. However, the nanocrystal materials obtained from these early procedures had large particle size distributions (PSD > 15%) and low fluorescence quantum yields. Due to the polydispersity within these samples, the size-dependent properties of these QDs were difficult to resolve. The situation changed dramatically when Murray et al. introduced a colloidal synthesis using organic media and organometallic precursors [19]. Samples produced using this procedure showed a high degree of monodispersity (PSD < 5%), excellent crystallinity, and were nearly free from structural defects. However, the fluorescence quantum yields hovered around the ~10% level.

It was later discovered that defects on the QD particle surface and poor surface passivation were the main culprits causing the poor fluorescence yields. This finding led several research groups to devise efficient methods for improving the surface quality and passivation. The first successful routes involved surface passivation via the deposition of an inorganic capping layer (or shell) composed of a semiconductor material of wider band gap than the core material. These (core)shell structures achieved efficient surface passivation as well as carrier confinement within the QD core, which decreased the likelihood of recombination via non-radiative pathways involving surface electronic states [20–22]. These relatively simple “capping” procedures were quite successful in increasing the fluorescence yields. Due to the high surface curvature on the QD surface, constraints on lattice-matching requirements for the creation of a heterojunction are somewhat relaxed, allowing materials that would be mismatched for bulk semiconductor applications to work for heterojunctions created on nanoscale structures. As a result, it is relatively simple to find core and shell materials with appropriate band structures that will also be lattice-matched and thereby obtain highly fluorescent nanoparticles.

Over the past decade a variety of procedures have been developed for obtaining high-quality QDs, all of which are based on variations of the high-temperature pyrolytic reaction introduced by Bawendi and coworkers [19]. The essential elements of these procedures involve the combining of an appropriate metallic or organometallic precursor (zinc, cadmium or mercury species) with a corresponding chalcogen precursor (sulfur, selenium or tellurium species) in a coordinating solvent at high temperatures (Fig. 3). High-quality QDs have been obtained using solvents that are stable at high temperature and act as surfactant molecules for stabilization of the QD surface to prevent particle aggregation [10,19]. Specifically, tri-n-octylphosphine oxide (TOPO) is commonly used due to its high boiling point and its ability to coordinate both metal and chalcogen elements. Frequently, TOPO is used in combination with other surfactants or co-solvents such as tri-n-octylphosphine (TOP), hexadecylamine, or stearic acid [23–25]. Under these conditions, particle nucleation takes place rapidly, followed by epitaxial growth and nanocrystal annealing at slightly lower temperatures. During the growth period, the QD size can be monitored using a spectroscopic probe within the reaction flask or by examining aliquots taken at various intervals. Once the desired size has been obtained, growth is quenched.
by lowering the temperature of the reaction mixture. Growth rate and maximum particle size values can be manipulated to a certain extent by controlling the following parameters: the initial precursor concentration, the growth temperature and the length of the growth period. It is also possible to introduce additional precursor material into the reaction vessel during the growth period in order to obtain larger QDs and improve the size distributions. Although the reactions carried out to produce the QDs must be performed under an inert atmosphere due to the reactivity of the precursor species with oxygen and water, the QDs themselves are stable in air. Therefore, post-synthetic manipulations can be carried out in air, making QDs relatively easy to work with.

To coat the QD cores, an appropriate mixture of capping material precursor can be added drop-wise to the raw reaction mixture following the annealing step (Fig. 3). This slow addition of shell precursor during this low temperature phase of the synthesis promotes epitaxial deposition of the material rather than nucleation of new nanocrystals. During this shell-growth period, aliquots can be analyzed to determine when the shell has reached its optimal thickness by observing the resulting fluorescence yield from the particles. The core/shell QDs obtained from these procedures are highly fluorescent, photostable, and sufficiently monodisperse for use as labels in biological studies. But they are not soluble in aqueous solution nor do they have appropriate moieties for conjugation to biomolecules. In order to make the QDs biocompatible the surface TOPO molecules must be replaced or modified with surface molecules that allow the QDs to be dissolved in aqueous media and linked to biomolecules.

Although there are procedures available for synthesizing QDs in aqueous solution, they suffer from broad size distributions and poor fluorescence efficiencies. As a result, the procedure of organic synthesis and capping followed by surface modification has been the preferred route for obtaining highly fluorescent water-soluble QDs.

Among the various techniques for surface modification, two general methods are shown in Fig. 4: (i) surface-exchange of hydrophobic surfactant molecules for bifunctional linker molecules [7], and (ii) phase-transfer methods using amphiphilic molecules that act as detergents for
solubilizing the QD coated with hydrophobic groups [17,26]. Both procedures have been employed using a wide variety of molecules that act in similar fashions to solubilize QDs and provide functional groups (carboxylic acid, amine, etc.) which are conjugated to biomolecules using well established protocols. The latter method has been particularly advantageous in that it allows for the retention of the native surfactant molecules, which appear to increase the stability and fluorescence efficiency over those samples where the native layer has been stripped away and replaced with a bifunctional linker molecule. Although the general properties of the nanocrystalline surface appear to be understood, the exact surface chemistry involved in such processes continues to be debated.

Nuclear magnetic resonance spectroscopy and X-ray photoelectron spectroscopy studies have been used to characterize the QD surface properties. However, more information is needed in order to understand how surface-surfactant molecule interactions are responsible for the observed

Fig. 4. Illustration of the two general strategies used to disperse hydrophobic QDs in aqueous solution. Organic molecules are drawn disproportionately large for clarity. (A) Ligands surrounding a TOPO-coated QD may be replaced with heterobifunctional ligands, like mercaptoacetic acid, and the QD may then be readily dispersed in aqueous solvents. Alternatively, silane functional groups may be used instead of carboxylic acids to grow a silica-shell around the QD, which can then be rendered water soluble with the growth of polar functional groups on the surface. (B) Native TOPO ligands on the QD surface may be retained and used to interact with an amphiphilic polymer like octylamine-modified polyacrylic acid. Hydrophobic interactions between TOPO and the octylamine side chain are believed to be responsible for the long-term stability of these particles.
differences in the efficiency of passivation/protection of the QD surface for certain surfactant molecules [27–29]. In contrast to the surface, the nanocrystal interior has been characterized much more thoroughly. High-resolution transmission electron microscopy and X-ray diffraction reveal the crystalline phase and faceted QD shape [4,19]. It has also been noted that the high surface curvature of the QD surface allows for slightly higher number densities of surface molecules per unit area on nanocrystal surfaces relative to bulk substrates, due to a reduction of the steric hindrance associated with the packing of molecules on the particle surface.

The following is a brief survey of the methods that have been used to produce biocompatible QDs, and highlights their main features. One of the first methods introduced involves the deposition of a silica coating onto the QD surface where the initial thiol-containing silane monomers displace the TOPO from the surface and create a silica shell. Subsequently, phosphonate-, poly(ethylene glycol)-, or ammonium-containing silane monomers, along with the thiol-containing monomer, can be added to increase the thickness of the shell, to impart hydrophilic character, and to add functional groups for modification and bioconjugation on the particle surface [6,30–32]. Although these QDs are reported to be stable, it is difficult to obtain large quantities of material using this procedure.

Simultaneous with the introduction of the silica-coating procedure, a much simpler route was demonstrated in which TOPO on the QD surface was displaced by the adsorption of bifunctional linker molecules, which provide both hydrophilic character and functional groups for bioconjugation. Simply by incubating the QDs for a short period with the bifunctional linker in solution, the QDs may be extracted from the organic solvent by centrifugation, and then re-dissolved in an appropriate conjugation buffer [7,33]. This approach was initially shown to work well for linker molecules such as mercaptoacetic acid, mercapto-succinic acid, dithiothreitol, glutathione and histidine, and was later demonstrated to be widely applicable for bifunctional compounds containing sulfhydryl groups [34–36]. The procedure takes only minutes to complete and can provide large quantities of biocompatible QDs. However, slow desorption of the linker molecules causes the colloids to precipitate, making long-term storage a problem, but the ease of carrying out these protocols lends them to making fresh samples as needed. Several variations of this method have been demonstrated whereby the surface TOPO molecules are replaced with small mercapto molecules, and subsequently these water-soluble QDs are incubated with thiol-containing biomolecules, which replace the mercapto compounds on the particle surface [34,37]. This approach also works well for small biomolecules that are soluble in polar organic solvents and can replace TOPO directly [38].

Recently, strategies to produce biocompatible QDs with long-term stability have been introduced. Examples include (a) the use of engineered recombinant proteins attached electrostatically to a QD surface which has been modified with dihydrolipoic acid [39–42], (b) the use of hydrophilic organic dendron ligands to create a hydrophilic shell around the QD [43], and (c) the use of a micellar encapsulation procedure in which phospholipid molecules surround the TOPO-coated QD surface. In the latter technique, the hydrocarbon tails of the phospholipid interdigitate with the alkyl chains extending from the particle surface, and the polar phosphate head groups extend out into the solution to create a water-stable micelle [26]. In addition, QDs conjugated to streptavidin via an amphiphilic polymer coating are now commercially available [17].

3. Biological applications

Following the nearly simultaneous reports of using QDs as labels in biological experiments by Alivisatos and co-workers at UC Berkeley and Chan and Nie at Indiana University in 1998 [6,7], the number of QD biological studies has increased exponentially. Quantum dot labels have been successfully used for a variety of bioanalytical purposes, such as DNA hybridization detection [31,34,37], immunoassays [40,41], and binding assays using fluorescence resonant energy transfer (FRET) to probe for target events [36]. These
well-established applications have employed organic dyes with good results, however, the use of QDs could allow for high-sensitivity multiplexed methods due to their narrow and intense emission spectra. Significant advances in the use of QDs as bioanalytical tools for in vitro work have been made in the areas of immunoassays and biosensors [44–46].

Fluorescence immunoassays detect the binding of a fluorophore-labeled antibody to an analyte molecule which has been attached to a support substrate. After a brief incubation period, the unbound antibody can be washed away and the quantity of bound antibody can be determined. Quantum dot-labeled antibodies have been used in such assays and were demonstrated to be generally applicable, however no increase in sensitivity over organic fluorophores was observed [40,46]. In another study, the benefits of using QD-based labels in immunoassays were realized by exploiting the multiplex capability of these nanocrystal fluorophores, i.e., the ability to excite and detect several labeled species simultaneously using a single light source [45].

In the area of biosensors, QDs are particularly attractive due to their long-term photostability, allowing real-time and continuous monitoring. One method for utilizing QDs in sensing applications is to create an “on/off” switching capability via FRET whereby nonradiative energy transfer occurs between the QD (donor) and an acceptor molecule [47,48]. QDs are promising donors for FRET-based applications due to their continuously tunable emissions that can be matched to any desired acceptor, and their broadband absorption, allowing excitation at a short wavelength that does not directly excite the acceptor. It has been recently reported that QDs can act as highly efficient FRET donors when coupled with a variety of acceptors, such as organic fluorophores or dyes [44,49,50], as well as other QDs or metallic nanoparticles [51,52]. An interesting application of FRET using a QD-based sensor has been demonstrated which does not require spatial reorganization of the donor–acceptor pair in order to initiate switching. Instead a photoactivated/deactivated acceptor was utilized [53]. Advances in the design of these types of integrated devices, which incorporate an emission unit with a quenching unit that can be modulated by a biological stimulus, could lead to the creation of powerful and compact sensors.

Another bioanalytical application is the use of QDs to create optically encoded polymer microspheres which could be used in high-throughput screening and analysis of genes, proteins and chemical libraries [54–56]. By encapsulating populations of QDs within the polymer bead, a unique spectroscopic signature can be assigned which identifies the particular biorecognition molecule that is attached to the bead. Later, upon exposure to a complex mixture of analyte molecules, those which bind to the microsphere can be identified. Due to the narrow emission profiles exhibited by QDs, it is possible for the encoded spectroscopic signature to contain as many as six colors. If 10 intensity levels were used for these individual colors, then a total of $10^6$ unique codes could be generated. In practical terms, 1000 unique codes would be more than adequate for state-of-the-art analyses since currently employed techniques using polymer microspheres dyed with organic fluorophore are limited to generating ~100 unique codes.

Shortly after this application was described by Han et al. [54], a similar approach was used to detect single nucleotide polymorphisms (SNPs), which are DNA sequences that differ at a single nucleotide [57]. This term describes frequently occurring genetic differences within populations of organisms, as opposed to those that are rare occurrences, i.e., mutations. This technique enabled the rapid and accurate identification of the SNPs present in specific alleles of the human cytochrome P450 gene family by using optically encoded beads in conjunction with a flow cytometry system. The fact that the QD-encoded beads had well resolved emission peaks and required only a single excitation source greatly simplified the instrumentation, and increased the reliability of this high-throughput analysis. It is hoped that by developing encoded microsphere libraries, scientists will soon be able to quickly and economically gather large quantities of genomic and gene expression data by using multiplexed detection [15].

QDs have seen increasing use as labels for cellular receptors and contrast agents for in vivo imaging [26,38,58]. In these applications, the high photostability of QDs relative to organic dyes allows
for long-term tracking of biological processes [42]. An impressive demonstration of this capability was illustrated by Dubertret et al. by microinjecting QD bioconjugates into Xenopus embryos and monitoring their partitioning into various cells during tadpole development over a period of several days [26]. In addition, the narrow emission spectra of QDs have allowed the simultaneous imaging of multiple targets inside or on the surface of live cells, providing the possibility for early detection and identification of malignant tumors based on multiple molecular markers [17]. Multicolor imaging using QDs could also be beneficial in the analysis of tissue samples by reducing the analysis time and increasing the number of biomarkers that can be examined [59]. The following paragraphs serve to highlight some of the recent developments in the area of biological labeling and imaging.

In 1998 the first major applications of QDs as biological labels were demonstrated by (i) the multicolor labeling of fixed mouse fibroblasts, where red QDs were modified to selectively stain cytoskeletal filaments and green QDs were linked to recognition molecules selective for the cell nucleus [6] and (ii) the uptake of transferrin-QD conjugates by live HeLa cells [7]. It has also been observed that in some cases QDs can enter cells via a nonspecific uptake mechanism [42,60,61]. In fact, this nonspecific uptake was used to monitor the movement of breast tumor cells across a support substrate coated with QDs. Depletion of the QDs on the substrate revealed the paths taken by the migrating cells [60]. All of these studies reinforced the notion that QDs can be imaged within living cells for extended periods of time, a significant advantage over conventional organic fluorophores.

In addition to fixed tissue/cell imaging, impressive examples of live cell-imaging have been accomplished using QDs. In a report by Dahan et al. [62], glycine receptors on neuronal membranes were labeled with QDs to create real-time video images. In these stunning video images the motion of the labeled receptors diffusing across the membrane surface is observed by signals emanating from single QD bioconjugates. Another example of live-cell imaging was demonstrated by Lidke et al. where QD-labeled epidermal growth factor (EGF) was used to probe EGF interactions with receptors on the membranes of live cells [63]. Single-molecule detection was accomplished in the monitoring of endocytosis of the QD-EGF conjugates in real time, revealing a previously unobserved transport mechanism. The increasingly popular application of QD-based labels for biological studies of living organisms has required that QD toxicity be examined. To date, none of the reports have observed any significant level of cytotoxicity [26,42,60,63,64]. However, more work specifically addressing this issue would be helpful since it is well known that QDs contain toxic elements. One study indicates that the low observed toxicity for QD bioconjugates is due to sufficient protection of the QD surface (by ligands and surfactants) from oxidation and release of cadmium ions [65].

Two interesting studies have utilized QDs to examine ATP-driven reactions. The application of QD bioconjugates in this area has permitted the direct observation of the release of QDs enclosed within the cavity of chaperone proteins [66] and the motorized motion of actin filaments [67]. In addition, QDs conjugated to peptides for targeting specific endothelial cell receptors (lung, tumor blood vessels and tumor lymphatic vessels) have been intravenously injected into mice, revealing accumulation of QDs in the targeted tissue. Whole organism imaging was not performed in this work, but was achieved later on small Xenopus embryos as mentioned previously [26]. High resolution and high contrast imaging has also been achieved by multiphoton excitation at near infrared wavelengths [68]. However, in this particular study, the QD fluorophore emitted visible photons which are not well suited for imaging deep within tissue sections or whole organisms. The ability to visualize the location and concentration of fluorescent probes within an entire organism requires excitation and detection at wavelengths capable of penetrating biological tissues [69].

A promising method for imaging structures deep within tissues is the use of QDs that absorb and emit in the near infrared region (650–2000 nm), allowing for deeper penetration of photons from the excitation source, as well as greater escape
depths for the QD emission signal [68,70,71]. Theoretical studies show that long wavelength probes benefit from low scattering and absorption by biological tissue, as well as minimal background noise since cellular autofluorescence is greatly reduced [72]. Unfortunately, there are few organic dyes that emit in this region and those that are available suffer from poor photostability and low quantum yields in biological media [73–76]. For this reason, QDs are a desirable alternative since there are several semiconductor materials available which can be tuned to emit in the near infrared region [12,13,77]. Quantum dot probes based on these materials are capable of quantum yields as high as 50% at room temperature, are stable in aqueous solution and compatible with the previously described bioconjugation techniques [12,78]. Near infrared-emitting QDs have been successfully used to image rat coronary vasculature, as well as porcine sentinel lymph nodes with a tissue penetration depth up to one centimeter [74,76]. Image generation for tissue samples can be based on either attenuation of radiation due to variations in tissue density or due to molecular differences within the tissue itself [79]. The latter technique has the potential for providing information-rich images, since specific molecular markers can be targeted. To this end, several fluorescent dyes and engineered proteins have been used for molecular imaging of tissues [75,80]. Near infrared-emitting QDs would be ideally suited to these types of studies since they have the potential for multiplexed detection in real time. This could open the door for studies which involve the monitoring of complex biological processes in vivo.

4. Future directions

The development of QDs as powerful tools for imaging living cells and living organisms may be complemented by new nanobiosensors. Current work is yielding evidence that organic dye-based sensors may make significant impacts in disease detection, providing a strong impetus for the development of analogous QD-based biosensors, which can take advantage of the unique properties of QDs [70]. Methods for controlling QD fluorescence in binary fashion (switching between “bright” and “dark” states) could lead to the development of sensing tools for probing a host of biological processes occurring at the cellular level.

The past decade has seen the development of QDs from a solid-state material into a powerful fluorescent probe. However, corresponding advances in targeting and delivery of QD-based probes to specific cellular or tissue constituents have lagged behind [26,42]. If these issues can be addressed during the next decade, QDs will be well on their way to delivering important insights into cellular processes, as well as providing the information needed in routine medical diagnostics. Molecular and cellular targeting research carried out using other types of nanoparticles should help research in QD delivery and targeting [81]. Advances in this direction will bring scientists closer to realizing the goal of developing “smart” multifunctional nanodevices. Great strides to this end have already been achieved in the directed assembly of nanoscale structures [37,82,83], but the “smart” responsive or reporting aspect of such devices has not been sufficiently demonstrated.

Current developments in the area of multifunctional nanodevices have allowed the use of QDs as labels for multimodal imaging, due to their ability to act as fluorescent tags for optical microscopy as well as contrast agents for electron microscopy [62,84]. Extending this multifunctionality to create a device with imaging and therapeutic capabilities would revolutionize the field of disease treatment. In fact, initial studies in this area are promising, revealing that QDs could be employed as photoactivated therapy agents [85].

A final area in which QD-based nanomaterials will surely impact the biological sciences is that of semiconductor diode lasers and detectors [86–89]. Advances in these rapidly developing technologies will benefit chemists and biologists by providing increased flexibility in the instrumentation available for biological studies, and allow further instrumental optimization for routine analyses of biological samples. Clearly, the pioneering work carried out by researchers in the physical sciences has laid a solid foundation for understanding the properties of nanomaterials, and their continued contributions will give the next generation of
engineers and technologists an excellent platform on which to design and build devices to solve a variety of problems in biology and medicine [90].

5. Concluding remarks

The popularity of QD-based fluorescent labels is increasing as researchers move to exploit the unique properties of this new class of fluorophores. This exploration is sure to open up new opportunities as well as old problems that might be addressed by using new QD probes. The breakthroughs and steady improvements made over the past 10 years in producing and modifying QDs for use as fluorescent labels have contributed to the successful implementation of this new and unique probe. Although they are unlikely to completely replace traditional organic fluorophores as biological labels, QDs have secured their place as a viable technology in the biological sciences. With their capability for single molecule and multiplexed detection, real-time imaging and biological compatibility, QDs represent a valuable new technology in the biologist’s toolbox.

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