REVIEW ARTICLE

Nanobio applications of quantum dots in cancer: imaging, sensing, and targeting

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Abstract In this article, the syntheses and optical properties of core/shell quantum dot (CdSe/ZnS) and their applications are reviewed. Nevertheless, the main focus is to provide an overview on biological applications of quantum dots that contain imaging, targeting, and sensing. We discuss the different synthetic methods, optical properties (photoluminescence intensity, absorption, and fluorescence spectra), and their dependence on shape, size, and inner structure of quantum dots. Also, the different mechanisms of quantum dots bio-targeting (passive and active mechanisms) are discussed. The impact of quantum dots in bioimaging is reviewed regarding its photoluminescence intensity, absorption and emission spectrum, and photo-stability on high-quality and sensitivity imaging. Further, the difference between near infrared and visible emission quantum dots in deep tissue imaging will be reviewed and some of done works are considered and compared with each other. And finally, the biosensing potential/application of quantum dots in medical diagnosis is going to be highlighted.

1 Introduction

In nanotechnology area, the "nano" appears to be a prefix for other sciences/technologies to highlight its integration with the merged field, in which the operation size range become an order of nanometer (1–100 nm) at a molecular level. In fact, due to the big ratio of surface-to-volume and quantum confinement effects, the most of material properties (e.g., electronic, optical, chemical, mechanical, and magnetic) differ from bulk materials when their sizes reach to nanoscale (Biju et al. 2008; Warburton 2002; Sharma et al. 2009). Such an approach has significantly promoted their scientific use in different applications such as military and optical electronic device (Kershaw et al. 2000; Wang et al. 2008c) and biological implementations such as bioimaging and biosensing (Ravindran Girija Aswathy et al. 2010; Debbage and Jaschke 2008; Frasco and Chaniotakis 2009; Hempen and Karst 2006; Willard et al. 2006), as well as bio-targeting (Gao et al. 2005; WeiboCai et al. 2007). From bioimaging and biosensing viewpoints, a nano-scaled particle can be categorized as an organic dye fluorophores and inorganic (i.e., semiconductor quantum dot (QD) (Mazumder et al. 2009) and metallic nanoparticle (NP) (Klaine et al. 2008; Suchita Kalele et al. 2006). The organic dyes were used for biological applications even though their efficiency was not high enough, perhaps due to narrow absorption spectrum. In fact, for the excitation, a tunable and fine wavelength of source is essential. The wide emission spectrum can cause aggregation of nanoparticles and overlap among different spectra. Moreover, the lack of photo-stability, photo-bleaching, and the variation of properties with the alteration of environment are other drawbacks of organic dyes (Murcia et al. 2008; Yu et al. 2006; Gao et al. 2005). Most problems associated with the organic dye fluorophores have been resolved by the emergence of QDs or NPs. In this article, we focus on QD nanocrystal with the cadmium selenide (CdSe) core. The wide absorption spectrum, narrow emission, photo-stability, lack of photo-bleaching, and high-quantum efficiency have made these nanostructures very attractive imaging/sensing materials in comparison with the dye fluorophores. Basi-

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cally, the intensity of fluorescence in imaging and targeting of biomarkers must be controlled that this can be attained with manipulating the size and shape of QDs (Jung and Yun 2008). Furthermore, the QDs nanocrystal used in biological application should be soluble in aqueous solutions thus various modifications have been imposed to improve the solubility and safety of QDs. The chemical surface characteristics dictate the condition of solubility in different solvents and control its functionalizing, quantum yield, and blinking (Okuyama and Lenggoro 2004; Dabbousi et al. 1997). Besides, the surfaces chemistry was shown to influence on hydrodynamic diameter that is one of fundamental parameters for the application of QD in diagnostic and therapy approaches (Lees et al. 2008). For the biological applications of QDs, it is notable to manage the surface of core with other semiconductor materials with higher band gap than the core as well as biocompatible polymer. In most of studies, as shown in Fig. 1, zinc sulfide (ZnS) has been used to cover the CdSe core. Such coverage

can result to increase quantum confinement effect, photo-stability, quantum yield, and colloidal stability, while minimizing the cadmium-based toxicity in in vivo imaging (Medintz et al. 2005; Vashist et al. 2006; Thurn et al. 2007). Due to a big surface-to-volume ratio of QDs, they can be labeled with different biomolecules (e.g., peptide, proteins, enzymes, antibodies, nucleic acid, oligonucleotides, and drugs) (Chen et al. 2008; Xing and Rao 2008; Frasco and Chaniotakis 2010; Wang et al. 2008b) by different methods. The significant advantages of QDs nanocrystal in biological application are their simultaneous use in accurate tumor targeting and high-sensitivity imaging. As a result, the high performance of imaging and targeting can be attainable since the small size and narrow emission of QDs result in a little overlap among their emission spectrums. In this current article, we review the revised synthesis methodologies, optical properties, and bio-impacts of QDs as an imaging/sensing agent for target therapy of cancer.
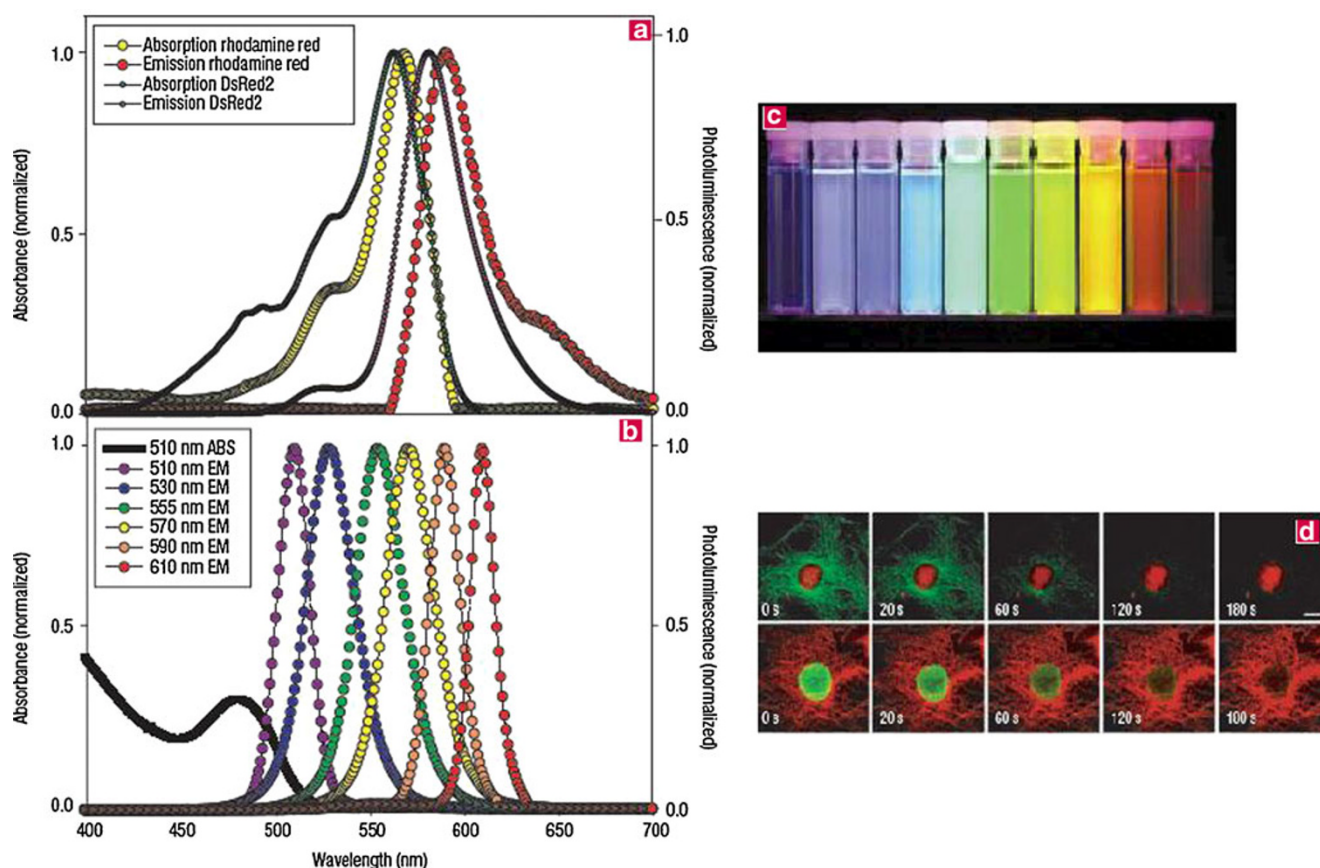

Fig. 1 Comparison between organic dyes (rhodamine red/DsRed2) and inorganic nanocrystal (different size of QDs). **a** Absorption (*Abs*) and emission (*Em*) of rhodamine red. **b** Absorption and emission of six different QD dispersions. **c** Photo demonstrating the size-tunable fluorescence properties and spectral range of the ten QD dispersions. **d** Nuclear antigens were labeled with QD 630–streptavidin (*red*), and microtubules were labeled with AlexaFluor 488 (*green*) simultaneously in a 3T3 cell. *Bottom row* Microtubules were labeled with QD 630–streptavidin (*red*) and nuclear antigens were stained *green* with Alexa 488. Continuous exposure times in seconds are indicated. Note the QD resistance to photo-bleaching under continuous illumination (Medintz et al. 2005)

The improvement and development of QDs for variation of application, we must manage the surface of core which carries out with covering core by other semiconductor materials with higher band gap than the core. In this article, we consider the ZnS coverage for the CdSe core of QD which its impacts result to increasing quantum confinement effect, photo-stability, quantum yield, colloidal stability, robust, and minimizing its toxicity in in vivo imaging (Fig. 2a) are investigated. Due to a big surface-to-volume ratio of QDs, the different bio-labeling such as DNA and RNA can be added, in addition to, it can be to link to biological molecules such as peptide, nucleic acid, oligonucleotides, and antibody (Fig. 2b) by different methods. The significant advantage of QDs nanocrystal in biological application is the simultaneous use of them in accurate tumor targeting and high-sensitivity imaging that the high performance of imaging and targeting can be attainable with consideration of small size and narrow emission of them because of weak overlap between their emission spectrums.

2 Syntheses and characterization of quantum dots

2.1 Syntheses

In this section, we briefly review the different methods of syntheses, surface-modified and optical properties. Since the discovery of quantum confinement effect and big ratio of surface-to-volume, colloidal semiconductor nanocrystals have been intensively studied due to their unique size- and shape-dependent physical properties. The selected nanocrystal constitutes of core (CdSe) and shell (ZnS) that separately produce with difference mechanisms dependence on application. In the growth processing, controlling of symmetric shape of quantum dots are very important. Since the growth of nanocrystal is almost uniform, the initial size distributions depend on time that the core of QD begins to grow. When CdSe nucleation take place, however, for CdSe with radii comprised among 1–10 nm, the value of the capillary length is approaching to particle radius, and the

particle solubility becomes non-linier against "$1/r$". Therefore, the particle growth can be described as diffusion-controlled process instead (Jiang 2008).

$$\frac{dr}{dt} = K\left(\frac{1}{r} + \frac{1}{\sigma}\right) \cdot \left(\frac{1}{r^*} - \frac{1}{r}\right) \qquad (1)$$

In Eq. 1, where dr/dt is the growth rate, K is the constant proportional to the diffusion constant of the monomer, σ is the thickness of diffusion layer, and r^* is the critical radius that nanocrystal solubility is exactly dependent the concentration of monomer in solution. This relation shows that small nanocrystal have the minus rate and dissolve in solvent, in contrast, the large ones have the positive rate. When the nanocrystal radius (r) is slightly bigger than r^*, the focus on size distribution can occur and the small nanocrystal can have swift growth rate than the bigger one if the monomer concentration remains at high level. With the depletion of monomers, defocusing (Ostwald ripping; Jiang 2008; Geissbuhler 2005) can occur that the small nanocrystals are dissolved and the bigger ones grow. In this synthetic process, it is very important to control the precursor rate, proportional injection, solvent symmetry, size and shape of QDs, and layer passivation which by accurate appointment of them, we can have the high-quality syntheses. Overall revision of the different methods of nanocrystal fabrication is shown in Table 1. But for QD syntheses, we most use of organometallic technique (Jiang 2008; Yang 2005; Protie're and Reiss 2006), which this technique and its sub-methods are illustrated and reviewed in Fig. 3. In this method, dimethyl cadmimum was considered as the precursor for the syntheses of high-quality QD (Hwang and Cho 2005). Anyway, because of the precursor, this approach is not popular. Therefore, lately, cadmium oxide (CdO) was reported as a safety precursor for QD syntheses (Peng and Li 2010) moreover, in this method, the temperature of interaction is very high (250–350°C). For attending of this point is very important which controlling of essential parameters such as QD's size and shape, photoluminescence intensity is possible with managing and regulating of action temperature, molar

Fig. 2 a Typical absorption and photoluminescence (*PL*) spectra of sample CdSe before and after overcoating with ZnS. **b** Schematic of methods for attaching antibodies and other proteins to DHLA-capped QDs (Sapsford et al. 2006)
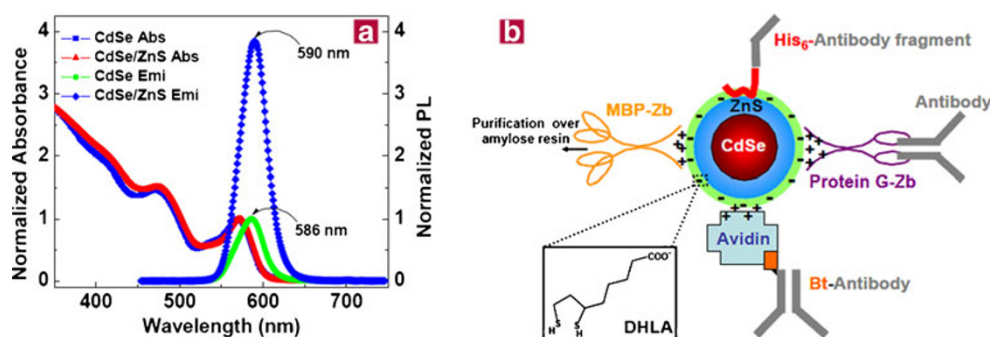
Table 1 Various fabrication techniques for nanostructure materials (Sharma et al. 2009)

Vapor phase synthesis	Wet chemical synthesis	Mechanical synthesis
Epitaxial deposition	Colloidal solution	Nanoscale milling
Thermal evaporation technique	Chemical solution deposition	
Sputtering technique	Electrochemical deposition	
Laser ablation		
Pulse laser deposition		

proportional, pH, and concentration effects (Jiang 2008; Geissbuhler 2005; Lu 2005).

Moreover, all the investigators astonishingly follow the procedure for increasing of quantum yield (proportional of emission photon to absorbance) and decreasing of number of QDs in an assay. The atoms in the QD surface can be defection (decreasing of QY factor) since they have not fully bonded but most of them eliminate by passivation in the synthetic method. For the passivation of QD surface, the use of other material (organic and inorganic) with bigger band gap than core is suggested and in this tactic, the covering of QD with inorganic layer is more robust than passivity by organic ones and higher stability in harsh condition. After the passivation step, not only most of dangling bond is fixed by layer but also the pair of electron and hole strictly confined by the big potential barrier. The varieties of core/shell nanostructure such as CdSe/ZnS, CdSe/ZnSe, and CdSe/CdS develop the quantum yields to 85%. Furthermore, one of the important parameters for the synthetic process is temperature because in the high temperature, the growth rate of the core of nanocrystal (CdSe) and following of Ostwald ripping affected on size distribution and became large but in low one, incomplete decomposition of precursor can occur and decrease the crystallizing of coverage layer (ZnS) then result to have any defect in crystal structure (Herz 2003; Drbohlavova et al. 2009). The different methods of (CdSe) QD synthesis and their important selected properties are shown in Table 2 and moreover, a few difference methods of CdSe/ZnS production are listed in Fig. 4.
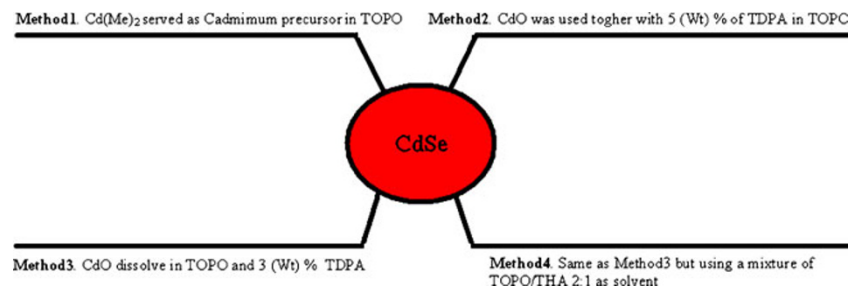
2.2 Optical properties

QDs optical properties (Jiang 2008; Dabbousi et al. 1997; Xing and Rao 2008) can be studied in the ensemble or single molecular of physical point view. The observations of single QDs [and analyzing with TEM (Dabbousi et al. 1997; Guo et al. 2008) (Fig. 5a)] permit to attain of most noticeable photo-physical phenomena such as absorption and emission spectrum, blinking, and other important properties. Any materials have distinct absorption and emission spectrum for themselves that can be used to recognize for them. They produce important data as stoke shift (the fluorescence emission spectrum is shifted by several nanometer towards lower energy transition compared to absorption maximum that the important result for that is enormous extending of QDs size) (Murcia et al. 2008; Machol et al. 1994), inhomogeneous broadening, and thermal spectrum. The inhomogeneous broadening arises from variety in QDs size and there is strongly related among electronic structure (Xing and Rao 2008; Schulz 2007), optical properties, and particle size. In the absorption spectrum, the decreasing of QD size shifts the onset of it to a visible region due to the increasing of band gap energy, moreover by alteration of the QD size, its emission wavelength and color can be adjusted, these phenomena are illustrated in Fig. 5c, d. The absorption is sensitive to several chemical and physical influences such as (Gao et al. 2005; Jiang 2008; Sounderya and Zhang 2008).

1. Spectrum broadening of QDs distribution that arise from inhomogeneous spread effect, concentration of crystalline defect, and inhomogeneous environment
2. The absorption spectrum can be affected by QDs' crystalline structure (FCC, BCC…)
3. The attachment of electrons lead to band flatted related to first exciton peak (Gotoh et al. 2005) and interband transmission
4. The covering of QDs surface with inorganic and organic layer can alter the spectrum absorption.

Temperature as well is a very significant parameter in the definition of optical characterization of materials that can impact on absorption and emission spectrums for example, in the cryogenic temperature (10 K), the spectrum has a

Fig. 3 A few difference sub-methods of organometallic technique for CdSe synthesizing (Geissbuhler 2005)

Method1. Cd(Me)₂ served as Cadmimum precursor in TOPO

Method2. CdO was used togher with 5 (Wt) % of TDPA in TOPO

CdSe

Method3. CdO dissolve in TOPO and 3 (Wt) % TDPA

Method4. Same as Method3 but using a mixture of TOPO/THA 2:1 as solvent

Table 2 Different synthesis (CdSe) methods and their optical and physical properties (Geissbuhler 2005)

Optical and physical parameters methods	Abs max emission (nm)	Stoke shift (nm)	FWHM (nm)	Quantum yield	Shape (from TEM)	Size distribution (%)
1. Cd(Me)2, TOPO	500/580 510/600	10–15	25–30	0.2–0.35	Dots	5–10
2. CdO, 5% TDPA, TOPO	524/555 540/575	16–20	30	0.15–0.2	Rods	≥10
3. CdO, 3% TDPA, TOPO	524/565 540/575	9–13	27–30	0.17–0.6	Dots	10
4. CdO, 3% TDPA, TOPO/HDA	507/543 520/553	9–13	26–28	0.4–0.54	Dots	5

$Cd(Me)_2$ dimethyl cadmimum, *TOPO* trioctylphosphineoxide, *TDPA* thiodipropionic acid, *HDA* 1-hexadecylamine, *FWHM* full width half maximum, *TEM* transmission electron microscope

sharp characteristic related to wavelength and can compare with expected of theory, whereas in the room temperature, we observe a vague of characterization that arises from thermal broadening (Khoon 2008). Similar to absorption, the alteration of temperature can influence on emission that optical feature of it such as FWHM and maximum peak can be changed. Furthermore, photoluminance (PL) intensity of QDs strictly depends on temperature fluctuation and their dependence related to the covering of QD surface. Different behavior of core and core/shell QDs in the thermal non-radiative activation theme reflects in PL intensity curve. These behaviors reveal when QDs used without coverage, the temperature alteration readily affected on carrier interaction, transmission, trapping, and other processing that can arise PL intensity decrement that refers to band gap increase. But when the core of QDs passivated with another inorganic layer, the effect of it strictly altered and has unusual behavior because of the low concentration of defect and transmission loss (Espinosa 2007). The increment of PL with increasing of temperature reveals that the non-radiative rate decreases and this manner of acting reminisced of luminescence temperature anti-quenching. Therefore, these alterations of features (absorption, emission, and PL) limit the application of QDs for example, in biological

application of QDs; the influenceable features of QDs must be controllable for better treatment and therapy (Fu et al. 2005; Vorgelegt 2006; Ted and Chin 2008). Besides, carrier localization is one of the significant parameters that severely depend on core and layer shape, size and potential distribution (Ted and Chin 2008; Burda et al. 2005). The lately theoretical modeling of CdSe/ZnS QD showed that the carrier localization is changed with the alteration of core and shell radius and moreover, it can manipulate the other optical properties. The covering of core in the QDs is another effectible parameter in optical properties alteration such as PL intensity and ref shift. When the core of nanocrystal cover by inorganic materials with higher band gap, because of quantum confinement effect (Burda et al. 2005), eliminating of trap, development of dangling bond, and astonishingly decrease of defect in the surface of core, the optical characterizations of QDs are improved (Fig. 5b, c, and d) and is shown in Table 3.

2.3 Surface modification and functionalization

We report most of QDs surface-modified methods that become water-soluble and functionalized to better interact with biomolecules as protein and DNA. Nanocrystals

Fig. 4 A few difference methods of CdSe/ZnS syntheses (Geissbuhler 2005; Protie're and Reiss 2006)
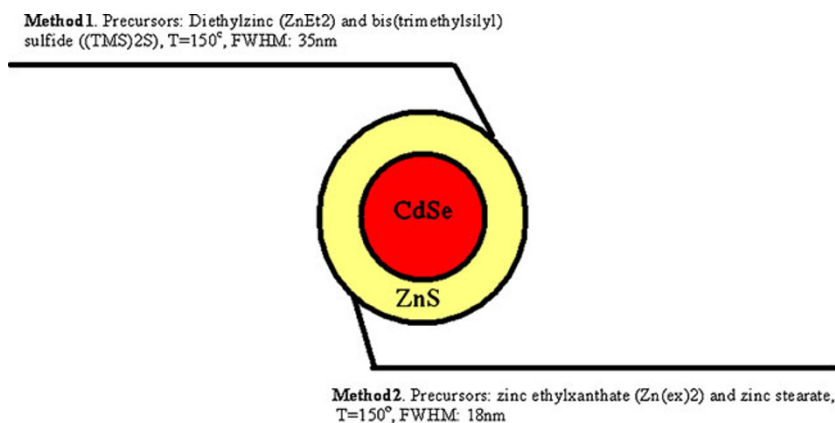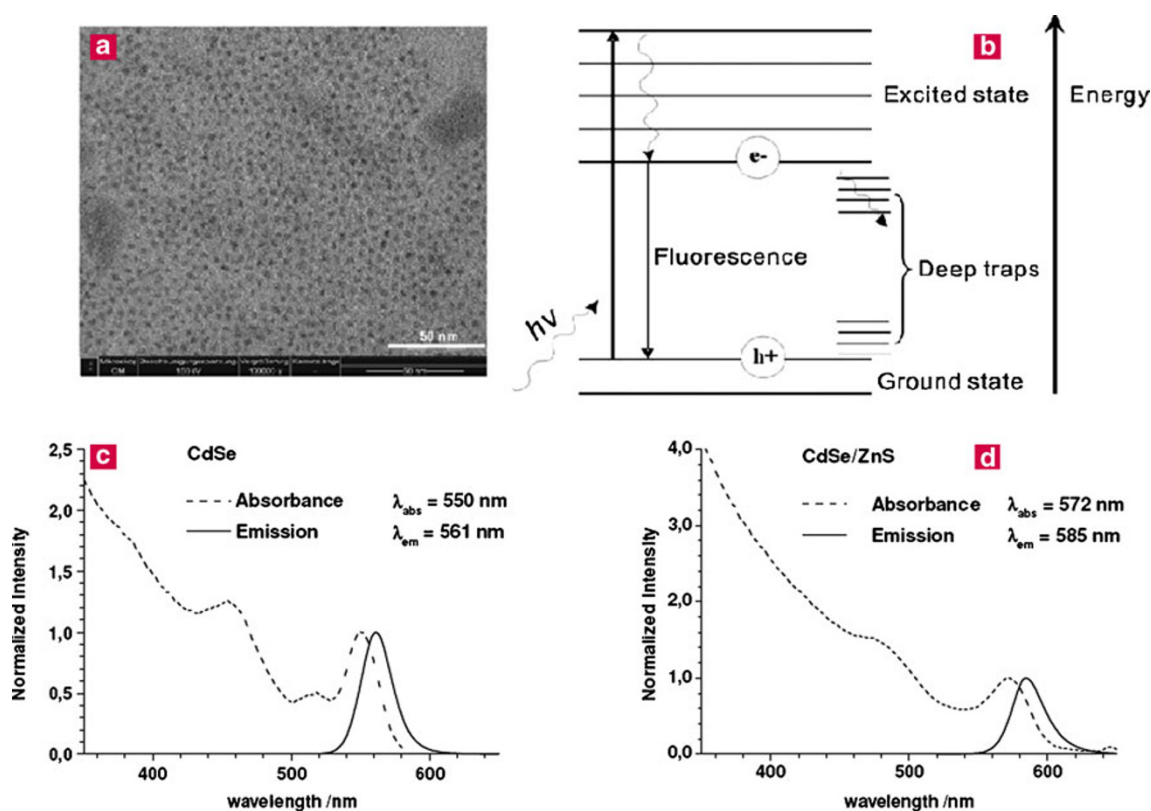
Fig. 5 a Transmission electron micrograph of QD 522 nm. b Schematic presentation of absorbance and fluorescence emission process and trap band in the band gap. c Absorbance and emission spectra of CdSe. d Absorbance and emission spectra CdSe/ZnS quantum dots (Lu 2005; Hezinger 2010)

become water-soluble if they have polar head group or charged group at their surface. QDs produced with high temperature have no water solubility and transferring to an aqueous solution phase needs to surface functionalizing with different water solubility methods which surface functionalizing carry out with ligand exchanging or nano-crystal capsulation. Many of different ligands can be used for replacing of QDs surface that have the different benefits and distinctive applications (Sapsford et al. 2006; Geissbuhler 2005; Medintz et al. 2005). Moreover, most of QD (CdSe, CdSe/ZnS) syntheses performed in an organic solvent in a high temperature which comeback to QD with surfactant covering and the head of surfactant group adds to inorganic surface that the hydrophobic chain of organic solvent (toluene and chloroform) bring into QD colloidal stability but the hydrophobic surface results to insolubility to aqueous

phase. However, because most of QD assays present in an aqueous phase and need to be a water-soluble particle, the surfactant layer of QDs should replace or cover with other layers. It is considerable that the columbic repulsion among QDs with same polarity prevents aggregation in solvent. There are several methods for water solubility of QDs, and this task carries out with different function which one end interacts with QD surface and other certifies the solubility in water. The hydrophilic head group used has thiol (−SH) and carboxyl (−COOH) functionality (Mazumder et al. 2009). In this article, we revise the several different methods for QDs water solubility that are illustrated in Fig. 6. Then, the total tactics for water solubility of QD divides to three categories: first, the exchanging of cap and consists of replacing of trioctylphosphineoxide/trioctylphosphine (TOPO/TOP) local ligand with bifunctional ligand. The second method involves

Table 3 The optical properties of five different CdSe/ZnS QDs (Lu 2005)

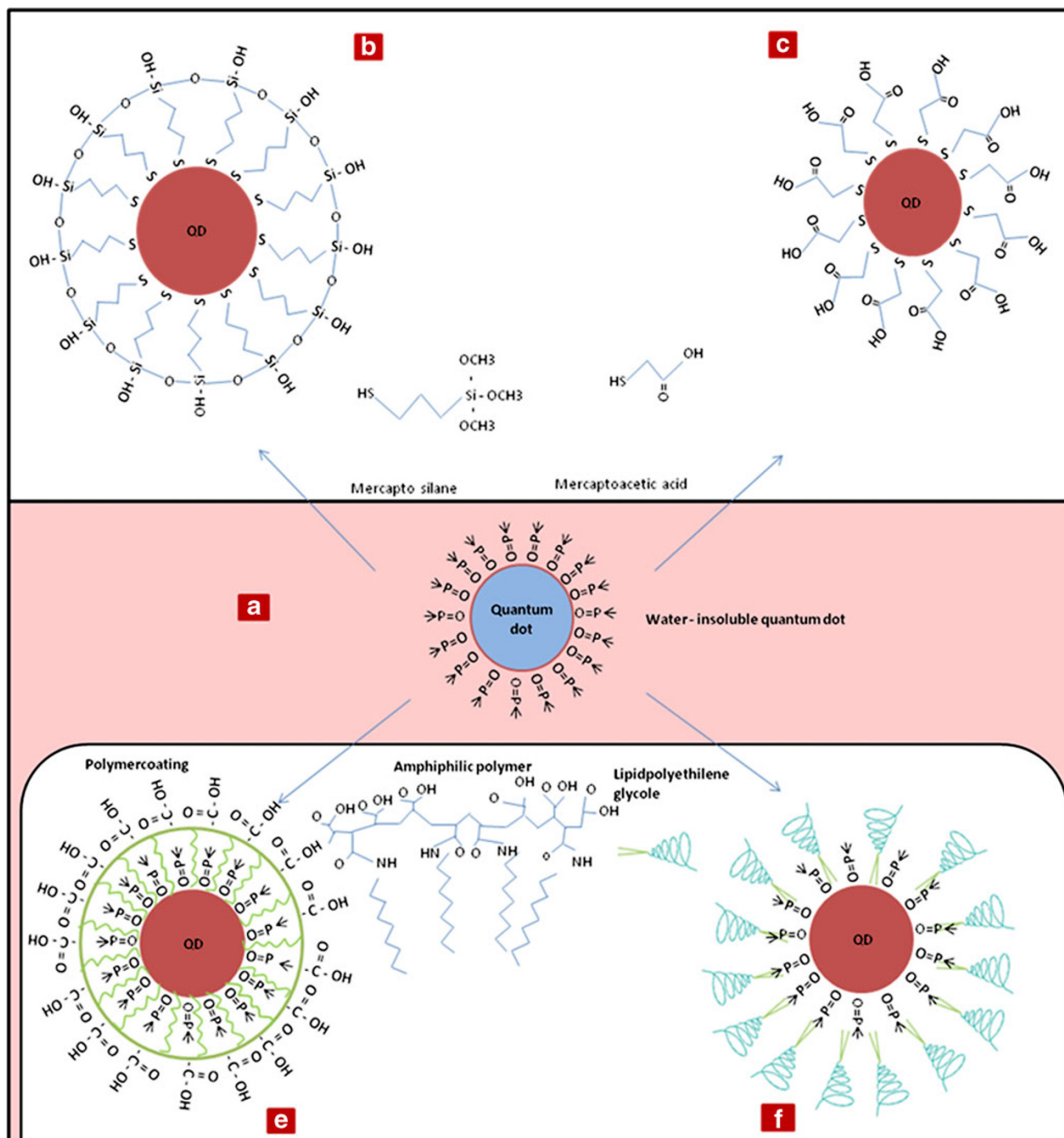| QDs	Abs/Emi max (nm)	Stoke shift (nm)	FWHM (nm)	QY	Core size (nm)
QD 522	504/522	18	39	0.56	2.7
QD 532	516/532	16	36	0.71	2.74
QD 554	539/554	15	35	0.34	3.31
QD 586	570/786	16	38	0.29	4.41
QD 625	600/625	25	40	0.2	4.66

QDs quantum dots, FWHM full width half maximum

Fig. 6 Distinct methods of QDs solubility (**a**) insoluble in water, (**b**) exchange ligand (mercator siliane), (**c**) exchange ligand (mercator acetic acid), (**d**) polymer covering (amphiphilic polymer), and (**e**) polymer covering (lipid polyethylene glycol)

constitute of silica layer polymer functionalized with polar groups that isolate QD surface, and the third procedure preserves the native TOP/TOPO on the QDs and uses variants of amphiphilic "diblock" and "triblock" copolymers and phospholipids to interleave tightly and interdigitate the alkylphosphine ligands through hydrophobic attraction, whereas the hydrophilic outer block permits aqueous

dispersion and further derivitization (Chan et al. 2002). The surface ligand exchange strategy is a direct method for the replacement of surface hydrophobic ligand with hydrophilic one such as dihydrolipoic acid (DHLA), mercaptor acetic acid, and mercaptorsiliane that transforms QDs to water-soluble state. For example, the DHLA-QD (Tran et al. 2002; Medintz et al. 2007) has a negative charge and is stable in an

acid solvent (pH>7) afford to the aggregation of QD and decreasing of PL. The decrement of PL (50–90%) is after ligand exchange with DHLA because of the reduction of passivation by DHLA ligand and its effect on trap, dangling band, and surface charge, and moreover, the diameter size of that composition gets by AFM (Lee et al. 2007; Eaton et al. 2007) is between 9.9−3.7 and 9.9+3.7 nm. The DHLA-QD permits the electrostatic adsorption of biomolecules with positive charge such as avidin or engineering one (poly histidine tag, maltose-binding protein) which is an important bio-linker for the attachment of QD to biomolecules such as protein or DNA on its surface (Eaton et al. 2007; Kim et al. 2004). Nonetheless, drawbacks of the mentioned procedure can limit its application, for example it needs an engineered protein with positive charge, the covalence bond of cross-linking because the attitude of DHLA to protonation is not effective, and in vivo stability and very low PL are other disadvantages of this procedure. The second strategy is capsulate and covering of QD with other layers that transform QDs to a water-soluble state such as amphiphilic polymer and lipid polyethylene glycol. Polyethylene glycol phospholipid (PEG-PL) is a composition that is used in this technique. However, the dilution of PEG-PLs aqueous brings to spherical micelles and is a nanometer size and produce possibility for covering of QD inside polymer.

Due to hydrophobic interaction between TOPO/TOP ligand and head group of PEG-PLs (Kim et al. 2004; Nie et al. 2007), the QDs are stable inside micelle hole. The PEG-PLs in aqueous have low non-specific interaction and because of nontoxicity, these cannot distort the protein and other biomolecules. For example, we report the properties of PEG2000-QD, here, the quantum efficiency of that remains at 40–80% of non-capsulate QD. Moreover, the size of functionalized QD of this procedure due to long chain of PEG2000 is big and limits its application that the hydrodynamic diameter has high range (14–24 nm). Another strategy reports the covering of QD by PLs for eliminating PEG2000-PLs-QD defect that the advisable advantage of this method is the decreasing of PLs-QD size and considered for the most biological application (Jamiesona et al. 2007), and the final size of QD has ranged between 9 and 12 nm in this technique. Furthermore, the PLs-QD refine and wash by cut off concentrator, dialyze but the decrement of PL in this method is big (22–60% of QD PL), the variation of PL in abovementioned methods comeback to type, shape, position, structure, and state of surface ligand and effects of ligand layer on TOPO/TOP molecule (Lu 2005; Sperling 2008; Xia and Rao 2009). The comparisons among optical and electronic properties of methods are illustrated in Fig. 7.

After the solubility of QD, it is ready for attachment of biomolecules to surface for bio-functionalizing which is

done due to: increment of solubility in water for long time, the presence of accessible function group for biomolecular binding, biocompatibility, and decreasing of interfacing with native organic nanoparticles. Applying of QD to biological system, the special biomolecule adds to QD surface without optical property devastation which attaches to QDs by a cross-linker with hydrophilic surfactant layer by active group such as –NH$_2$, –COOH, or –SH (Mazumder et al. 2009; Medintz et al. 2007). Attaching carried out by different techniques including direct linkage, covalent linkage, and electrostatic interaction (Huh et al. 2005) is illustrated in Fig. 8.

At the first method, the biomolecules consist of a thiol group that can be linked to QD surface by mercapto-exchanging process but the cross-linker between Zn and thiol is not tight and dangled, therefore they easily dissociate of QD surface and result to the aggregation of it. Moreover, small molecules such as oligonucleotides, deferent serum albumin readily adsorb to QD surface that it depends on pH (Gao et al. 2002), temperature, and surface charge. In the second method, many scientists demonstrated the technique for the attachment of protein to QD surface with electrostatic interaction that considered an engineered protein (maltose-binding protein; Tran et al. 2002; Zhao et al. 2008) with positive charge to reveal electrostatic interaction with negative charge on DHLA-QD surface but is not sufficiently specific and introduces biological milieu. Moreover, the functionalized QD is not suitable for in vivo application due to the interference of protein with other positive charges, low QY, and the application of DHLA-QD in a specific environment. The last procedure (covalent linkage) displays a very stable binding between QD and biomolecules with the use of a bio-linker and this method is too used for QD functionalizing for in vivo application such as labeling and imaging. Because most of water solubility methods bring out the covering of QD such as carboxylic acid, amino, or thiol group, QDs easily linked to a functional group and can be used for distinctive application. Therefore, the use of QDs in biological application strictly depends on bio-linker and biomolecules that the difference of a cross-linker such as 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide usually used for binding of –NH$_2$ and –COOH and SMCC (4-(N-maleimidomethyl)-cyclohexanecarboxylic acid N-hydroxysuccinimideester) used for –SH and –NH$_2$, by using the third method, the distinction of biomolecules such as biotin, peptide, and protein including streptavidin, avidin, albumin, and antibody is possible to conjugate nanoparticles with ligands, peptides, carbohydrates, nucleic acid, protein, lipids, and polymers (Sapsford et al. 2006; Geissbuhler 2005; Sperling 2008; Xia and Rao 2009; Mulder et al. 2006; Rhyner et al. 2006; Yu et al. 2007a, b; Smith and Nie 2004; Aihua Fu et al. 2005). But there are some distinctive procedures for surface changing

Fig. 7 Normalized PL spectra comparison of two QD samples before and after surface overcoating with (**a**) dihydrolipoic acid (*DHLA-QD*), (**c**) PEG-PLs-QD (PEG2000), (**e**) non-PEG-PLs-QD, (**b**) AFM image of DHLA-QD625 on Mg2+-modified mica, (**d**) TEM images of PEG2000-PLs encapsulated QDs with emission at 586 nm, (**f**) TEM images of PLs-QDs with emission at 586 nm. (Lu 2005)
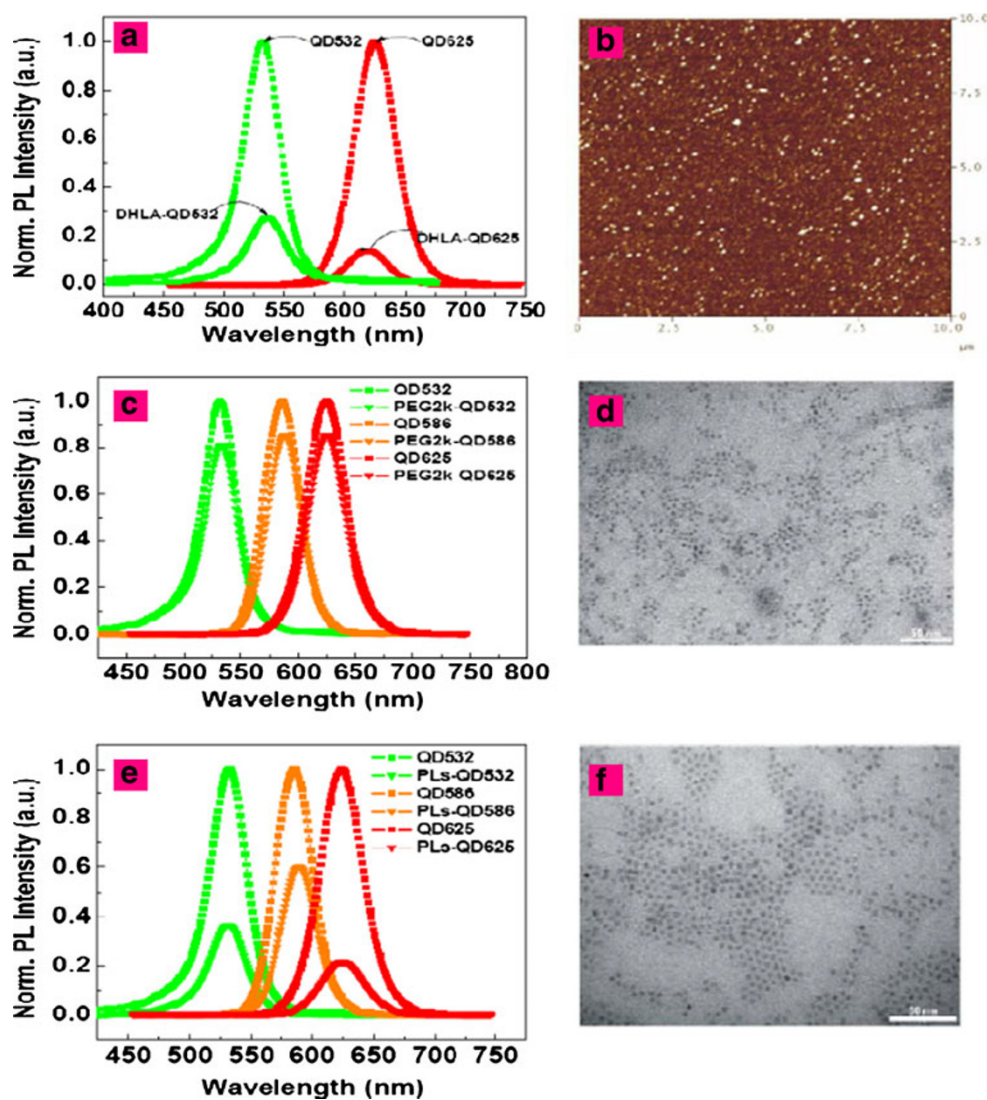
of QD that are summarized in Fig. 9, and biomolecule attached and their applications are listed in Table 4.

3 Nano-biological applications

Human cancer is a complex disease that is brought by unstable genes and alteration of multiple aggregative molecules. The customary diagnostic and beforehand of cancer cannot give complete details of cancer location, therefore the traditional methods for cancer diagnosis such as medical imaging and tissue biopsy have low efficiency and sensitivity, and most of cancer antigen agents cannot differentiate between cancerous and normal cells which become toxic and result to normal cell death. Besides, cancer is often recognized late, and we only detect the cancerous site when its size reach 1 cm in diameter and the cancerous cell has metastasized into other parts of body which in this stage, controlling and destroying them are not

attainable, for example the breast and prostate cancer. Because of those reasons, human cancer is identified as a deadly disease. For solving the problem and selecting the method for complete destruction of the cancerous cells, we need systems that do three important tasks: (a) accurate detection and sensing, (b) tune targeting and obvious imaging, and (c) fine delivery of a drug. With consideration to the above cases, only functionalized QDs with astonishing properties can explain cancer disease and in this section of article, we review and report the three important characteristics of QDs as sensing, targeting, and imaging which are done in a different institute and laboratory (Nie et al. 2007; Smith et al. 2006; Corlu et al. 2007). With regard to QD application in a biological field, we can divide into three categories: biosensing (DNA, protein, and sugar sensing and immunoassays), bio-targeting (passive and active), and bioimaging (live cells, in vitro, single molecule, and in vivo imaging) (Drbohlavova et al. 2009; Xia and Rao 2009). Therefore, QDs are the best candidates for
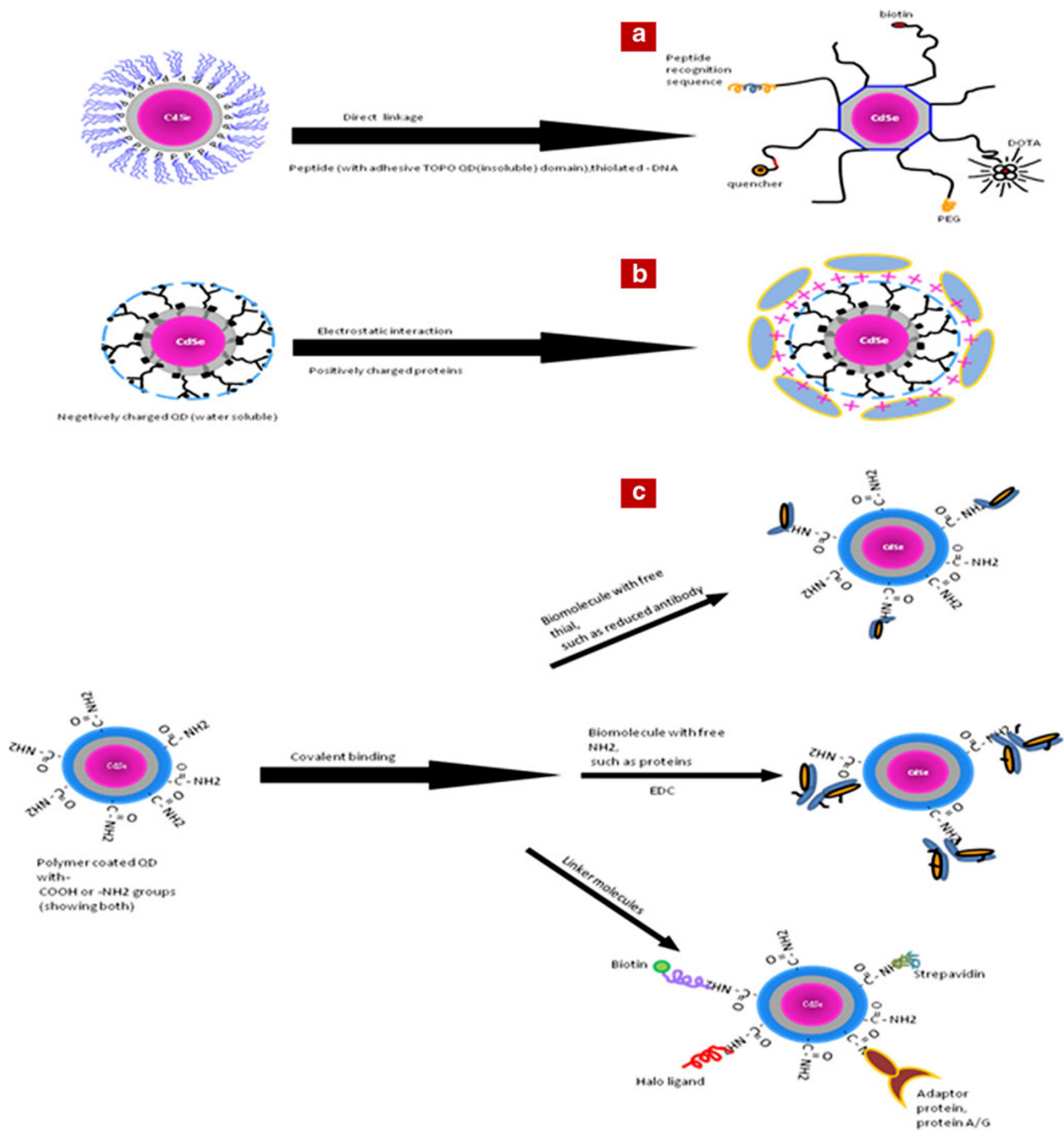
Fig. 8 Common methods used for the QD biofunctionization including: (**a**) direct linkage to the TOPO-coated QDs [biomolecules can be linked including thiolated DNA (ligand exchange)] or peptides with adhesive domains, (**b**) electrostatic interaction, and (**c**) covalent linking (Xing and Rao 2008)

biological application because of their optical and physical properties (the big absorption cross-section, broaden absorption spectra, narrow emission spectra, high-quantum efficiency, resistance to photo-bleaching, photo-stablity, brightness, and the tunable of peak of emission wavelength) and the big volume-to-surface ratio that causes to attach of most biological molecule to QDs surface and the methods of QDs functionalized are explained and revised in Section 2.3 and most of the QD functions that are reviewed are listed in Table 4. Then, in the following of sensitive methods for the detection and diagnostic of cancer, nanotechnology is identified as a big promise which their
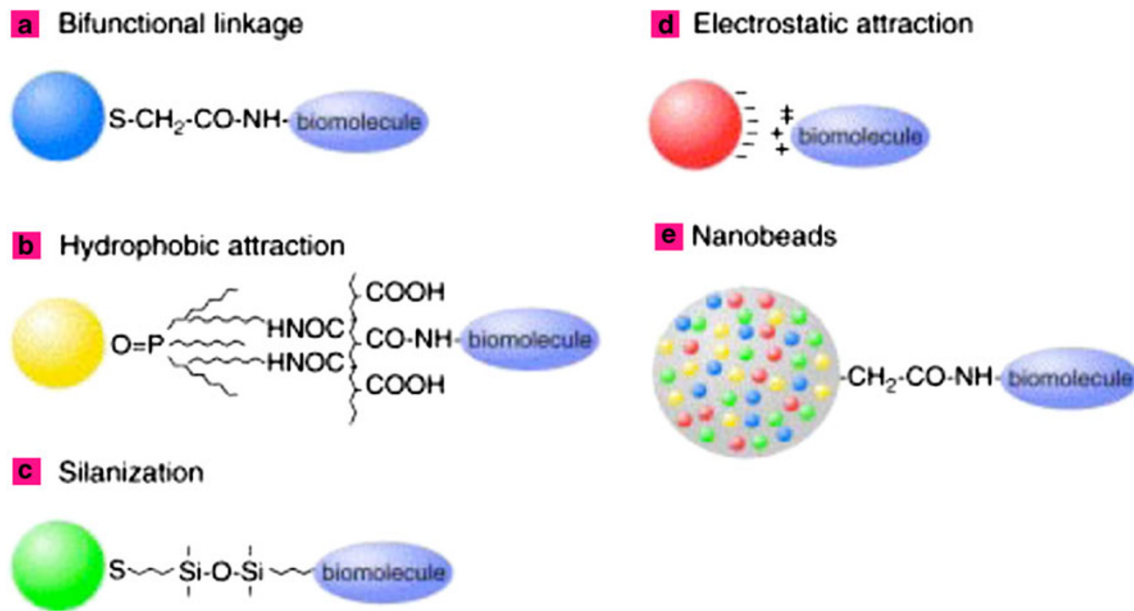
Fig. 9 Schematic illustration resuming the different bioconjugation methods. **a** Use of a bifunctional ligand such as mercaptoacetic acid for covalent linkage of NCs to biomolecules. **b** TOPO-capped NCsbound to a modified acrylic acid polymer by hydrophobic interaction. Then, biomolecules are covalently attached. **c** NC solubilization and bio- conjugation by exchanging TOPO against mercaptosilane, additional silanization and finally covalent linkage to a biomolecule. **d** Creation of negatively charged NCs through ligand exchange, then adsorption of biomolecule via electrostatic interactions. **e** Incorporation of NCs intonanobeads, then linkage to biomolecules (Geissbuhler 2005)

unique properties enable contrast and detectives in order of 10–100 magnitude, then of traditional biomarker in bio- imaging and blood assay. The heart of this technology lies in ability for the decreasing of device size and the construction of nano device in the range between bimolecules and atoms.

3.1 Nano-biosensing applications

The biosensors are a novel class of developed probes that are used for biomarker detection in the real-time form, and the many applications of biosensors relate to DNA, protein, and sugar sensing and immunoassays which the biosensors can be significant for the diagnosis of cancer site due to high operation rate, easy use, low price, and the surprising enabling in high selection rate of biomarkers. The QDs are ideal for biosensing application because of their resistance in photo-bleaching and real-time performance. The func- tionalized QDs can be used in the base of fluorescence resonance energy transfer (FRET is a process in which energy is transferred by a non-radiative, long-range dipole– dipole coupling from fluorophores in an excited state serving as a donor to another proximal ground state acceptor) mechanism that elucidates the ligand receptor binding and the alteration of molecular structure. In the FRET mechanism, QDs play donor role and acceptors can be the dye molecules; in this system, the distance between a donor and an acceptor is a 1–10-nm scale and QDs offer several advantages when used as a donor in FRET system

such as tunable size and narrow emission spectra which noticeably decrease the overlapping among adjacent spec- tra, and moreover expand absorption spectra allow to select an excitation source that relates to minimum absorption of an acceptor and decreasing of direct excitation. Several studies reveal the effective use of QD-FRET for the detection of an analyte by using traditional strategy that implies to binding of QD to target acceptor such as proteins, antibody, or DNA aptamer (Sapsford et al. 2006; Kim et al. 2004; Tran et al. 2002; Basabe-Desmonts et al. 2007). By implementation of the FRET mechanism, the labeled targets lie in the near of QDs and cause to saturate the PL of QD for a limited number of acceptors, therefore the presentation of target to the FRET system brings about decreasing of quantum efficiency and continually increase of QD's PL then with those alteration, therefore, we can sense the multiple important target including the sensing and detecting of different analyte as nutrient maltose and explosive TNT. Moreover, in the FRET systems, as depicted in Fig. 10a, the rate of energy transfer depends on the overlap of fluorescence spectrum of the donor and absorption spectrum of the acceptor, quantum yield of the donor, relative orientation of the donor and acceptor transition dipoles, and the distance between the donor and the acceptor. This allows to measure: (a) interaction among molecules, for example proteins or a protein and a ligand and (b) distances between two sites in a macromolecule. Overall, the important parameters that control the FRET systems are excited-state life time, medium refractive index,

Table 4 QDs biomolecule attached and their application

QD–functions	Applications	Ref.
QD–RGD peptide	Labeling and imaging	(Mazumder et al. 2009)
QD–streptavidin	Immunolabeling	(Mazumder et al. 2009)
QD–AFP-Ab	Imaging and targeting	(Chen et al. 2008)
QD–oligonucleotides	Cell labeling	(Sapsford et al. 2006)
QD–streptavidin/biotinylated DNA	FISH detection	(Sapsford et al. 2006)
QD–DNA	Hepatitis B and C and SND detection and biosensing	(Sapsford et al. 2006; Medintz et al. 2005)
QD–avidin	Labeling	(Sapsford et al. 2006)
QD–anti-TNT	Immunodetection	(Sapsford et al. 2006)
QD–antibody	Biosensing and small molecular detection	(Sapsford et al. 2006)
QD–aptamer	ATP detection	(Drbohlavova et al. 2009)
QD–protein	Biosensing	(Smith et al. 2006)
QD–MBP-Cy3-β-CD-Cy3.5	Biosensing	(Toshihide and Kayozabo 1992)
QD–TAT	Endothelial cell targeting and labeling	(Stroh et al. 2005)
CHP–QD–Hela	Cervical cancer	(Wang et al. 2008a)
QD–Luc8	BRET system	(Xia and Rao 2009)
QD–PSMA	Prostate cancer	(Fu et al. 2005)
QD–PEG–PLA	Biomedical imaging and detection	(Manda et al. 2005)
QD–PEG–antibody	Prostate cancer detection	(Jamiesona et al. 2007)
QD–PEG–DSPE	Magnetic imaging	(Mulder et al. 2006)
QD–peptide	In vivo vascular tumor targeting	(Fu et al. 2005)
QD–CA 125	Ovarian cancer	(Peng and Li 2010)
QD–HER2	Breast cancer	(Peng and Li 2010)
QD–PSA	Prostate cancer	(Peng and Li 2010)
QD–anti-claudin-4	Pancreatic cancer	(Peng and Li 2010)
QD–AFP	HCC (hepatocelluar)	(Peng and Li 2010)

QD quantum dot, *AFP* alpha-fetoprotein, *PSA* prostate-specific antigen, *MBP* maltose-binding protein, *FISH* fluorescence in situ hybridization, *PSMA* prostate-specific membrane antigen, *HER2* human epidermal growth factor receptor 2, *CA 125* carbohydrate antigen 125, *PEG* polyethylene glycol, *DSPE* 1,2 distearoyl-sn-glycero-3-phosphatidylethanolamine, *PLA* polycaprolactone, *Luc 8* luciferase, *RGD* arginine–glycine–aspartic acid, *DNA* deoxyribonucleic acid, *BRET* bioluminescence resonance energy transfer, *ATP* adenosine triphosphate

quantum yield of donor, relative orientation of donor–acceptor dipole, integration of spectrum overlap between the donor and the acceptor, and the number of acceptors attached at each QD. In this section, we report several examples of QD biosensing applications: (a) Goldman and coworkers used of QDs conjugated to an antibody for small molecular detection. (b) QDs are used in monitoring of protein biomarkers in stationary cells including the measurements of antigen cells B and T with different colors and proliferation monitor in PMP70. (c) Hahn et al. revealed that the improvement of QDs' sensitivity compare to dye organic for detection of *Escherichia coli* 0157:H7. (d) The use of sandwich immunoassays for simultaneous detection of four toxins cholera, ricin, shiga-like toxin 1, and staphylococcal enterotoxin B is reported. (e) Another example displayed the use of QD-antibody for the sensing of difference between diphtheria and tetanus toxins. (f) Yang et al. showed the concurrent detection of bacteria and *Salmonella typhimurium* by the use of QDs' different colors. (g) The use of QD probes in fluorescence in situ hybridization for the detection of DNA and mRNA is reported. (h) Panthak et al. report the labeling of Y chromosome in human sperm cells employed by QD-oligonucleotide probes. (i) Xiao and coworkers used QD–streptavidin at labeling of special probes biotinylated oligonucleotides for HER2 localization. (j) Moreover, the QD-FRET used for DNA detection is reported. (k) Chen and Gerion observed that the viral peptides called nuclear localization signals conjugated with CdSe/ZnS QDs has no toxic effect in HeLa cells transfected with the peptide-coated QDs and shown in Fig. 10b (Geissbuhler 2005; Drbohlavova et al. 2009; Medintz et al. 2007; Peng and Li 2010; Smith et al. 2006).

For conclusion, the mention of this point is noticeable that FRET measurements enable to convey the important data from donor–acceptor interaction. However, there are
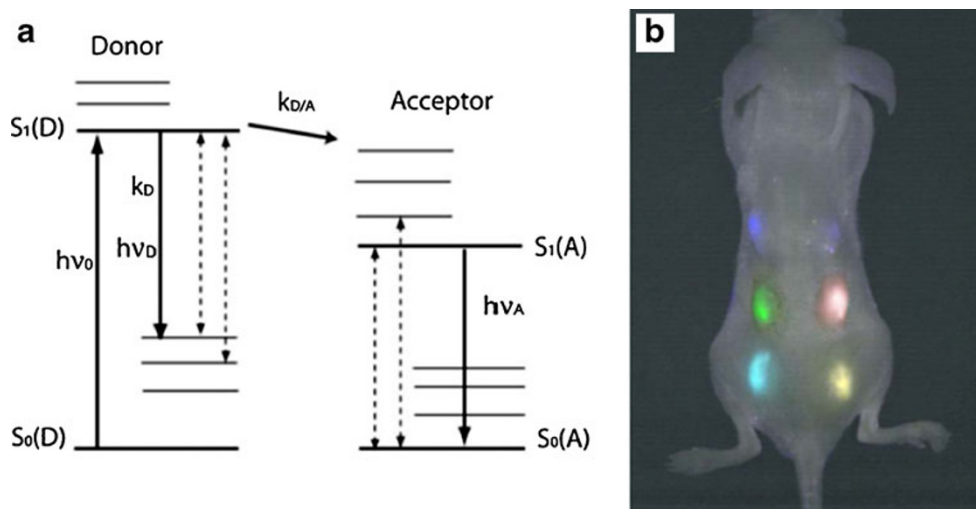
Fig. 10 FRET mechanism. **a** Energy diagram for the non-radiative energy transfer. $S_0(D)$ and $S_1(D)$ are the ground and first excited singlet states of the donor; k_D and k_D/A are the rate constants for the radiative and non-radiative energy transfer processes, respectively. *Solid lines* depict photon-participated transitions; *dashed lines* depict resonant transitions in the electronic structures of the donor and acceptor. **b** Further utility of QDs have been found in labeling of nucleus in live cells, however, this issue has not been not fully studied. (Geissbuhler 2005; Drbohlavova et al. 2009)

several problems that can disrupt the FRET systems operation including: (a) the QDs that bring out of the same synthetic method have different structure and spectra because of more stage of QD synthesizing and small fluctuation for defect present in core and layer. These defects have a significant effect on photo-physical properties of QD, peak situation of spectra distribution, and spectra median of QDs that affected on Förster radius of FRET system. (b) Another annoying parameter that can affect on FRET parameters is blinking. The QD blinking is associated to charge trapping and un-trapping at surface defects during excitation and results in alternation (at all timescales) of bright and dark states during which no photons are emitted. For the last case, we must mention that QDs have a longer life time (20–30 ns) than dye fluorophores (1–4 ns) and auto-fluorescence (2 ns). Because the fluorescence decay of QDs is long enough, the auto-fluorescence signal (is one of the noise source and reason for decreasing of FRET system sensitivity) has vanished and QDs still emit photons (Stroh et al. 2005).

3.2 Nano-bio-targeting impacts

The cancer stem cells are the set of cells that contain the self-reproducible properties. Lately, the therapy of cancer may be very effective if the stem of cancer cells are fine targeted and this task need for a device similar to molecule and atom size that can easily move and have unique properties to satisfy the tune-targeting parameters such as tunable size, photo-stability, resistance to photo-bleaching, and robust (Juzenas et al. 2008; Meijering et al. 2006) was hypothesized. By reviewing several reports, we reveal that most of cancer antigen agents cannot differentiate between normal and cancerous cells and cause to be toxic of them; therefore, nanotechnology offers some distinctive methods for targeting and can produce significant advantage for cancer patient therapy. In fact, the use of nanoparticles for targeting is an important application of nanotechnology in cancer that proposes two methods for that: passive and active targeting.

3.2.1 Passive targeting

The cancerous tissues include two arrogant factors because of them. The QDs easily accumulate and aggregate in tumor site. The factors necessary for passive targeting are: (a) the growth of tumor site produces vascular endothelial growth agent to promote the angiogenesis. (b) Most of tumor sites lack lymphatic drainage systems which cause to accumulate QDs to targeted location. For passive targeting, the size and surface properties of nanoparticle must be controlled, therefore for the improvement of targeting time, the optimum size of QDs should be smaller than 100 nm in diameter and the surface of QDs must be amphiphilic. In this targeting strategy, the normal tissues are connected by endothelial cells and QDs cannot pervade into cells but the tumor cells have most leakage site and cause to penetrate QDs into vascular cells. However, in some cancers such as lung, passive targeting is an inefficient method because in this cancer, tumor site accessibility is very hard and this method is not used (Sharma et al. 2009; Yu et al. 2007b). The scheme of passive targeting method is illustrated in Fig. 11a.

Fig. 11 a Permeation and retention of QD probes via leaky tumor vasculatures (passive targeting). **b** High affinity binding of QD–antibody conjugates to tumor antigens (active targeting) (Gao et al. 2004)
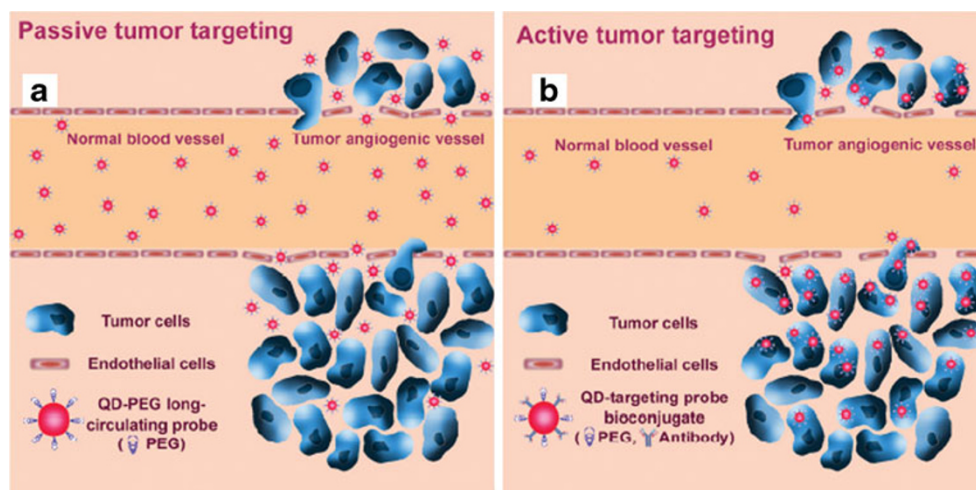
3.2.2 Active targeting

The active targeting is usually attained by binding of QDs to targeting element that produces superiority accumulation of QDs in tumor organs, tumor, cancer cells, or interstitial tumor cells. This procedure is in the base of especial interaction as antibody–antigen, ligand–receptor, and lectin–carbohydrate. In this method, because the use of attached particle in QDs surface, the targeting characteristics such as efficiency and speed are high. The targeting proposition is one of the significant problems in cancer therapy in which the precision and high-speed performance targeting are affected on accurate diagnostics of tumor site and decreasing normal cell destruction. The scheme of active targeting of tumor site is illustrated in Fig. 11b.

In the in vivo state, the QD probes can be delivered to tumor site both by passive targeting mechanism and active targeting. In the passive targeting, big molecule and particle accumulate in tumor area with preference regarding through permeability development and retain effect but active targeting use of specific antibody attached to QD surface for targeting the considered point. For example, when QD-anti-AFP for targeting was used, we can reveal the obvious fluorescence of an area and then easily analyze data, but in the passive targeting mode, a few of QDs can be reach to a target point and we have no obvious targeting, therefore this distinction between the targeting methods and QDs or QD-anti-AFP fluorescence are illustrated in Fig. 12a, b, and c. Moreover, when the QDs targeted the tumor and accumulate in that area, we can arrange contour map of fluorescence intensity of QDs in the cancerous tumor. The contour map (Fig. 12d) is a fluorescence intensity map that organizes by the measurements of intensity detected site by site. The different colors in the map show the inhomogeneous distribution of cancer cells in the targeted point. The cold colors display the low intensity of fluorescence which

is because of low population of QDs in tumor site and vice versa the hot color. Therefore, the numbers of QDs arrived to tumor site perfectly depend on the targeting method and if we used active targeting, most of injected QDs can be reach to a cancerous tumor and we have a very bright contour map. Furthermore, the map shows the complexity of tumor site (Gao et al. 2004; Yu et al. 2007a, b).

3.3 Nano-bioimaging implementations

The nanoparticles have optical properties that make them suitable for high-quality imaging and in this category of application, the nanoparticle specifically QDs are used as fluorescence marker of live cell receptors and depended marker to oncologic. The QDs absorb white light and re-emit that in few nanoseconds which have tunable wavelength dependent on size, semiconductor natures, and the proportional composition of material used in structure which spreads the wavelength between UV to infrared (IR) (Kairemo et al. 2008; Ballou et al. 2004). In the past years, several techniques are used for imaging and imply to signal that emits from tissue by the use of an ultrasound wave, X-ray wave, gamma rays, and radio wave and the contrast of image (the most of different tumor is identified in the base of image contrast) produced by the difference of attenuation of signals which usually are function of tissue and anatomy structures. However, none of attained image can totally analyze the cancerous tumor site that may do with quantitative in vitro assay and tissue biopsy evaluation, besides the multiple detection of biomarker becomes very hard by the use of those traditional techniques and none of them have no possibility of an inherent high-spatial resolution of small tumor site. As a result, the production of highly accurate spatial image of low population of biomarker can astonishingly trend to detection and diagnosing of cancer and especially for metastases sites (Willard
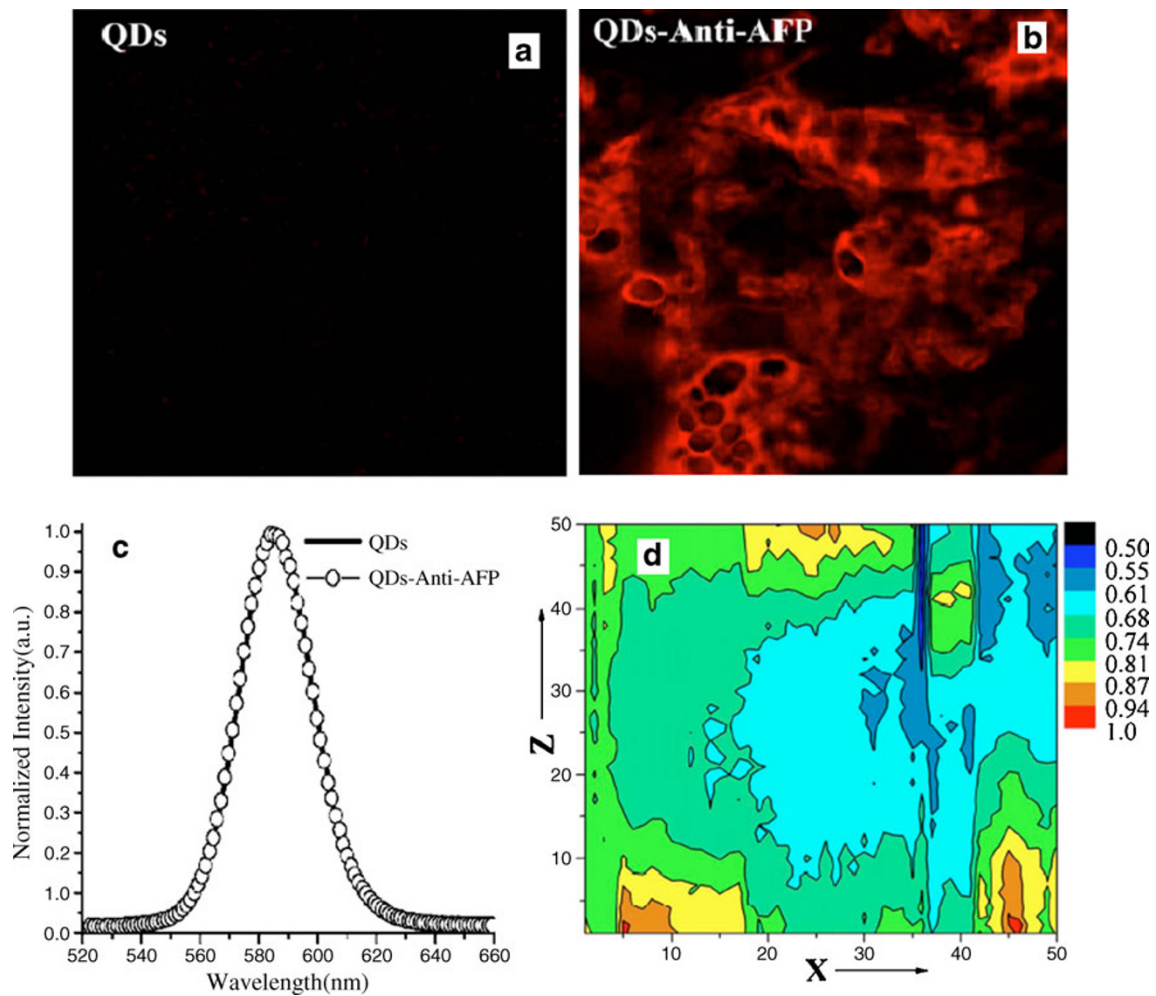
Fig. 12 Histological examination of QD passive and active targeting ability. **a** Passive targeting. **b** Active targeting **c** Fluorescence spectral comparison between QDs and QDs-anti-AFP. **d** Fluorescence intensity contour map of a detected cancerous area in the QDs-tagged tumor. Although all the sampling sites are in the tumor, their fluorescence intensities are different and the map exhibits the inhomogeneous distribution of the fluorescence intensities in the detected area of the tumor; (Yu et al. 2007a, b)

et al. 2006; Sperling 2008). With the introduction of the above important point, because QDs have the photostability greater than organic dye, this unique property allows them to construct high-rate imaging and 3D image with high resolution. Moreover, resistance to photobleaching became very important, if the assay for detection and imaging of live cell alteration needs a very long time in order of days or weeks. In contrast to dye fluorophores, QDs have wide photon absorption spectra and narrow emission tunable spectra that the simultaneous detection and imaging of multiple targets become possible. Recently, the novel QDs are presented that have expanded absorption spectra (UV-IR), therefore the multicolor imaging of targets is attained and reached images are easily analyzed with important details (Peng and Li 2010; Pinaud et al. 2006). In this section, we only review the in vivo imaging. The unique optical properties of QDs cause them to be a very attractive device as the fluorophores in the in vivo imaging,

whereas the customary fluorescence in the base of an organic molecule produces slight stability and small possibility in simultaneous detection of multiple targets (Sounderya and Zhang 2008; Medintz et al. 2005; Sperling 2008; Xia and Rao 2009; Jaiswal et al. 2004). Therefore, in contrast with traditional in vivo imaging probes such as positron emission tomography, single photon emission computed tomography, and MRI (Zhao et al. 2008; Mulder et al. 2006), QDs antibody labeled and targeted produce several features and unique capabilities: (a) optical and electronic properties depended on size and are tunable with particle size alteration which produces the expand range of nanoparticle for simultaneous detection and imaging of cancerous cell biomarkers. (b) The QDs have big surface-to-volume ratio to accumulate several different functional groups that can use to diagnose multiple targets, therefore this condition obligates to design of multifunctional nanoparticles for high-quality imaging. (c) The wide researches

have been shown that the nanoparticle in size (10–100 nm) without antibody attached aggregated in tumor site because of permeability and retention reasons (Nie et al. 2007). Furthermore, the high brightness of QDs and its resistance to photo-bleaching enable them to continually emit for a long time present them as important agent for in vivo imaging, as well as in nanoparticle syntheses improvement, covering and surface modification significantly enhanced them application in targeting and imaging. With the use of a suitable cover, we can attain long exposure time, high stability, and decreasing of QDs depositing that are very important in vivo parameters. One of the important properties of QDs is the big absorption cross-section that enables them for more efficient performance of deep tissue specimen by multi-photon excitement. With the use of this technique, the fluorescence signals can be detected in depth of several microns through live mice at an in vivo imaging. For example, the results of NIE groups showed that the

potential use of QDs for design of remote particle in targeting and in vivo imaging of live animals. Another report shows the use of QDs conjugated to specific antibody for labeling on cancerous prostate cells (PSMA). As a result of QDs properties (big absorption cross-section, long life time, and photo-stability), in vivo imaging constructed by QD agents is very sensitive and blithe but, auto-fluorescence emitted from substrate (noise) are a caution for this procedure and can be an important limitation factor. For elimination of this factor, more strategy is suggested: (a) one method is an emission scanning microscopy that is used for separation of fluorescence emission of QDs and auto-fluorescence because of narrow emission of QDs. (b) The effective method is a spectral displacement visible to near infrared (NIR) because most of the chromosphere organs absorb slight light in high wavelength and another profit of this method is used in deep tissue imaging (Jamiesona et al. 2007; Fu et
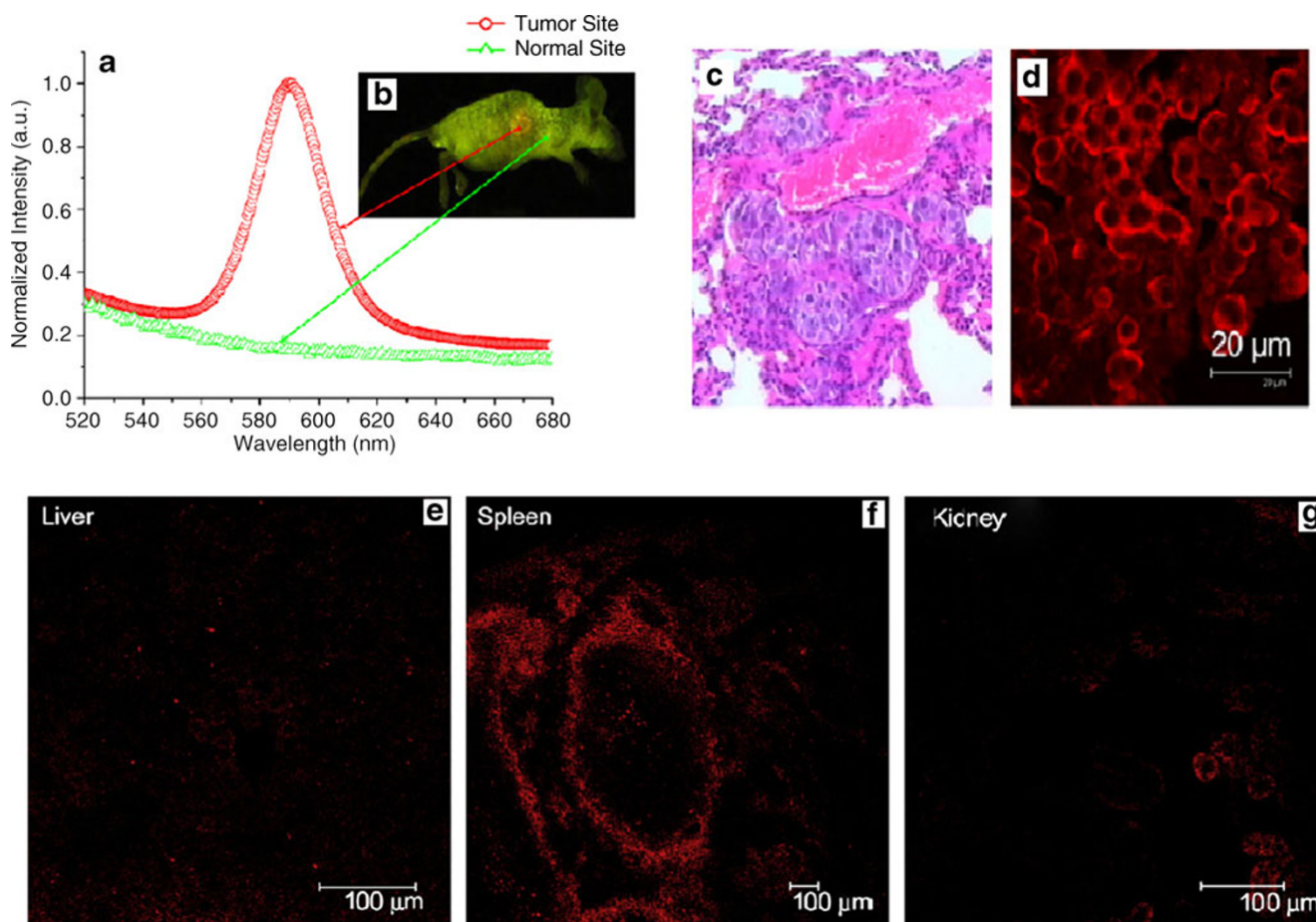

Fig. 13 **a** In vivo targeting and imaging subcutaneous tumor model with QD–AFP–Ab probes the spectra analysis of the tumor site (*red arrow*) and the normal tissue adjacent to the tumor site (*green arrow*). The fluorescence spectra of tumor site were the same with those of QD–AFP–Ab probes, but there was no characteristic 590-nm peak of the QD at the normal tissue site. **b** The HE staining of the tumor

section. **c** The confocal microscopic imaging of the tumor section showed the specific binding of QD–AFP–Ab probes to tumor cells. **e, f, g** The QD distribution in the liver, spleen, and kidneys. The tissue sections were observed with CLSFM. As shown in the figures, QD590 was mainly distributed in the liver, spleen, and kidneys (Chen et al. 2008)

al. 2005). Tissue imaging with NIR and IR excitation eliminate some of visible imaging problems such as slight transfer of visible light through depth tissue. Because in the NIR window spectrum, the Rayleigh scattering is decreased, besides the absorption due to water and hemoglobin has the minimum quantity. Moreover, there is small amount of dye molecule that emits light between NIR, then background noise significantly decreased (Rhyner et al. 2006; Smith and Nie 2004; Smith et al. 2006; Zhao et al. 2008; Lim et al. 2003; SalmanOgli and Rostami 2010). One of the in vivo assays report showed the use of QDs conjugated to AFP-Ab for in vivo imaging and histological examination of QD and QD-AFP-Ab are shown in Fig. 11. Nonetheless, diagnostic of small metastases site is a very important case in cancer which in above example the QD-AFP-Ab is injected to live mice for lung metastases imaging. In this assay, the spectral analyses reveal that normal organ fluorescence spectra is similar to cancerous one but has not the intensity peak and moreover, specific binding probes to metastases confirm by Fig. 13 and their reports display the QD-AFP-Ab probes can be used to detects of small lung metastases and HCC lung metastases model (Chen et al. 2008; Yu et al. 2007a, b). Another report of an in vivo cancer detection explains the specific conjugation of QD to anti-AFP binding to hepatoma and they use QD anti-AFP for AFP that is the original element of mammalian fetal serum and the alteration of AFP blood level determines the hepatocelluar carcinoma, therefore the aggregation and retention of AFP in the tumor site are essential for detection and imaging for cancer therapy (Yu et al. 2007a, b). In the next assays of in vivo imaging and targeting, the use of surface ligand PEG with QDs is reported that used for performance time improvement, decreasing of dosage, and targeting development (Manda et al. 2005; Stroh et al. 2005; Zhao et al. 2008). Recently, the self-illuminating QDs conjugated to new probes for in vivo imaging are reported.

4 Conclusion

In this article, we revised the distinct methods of syntheses, optical properties and surface modification and functionalization of QDs (CdSe/ZnS) for specific biomedical applications such as detecting and sensing and targeting and imaging. With regard to late reports and assays, we revealed that: (a) the different methods of syntheses significantly affected on optical properties (peek absorption distribution, FWHM of emission spectra, and coordination of absorption and emission spectra), physical properties (size, inhomogeneity of QDs structure), (b) the distinct functionalized procedures carry out by attention to specific application and the QDs size must be controlled, (c) the functionalized

particle must be confirmed by considering some vital parameters such as photo-stability, photo-bleaching, biocompatibility, and non-toxicity, (d) the separate composition of functionalized QDs can be used in FRET mechanism for biosensing application, (e) the active targeting is an effective method which performed with high speed and accurate targeting and easily used for cancerous site targeting, (f) imaging with QDs functionalized is done for high resolution and precision and attained imaging disclose the small cancerous site with majority details that help me for cancer therapy.

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